Public Assessment Report

Mutual Recognition Procedure

CONCERTA® XL 27 MG PROLONGED-RELEASE TABLETS

(methylphenidate hydrochloride)

UK/H/0544/004/MR

UK licence no: PL 00242/0400

Janssen-Cilag Limited

Medicines and Healthcare Products Regulatory Agency

CONCERTA® XL 27 MG PROLONGED-RELEASE TABLETS

PL 00242/0400

UK/H/0544/004/MR

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Concerta XL 27 mg prolonged-release tablets (Product Licence number 00242/0400). It explains how Concerta XL 27 mg prolonged-release tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Concerta XL 27 mg prolonged-release tablets. For practical information about using Concerta XL 27 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

- **What are Concerta XL 27 mg prolonged-release tablets and what are they used for?**

Concerta XL 27 mg prolonged-release tablets contain the active ingredient methylphenidate hydrochloride, which is a psychostimulant that belongs to a group of medicines called centrally acting sympathomimetics.

Concerta XL 27 mg prolonged-release tablets are used to treat 'attention deficit hyperactivity disorder' (ADHD). It is used in children and young people between the ages of 6 and 18, and only after trying treatments which do not involve medicines (such as counselling and behavioural therapy).

Concerta XL is not for use as a treatment for ADHD in children under 6 years of age or for initiation of treatment in adults. When treatment was started at a younger age, it might be appropriate to continue taking Concerta XL when you become an adult. Your doctor will advise you about this.

- **How are Concerta XL 27 mg prolonged-release tablets used?**

The medicines can only be obtained with a prescription.

- **How do Concerta XL 27 mg prolonged-release tablets work?**

Concerta XL 27 mg prolonged-release tablets work by improving the activity of certain parts of the brain which are under-active. The medicine can help improve attention (attention span), concentration and reduce impulsive behaviour.

The medicine is given as part of a treatment programme, which usually includes psychological, educational and social therapy.

It is prescribed only by doctors who have experience in children or young people's behaviour problems. Although there is no cure for ADHD, it can be managed using treatment programmes.

- **How have Concerta XL 27 mg prolonged-release tablets been studied?**

Clinical studies have already been submitted for the approval of marketing authorisations (licences) for Concerta XL 18, 36 and 54 mg prolonged-release tablets (Product Licence numbers 00242/0372-4). As the non-clinical and clinical data required for the grant of a marketing authorisation for this product have already been submitted for Concerta XL 18, 36 and 54 mg prolonged-release tablets, no new non-clinical or clinical data were submitted with this application.

- **What is the risk associated with Concerta XL 27 mg prolonged-release tablets?**

There are several side effects that could be serious and for which you would need to see a doctor straight away. These include common side effects (may affect up to 1 in 10 people), such as uneven heartbeat (palpatations), mood changes/swings or changes in personality; uncommon side effects (may affect up to 1 in 100 people), such as thinking about or feeling like killing yourself, seeing, feeling, or hearing things that are not real (these are signs of psychosis), uncontrolled speech and body movements (Tourette's), signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing; rare side effects (may affect 1 in 1000 people), such as feeling unusually excited, over-active and uninhibited (mania); and very rare side effects (may affect 1 in 10000 people), such as heart attack, sudden death, suicidal attempt, fits (seizures, convulsions, epilepsy), skin peeling or purplish red patches, inflammation or blocked arteries in the brain, muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system -due to a temporary lack of blood supply to the brain, decrease in number of blood cells (red cells, white cells and platelets) which can make you more likely to get infections, and make you bleed and bruise more easily; a sudden increase in body temperature, very high blood pressure and severe convulsions ('Neuroleptic Malignant Syndrome').

There are also the following side effects that have an unknown risk (frequency cannot be estimated from the available data): unwanted thoughts that keep coming back; unexplained fainting, chest pain, shortness of breath (these can be signs of heart problems); paralysis or problems with movement and vision, difficulties in speech (these can be signs of problems with the blood vessels in your brain) be taken in combination with methylphenidate.

If you experience any of these side effects while taking Concerta XL 27 mg prolonged-release tablets, you must contact your doctor immediately.

For a full list of all side effects reported with Concerta XL 27 mg prolonged-release tablets, please see the package leaflet.

Concerta XL 27 mg prolonged-release tablets should not be used in people who are hypersensitive (allergic) to methylphenidate hydrochloride or any of the other ingredients. This product has an influence on the ability to drive and use machines (dizziness and fatigue is experienced commonly). You also must not drink alcohol while taking this medicine. This product contains lactose; you should consult your doctor before you take this medicine if you cannot tolerate or digest lactose.

You must consult your doctor before taking this medicine if you are having sex, pregnant (or think you might be pregnant) or breast-feeding. Also you should not take this medicine if you have taken a medicine called a "monoamine oxidase inhibitor" (MAOI) in the last 14 days. You should also consult your doctor before taking this medicine if you have been taking medicines for depression, severe mental health problems, epilepsy, to reduce or increase blood pressure, cough/cold remedies that affect blood pressure, medicines that thin blood to prevent clots.

You should inform your doctor if you are going to have an operation, as some anaesthetics can cause a sudden rise in blood pressure.

- **Why is Concerta XL 27 mg prolonged-release tablets approved?**

It was concluded that the effect of Concerta XL 27 mg prolonged-release tablets to treat the symptoms of ADHD in patients between the ages of 6 and 18, and only after trying treatments which do not involve medicines (such as counselling and behavioural therapy) had been shown.

It was considered that the benefits of Concerta XL 27 mg prolonged-release tablets outweigh their risks and the grant of a marketing authorisation was recommended.

What measures are being taken to ensure the safe and effective use Concerta XL 27 mg prolonged-release tablets?
A risk management plan has been developed to ensure that Concerta XL 27 mg prolonged-release tablets are used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Concerta XL 27 mg prolonged-release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

- **Other information about Concerta XL 27 mg prolonged-release tablets**

Austria, Belgium, Germany, Greece, Spain, Finland, France, Ireland, Iceland, Luxembourg, the Netherlands, Norway, Portugal and Sweden agreed to grant Marketing Authorisations for Concerta XL 27 mg prolonged-release tablets on 6 May 2008. A national licence had previously been granted in the UK on 9 March 2007.

For more information about treatment with Concerta XL 27 mg prolonged-release tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in 11-2013.

The full PAR for Concerta XL 27 mg prolonged-release tablets follows this summary.

CONCERTA® XL 27 MG PROLONGED-RELEASE TABLETS

PL 00242/0400

UK/H/0544/004/MR

TABLE OF CONTENTS

Module 1
Information about initial procedure

Product Name	Concerta XL 27 mg prolonged-release tablets
Type of Application	Full dossier, Article 8.3
Active Substance	Methylphenidate hydrochloride
Form	Prolonged-release tablets
Strength	27 mg
MA Holder	Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK
Reference Member State (RMS)	United Kingdom
Concerned Member State (CMS) countries	Austria, Belgium, Germany, Greece, Spain, Finland, France, Ireland, Iceland, Luxembourg, the Netherlands, Norway, Portugal and Sweden
Procedure Number	UK/H/0544/0004/MR
Timetable	Day 90 – 6 May 2008

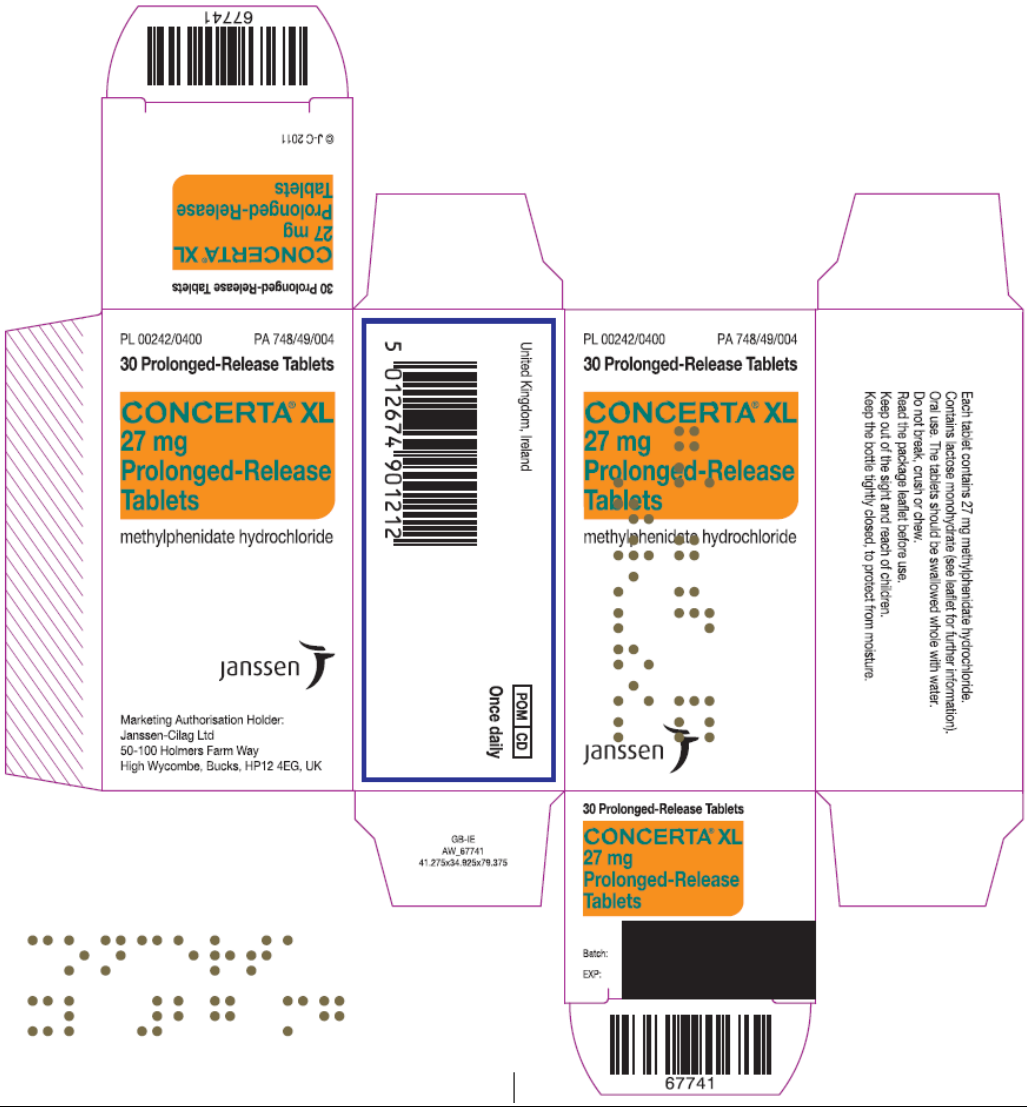
Module 2
Summary of Product Characteristics

The current approved UK versions of the Summary of Product Characteristics (SmPCs) for this product is available on the MHRA website.

Module 3
Patient Information Leaflet

The current approved UK versions of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.

Module 4
Labelling



Module 4
Scientific Discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS and CMS countries agreed to grant a Marketing Authorisation to Janssen-Cilag Limited for the medicinal product Concerta XL 27 mg prolonged-release tablets (PL 00242/0400; UK/H/0544/004/MR) on 6 May 2008. A national licence had previously been granted in the UK on 9 March 2007. This product is only available as a prescription-only medicine.

This application for a mutual recognition procedure (MRP) is for prolonged-release tablets containing 27mg of the psychostimulant, methylphenidate hydrochloride. The application has been submitted under Article 8.3 of Directive 2001/83/EC, a full-dossier application of a line extension to the existing Marketing Authorisations for Concerta XL 18, 36 and 54 mg prolonged-release tablets (PL 00242/0372-4), which were granted in the UK to Janssen-Cilag Limited in February 2002. The RMS for this procedure was the UK and the CMS countries were Austria, Belgium, Germany, Greece, Spain, Finland, France, Ireland, Iceland, Luxembourg, the Netherlands, Norway, Portugal and Sweden.

The proposed indication for Concerta XL 27 mg Prolonged-Release Tablets is the same as the indication approved for the three authorised tablet strengths (18 mg, 36 mg and 54 mg). It is indicated as part of a comprehensive treatment programme for attention deficit hyperactivity disorder (ADHD) in children over 6 years of age and adolescents when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

Methylphenidate HCl is a central nervous system (CNS) stimulant and has been used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) for several decades. The mode of therapeutic action in ADHD is not entirely understood. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space.

The rationale for the 27 mg tablet is to provide prescribing physicians with additional options to more gradually titrate the dose upwards between the 18 mg and 36 mg doses, based on a careful assessment of efficacy and tolerability on an individual-by-individual basis. These products are designed for once-daily dosing.
No new preclinical studies were conducted, which is acceptable given that the application was based on an active substance whose pharmacokinetic, pharmacodynamic and toxicological properties are well-known.

As the clinical data required for the grant of this licence have already been submitted for the 18, 36 and 54 mg strength prolonged-release tablets, no new clinical data were submitted with this application and none were required. Kinetics are linear over the

therapeutic range (Modi *et al.* Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system *Journal of Clinical Pharmacology* 2000, vol 40, pp1141-9) hence no bioequivalence study is required since the product is a proportional pharmaceutical scale up.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

II. ABOUT THE PRODUCT

Name of the product in the RMS	Concerta XL 27 mg prolonged-release tablets
Name(s) of the active substance(s) (INN)	Methylphenidate hydrochloride
Pharmacotherapeutic classification (ATC code)	Methylphenidate (N06 BA04)
Pharmaceutical form and strength(s)	27 mg prolonged-release tablets
Reference numbers for the DCP	UK/H/0544/004/MR
Reference Member State (RMS)	United Kingdom
Concerned Member States (CMS)	Austria, Belgium, Germany, Greece, Spain, Finland, France, Ireland, Iceland, Luxembourg, the Netherlands, Norway, Portugal and Sweden
Marketing Authorisation Number(s)	PL 00242/0400
Name and address of the authorisation holder	Janssen-Cilag Limited, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, UK

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. ACTIVE SUBSTANCE

Methylphenidate hydrochloride

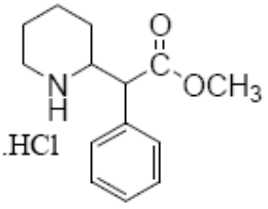
rINN: Methylphenidate hydrochloride

Chemical Name: 2-piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride (R*,R*)-(±)

Methyl α-phenyl-2-piperidineacetate hydrochloride

CAS: 298-59-9

Structure:



Molecular Formula: $C_{14}H_{19}N0_2$, HCl

Molecular Weight: 269.8

General Properties: White to off-white, crystalline powder. Freely soluble in water and in methanol, soluble in alcohol, slightly soluble in chloroform and in acetone.

Methylphenidate hydrochloride is a white to off-white, odourless, crystalline powder that is freely soluble in water and methanol, soluble in alcohol and slightly soluble in chloroform and in acetone. Its melting point is 224-226°C.

Methylphenidate contains two chiral centres and, therefore, has four stereoisomers. The drug substance is a racemic mixture (*dl-threo* form of two enantiomers) consisting of RR and SS configurations in an approximately 1:1 ratio. Only the *d-threo* (RR) enantiomer has activity against hyperkinetic syndrome.

Methylphenidate hydrochloride is relatively stable under acidic conditions. Hydrolytic degradation occurs at a pH above 4.

An appropriate specification based on the USP has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

Details of the reference standards used for the evaluation of the active substance are provided.

P. MEDICINAL PRODUCT

Description and composition of the drug product

The excipients comprise butylhydroxytoluene (E321), cellulose acetate 398-10, hypromellose 3cp, phosphoric acid concentrated, poloxamer 188, polyethylene oxides 200K and 7000K, povidone K29-32, sodium chloride, stearic acid, succinic acid, black iron oxide (E172), and ferric oxide red and yellow (E172).

The film coat is made with black iron oxide (E172), hypromellose 15cp, lactose monohydrate, titanium dioxide (E171), and triacetin. The clear coat consists of carnauba wax, hypromellose 6cp, and macrogol 400. And the ingredients of the printing ink are black iron oxide (E172), hypromellose 6cp, isopropyl alcohol, propylene glycol, and purified water.

All excipients used in the 27 mg tablet are identical to those used in the approved strength tablets (18 mg, 36 mg, and 54 mg) except for an additional colorant. The excipients, that have been previously reviewed and approved, comply with the appropriate compendial monographs and the manufacturer's specifications, except for succinic acid, which is a referenced material in the ACS (American Chemical Society). Certificates of Analysis for each excipient have been provided.

Appropriate TSE certification is provided which states that only two excipients, lactose and stearic acid, are of potential animal origin. Stearic acid is produced from bovine and/or porcine tallow originating from North America only. A current TSE

Certificate of Suitability has been provided. Lactose for use in the Opadry colourings is manufactured in accordance with EMEA/410/01 Rev 2**.**

A manufacturing overage is included in the batch formula

Manufacture
The manufacturing process for the 27 mg strength tablets is essentially the same as for the other three currently approved strengths (18 mg, 36 mg, and 54 mg) and has been adequately described. A flowchart identifies the different sites involved in the manufacturing process.

Satisfactory in process controls are provided for the steps of the manufacturing process. Formal validation studies have been conducted on batches manufactured at typical production scale. Each operation has been validated according to current guidelines in an approved protocol. The validation is thorough, confirming that the process is adequately controlled and that batches can be manufactured consistently within these controls. Batch analysis data on validation batches show consistent compliance with the finished product specification and provide further confirmation of the validity of the manufacturing process.

Finished product specification
The release and shelf life specifications for Concerta 27mg Prolonged Release Tablets are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Generally, the methods of the United States and European Pharmacopoeia are employed. Test methods have been described and have been adequately validated, as appropriate. Batch analyses from relevant drug product batches used to establish the specification and evaluate the consistency in manufacturing have been provided. All batches comply with the specification. Details of the reference standards that have been used in the testing of Concerta Prolonged Release Tablets 27 mg strength have been provided.

Container-closure system
The product is stored in a high-density polyethylene (HDPE) bottle with a child-resistant polypropylene closure with one or two desiccants enclosed. The number of tablets in each bottle is 28 or 30. Satisfactory specifications and drawings of the packaging materials have been provided. The applicant states that the packaging materials are used commonly for solid dose preparations and meet EC requirements. No specific compatibility studies should therefore be necessary; the satisfactory stability data confirm their suitability for use.

Stability
Stability data have been provided for production scale batches in accordance with current guidelines. Long term and accelerated conditions were tested and the data generated support the shelf-life of 2 years. This medicinal product does not require any special storage conditions but the bottle should be kept tightly closed.

Product literature
The Summary of Product Characteristics (SmPC) and labelling for this product is satisfactory. The Patient Information Leaflet (PIL) is in compliance with current guidelines and user testing results have been submitted. The results indicate that the

PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusions
The product is pharmaceutically satisfactory and granting of a licence is recommended.

III.1 NON-CLINICAL ASPECTS
No new non-clinical data have been supplied with this application and none are required for an application of this type.

III.3 CLINICAL ASPECTS
INTRODUCTION
This product is indicated for a paediatric population. All clinical data and some clinical pharmacology data were collected from paediatric patients.

CLINICAL PHARMACOLOGY
Pharmacokinetics
Kinetics are linear over the therapeutic range (Modi *et al.* Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system *Journal of Clinical Pharmacology* 2000, vol 40, pp1141-9) hence no bioequivalence study is required since the product is a proportional pharmaceutical scale up.

Pharmacodynamics
Data have been provided for the currently authorised strengths. No new clinical data are required for the new strength.

EFFICACY AND SAFETY
Data have been provided for the currently authorised strengths. No new clinical data are required for the new strength.

PRODUCT LITERATURE
Summary of Product Characteristics (SmPC)
The SmPC for Concerta XL 27 mg Prolonged-Release Tablets is consistent to those approved for the three authorised tablet strengths (18 mg, 36 mg and 54 mg) and is satisfactory.

Patient Information Leaflet (PIL)
The proposed PIL is essentially identical to that approved for the three authorised tablet strengths and it is, therefore, satisfactory.

Labelling
All labelling is satisfactory.

DISCUSSION
No new clinical data are required for this new tablet strength and, as kinetics are linear over the therapeutic range, no bioequivalence study is required. The proposed

SmPC and PIL are consistent to those approved for the three authorised tablet strengths and are, therefore, satisfactory.

OVERALL CONCLUSION
A Marketing Authorisation may be granted for this product.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of the product are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY
The efficacy of methylphenidate hydrochloride tablets has been well-documented in the past. No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The benefit/ risk ratio is considered to be positive.

Module 6

STEPS TAKEN AFTER THE MUTUAL RECOGNITION PROCEDURE - SUMMARY

All non-safety variations of clinical significance granted after the mutual recognition procedure are presented below:

Date submitted	Application type	Scope	Outcome
05/03/2010	II	To add to section 4.2 (Posology and method of administration), "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 in adults is not appropriate" and update 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the SmPC have been updated.	Granted 26/05/2011

Mutual Recognition Procedure

Type II variation

Preliminary Variation Assessment Report

ConcertaXL
Methylphenidate

UK/H/0544/001/II/056

Marketing Authorisation Holder: Janssen-Cilag

Date: 14/07/10

I. RECOMMENDATION

Based on the review of the data on safety and efficacy the RMS considers that the variation application UK/H/0544/001/II/056 for Concerta (Methylphenidate MR), in the treatment of ***adult ADHD***, for the following proposed changes:

CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD***). It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.***

is not approvable since potential serious risks to public health (see section V.1) have been identified which preclude a recommendation for such variation and recommend that the variation to the terms of the Marketing Authorisation should be refused.

II. EXECUTIVE SUMMARY

Introduction: This is a Type II Complex variation undergoing a Mutual Recognition Procedure with the UK as Reference Member State (RMS). The MAH are seeking a new indication of use in adults with Attention Deficit Disorder (ADHD).

Current indication: Methylphenidate has recently been through a harmonisation procedure for its current indication of the treatment of ADHD as part of a comprehensive treatment programme in children aged 6 years or older.

Evidence submitted:

- Environmental Impact Assessment
- Non-clinical Studies
- Pharmacokinetic (3) and Abuse Potential Studies (3)
- Two European fixed-dose placebo controlled studies (Studies 3002 and 3013)
- One US flexible dosing study (Study 02-159)
- One withdrawal study (Study 3004)
- Open-label safety studies
- Literature review

Efficacy: Studies 3002 and 02-159 demonstrate efficacy over placebo and Study 3013 demonstrated efficacy for the higher dose (72mg) of methylphenidate (MPH) but not the lower dose (54mg). There is a concern over the handling of missing data. The withdrawal study failed to demonstrate longer-term efficacy as the benefit over placebo was small and the numbers completing the study were small. The optimum duration of treatment is not clear.

Safety: Concerns are raised over the extent of psychiatric adverse events in the adult population. The proportion of subjects with a sustained increase in heart rate and blood pressure has not been presented.

RMP assessment: Many concerns are raised over the psychiatric adverse events, effect of sustained increases in heart rate and blood pressure and clinically significant weight loss. The greater exposure of women with child bearing potential has not been addressed particularly in view of the possible spina bifida signal. There is a need for contraceptive advice and a pregnancy registry.

Conclusion The efficacy for the proposed indication has not been clearly demonstrated. The currently proposed indication would result in inappropriate usage as it is not consistent with DSM IV diagnostic criteria.

II.1 Scope of the variation

The MAH are applying for a new indication of ADHD in adults who were first diagnosed in childhood but whose symptoms have persisted into adulthood.

III. SCIENTIFIC DISCUSSION

Background

The MAH are seeking a new indication of use in adults with Attention Deficit Disorder (ADHD). The MAH estimates a prevalence of adult ADHD of 3.7% based on a prospective study in 1100 individuals by Fayyad 2009 (Clinical Overview). In a European guideline (Taylor et al 2004) the prevalence of childhood ADHD was thought to be between 3-5% and should 30-60% continue into adulthood, this estimate may be too high.

The concept of adult ADHD is generally accepted but the robustness of the diagnosis generates much more concern. One of the key diagnostic symptoms of hyperactivity is not so apparent in adults and they tend to present more with the problems associated with inattention. For a diagnosis of ADHD in children symptoms should have been present from a young age, often less than 2 years. Thus establishing the age of onset retrospectively is another challenge to the diagnosis of individuals that first present in adulthood. There is a CHMP Guideline on the Clinical Investigation of Medicinal Products for the Treatment of ADHD EMEA/CHMP/EWP/431734/2008. Atomoxetine is the only active substance with an indication for adult ADHD, although evidence based guidelines such as British Association for Psychopharmacology and NICE, do support the use of methylphenidate in adult ADHD.

The MAH have sought Scientific Advice on several occasions. The problems surrounding the diagnostic robustness of the studied populations has led the MAH to apply for an indication of ADHD in adults who were first diagnosed in childhood but whose symptoms have persisted into adulthood. The study programme consisted of a mixed adult ADHD population and thus the data that have been presented consist of a retrospective subgroup analysis. This variation assessment report considers the robustness of this approach.

III.1 Quality aspects

N/A

Environmental Impact

The MAH has conducted a satisfactory Environmental Risk Assessment. The results indicate that the increase in production of methylphenidate to supply the new patient population is unlikely to pose a risk to the environment.

III.2 Non-clinical aspects

No new studies have been undertaken for this indication but a series of non-clinical studies were conducted for the Japanese Regulatory Authorities. In addition there is one study that is conducted in lactating rats which is deemed relevant to the application. Generally it is assessed that the human data is now available and takes precedence over the animal data but for the study in lactation only 1 human case in mentioned in Section 4.6 and it is proposed that the following sentence is added:

> ***In rats, methylphenidate-associated radioactivity was found in the milk at concentrations up to around 1.5 times that in the plasma.***

In addition the wording to Section 5.3 should be clarified as follows:

> **Pregnancy-embryonic/foetal development**

Methylphenidate is not considered to be teratogenic in rats and rabbits. Fetal toxicity ***in the form of total litter loss*** was noted in rats at maternally toxic doses

III.3 Clinical aspects

III.3.1 Clinical pharmacology

A list of the clinical studies submitted is presented below:

Study	Study Design / Subject Population	Objectives	Treatments/dosing
02-160	Open-label, fixed-sequence, single- and multiple dose pharmacokinetics and safety study / 27 (20 M/7 F) Healthy adults	To assess single- and multiple-dose PK and safety of high doses of CONCERTA	CONCERTA 54 mg, 72 mg, 108 mg, 144 mg / oral dosing once daily for 4 days
12-004	Open-label, single-dose, randomized, crossover pharmacokinetic study / 19 (14 M/5 F) Healthy adults	To determine the PK of methylphenidate from whole and crushed CONCERTA Tablets and crushed RITALIN tablets	CONCERTA 18 mg (whole and crushed), RITALIN 20 mg (crushed)/oral single dose
12-302	Double-blind, randomized, placebo-controlled, crossover study / 18 (16 M/2 F) Healthy adults with a recent history of substance abuse	To assess the abuse potential of CONCERTA as compared to RITALIN and placebo	RITALIN 60 mg; placebo; CONCERTA 108 mg/oral single dose
12-005	Double blind, placebo-controlled, randomized, crossover study / 49 (37 M/12 F) Healthy adults with a history of recreational stimulant use	To evaluate the abuse potential of CONCERTA as compared to RITALIN and placebo; and to assess the PK-PD relationships (PK-PD) of methylphenidate when dosed as CONCERTA and RITALIN	RITALIN 60 mg; placebo; CONCERTA 108 mg/oral single dose
12-007	Double-blind, placebo-controlled, randomized, crossover study with a qualifying and a treatment phase / 55 (42 M/ 13 F) Healthy normal adults with a history of light (occasional) stimulant drug use	To assess abuse potential of CONCERTA as compared to RITALIN and placebo at comparable doses.	RITALIN 50 and 90 mg; placebo; CONCERTA 54 and 108 mg/oral single dose
12-001	Open-label, multiple-dose, parallel design, pharmacokinetic study / 26 (19 M/7 F) Healthy adolescents with ADHD	To assess the multiple-dose PK of CONCERTA.	CONCERTA 18 mg, 27 mg, 36 mg, 54 mg, 72 mg,/oral dosing once daily for 6 days

Study 02-160 (pharmacokinetics healthy adults)
This was an open-label, fixed sequence, four-period crossover single- and multiple-dose pharmacokinetics and safety/tolerability study in healthy male and female adult subjects. In each period, subjects received single oral daily doses of CONCERTA for four days, with sequential dose escalation for each period. The doses evaluated in the study were 54, 72, 108 and 144 mg given as combinations of CONCERTA 36 and 54 mg tablets. On Days 1 and 4 of each period blood samples were collected over 24 hours for characterizing the pharmacokinetics of total methylphenidate (non-chiral assay for d- and l- isomers combined) and its major metabolite, α-phenyl piperidine acetic acid (PPAA, also abbreviated as PPA in some reports; non-chiral assay for d- and l- isomer combined), which has little or no pharmacologic activity. Dosing in study periods was separated by a 3-day washout period. Plasma was isolated from the blood samples and analyzed for MPH and PPAA using validated LC/MS/MS methods.

Twenty-seven subjects participated in the study; seven subjects in the weight range of 55 to 73 kg; ten subjects in the weight range of 74 to 91 kg and ten subjects in the weight range of 92 to 109 kg, such that all subjects received methylphenidate doses in the 1 to 2 mg/kg range in some period. Pharmacokinetic data were available and analyzed from 25 subjects who completed blood sampling in all four treatment periods. Two subjects withdrew due to adverse events.

Due to the short half-life of about 3.5 hours, there is minimal accumulation of methylphenidate upon multiple dosing. Hence, pharmacokinetic parameters obtained from Day 4 represent steady-state.

The mean age of the subjects was 29 years (range 20-50).

The mean (and standard deviation) plasma pharmacokinetic parameters for total methylphenidate for subjects who completed blood sampling in all four treatments are presented below:

Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{inf} (ng.h/mL)	CL/F (L/h/kg)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{tau}/AUC_{inf})*
DAY 1						
54	12.0	6	130	5.28	3.58	1.08[c]
	(3.54)	(1-10)	(32.4)	(1.48)	(0.63)	1.02, 1.14
72	17.1	6	196	4.80	3.57	0.96
	(5.80)	(5-10)	(65.7)	(1.50)	(0.62)	0.93, 1.00
108	26.3	6	293[c]	4.73[c]	3.59[c]	1.07[c]
	(6.38)	(5-12)	(76.5)	(1.32)	(0.54)	0.97, 1.04
144	35.8	6	381[d]	4.80[d]	3.65[d]	1.08[d]
	(9.72)	(1-12)	(105)	(1.27)	(0.60)	1.02, 1.14
DAY 4						
Dose (mg)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$[a] (h)	AUC_{tau} (ng.h/mL)	CL_{ss}/F (L/h/kg)	$T_{½}$ (h)	$C_{min,ss}$ (ng/mL)
54	12.5	6	139[c]	4.81[c]	3.60	0.496
	(2.84)	(1-10)	(33.6)	(1.19)	(0.84)	(0.305)
72	16.1	6	185	4.94	3.63	0.807
	(4.60)	(5-8)	(49.0)	(1.27)	(0.49)	(0.428)
108	26.0	6	291	4.70	3.60	1.23
	(6.99)	(5-10)	(71.1)	(1.19)	(0.56)	(0.607)
144	36.9	6	419	4.55	3.42	1.73
	(11.3)	(1-8)	(137)	(1.77)	(0.50)	(0.894)

[a] Median and range are listed
[b] Mean and 95% confidence interval are listed
[c] N = 24
[d] N = 23
* AUC_{tau} – area under the curve over a dosing interval at steady-state; AUC_{inf} – area under the curve after first dose extrapolated to infinity

The mean (and standard deviation) plasma pharmacokinetic parameters for total PPA for subjects who completed blood sampling in all four treatments are presented below:

Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{inf} (ng.h/mL)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{tau}/AUC_{inf})*
DAY 1					
54	477	8	8068	8.04	1.00[c]
	(108)	(5-10)	(1405)	(1.29)	0.96, 1.04
72	609	10	10713	8.01	1.01
	(95.8)	(5-10)	(1634)	(1.29)	0.99, 1.04
108	937	10	16766[d]	8.09[d]	1.00[d]
	(144)	(5-12)	(2399)	(1.17)	0.96, 1.04
144	1220	8	21429[d]	8.16[d]	1.05[d]
	(212)	(5-12)	(3071)	(1.32)	1.00, 1.10
DAY 4					
Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{tau} (ng.h/mL)	$T_{½}$ (h)	$C_{min,ss}$ (ng/mL)
54	536	8	7941[c]	8.23[c]	120
	(84.7)	(5-12)	(1172)	(2.04)	(45.1)
72	706	8	10788	8.22[c]	167
	(106)	(5-12)	(1446)	(1.03)	(45.3)
108	1061	8	16465	8.45[c]	271
	(165)	(5-12)	(2497)	(1.21)	(81.2)
144	1430	8	22288	9.06[e]	379
	(216)	(1-12)	(3092)	(2.79)	(99.8)

[a] Median and range are listed
[b] Mean and 95% confidence interval are listed
[c] N = 24
[d] N = 22
[e] N = 23
* AUC_{tau} – area under the curve over dosing interval at steady-state; AUC_{inf} – area under the curve after first dose extrapolated to infinity

Safety

The mean systolic blood pressure (mmHg) by day of treatment and time after treatment with OROS methylphenidate HCl is presented below:

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	130.3				
Check-in[b]	129.1	121.6	116.0	122.4	<0.001
Before treatment[c]	120.1	116.1	109.9	114.5	<0.001
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	119.4	119.0	120.4	122.5	0.626
8 hours after dosing	121.3	122.8	124.9	127.9	0.136
12 hours after dosing	127.0	126.1	127.8	127.5	0.842
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	120.8	123.1	124.5	129.5	0.044
8 hours after dosing	126.8	127.1	127.3	126.2	0.965
12 hours after dosing	127.0	131.2	128.1	131.7	0.017
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	123.2	127.0	124.6	119.7	0.016
8 hours after dosing	122.2	123.6	125.4	127.7	0.286
12 hours after dosing	134.0	129.1	126.7	129.6	0.077
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	118.1	121.0	122.6	124.5	0.108
8 hours after dosing	127.1	122.7	125.4	123.3	0.074
12 hours after dosing	127.3	130.4	126.2	128.7	0.224
End of Study				n = 27	
After Day 4, Period 4[d]				124.3	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

The mean diastolic blood pressure (mmHg) by day of treatment and time after treatment with OROS methylphenidate HCl is presented below:

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	70.5				
Check-in[b]	76.4	72.6	70.3	73.5	0.005
Before treatment[c]	73.5	71.7	68.2	71.2	0.006
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	73.2	72.4	71.6	76.4	0.003
8 hours after dosing	73.4	74.5	74.7	77.0	0.235
12 hours after dosing	75.5	75.0	76.7	77.6	0.359
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	71.8	75.3	76.3	76.5	0.014
8 hours after dosing	74.0	76.4	76.5	77.7	0.090
12 hours after dosing	76.4	81.3	77.3	80.0	<0.001
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	73.6	75.9	76.0	73.9	0.094
8 hours after dosing	75.1	76.3	77.4	77.9	0.483
12 hours after dosing	82.1	77.3	78.3	80.0	0.001
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	72.7	72.7	75.3	76.0	0.147
8 hours after dosing	76.6	76.1	78.0	77.5	0.501
12 hours after dosing	77.7	79.4	77.4	78.3	0.348
End of Study				n = 27	
After Day 4, Period 4[d]				76.0	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

The mean heart rate (beats per minute) by day of treatment and time after treatment with OROS methylphenidate HCl is presented below:

	54 mg (Period 1)	72 mg (Period 2)	108 mg (Period 3)	144 mg (Period 4)	p-Value[a]
Screening	70.2				
Check-in[b]	77.3	79.6	80.6	79.3	0.611
Before treatment[c]	76.1	70.1	67.7	74.1	<0.001
Day 1	n = 27	n = 27	n = 27	n = 26[e]	
4 hours after dosing	70.8	73.1	78.7	82.1	0.004
8 hours after dosing	83.7	85.3	90.3	93.9	0.017
12 hours after dosing	83.9	87.0	94.3	99.0	<0.001
Day 2	n = 27	n = 27	n = 27	n = 26	
4 hours after dosing	77.8	86.5	87.7	94.1	<0.001
8 hours after dosing	85.0	90.3	89.3	96.5	0.005
12 hours after dosing	87.2	94.3	91.9	98.2	0.007
Day 3	n = 27	n = 27	n = 27	n = 25	
4 hours after dosing	82.0	87.7	90.7	90.1	0.002
8 hours after dosing	83.5	85.6	89.1	93.7	0.046
12 hours after dosing	92.2	94.9	95.8	99.2	0.136
Day 4	n = 27	n = 27	n = 26	n = 25	
4 hours after dosing	76.8	77.5	79.7	89.6	<0.001
8 hours after dosing	83.5	86.9	90.3	96.1	0.002
12 hours after dosing	88.7	92.7	95.0	98.6	0.008
End of Study				n = 27	
After Day 4, Period 4[d]				85.0	

a: Repeated measures ANOVA for differences among treatments
b: Subjects were required to check-in on the day before each treatment period. This usually occurred during the late afternoon or early evening.
c: The measurement before treatment was generally performed about 30 to 45 minutes before drug was administered (at 8:00 AM). This value refers to the measurement performed before the first dose of each study period.
d: This measurement was obtained on the day following the last day of Period 4.
e: Subject 22 took 108 mg instead of 144 mg on Day 1 Period 4 and discontinued after that point. Subject 12 did not take doses for Period 4, Days 3 and 4.

A list of subjects with abnormal Holter monitor results during dosing with OROS methylphenidate HCl is presented below:

Period	Subject No.	Finding	Investigator Comment
1	014	Frequent SVT	Possible drug effect
2	011	Vagally Mediated Sinus Slowing with Wenckebach	Unlikely drug effect
	014	SVT-Probable Atrial Tachycardia Junctional Rhythm	Possible drug effect Unlikely drug effect
	027	Transient Junctional Rhythm	Unlikely drug effect
3	009	Frequent Wenckebach	Unlikely drug effect
	011	Frequent Wenckebach	Unlikely drug effect
4	007	1 Episode of Mobitz I Block	Unlikely drug effect
	011	Several episodes of Simultaneous Sinus Slowing and Mobitz I AV Block Frequent Mobitz I Block	Unlikely drug effect Unlikely drug effect
	012	VT-NS	Possible drug effect
	014	Frequent Short Runs of SVT	Possible drug effect
	023	Transient Junctional or Ectopic Atrial Rhythm (HR was 68 beats per minute)	Possible drug effect
	027	Transient Junctional Rhythm Junctional Rhythm; Atrial Tachycardia with Block	Unlikely drug effect Possible drug effect

Abbreviations: SVT = supraventricular tachycardia, VT-NS = Ventricular tachycardia, nonsustained, AV = atrioventricular

The MAH concluded:

- CONCERTA produced linear and dose-proportional pharmacokinetics of total MPH and its major metabolite, PPAA, for CONCERTA doses of 54 to 144 mg/day
- The pharmacokinetics of both MPH and PPAA were similar for both genders
- The pharmacokinetics of both MPH and PPAA were similar after single and multiple dosing
- There was minimal accumulation of MPH after multiple dosing

Assessor's comments

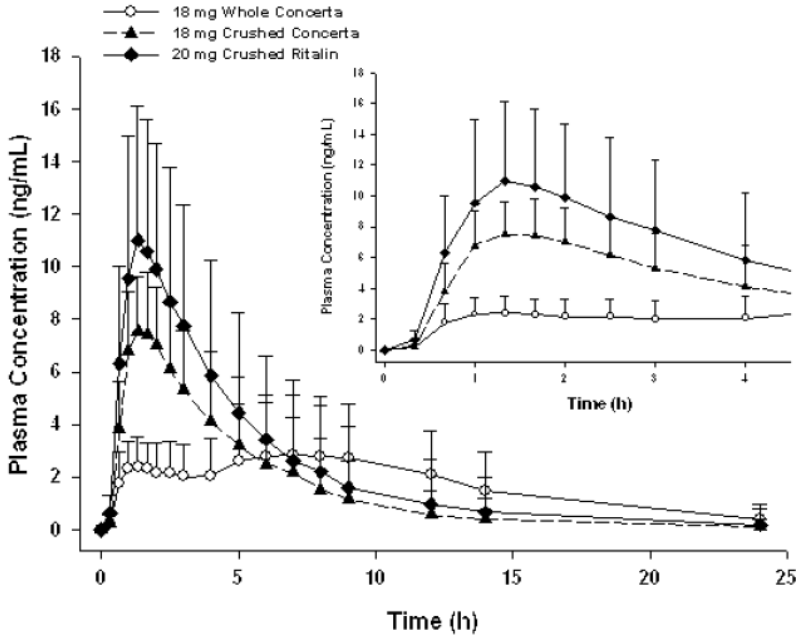
The pharmocokinetic study demonstrates linear kinetics for MPH and PPAA. The individual patient pharmacokinetic results have not been presented and will be asked for. Bioequivalence limits were met in mg equivalent comparison by Day 4 for the 72mg dose when compared to 54mg dose. HR was measured continuously. Subjects received doses of Concerta in ascending strength. HR and BP did not return to baseline levels in between dosing periods, thus increases observed in HR and BP with higher doses may be less than if subjects had been monitored in a MPH naïve state. The baseline HR and BP for each treatment period and at study end should be presented for each subject. In addition, individual subject data for BP increases greater than 5mm Hg should be presented for each study period.

There were four subjects who had ST changes during treatment. These were not described and could have been ST elevation or non-specific. In addition there were dysrhythmias observed in three subjects. Further scrutiny of these cases is warranted.

Study 12-004 Concerta Crushed

This open-label study was done in 18 healthy volunteers (M/F 13/5). One individual dropped out for personal reasons and was replaced and Subject 17 had an aberrant result much higher than the 2 either side. This was thought to be a sample labelling error. The results were not included.

The mean (and standard deviation) plasma time profiles of d-methylphenidate following single doses of crushed and intact CONCERTA and crushed Ritalin (IR MPH) is shown below:



The mean (and standard deviation) pharmacokinetic profiles of d-methylphenidate following single doses of crushed and intact CONCERTA and crushed Ritalin (IR MPH) is shown below:

	18 mg Whole CONCERTA (Treatment A)	18 mg Crushed CONCERTA (Treatment B)	20 mg Crushed IR MPH (Treatment C)
C_{max} (ng/mL)	3.55 (2.25)	8.17 (2.59)	11.6 (5.01)
T_{max}[a] (h)	6.00 (0.66 - 12.00)	1.33 (0.66 - 2.50)	1.33 (1.00 - 3.00)
AUC_{0-2h} (ng.h/mL)	3.39 (1.56)	9.79 (2.76)	14.4 (6.76)
AUC_t[#] (ng.h/mL)	39.7 (31.0)	37.1 (24.3)	54.5 (48.5)
AUC_{inf} (ng.h/mL)	42.8 (36.2)[$]	38.2 (26.0)[$]	55.1 (51.5)[$]

* N=18 subjects completed the study, however, data from one subject who had a strange PK profile was not included in the PK summary below due to reasons summarized in the report, hence data from N=17 is reported for the primary endpoints of C_{max}, T_{max}, AUC_{0-2h} and AUC_t.

[a] Median (range)

[#] t = 24h

[$] N=18 for CONCERTA treatment arms and N=19 for RITALIN (IR MPH)

A summary of the post hoc statistical analysis of relative bioavailability of d-theo-methylphenidate following single doses of crushed and intact CONCERTA and crushed Ritalin (IR MPH) is shown below:

Pharmacokinetic Parameter	Ratio[a] (%)	90% Confidence Intervals	p value
CMAX/Dose (ng/mL/mg)	81.46	(74.75, 88.78)	0.0008
CMAX (ng/mL)	72.68	(66.68, 79.22)	< 0.0001
AUC_{0-2h}/Dose (ng.h/mL/mg)	80.13	(71.10, 90.31)	0.0054
AUC_{0-2h} (ng.h/mL)	71.49	(63.41, 80.61)	0.0002
AUCMEDIAN/Dose (ng.h/mL/mg)	79.29	(66.33, 94.78)	0.0376

A: Ratio between adjusted geometric means (Test/Reference).

Assessor's comments

Concerta does not appear to have a pharamocokinetic profile when crushed that increases its abuse potential compared to Ritalin when crushed. Crushed Concerta is assessed as not demonstrating a less safe profile compared to Crushed Ritalin in this regard. The Cmax of crushed Concerta would appear of a similar order of magnitude to that obtained from IR. The pharmacokinetic data of crushed Concerta would suggest that the abuse potential of Concerta is similar to MPH IR; however, the studies exploring the potential of abuse were done using intact Concerta and thus may underestimate this. The data on MPH IR is available from these studies so it is possible to gauge the likely effect.

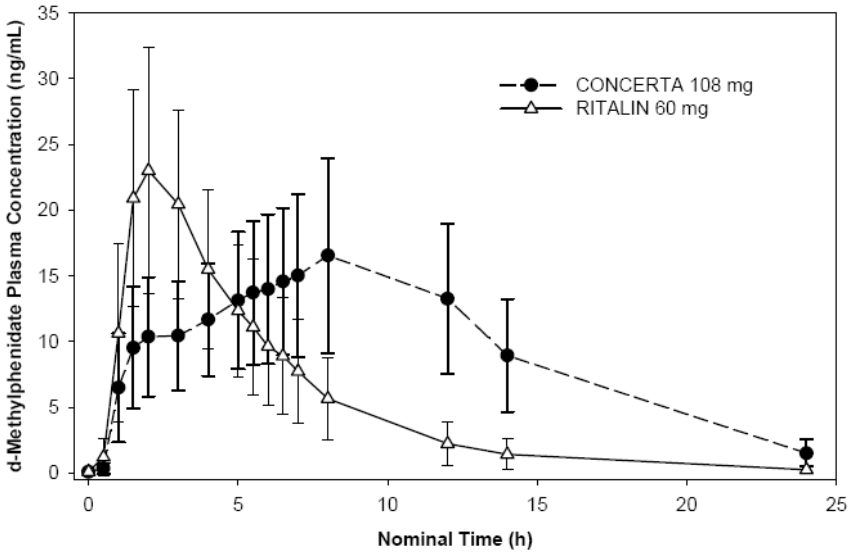
Study 12-302 (Individuals with recent Hx of Substance Abuse)

This was a double-blind, randomized, placebo-controlled, three-period crossover study to assess the pharmacokinetic and pharmacodynamic effects related to abuse potential of single oral doses of placebo, 60 mg immediate release methylphenidate (RITALIN) and 108 mg OROS methylphenidate (CONCERTA) in adults with a diagnosis of substance abuse, based on Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM) IV criteria. Eighteen subjects participated in the study. Over a 24-hour period from dosing, subjects completed Drug Rating Questionnaire. Subject (DRQS), study staff completed Drug Rating Questionnaire. Observer (DRQO), and blood samples were collected for estimation of

methylphenidate plasma concentrations (both d- and l- isomer were measured, but PK analysis was performed only for the active d- isomer). In addition, on the final treatment day (at the end of period 3), after last sample collection, subjects completed a Treatment Enjoyment Assessment Questionnaire (TEAQ), where they were asked to provide information on which drug treatment (placebo, RITALIN, CONCERTA), if any, they would prefer to take again. They had a choice of indicating if none of the treatment options from the study were preferred.

This study was designed to assess abuse liability of single doses of CONCERTA versus RITALIN and placebo, with the primary endpoint being time to maximum change from baseline Liking score (question 2 of the DRQS "Do you like the drug effect you are feeling now?"), the working hypothesis being that the maximum effect for both drugs will be observed when maximum plasma concentrations are reached, hence, CONCERTA would have a longer time to maximum change from baseline for Liking. To examine the primary hypothesis, the statistical analyses used an ANOVA, with step-down pairwise comparisons between RITALIN and placebo, as a measure of assay sensitivity, and if p . 0.05, the RITALIN versus CONCERTA. As per protocol, CONCERTA was not compared with placebo.

The mean (and standard deviation) plasma time profiles of d-methylphenidate following single doses of CONCERTA (OROS MPH) and Ritalin (IR MPH) is shown below:

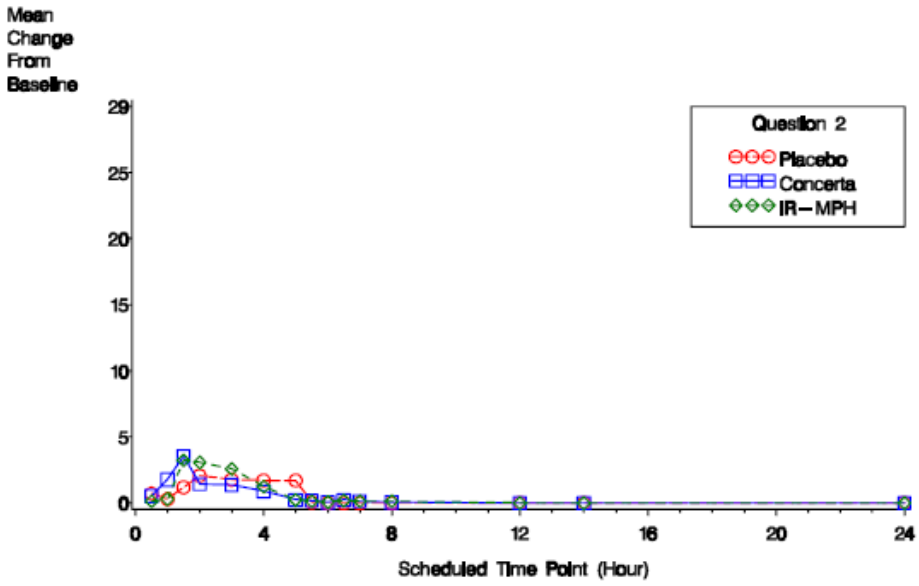


A summary of mean (and standard deviation) d-methylphenidate pharmacokinetic parameters following single doses of CONCERTA (OROS MPH) and Ritalin (IR MPH) is shown below:

Parameter	CONCERTA (OROS MPH) (N= 17)*	IR MPH (N= 17)*
C_{max} (ng/mL)	17.1 (7.11)	24.5 (9.46)
T_{max} (h)	7.56 (2.46)	2.09 (0.566)
AUC_{inf} (ng.h/mL)	220 (95.0)	128 (57.6)
$T_{1/2}$ (h)	3.71 (0.504)	3.62 (0.419)
C_{max} / AUC_{inf}	0.078 (0.009)	0.196 (0.032)

* One subject withdrew from the study after receiving IR MPH treatment, hence, data from N=17 subjects who completed all periods are included in this summary.

The DRQS mean change from baseline with time for Question 2 (0-29 scale) is presented below:



The treatment enjoyment assessment questionnaire (TEAQ) in patients completing is shown below:

Preferred Treatment	N of Subjects	Observed (N=17)	Expected (N=17)	p-Value[a]
CONCERTA	1	5.88%	25%	0.181
IR MPH	7	41.2%	25%	
Placebo	2	11.8%	25%	
None	7	41.2%	25%	

[a] p-Value based on Continuity Corrected Chi Square test assuming equal preference among all four choices.

Assessor's comments

There was a very low rating on Item 2 of the DRQS for enjoyment whether with Concerta, MPH-IR or placebo. No concern is raised from this study but it is unlikely that anyone would take Concerta in this fashion should they wish to abuse it. Assessment of a meaningful liking effect was not possible in this population.

Study 12-005 (Recreational Drug Users)

In this single-dose, double-blind, randomized, three-way crossover study in healthy subjects with a history of recreational stimulant use, forty-nine healthy adults, ages 18 to 48 were enrolled. The history of recreational stimulant use was defined as at least ten occasions of use in the previous five years and at least one occasion of use in the previous year. The relevant stimulant drugs were: cocaine, mixed amphetamine salts, methamphetamine, methylenedioxy-methamphetamine (ecstasy; MDMA), methylphenidate (RITALIN).

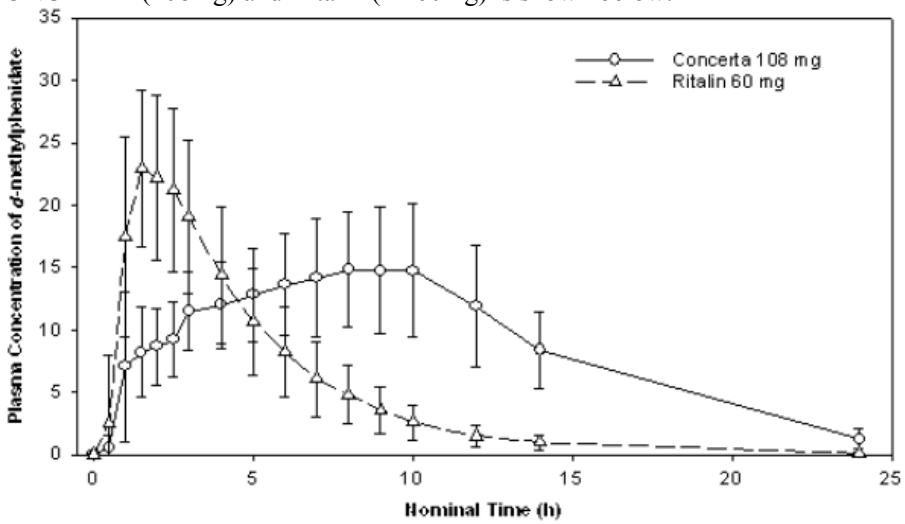
Subjects were excluded if they were considered substance-dependent per DSM-IV criteria. They received single doses of CONCERTA 108 mg, RITALIN 60 mg, and placebo in a randomized fashion, followed by pharmacokinetic sampling, pharmacodynamic assessments related to drug abuse, and safety assessments over a 24-hour period from dosing. Pharmacodynamic effects related to drug abuse were assessed using Cole/Addiction Research Center Inventory (ARCI), Drug Rating Questionnaire (Subject) - Visual Analog Scales(DRQS-VAS), and Subjective Drug Value Procedure (SDVP). The primary endpoint was maximum value (Emax) of Liking as scored by a subject's response to question 2 ("Do

you like the drug effect you are feeling now?") on the DRQS-VAS. Additional parameters used for evaluations included TEmax (time to maximum effect), AUE (area under the response curve) and partial AUEs.

Previous Drug Use

Of subjects in the Randomized population, the primary substances used in the past were cocaine (43 subjects [87.8%]), methylenedioxy-methamphetamine (38 subjects [77.6%]), and methamphetamine (12 subjects [24.5%]). Similarly, in the Completed population, 34 (85.0%) of subjects had used cocaine and methylenedioxy- methamphetamine, and 11 (27.5%) subjects had used methamphetamine. Only three subjects (6.1%) in the Randomized population and two subjects (5.0%) in the Completed population had ever used methylphenidate.

The mean (and standard deviation) d-methylphenidate plasma profiles following single doses of CONCERTA (108mg) and Ritalin (IR 60mg) is shown below:



The key positive effects measures for placebo, Concerta and Ritalin (IR MPH) are presented below:

Positive Effects Measure	Placebo	CONCERTA 108 mg N=40	IR MPH 60 mg N=40
VAS Liking			
E_{max}, Geometric mean (%CV)	13.7 (1326)*	46.8 (133)	56.6 (125)
$AUE_{0\text{-}MTEmax}$[a], Geometric mean (%CV)	13.5 (3222)*	32.6 (724)	68.1 (233)
1-hour score, Mean (SD)	31.0 (29.8)*	43.8 (32.6)	55.3 (29.0)
2-hour score, Mean (SD)	35.6 (31.0)*	42.8 (27.8)	54.4 (27.4)
Cole/ARCI – Stimulation Euphoria			
1-hour score, Mean (SD)	4.9 (6.63)*	10.2 (10.4)$	14.2 (11.9)
2-hour score, Mean (SD)	5.4 (7.22)*	9.4 (8.06)$	15.5 (11.6)
Cole/ARCI - Abuse Potential			
1-hour score, Mean (SD)	2.0 (2.97)*	4.6 (4.41)	5.4 (3.93)
2-hour score, Mean (SD)	2.2 (2.97)*	3.7 (4.00)	4.0 (4.91)
ARCI Amphetamine			
1-hour score, Mean (SD)	4.9 (4.90)*	8.8 (7.05)$	10.9 (7.62)
2-hour score, Mean (SD)	5.2 (5.07)*	8.9 (5.94)$	11.8 (7.34)
ARCI Morphine Benzedrine group#			
2-hour score, Mean (SD)	6.1 (7.98)*	10.7 (9.20)$	16.7 (12.4)
Subjective Drug Value Procedure			
Subjective drug value ($)[b], Mean (SD)	6.39 (15.5)	6.49 (13.3)	7.85 (14.4)

[a] Calculated with reference to median time to peak effect (TE_{max}) for IR MPH
[b] Canadian dollars (At the time of the study, the exchange value of the local, Canadian dollar was approximately $0.80 to 0.83 in U.S. dollars)
* Significant difference between placebo and IR MPH ($p<0.05$)
$ Significant difference between CONCERTA and IR MPH ($p<0.05$)
# Not assessed at 1 hour

The ARCI short form [17] consists of 77 questions extracted from the much larger (550 question) ARCI. The short form contains the following five subscales that are important to the evaluation of abuse potential:

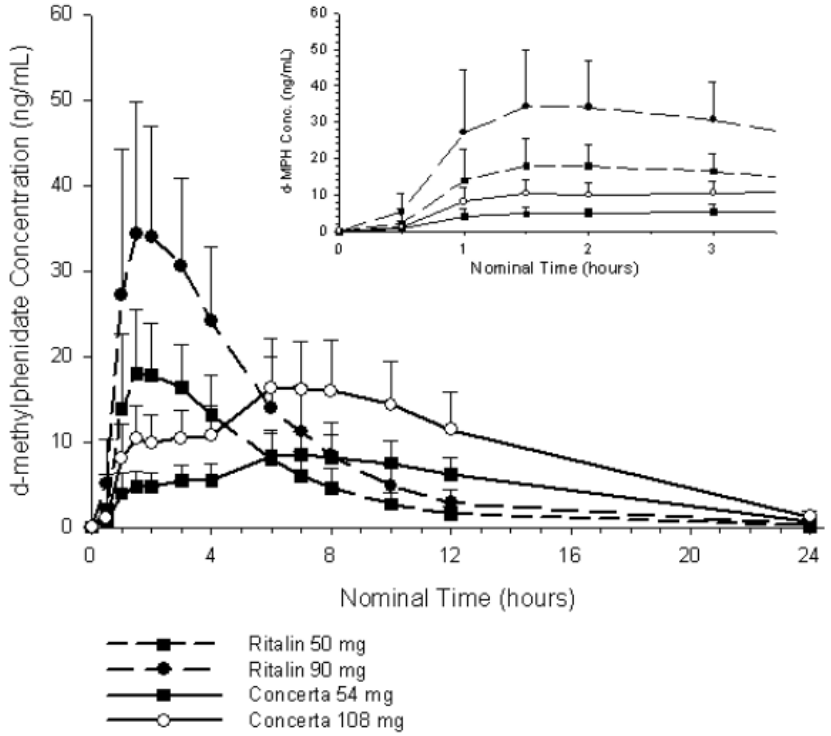
- o Morphine-Benzedrine Group scale (the MBG or .euphoria. scale);
- o Amphetamine (A) scale;
- o Benzedrine Group scale (the BG or .stimulant. scale);
- o Lysergic Acid Diethylamide scale (the LSD or .dysphoria. scale);
- o Pentobarbital-Chlorpromazine-Alcohol Group scale (the PCAG or .sedation. scale).

A different subset of the original ARCI was later developed [18], using a new factor analysis of responses to some of the 550 questions. This newer form includes seven scales, Sedation.Motor, Sedation.Mental, Unpleasantness.Physical, Unpleasantness.Mental, Stimulation.Motor, Stimulation.Euphoria, and Abuse Liability. The questions in the two stimulation scales do not overlap with each other but do overlap with the Cole/ARCI Abuse Liability and ARCI Amphetamine scales.

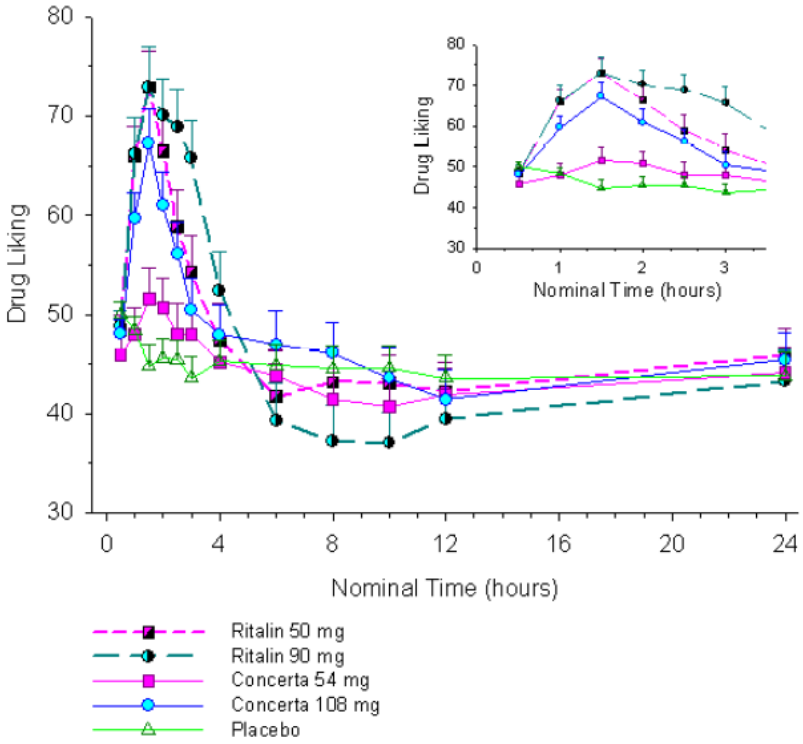
Assessor's comments
The primary endpoint was the comparison of Emax between IR MPH and Concerta. This was based on DRQS-VAS Item 2 'Liking' (0-100 scale). This failed to reach significance. The results clearly suggest that even when Concerta is not crushed (a more likely scenario of abuse) that this imparts a pleasant effect in this population of recreational drug users. If the 72mg Concerta was crushed it would be likely to give Cmax levels around that seen for MPH IR 60mg and thus similar enjoyment rating.

Study 12-007 Abuse Potential in Light (occasional) Drug Users
This was a double-blind, placebo-controlled, randomized, five-way crossover study in 49 healthy subjects with a history of occasional recreational stimulant use. Qualified subjects received single doses of placebo, 54 and 108 mg OROS methylphenidate (CONCERTA), and 50 and 90 mg immediate release methylphenidate (RITALIN). For each treatment, pharmacokinetics, pharmacodynamics and safety were assessed for 24 hours. Pharmacodynamic (subjective) data were collected through standard questionnaires (Addiction Research Center Inventory (ARCI) and visual analog scales (VAS) for positive, stimulant, negative and other effects. The VAS Liking and ARCI/MBG scales were predefined as primary dependent variables. IR and OROS MPH produced expected plasma concentration time profiles of d-methylphenidate. IR MPH (50 and 90 mg) produced statistically significant differences ($p<0.05$) from placebo for primary and secondary subjective measures. For most measures, 108 mg OROS MPH produced statistically significant differences ($p<0.05$) from placebo, while most differences for the 54 mg dose versus placebo were not statistically different. The consistent rank order for magnitude of positive, negative, and stimulant effects was (highest to lowest): IR 90 mg > IR 50 mg > OROS 108 mg > OROS 54 mg > placebo. Most measures showed significant differences ($p<0.05$) between comparable doses of IR and OROS MPH. The linear correlation of concentration with effect (PK-PD) was modest for IR and poor for OROS MPH. In conclusion, for comparable total dose levels, IR MPH had greater subjective effects than OROS MPH, supporting the hypothesis that a formulation can modulate abuse potential by controlling the rate and extent of drug delivery.

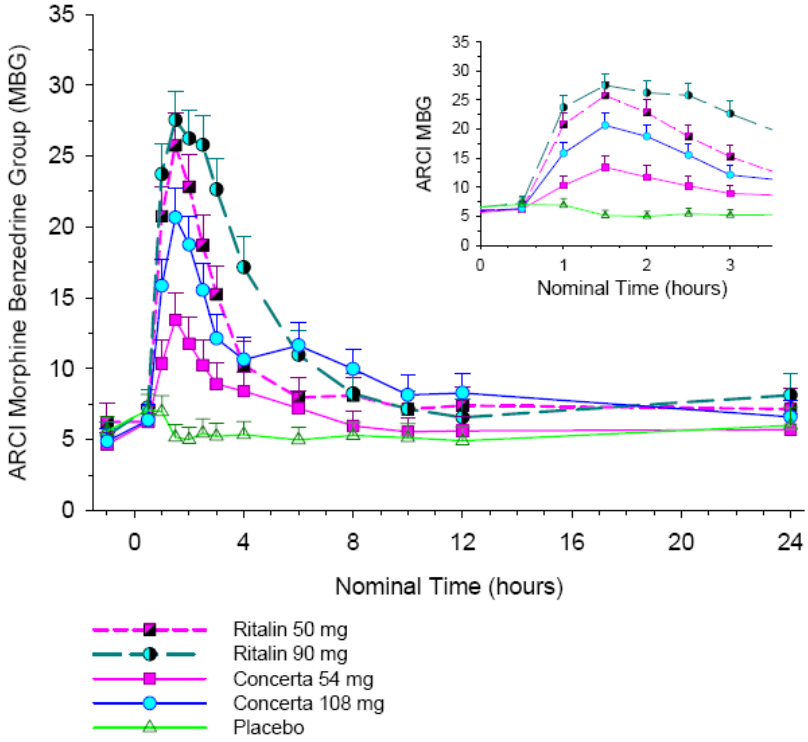
The mean (and standard deviation) d-methylphenidate plasma profiles following single doses of CONCERTA (54mg and 108mg) and Ritalin (50mg and 90mg) is shown below:



The mean (and standard deviation) time course of DRQS-VAS drug liking scores (0=Max Dislike, 50=Neutral, 100=Max Like) are presented below:



The mean (and standard deviation) time course of ARCI Morphine Benzedrine Group (MBG, ranging from 0-51) scores are presented below:



The summary of the mean primary dependent variables by treatment (positive effects) following single doses of CONCERTA, Ritalin (IR MPH) and placebo is shown below:

Subjective Measure		Placebo	CONCERTA 54 mg	CONCERTA 108 mg	IR MPH 50 mg	IR MPH 90 mg
DRQS-VAS Drug Liking ('at this moment')	AUE_{0-1h}	24.5	23.4[a]	26.9	28.6*	28.8*
	AUE_{0-2h}	70.4	74.0[a]	90.7*	98.2*	99.5*
	AUE_{0-3h}	116	123[a]	147*[b]	158*	168*
	E_{max}	51.7	60.0*[a]	73.8*[b]	78.1*	84.7*
Overall Drug Liking	12 h	40.4	43.0[a]	48.7	53.4*	50.6*
	24 h	38.2	42.1[a]	44.3	53.0*	48.0*
	E_{max}	42.7	46.3[a]	53.3*	58.2*	56.6*
ARCI MBG	AUE_{0-1h}	6.7	6.9[a]	8.4*[b]	9.9*	10.9*
	AUE_{0-2h}	12.2	19.1*[a]	27.3*[b]	33.6*	37.2*
	AUE_{0-3h}	17.5	29.4*[a]	42.8*[b]	52.5*	62.3*
	E_{max}	9.4	17.4*[a]	24.0*[b]	28.8*	33.8*

[a] Significant difference between CONCERTA 54 mg and IR MPH 50 mg ($p<0.05$)
[b] Significant difference between CONCERTA 108 mg and IR MPH 90 mg ($p<0.05$)
* Significantly different from placebo ($p<0.05$)
Statistical significance for VAS Drug Liking, Overall Drug Liking assessed using ANOVA; ARCI MBG assessed using ANCOVA

Assessor's comments

Although the Assessor agrees with the following MAH conclusion:
Overall, a consistent rank order was observed for all subjective measures of abuse as follows:

IR MPH 90 mg > IR MPH 50 mg > CONCERTA 108 mg > CONCERTA 54 mg > placebo

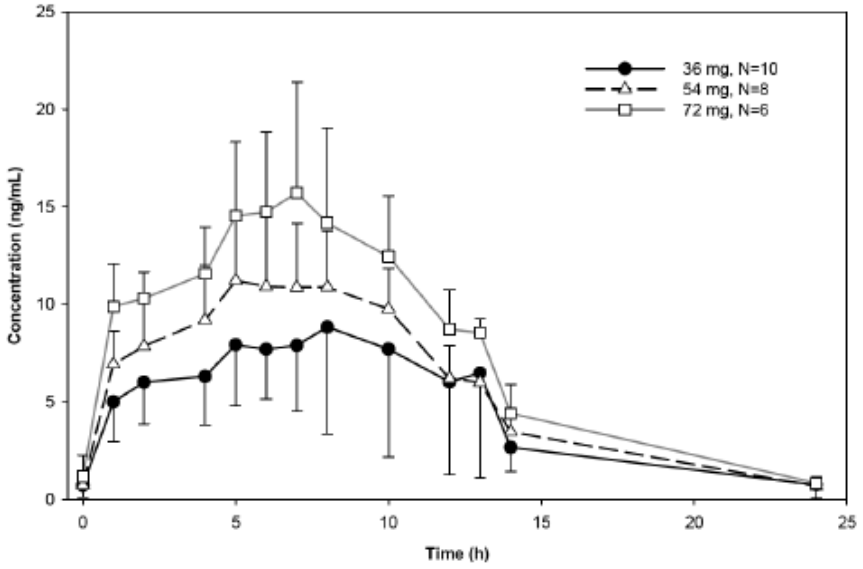
It would appear more likely that if abused the drug would be crushed. Even uncrushed in this naïve population the DRQS Drug Liking Score is higher than in the previously studied

populations. Some addiction potential has been demonstrated and also pleasurable effects which raises the question of how much the action seen in the RCTs is due to the euphoric effects of the Concerta.

Conclusion on Abuse Potential
Concerta consumption in light and recreational drug users appears to confer a positive effect on the 'Liking' element of the DRQS. This appears to be related to Cmax. If the tablets are crushed then the effects are likely to be heightened. The effect of augmentation of the effects of other drugs of misuse is not known and it is known that diversion is a significant problem (see RMP assessment).

Study 12-001
This was an open-label, multiple dose, five-dose parallel pharmacokinetic study. Healthy male and female subjects, ages 13 through 17 years, who were already taking CONCERTA® for the treatment of ADHD were enrolled. Subjects were instructed to take single oral daily doses of CONCERTA at the same time each day for five days while at home. On Day 6, subjects reported to the study center and received a final dose of study medication. The CONCERTA doses evaluated in the study were 18-, 27-, 36-, 54- and 72-mg. On Day 6, blood samples were collected over 24 hours for characterizing the pharmacokinetics of d- and l-methylphenidate and the major metabolite, d- and l-ritalinic acid (PPA), using validated assays.

The mean (and standard deviation) d-methylphenidate plasma profiles on Day 6 following once daily Concerta dosing is presented below:



Note: Data from 18- and 27-mg dose groups are not displayed, only 1 subject was dosed at each of these levels.

The mean (and standard deviation) plasma pharmacokinetic parameters for total d- and l-methylphenidate are presented below:

Dose (mg)	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{tau} (ng.h/mL)	CL_{SS}/F (L/h)	$T_{½}$ (h)	Vz/F (L)	Exposure Ratio[c]
				d-MPH				
36	10	9.5	7.2	110	189	4.60	1221	0.0475
		(5.2)	(1.6)	(53.0)	(68.6)	(2.88)	(682)	
54	8	12.2	6.8	137	208	3.62	1059	0.0335
		(3.3)	(1.7)	(34.6)	(54.4)	(0.45)	(154)	
72	6	17.6	7.0	182	203	3.55	1037	0.0328
		(4.6)	(1.8)	(34.6)	(37.8)	(0.50)	(210)	
				l-MPH				
36	10	0.417	6.5	2.51	18179	5.93	148427	0.0010
		(0.47)	(2.3)	(3.12)	(16087	(5.23)[a]	(202304)[a]	
54	8	0.681	5.8	3.30	35153	1.83[b]	3777[b]	0.0010
		(1.50)	(1.0)	(6.34)	(33954)	(NR)	(NR)	
72	6	0.457	5.7	3.45	30368	4.73[b]	17697[b]	0.0007
		(0.52)	(0.5)	(5.16)	(24044)	(NR)	(NR)	
				Total MPH				
36	10	9.9	7.0	112	372	4.29	2257	0.0229
		(5.5)	(2.1)	(55.9)	(137)	(2.03)	(1033)	
54	8	12.8	6.8	141	406	3.58	2040	0.0177
		(3.4)	(1.7)	(34.3)	(108)	(0.46)	(296)	
72	6	17.8	7.0	186	399	3.54	2025	0.0175
		(4.5)	(1.8)	(33.9)	(73.9)	(0.49)	(391)	

[a] n=2; [b] n=1

[c] Parent to metabolite ratio (MPH AUC_{tau}/PPA AUC_{tau})

Data from 18- and 27-mg dose groups are not displayed, only 1 subject was dosed at each of these levels.

Assessor's comments

The study in adolescents is only relevant to the application in terms of providing a review of the pharmacokinetic data across ages from children to adults and is not considered further.

CLINICAL EFFICACY

Main Studies

The double-blind controlled Phase III studies of Concerta in adults with ADHD are summarised below:

Protocol No.	No. Sites Enrolling Subjects Region (Country)	Study Design	Daily Dose and Study Duration	Subjects In Efficacy Analyses (M/F)[a]
Placebo-Controlled Studies				
42603ATT3002 (3002)	57 sites Europe: (Great Britain, Germany, Sweden, Denmark, Norway, Finland, Czech Republic, Greece, France, The Netherlands, Spain, Portugal, Switzerland)	Randomized, 5-week double-blind, placebo-controlled, parallel group phase using 3 fixed doses of CONCERTA (18, 36 and 72[b] mg) followed by an open-label extension period of 7-week duration with flexible dosing (18 to 90 mg/day)	Placebo CONCERTA 18 mg 36 mg 72 mg	95 (59/36) 99 (56/43) 101 (46/55) 99 (53/46)
02-159	27 sites United States	Randomized, 7-week double-blind, placebo-controlled, parallel group, dose-titration study of CONCERTA (36 – 108 mg/day)	Placebo CONCERTA (final mean dose = 68 mg/day)	116 (64/52) 110 (63/47)
42603ATT3013 (3013)	42 sites Europe: (Belgium, Denmark, Finland, France, Germany, Great Britain, The Netherlands, Norway, Spain, Sweden, Switzerland)	Randomized, 13-week, double-blind, placebo-controlled, parallel group, dose response study of 2 fixed doses of CONCERTA (54 or 72 mg/day)[c]	Placebo CONCERTA 54 mg 72 mg	97 (52/45) 90 (44/46) 92 (50/42)
Maintenance of Effect – Randomized Withdrawal Study Phase				
42603ATT3004 (3004)[d,e]	14 sites Europe: (Germany, The Netherlands, Spain, Portugal, Switzerland)	Randomized, 4-week, double-blind, placebo-controlled withdrawal phase following at least 52 weeks of open-label treatment; CONCERTA given at dose achieved at end of open-label treatment.	Placebo CONCERTA (mean dose during withdrawal phase = 43 mg/day)	22 (7/15) 23 (11/12)

[a] A total of 899 adult subjects with ADHD were evaluated in the 3 placebo-controlled studies and 45 adult subjects with ADHD were evaluated in the randomized withdrawal phase of Study 3004.

[b] Subjects assigned to CONCERTA 72 mg group were titrated from a starting dose of 36 mg/day for 4 days, to 54 mg/day for 3 days (end of Week 1), after which the assigned final dosage of 72 mg/day was administered for 4 weeks.

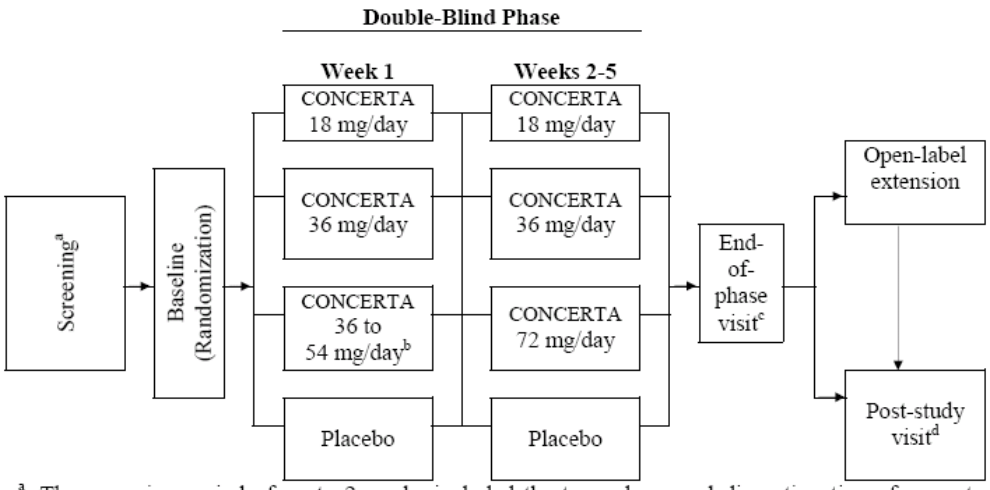
[c] Subjects assigned to CONCERTA were titrated from starting dose of 36 mg/day for 1 week to assigned target dose of 54 or 72 mg/day beginning on Day 8.

[d] Subjects had been treated in Study 3002 prior to enrollment in Study 3004.

[e] Subjects received up to 108 weeks of open-label treatment with CONCERTA prior to randomized withdrawal phase.

Methods - Study design

Figure 1: Design of Study 3002



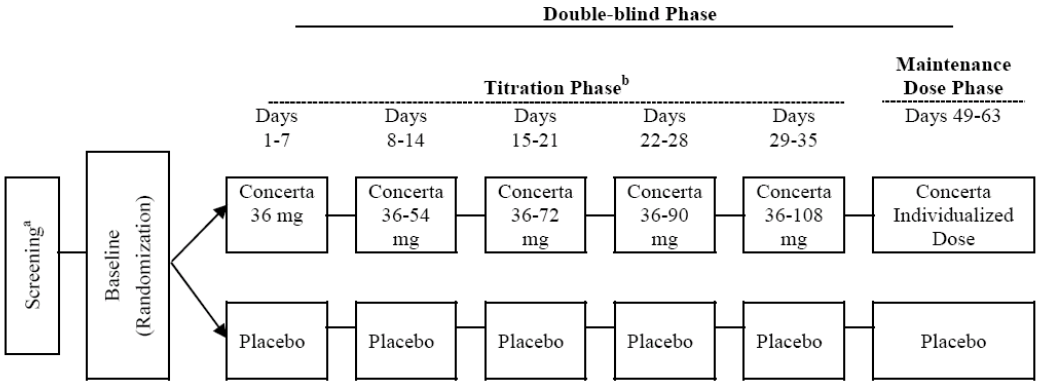
[a] The screening period of up to 2 weeks included the taper down and discontinuation of current disallowed treatment (except if fluoxetine or monoamine oxidase inhibitors needed to be tapered off, then a screening period of 4 weeks was allowed).

[b] Subjects assigned to 72 mg CONCERTA were titrated from a starting dose of 36 mg/day for 4 days, to 54 mg/day for 3 days (end of Week 1), after which the assigned final dosage of 72 mg/day was administered for 4 weeks.

[c] All subjects, including those who withdrew prematurely from the double-blind phase, had end-of-phase procedures performed.

[d] For those subjects not continuing in the open-label extension, the post-study visit was scheduled 1 week after the final dose of study drug in the double-blind phase. For those subjects who continued in the open-label extension, the post-study visit was scheduled 1 week after the final dose of study drug in the open-label extension.

Figure 2: Design of Study 02-159



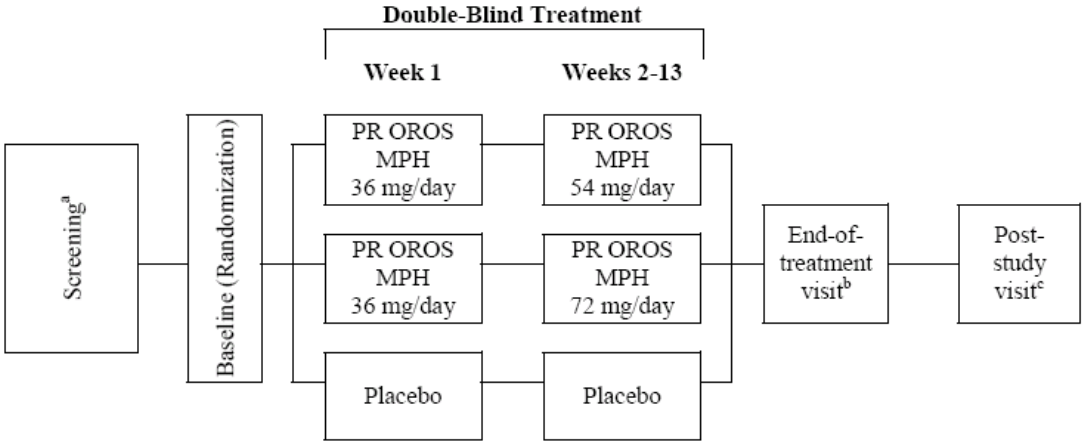
[a] Subjects who were being treated for ADHD at screening had to washout from all ADHD medication for 7 to 14 days. Subjects on atomoxetine hydrochloride returned for baseline visit within a 10 to 14 day window.

[b] Doses were titrated until the individualized dose was achieved. All visits were required, even if a subject had achieved an individualized dose.

All subjects will initiate treatment with 36 mg and continue with incremental increases of 18mg of CONCERTA every seven days (+/- 2 days) until an individualized dose is achieved. The individualized dose is the dose when: AISRS decreases by 30 percent and a Clinical Global Impression-Improvement (CGI-I) rating of 1 or 2 is achieved, or titration to the maximum dose of 108 mg has been achieved. Dose reduction by 18 mg/day for safety reasons was permitted only once during the double-blind phase, and a subsequent dose increase was not allowed. A dose reduction was required for resting heart

rate > 100 bpm, systolic blood pressure > 140 mmHg, or diastolic blood pressure > 90 mmHg (average of triplicate measurements), and for adverse events at the discretion of the investigator.

Figure 3: Design of Study 3013



[a] The screening period of up to 2 weeks included the tapering and discontinuation of current forbidden treatment (except if fluoxetine or monoamine oxidase (MAO) inhibitors needed to be tapered, in which case a screening period of 4 weeks was allowed).
[b] If a subject was withdrawn early, every attempt had to be made to complete the end-of-treatment procedures.
[c] The post-study visit was scheduled 1 week after the final dose of study drug.

Population

ADHD was diagnosed using DSM-IV by qualified mental health professionals experienced in ADHD diagnosis and trained in the use of structured interviews to confirm the diagnosis. Specified axis I disorders and elderly (> 65 years of age) were excluded. Subjects were required to demonstrate a chronic course of ADHD symptomatology from childhood to adulthood, with some symptoms present before the age of 7 years. Description of the chronicity of ADHD symptoms could be subject- or informant-based; if available, documentation of previous diagnosis or onset of symptoms in childhood was obtained from medical and/or psychiatric records, school records, and family member reports. In Studies 3002 and 3013, the Connors' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was used to confirm the diagnosis while in Study 02-159, the Adult ADHD Clinical Diagnostic Scale (ACDS), version 1.2 was employed.

Statistical Assessor's Comment:
The patient population enrolled does not reflect the population for which the applicant is seeking an indication. In Study 3002 approximately 20% of patients enrolled had a diagnosis of ADHD before the age of 18. It is unlikely that statistically significant results in this sub-population will be obtained (shown later) as the trial is not powered to detect this difference. If no differences between the sub-groups based on age of diagnosis are found, it is a matter of clinical judgement whether an overall positive study is sufficiently supportive of the narrower indication.

Exclusion criteria (see Appendix III)

These were very extensive and excluded any significant psychiatric or physical co-morbidity drug or alcohol abuse.

Endpoints (see Appendix IV)
Randomisation was centrally implemented by computer and stratified by treatment centre. There were very few patients randomised per centre.

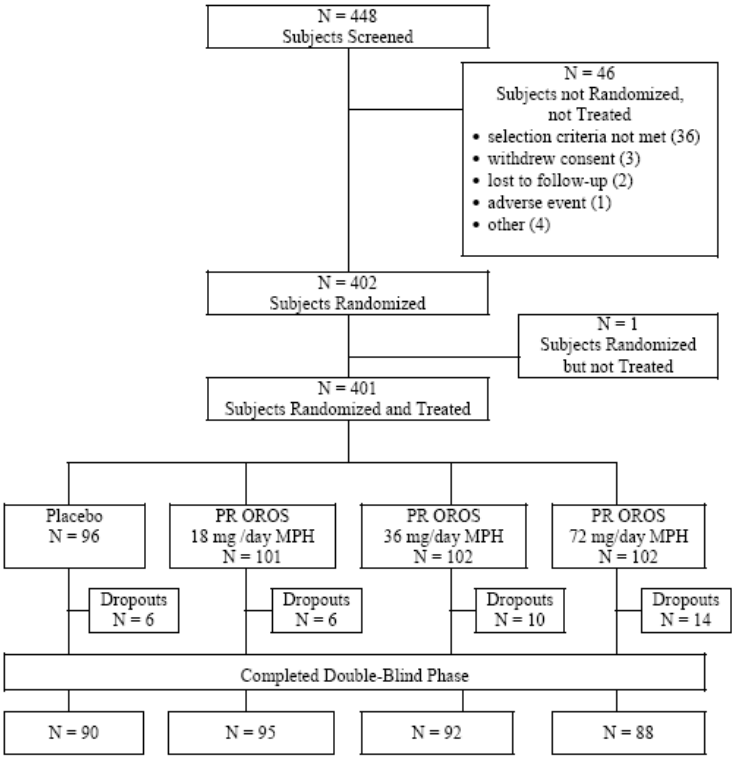
Statistical Methods
ANCOVA was used to analyse the primary endpoints of CAARS (or AIRSS) score, with treatment, country and baseline primary efficacy variable (although see below). Due to the small number of patients per treatment centre, centres were grouped by country and this was then included as a covariate. LOCF was the primary method for handling missing data, with BOCF used in study 059 for patients with no post-baseline measurements. Sensitivity analyses using MMRM and using the per-protocol populations were provided.

Statistical Assessor's Comment
The use of ANCOVA is acceptable for this endpoint. The decision to include country instead of the pre-specified covariate of investigator is understandable and supported. However there is concern that arbitrary *post hoc* covariates have been introduced into the final model in some of the trials, which was not specified in the SAP, and is not acceptable.. It is unclear why gender has been included in the model in Study 3002, and age has been included in study 3013, and the applicant should repeat the analysis to provide reassurance that the *post hoc* inclusion of the covariate does not affect the interpretation of the results.

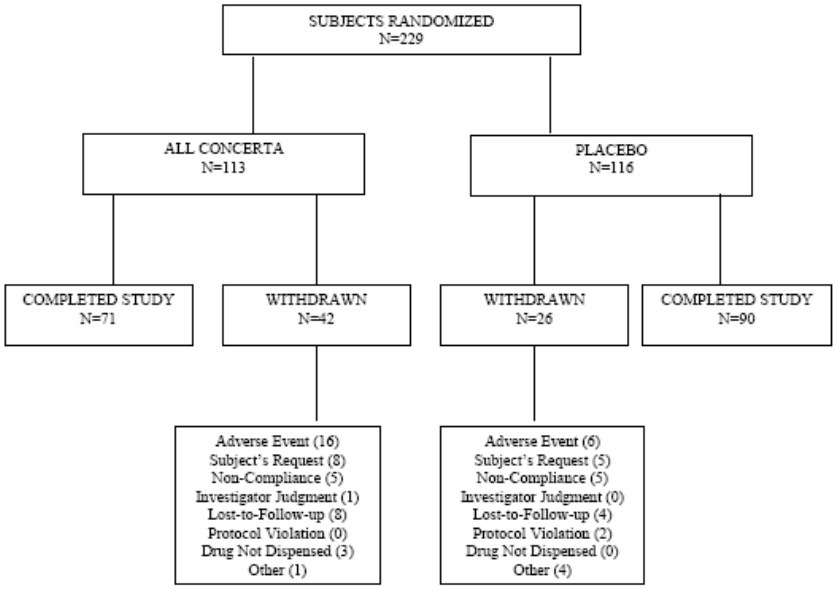
It is unclear whether LOCF is a suitably conservative analysis to handle the missing data. Although the results of the per-protocol analysis and the MMRMM sensitivity analysis have an even more extreme significance, this does not rule out the possibility that neither the per-protocol nor the LOCF method are conservative. The responder analysis may be the most appropriately conservative method to assess the missing data. In Study 3002, the additional *post hoc* definition of a CAARS decrease of 50% indicating response, as well as the pre-specified change of 30% is supported. However what is not clear from the data is how patients who dropped out of the trial have been handled in the responder analysis. The applicant state that "a treatment responder was defined as a subject with a 30% or greater reduction from baseline in CAARS total score at double-blind end point." They go on to define the "the primary end point in the double-blind treatment phase was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated CAARS from baseline to the last post-randomization assessment in the double-blind treatment period." One interpretation of this is that all data is considered as LOCF, and therefore even if a patient drops out of the study, they may have been considered a responder if they had a 30% change when they dropped out. This is not an appropriately conservative analysis and the applicant should clarify if this is method used. If so, the applicant should repeat the responder analysis including all patients who dropped out as failures. They should provide the point estimates per treatment group, as well as confidence intervals for the differences between the 3 active dose groups and placebo, and the associated Dunnet adjusted p-values. The same applies for the additional *post hoc* definition of responder of a 50% decrease in CAARS.

Results

Disposition - Study 3002

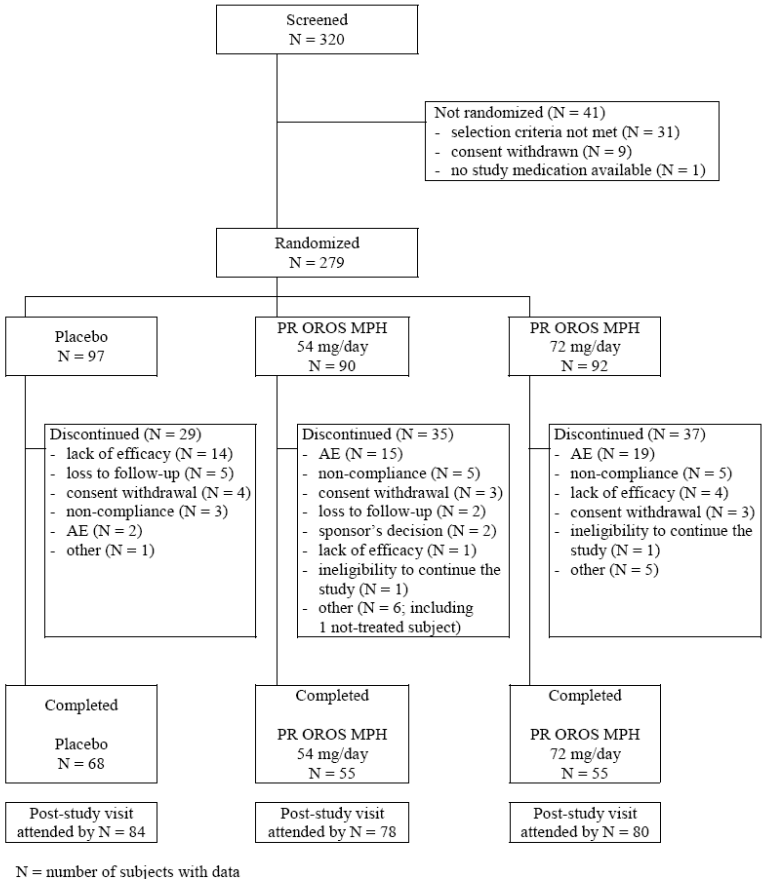


Disposition - Study 02-159



Subjects Completing the Study, N=161

Disposition - Study 3013



Statistical Assessor's Comment:

Across all studies, the withdrawal rates for Concerta were higher for that of placebo and there is no evidence that the withdrawals happen earlier rather than later (or vice versa) (graphs not shown). There is a clear imbalance between the arms, which leads to the possibility that the primary analysis method (and also the MMRM sensitivity analyses) may not be suitably conservative. In study 3013, there is an incredibly high dropout rate, with 30% of patients not completing in the placebo group, and 40% in the active group. The implications of this are discussed further in the results section.

Demographics - Study 3002

42603ATT3002: LAMDA: FINAL ANALYSIS

DISPLAY GEN.1: INVESTIGATORS: TABULATION

POPULATION: ALL SUBJECTS / DOUBLE BLIND
TABULATION BY COUNTRY

COUNTRY	MPH 18mg OD		MPH 36mg OD		MPH 72mg OD		Placebo		OVERALL	
	N	%	N	%	N	%	N	%	N	%
CZECH REPUBLIC	3	3.0	3	2.9	5	4.9	4	4.2	15	3.7
DENMARK	8	7.9	10	9.8	8	7.8	7	7.3	33	8.2
FINLAND	7	6.9	7	6.9	8	7.8	8	8.3	30	7.5
FRANCE	5	5.0	5	4.9	4	3.9	4	4.2	18	4.5
GERMANY	31	30.7	28	27.5	31	30.4	29	30.2	119	29.7
GREAT BRITAIN	4	4.0	2	2.0	3	2.9	2	2.1	11	2.7
GREECE	2	2.0	3	2.9	2	2.0	1	1.0	8	2.0
NETHERLANDS	7	6.9	8	7.8	8	7.8	7	7.3	30	7.5
NORWAY	6	5.9	7	6.9	6	5.9	7	7.3	26	6.5
PORTUGAL	4	4.0	4	3.9	5	4.9	5	5.2	18	4.5
SPAIN	7	6.9	7	6.9	7	6.9	7	7.3	28	7.0
SWEDEN	10	9.9	11	10.8	10	9.8	9	9.4	40	10.0
SWITZERLAND	7	6.9	7	6.9	5	4.9	6	6.3	25	6.2
** TOTAL **	101	100.0	102	100.0	102	100.0	96	100.0	401	100.0

Study 02-159 – US only Demographics - Study 3013

ANALYSIS SET: INTENT TO TREAT
TABULATION BY COUNTRY

COUNTRY	PLACEBO		54 MG/DAY		72 MG/DAY		OVERALL	
	N	%	N	%	N	%	N	%
BELGIUM	5	5.2	3	3.3	4	4.3	12	4.3
DENMARK	4	4.1	3	3.3	5	5.4	12	4.3
FINLAND	9	9.3	9	10.0	10	10.9	28	10.0
FRANCE	10	10.3	6	6.7	6	6.5	22	7.9
GERMANY	22	22.7	23	25.6	20	21.7	65	23.3
GREAT BRITAIN	4	4.1	3	3.3	3	3.3	10	3.6
NETHERLANDS	5	5.2	4	4.4	6	6.5	15	5.4
NORWAY	8	8.2	9	10.0	9	9.8	26	9.3
SPAIN	12	12.4	14	15.6	12	13.0	38	13.6
SWEDEN	17	17.5	15	16.7	16	17.4	48	17.2
SWITZERLAND	1	1.0	1	1.1	1	1.1	3	1.1
** TOTAL **	97	100.0	90	100.0	92	100.0	279	100.0

Key Demographic Characteristics

	Study 3002				Study 02-159		Study 3013		
		CONCERTA						CONCERTA	
	Placebo (N=95)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)	Placebo (N=116)	CONCERTA (N=110)	Placebo (N=97)	54 mg (N=90)	72 mg (N=92)
Age, yrs									
Mean	34.6	34.5	33.9	33.7	38.2	39.9	35.5	35.8	35.8
Range	18-57	18-60	18-60	18-63	19-64	18-65	18-57	18-64	18-60
Sex, n (%)									
Male	59 (62.1)	56 (56.6)	46 (45.5)	53 (53.9)	64 (55.2)	63 (57.3)	52 (53.6)	44 (48.9)	50 (54.3)
Race, n (%)									
Caucasian	93 (97.9)	98 (99.0)	98 (97.0)	96 (97.0)	99 (85.3)	96 (87.3)	93 (95.9)	85 (94.4)	89 (96.7)
ADHD Subtype, n (%)									
Combined type	67 (70.5)	62 (62.6)	75 (74.3)	74 (74.7)	94 (81.0)	87 (79.1)	73 (75.3)	60 (66.7)	62 (67.4)
Inattentive type	23 (24.2)	32 (32.3)	19 (18.8)	22 (22.2)	21 (18.1)	22 (20.0)	23 (23.7)	27 (30.0)	28 (30.4)
Hyperactive/ Impulsive type	2 (2.1)	4 (4.0)	7. (6.9)	3 (3.0)	1 (0.9)	1 (0.9)	1 (1.0)	3 (3.3)	2 (2.2)
NOS	3 (3.2)	1 (1.0)	0	0	0	0	0	0	0
Age at ADHD Diagnosis, yr[a]									
N	94	98	101	99	53[a]	55[a]	96	90	91
Mean	31.6	30.8	29.1	28.9	27.1	31.1	31.9	30.8	32.4
Range	4 - 57	4 – 60	0 - 59	2 - 63	5 - 59	4 - 63	3 – 57	3 – 63	3 – 60
Prior Use of ADHD Drugs, n(%)[a,b]									
N	96	101	102	102	116	113	97	90	92
Yes	11 (11.5)	8 (7.9)	6 (5.9)	10 (9.8)	42 (36.2)	39 (34.5)	10 (10.3)[c]	11 (12.2)[c]	3 (3.3)[c]
Co-morbid mood/anxiety disorder, n (%)[a]									
N	96	101	102	102	116	113	97	90	92
Yes	10 (10.4)	10 (9.9)	11 (10.8)	17 (16.7)	15 (12.9)[d]	6 (5.3)[d]	12 (12.4)	13 (14.4)	9 (9.8)

NOS = not otherwise specified.
[a] Based on all randomized subject population.
[b] Defined as within the past 3 months prior to enrollment for Study 3002 and 3013; defined as within 30 days of the screening visit and prior to the first dose of double-blind study medication for Study 02-159.
[c] Defined as prior use of MPH for Study 3013.
[d] Combined number of subjects with anxiety and depression.

Psychiatric Co-morbidity

Study 3002 There were very low levels of co-morbidities apart from anxiety: alcohol (currently active 0.7%: history 13.5%), Mood and Anxiety (currently active 12.0%: history 29.9%), Personality Disorder (currently active 1.0 %) with 91% of the study population was methylphenidate naïve.

Study 02-159 Approximately 35% had taken some form of medication for their ADHD before randomisation which was stopped 30 days prior to randomisation.

Study 3013 Similar pattern to Study 3002: 8.6% stopped methylphenidate prior to randomisation.

Concomitant Therapy

Concomitant therapy with antidepressants was permitted but the dose had to be stable for the last 3 months. MAOIs were not permitted.

Study 3002 There were 10% subjects comedicated with psychoanaleptics and 5% with psycholeptics.

Study 02-159 There were low levels of co-medication with benzodiazepine or related drugs (1.8%), SSRIs up to 9% but high levels of anilide use(up to 20%).

Study 3013 There were 16.8% subjects comedicated with psychoanaleptics and 8.6% with psycholeptics.

Compliance

In Study 02-159 compliance was 73% in the CONCERTA group and 85% in the placebo group being at least 90% compliant (percentage of days that the full dose was taken). There were less stringent definitions of compliance based on total tablet count and thus >90% of subjects were deemed to be compliant in studies 3002 and 3013.

Exposure

The dose received per treatment group is presented below:

	Dose (mg)	CONCERTA (N=110)	Placebo (N=116)
Maximum dose, n (%)	36	32 (29.1)	11 (9.5)
	54	18 (16.4)	19 (16.4)
	72	15 (13.6)	12 (10.3)
	90	16 (14.5)	6 (5.2)
	108	29 (26.4)	68 (58.6)
Mean Maximum Dose (mg) (SD)		70.7 (28.72)	87.7 (26.70)
Final dose, n (%)	36	36 (32.7)	15 (12.9)
	54	16 (14.5)	16 (13.8)
	72	19 (17.3)	11 (9.5)
	90	16 (14.5)	6 (5.2)
	108	23 (20.9)	68 (58.6)
Mean Final Dose (mg) (SD)		67.7 (27.90)	86.9 (27.81)

Primary Endpoint

The Intent-To-Treat (ITT) population, defined as those who had taken one dose of medication and have one post baseline assessment.

Statistical Assessor's Comment

The definition of ITT that is most appropriate is patients who have received study medication. The decision to exclude patients who did not have a post-baseline measurement is not supported. However, there are so few of these patients across the trials, that it is unlikely in the extreme that their inclusion would change the interpretation of the results to any meaningful degree

Study 3002

CAARS ADHD symptoms total sore: Actual values and change from baseline to double-blind endpoint – Last observation carried forward (LOCF) – ITT population, is presented below:

		CONCERTA		
	Placebo (N=95)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)
Baseline				
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Range	24, 51	24, 53	25, 51	24, 52
Double-Blind End Point				
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Range	4, 50	4, 51	4, 52	1, 50
Change From Baseline to Double-Blind End Point				
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Range	-45, 8	-35, 16	-37, 8	-40, 8
p-value (vs. Placebo)[a]		0.0146	0.0131	<0.0001
Difference of LS means		-3.99	-4.03	-6.59
95% CI		(-7.35, -0.64)	(-7.38, -0.69)	(-9.93, -3.25)

A negative change from baseline indicates an improvement.

[a] Based on ANCOVA model with factors for treatment, gender, and country and baseline value as a covariate. Dunnett's procedure was used to adjust for comparisons between each CONCERTA dose group and placebo.

Study 02-159

AISRS total sore: Actual values and change from baseline to double-blind endpoint – Last observation carried forward (LOCF) – ITT population, is presented below:

	Placebo (N=116)	CONCERTA (N=110)
Baseline		
Mean (SD)	38.1 (7.31)	38.6 (6.85)
Range	24, 54	24,54
Double-Blind End Point		
Mean (SD)	31.3 (12.38)	27.6 (13.17)
Range	3, 54	0, 52
Change From Baseline to Double-Blind End Point		
Mean (SD)	-6.8 (11.45)	-10.9 (11.75)
Range	-38, 12	-48, 13
p-value (vs. Placebo)[a]		0.012
Difference of LS means		-3.8
95% CI		(-6.80, -0.86)

A negative change from baseline indicates an improvement.

[a] Based on ANCOVA model with factors for treatment and site and baseline value as a covariate. A step-wise procedure was used to control the overall Type I error rate.

Study 3013

CAARS ADHD symptoms total sore: Actual values and change from baseline to double-blind endpoint –ITT population, is presented below:

		CONCERTA	
	Placebo (N = 97)	54 mg (N = 90)	72 mg (N = 92)
Baseline[a]			
Mean (SD)	36.5 (6.05)	35.6 (6.75)	37.3 (6.35)
Range	24 - 51	25 – 54	23 - 50
End point			
Mean (SD)	26.1 (10.59)	23.0 (11.07)	21.6 (10.21)
Range	0 - 52	2 – 52	2 - 44
Change from Baseline to End point			
Mean (SD)	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)
Range	-43 - 7	-37 – 11	-39 - 10
p-value (vs. Placebo)[b]		0.1356	0.0024
Difference in LS means[b]	-	-2.69	-4.89

[a] In case of missing values, the baseline value was imputed with the screening value.

[b] Based on ANCOVA model with factors for treatment, gender, and country, and age and baseline value as a covariate. Comparisons of each dose group with placebo adjusted for multiplicity using Dunnett's procedure.

The CAARS demonstrated numerical improvement above placebo for both subsections inattention and hyperactivity/impulsivity.

Responder Rates The definition of responder is less rigorous in Study 3002 and Study 3013, with only a requirement to demonstrate a 30% improvement on the CAARS and no reference to CGI.

Study 3002 – Responder rates: percentage of subjects with 30% or more reduction from baseline in CAARS total score at double-blind endpoint

		PR OROS MPH		
Timepoint	Placebo (N=95)	18 mg (N=99)	36 mg (N=101)	72 mg (N=99)
Double-Blind End Point				
Responders: n (%)	26 (27.4)	50 (50.5)	49 (48.5)	59 (59.6)
Non-responders: n (%)	69 (72.6)	49 (49.5)	52 (51.5)	40 (40.4)
p-value[a] (comparison versus placebo)		0.0020	0.0074	<0.0001

[a] 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

Study 02-159 – Number (%) of responders by visit based on the AISRS total score and CGI Improvement Scale

Visit[a]	CONCERTA	Placebo	Odds Ratio[b]	95% CI	p-value[c]
Titration Visit 1, n/N (%)	20/103 (19.4)	6/115 (5.2)	3.60	(1.42, 9.14)	0.002
Titration Visit 2, n/N (%)	23/98 (23.5)	13/108 (12.0)	2.18	(1.03, 4.65)	0.037
Titration Visit 3, n/N (%)	30/91 (33.0)	19/103 (18.4)	2.13	(1.08, 4.21)	0.028
Titration Visit 4, n/N (%)	35/85 (41.2)	21/97 (21.6)	2.75	(1.38, 5.50)	0.003
Titration Visit 5, n/N (%)	40/81 (49.4)	22/93 (23.7)	3.31	(1.68, 6.55)	<0.001
Two 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]: All subjects initiated treatment with 36 mg of study medication and continued with incremental increases of 18 mg every 7 days until an individualized dose. The mean final dose of CONCERTA was 67.7 mg.

[b] The odds ratio of achieving response for All CONCERTA versus placebo, adjusted for pooled study site.

[c]: 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.

The applicant has also provided a table for the dose at which patients first responded, although this is a post hoc analysis with number (%) of responders by dose based on AISRS total score and CGI improvement scale:

	CONCERTA		Placebo	
Dose Level (mg/day)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)
36	103	21 (20.4)	115	9 (7.8)
54	78	11 (14.1)	103	11 (10.7)
72	59	12 (20.3)	85	6 (7.1)
90	44	8 (18.2)	71	1 (1.4)
108	29	5 (17.2)	67	3 (4.5)

The applicant has presented a sensitivity analysis using MMRM on the change from baseline data. In particular, this results in the baseline data not being included in the model. The treatment effect was significant in this model, and the applicant notes that the treatment by time interaction was not.

Statistical Assessor's Comment:
It is unclear from the data presented what precisely is happening. Patients are not up-titrated if they respond, and in total 57 patients responded at any time on Concerta, although there were only 38 responders at the end of the trial. If the applicant considers missing data to be non-responders, this may explain a lot of this apparent discrepancy. The other alternative is that patients are responding throughout the trial but then fail at the final visit. This would raise questions about the longer term efficacy, especially in light of the results of the randomised withdrawal trial. The applicant should clarify the reasons why there is a difference between the total number of responders at the end of the double-blind period, and the total of all responders in the *post hoc* analysis.

The numerator should only be considered in the table above since LOCF has been used at final visit. The data require further scrutiny treating all dropouts as non-responders to gain a more realistic view on the degree of efficacy.

The usual method of interpreting the MMRM analysis is to consider the treatment by time interaction test. However, because the applicant has presented a change from baseline analysis, which excludes baseline, it is the treatment effect which is the most important in assessing the efficacy of the product. The interaction test would show whether the improvement from baseline increases as the trial continues, whereas the treatment effect shows whether there is any difference between the 2 treatments. Therefore the sensitivity analysis does not provide evidence against efficacy, although it is still arguable that neither method provides a suitably conservative analysis.

The dosing regimen used in the trial does not support the proposed dosing regimen in the SmPC, with much higher doses being permitted in this trial. However efficacy does seem to be demonstrated at the lower dose groups, as shown in the *post hoc* analysis above.

Study 3013 - Disposition

DISPLAY EFF.28: RESPONDER RATE: DESCRIPTIVE STATISTICS
ANALYSIS SET: INTENT TO TREAT
A) TABULATION OF RESPONSE AT DOUBLE-BLIND ENDPOINT

	RESPONSE?					
	NO		YES		TOTAL	
	N	%	N	%	N	%
PLACEBO	53	54.6	44	45.4	97	100.0
54 MG/DAY	40	44.4	50	55.6	90	100.0
72 MG/DAY	33	35.9	59	64.1	92	100.0
ALL MPH	73	40.1	109	59.9	182	100.0

		PR OROS MPH		
	Placebo (N = 97) n (%)	**54 mg/day (N = 90) n (%)**	**72 mg/day (N = 92) n (%)**	**Total (N = 279) n (%)**
Completed	68 (70.1)	55 (61.1)	55 (59.8)	178 (63.8)
Discontinued	29 (29.9)	35 (38.9)	37 (40.2)	101 (36.2)
Adverse event	2 (2.1)	15 (16.7)	19 (20.7)	36 (12.9)
Lack of efficacy	14 (14.4)	1 (1.1)	4 (4.3)	19 (6.8)
Non-compliance	3 (3.1)	5 (5.6)	5 (5.4)	13 (4.7)
Consent withdrawal	4 (4.1)	3 (3.3)	3 (3.3)	10 (3.6)
Loss to follow-up	5 (5.2)	2 (2.2)	0	7 (2.5)
Sponsor's decision	0	2 (2.2)	0	2 (0.7)
Ineligibility to continue the study	0	1 (1.1)	1 (1.1)	2 (0.7)
Other	1 (1.0)	6 (6.7)	5 (5.4)	12 (4.3)

Statistical Assessor's Comment:
The most appropriate method for handling missing data is to consider those that drop out as treatment failures. As noted earlier there is an incredibly high dropout rate in this study, with 30% of patients not completing in the placebo group, and 40% in the active group. It is clear from the data presented that in this trial the applicant has not treated missing as failure, as more patients appear to have responded than actually finished the trial in the 72 mg/day group. Whilst it is accepted that this study is longer in duration than the other efficacy studies and thus it may be reasonable to expect a higher dropout, there is so much missing data that the robustness of the results could be called into question. Furthermore, it adds weight to the concern that carrying forward a good value using LOCF when a patient drops out for a safety-related AE is not a suitably conservative analysis.

CGI-I summary statistics at double-blind endpoint – ITT population

		CONCERTA				
CGI-I Rating	Placebo	18 mg	36 mg	54 mg	72 mg	All Concerta
Study 3002						
N	93	97	100		98	295
Mean (SD) score at LOCF end point	3.4 (0.92)	2.8 (0.90)	3.0 (1.04)		2.7 (1.08)	2.8 (1.02)
p-value (vs. Placebo)[a]		0.0004	0.0108		<0.0001	<0.0001
CGI-I Scores, n (%)						
Much or very much improved	17 (18.3)	37 (38.2)	36 (36.0)		47 (47.9)	120 (40.7)
Minimally improved	30 (32.3)	35 (36.1)	29 (29.0)		26 (26.5)	90 (30.5)
No change	41 (44.1)	24 (24.7)	30 (30.0)		21 (21.4)	75 (25.4)
Minimally - Much worse[b]	5 (5.4)	1 (1.0)	5 (5.0)		4 (4.1)	10 (3.4)
Study 02-159						
N	115					103[c]
LS Mean (SE) score at LOCF end point[d]	3.43 (0.11)					3.02 (0.11)
p-value (vs. Placebo)[e]						0.008
CGI-I Scores, n (%)						
Much or very much improved	25 (21.8)					39 (37.9)
Minimally improved	17 (14.8)					23 (22.3)
No change	68 (59.1)					34 (33.0)
Minimally - Much worse[b]	5 (4.3)					7 (6.8)
Study 3013						
N	93			84	92	176
Mean (SD) score at end point	3.0 (1.17)			2.7 (1.17)	2.5 (1.18)	2.6 (1.15)
p-value (vs. Placebo)[a]				0.0518	0.0018	0.0034
CGI-I Scores, n (%)						
Much or very much improved	31 (33.4)			42 (50.0)	56 (60.9)	98 (55.7)
Minimally improved	26 (28.0)			14 (16.7)	15 (16.3)	29 (16.5)
No change	30 (32.3)			25 (29.8)	17 (18.5)	42 (23.9)
Minimally - Much worse[b]	6 (6.5)			3 (3.6)	4 (4.4)	7 (4.0)

A lower mean CGI-I score indicates greater improvement relative to baseline.
Shaded area indicates treatment group was not represented in that study.

[a] Based on ANOVA model on ranks controlling for country and gender. Comparison between each CONCERTA dose group and placebo adjusted using Dunnett's procedure for Study 3002; comparisons unadjusted for mulitiplicity in Study 3013.

[b] No subject in any treatment group had a CGI-I rating of very much worse at double-blind end point.

[c] Mean final dose of 68 mg/day.

[d] Data represent LS mean (± SE).

[e] Based on ANOVA model with factors for treatment and site. A step-wise procedure was used to control the Type I error rate.

Overview of Primary and Secondary Endpoints – ITT Population
Study 3002

Efficacy Variable	Placebo	CONCERTA 18 mg	CONCERTA 36 mg	CONCERTA 72 mg
Primary Efficacy Variable				
CAARS ADHD symptoms total Score, n	95	99	101	99
Mean change (SD)[a]	-7.6 (9.93)	-10.6 (10.34)*	-11.5 (9.97)*	-13.7 (11.11)*
Secondary Efficacy Variables				
CAARS Inattention Subscale, n	95	99	101	99
Mean change (SD)[a]	-3.7 (5.23)	-5.9 (5.76)*	-6.5 (5.92)*	-7.6 (6.29)*
CAARS Hyperactivity/Impulsivity Subscale, n	95	99	101	99
Mean change (SD)[a]	-3.9 (5.46)	-4.7 (5.54)	-4.9 (5.04)	-6.0 (6.18)*
CAARS-S:S Total Score, n	91	93	95	92
Mean change (SD)[a]	-5.8 (11.26)	-10.4 (12.90)*	-11.3 (12.42)*	-14.4 (15.52)*
CGI-S, n	93	97	100	98
Median change (range)[a]	0.0 (-3, 1)	-1.0 (-4, 1)*	-1.0 (-4, 1)*	-1.0 (-4, 1)*
CGI-I, n	93	97	100	98
Mean value (SD)[c]	3.4 (0.92)	2.8 (0.9)*	3.0 (1.06)*	2.7 (1.08)*
SDS Total Score, n	74	76	79	75
Mean change (SD)[a]	-2.2 (3.90)	-4.8 (6.25)*	-4.1 (5.62)	-5.1 (6.96)*
Q-LES-Q-SF Total Score, n	78	82	86	78
Mean change (SD)[b]	5.0 (14.17)	5.6 (12.30)	4.7 (15.68)	6.7 (18.97)
GAE, n	93	97	100	98
Median value (range)[d]	0.0 (0, 3)	1.0 (0, 3)	1.0 (0, 3)	1.0 (0, 3)

[a] Negative change from baseline value indicates improvement relative to baseline value.
[b] Positive value or change from baseline value indicates improvement relative to baseline value.
[c] CGI-I scale ranged from 1 (very much improved) to 7 (very much worsened).
[d] GAE was rated using 4-point scale (0 = poor to 3 = excellent).
* Denotes a statistically significant (p-value<0.05) difference relative to placebo, adjusted for comparisons between each CONCERTA dose group and placebo using Dunnett's procedure.

Study 02-159

Variable[a]	CONCERTA	Placebo	p-value[b]
AISRS Total Score (primary variable), n	110	116	
Mean change (SD)	-10.9 (11.75)	-6.8 (11.45)	0.012
CGI-I, n:	103	115	
LS Mean (SE)[b]	3.0 ± 0.11	3.4 ± 0.11	0.008
CAARS-S:S Total Score:, n	102	115	
Mean change (SD)	-13.3 (15.81)	-8.8 (13.19)	0.029
Treatment Responder Rate[c]:			
% (n/N)	36.9 (38/103)	20.9 (24/115)	0.009
SDS Work Subscale Score, n	90	99	
Mean change (SD)	-1.4 (2.79)	-1.0 (2.44)	0.397
CGI-S, n	103	115	
Mean change (SD)	-1.0 (1.22)	-0.5 (1.00)	0.009[d]
AIM-A: Work/Home/School Domain, n	94	107	
Mean change (SD)	17.4 (26.68)	9.6 (22.53)	0.016[d]

[a] Lower values indicate greater improvement for AISRS Total score, CGI-I, CAARS-S:S Total score, SDS - Work subscale score, and CGI-S. Higher values indicate greater effectiveness for AIM-A Work/Home/School Domain score.
[b] Data represented as LS mean (± standard error).
[c] Treatment responder defined as subjects with 30% improvement in AISRS total score and a CGI-Improvement rating of much or very much improved.
[d] Nominal p-values. Formal testing was not performed due to multiple-testing hierarchy.
Note: The number of subjects reported for each variable is not the same because the baseline value was carried forward to final visit only for the AISRS total score for subjects with missing post-baseline assessments.

Study 3013:

Efficacy Variable	Placebo	CONCERTA 54 mg	CONCERTA 72 mg
Primary Efficacy Variable			
CAARS ADHD symptoms total Score, n	97	90	92
Mean change at end point (SD)[a]	-10.4 (11.03)	-12.5 (10.38)	-15.7 (10.80)*
Secondary Efficacy Variables			
CAARS Inattention Subscale, n	97	90	92
Mean change at end point (SD) [a]	-5.5 (6.35)	-7.0 (6.14)*	-8.9 (6.37)*
CAARS Hyperactivity/Impulsivity Subscale, n	97	90	92
Mean change at end point (SD) [a]	-4.9 (5.84)	-5.6 (5.19)	-6.8 (5.67)*
CAARS-S:S Total Score, n	94	85	90
Mean change at end point (SD) [a]	-8.5 (11.64)	-12.8 (13.42)*	-12.6 (13.84)*
CGI-S, n	97	90	92
Mean change at end point (SD)[a]	-0.9 (1.35)	-1.0 (1.19)	-1.4 (1.31)*
CGI-I, n	93	84	92
Mean value at end point (SD)[b,c]	3.0 (1.17)	2.7 (1.17)	2.5 (1.13)*
SDS Total Score, n	88	77	83
Mean change at end point (SD)[a]	-3.6 (5.33)	-4.4 (6.35)	-4.6 (6.58)
AIM-A: Work, Home, & School – Performance and Daily Functioning, n	97	88	92
Mean change at end point (SD)[b]	10.3 (18.95)	16.4 (22.95)*	19.8 (22.47)*
AIM-A: Living with ADHD, n	97	88	92
Mean change at end point (SD)[b]	2.0 (11.91)	4.3 (13.24)	5.9 (12.11)*
AIM-A: Impact of Symptoms on Daily Life, Daily Interference Scale, n	96	88	90
Mean change at end point (SD)[b]	12.7 (19.37)	17.5 (22.57)*	17.6 (21.63)*
AIM-A: General Well-Being, n	97	88	92
Mean change at end point (SD)[b]	4.7 (14.95)	9.5 (16.69)*	8.7 (16.48)
AIM-A: Relationships/Communication, n	97	88	92
Mean change at end point (SD)[b]	5.7 (20.96)	9.5 (18.88)	13.5 (21.17)*
AIM-A: Impact of Symptoms on Daily Life, Bother/Concern, n	97	88	92
Mean change at end point (SD)[b]	13.4 (19.53)	16.8 (21.28)	16.6 (24.62)

[a] Negative change from baseline indicates improvement relative to baseline value.
[b] Positive value or change from baseline indicates improvement relative to baseline value.
[c] CGI-I scale ranged from 1 (very much improved) to 7 (very much worsened).
* Denotes a statistically significant (p-value≤0.05) difference relative to placebo, adjusted for comparisons between each CONCERTA dose group and placebo; Dunnett's procedure was used for the primary efficacy variable.

Subgroup Analysis in special populations

	Study 3002 Diff in LS Mean Change (N)[a]			Study 3013 Diff in LS Mean Change (N)[b]		
Subgroup/ Treatment Group	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 1	Subgroup 2	Subgroup 3
Age at ADHD Diagnosis	**<18 yrs**	**≥18 yrs**	**N/A**	**<18 yrs**	**≥18 yrs**	**N/A**
CONCERTA 18 mg	-5.7 (16)	-4.4 (82)				
CONCERTA 36 mg	-6.8 (21)	-3.8 (80)				
CONCERTA 54 mg				-2.2 (18)	-4.2 (72)	
CONCERTA 72 mg	-6.6 (17)	-6.6 (82)		-12.9 (11)	-5.0 (80)	
ADHD Subtype	**Combined**	**Inattention**	**Hyperactive/ Impulsivity**	**Combined**	**Inattention**	**Hyperactive/ Impulsivity**
CONCERTA 18 mg	-4.3 (62)	-2.7 (32)	NE			
CONCERTA 36 mg	-4.6 (75)	-1.6 (19)	NE			
CONCERTA 54 mg				-2.2 (60)	-5.7 (27)	NE
CONCERTA 72 mg	-6.4 (74)	-4.1 (22)	NE	-4.2 (62)	-8.0 (28)	NE
Age at Study Entry	**18-24 yrs**	**24-35 yrs**	**36-49 yrs**	**18-24 yrs**	**24-35 yrs**	**36-49 yrs**
CONCERTA 18 mg	-5.6 (21)	-5.5 (31)	-3.6 (37)			
CONCERTA 36 mg	-3.8 (28)	-4.0 (27)	-6.5 (40)			
CONCERTA 54 mg				-2.2 (18)	-0.6 (32)	-5.1 (28)
CONCERTA 72 mg	-5.6 (22)	-5.4 (35)	-9.3 (36)	-1.3 (13)	-2.6 (35)	-9.2 (34)
Age in Study Entry	**50-65 yrs**			**50-65 yrs**		
CONCERTA 18 mg	-2.0 (10)					
CONCERTA 36 mg	3.6 (6)					
CONCERTA 54 mg				-7.4 (12)		
CONCERTA 72 mg	-5.7 (6)			-7.6 (10)		
Gender	**Male**	**Female**	**N/A**	**Male**	**Female**	**N/A**
CONCERTA 18 mg	-4.2 (56)	-3.7 (43)				
CONCERTA 36 mg	-3.9 (46)	-4.6 (55)				
CONCERTA 54 mg				-3.4 (44)	-2.4 (46)	
CONCERTA 72 mg	-5.8 (53)	-7.0 (46)		-5.6 (50)	-4.1 (42)	
BMI at Study Entry (kg/m^2)	**< 25 (normal)**	**25-<30 (overweight)**	**≥ 30 (obese)**	**< 25 (normal)**	**25-<30 (overweight)**	**≥ 30 (obese)**
CONCERTA 18 mg	-3.5 (49)	-3.6 (30)	-3.7 (18)			
CONCERTA 36 mg	-2.2 (55)	-5.2 (31)	-6.6 (15)			
CONCERTA 54 mg				-1.5 (40)	-4.3 (35)	-1.4 (15)
CONCERTA 72 mg	-5.2 (48)	-6.9 (37)	-9.6 (14)	-3.2 (40)	-6.1 (34)	-2.8 (17)
Current Psychiatric Comorbidity	**Yes**	**No**	**N/A**	**Yes**	**No**	**N/A**
CONCERTA 18 mg	-4.0 (14)	-4.1 (85)				
CONCERTA 36 mg	-5.3 (18)	-4.1 (83)				
CONCERTA 54 mg				-0.3 (20)	-3.8 (70)	
CONCERTA 72 mg	-4.6 (18)	-6.8 (81)		-6.2 (18)	-4.5 (74)	
History/Current Psychiat. Comorbid.	Yes	No	N/A	Yes	No	N/A
CONCERTA 18 mg	-2.6 (46)	-4.9 (53)				
CONCERTA 36 mg	-1.9 (55)	-5.9 (46)				
CONCERTA 54 mg				-1.9 (49)	-3.5 (41)	
CONCERTA 72 mg	-4.3 (49)	-8.3 (50)		-4.5 (48)	-5.1 (44)	
Prior MPH Exposure	**Naive**	**Non-naive**	**N/A**	**Naïve**	**Non-naive**	**N/A**
CONCERTA 18 mg	-3.7 (91)	-3.5 (8)				
CONCERTA 36 mg	-4.0 (95)	-1.7 (6)				
CONCERTA 54 mg				-2.5 (79)	-4.9 (11)	
CONCERTA 72 mg	-6.2 (90)	-5.6 (9)		-5.3 (89)	1.8 (3)	

NE = LS mean difference could not be estimated because of too few subjects.

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

[b] The difference in LS means is based on an ANCOVA model with treatment, country, and gender as factors, and age and baseline score as a covariate.

Light shaded areas indicate treatment group not represented in that study.

The applicant has also presented an analysis by age for Study 02-159:

Subgroup	All CONCERTA LSMean ± SEM (N)	Placebo LSMean ± SEM (N)	p-Value[a]
Male	-12.1 ± 1.56 (63)	-6.6 ± 1.46 (64)	0.009
Female	-9.9 ± 1.95 (47)	-6.7 ± 1.80 (52)	0.231
Age 18 to 35	-9.2 ± 2.01 (42)	-7.5 ± 1.85 (47)	0.510
Age 36 to 49	-11.3 ± 1.87 (40)	-7.0 ± 1.79 (48)	0.089
Age 50 to 65	-11.6 ± 2.93 (28)	-3.4 ± 3.45 (21)	0.092

Statistical Assessor's Comment
The analysis by age in Study 02-159 suggests that there is a much stronger effect in older patients compared to younger patients. The response to active increases as age increases, and the response to placebo decreases. If there is a correlation between age in study and age of diagnosis, this could have important implications for the proposed wording. In particular it would suggest weaker efficacy in the indicated population and the applicant should investigate this further.

Dose Response – Placebo adjusted mean differences in key efficacy variables

(Study 3002; Intent-to-Treat Population)

Efficacy Variable Change at End Point[a]	LS Mean Difference vs. Placebo CONCERTA 18 mg	CONCERTA 36 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total score	-4.00	-4.03	-6.59
CAARS Inattention subscale	-2.80	-3.06	-4.16
CAARS Hyperactivity/Impulsivity subscale	-1.15	-0.97	-2.41
CAARS-S:S Total score	-6.08	-6.11	-9.23
SDS Total score	-2.77	-2.11	-3.02

[a] Based on ANCOVA on change from baseline at end point with treatment, country and gender as factors and baseline score as covariate.

(Study 3013; Intent-to-Treat Population)

Efficacy Variable Change at End Point	LS Mean Difference vs. Placebo CONCERTA 54 mg	CONCERTA 72 mg
CAARS ADHD Symptoms Total score	-2.69[a,b]	-4.89[a,b]
CAARS Inattention subscale	-1.90[a,b]	-3.21[a,b]
CAARS Hyperactivity/Impulsivity subscale	-0.80[a,b]	-1.73[a,b]
CAARS-S:S Total score	-4.25[a,b]	-4.43[a,b]
AIM-A Work, Home, School – Performance and Daily Functioning score	8.00[a,c,d]	9.76[a,c,d]
CGI-S score	13.53[b,c,d]	37.61[b,c,d]

[a] Based on ANCOVA on change from baseline at end point with treatment, country and gender as factors, and age and baseline score as covariate.
[b] A negative LS means difference indicates greater improvement in CONCERTA group compared to placebo group.
[c] Difference in LS means ranks based on ANCOVA on ranks, comparing each CONCERTA group with placebo.
[d] A positive LS means difference indicates greater improvement in the CONCERTA group compared to placebo group.

Assessor's comments
Although formal statistical testing with Johkheere-Terpestra trend test was negative for study 3002, there is a consistent numerical dose response in the main items seen in both studies. This is perhaps surprising as all doses clearly separate from placebo and there are clear numerical differences. There is heterogeneity in the subscales, possibly due to a lack of power.

Literature of short-term efficacy

Results from the three non-sponsor-initiated placebo-controlled studies of CONCERTA, involving a total of 211 adults with ADHD diagnosed using DSM-IV, reported larger symptomatic improvement with CONCERTA compared with placebo.

- In a 6-week study, adults with ADHD were randomly assigned to double-blind treatment with CONCERTA (n=67) or placebo (n=74). Dosing for both drugs was individualized and was initiated at 36 mg/day and titrated to optimal response based on efficacy and safety, up to a maximum dose of 1.3 mg/kg/day. The mean dose of study drug at Week 6 was 80.9 mg/day for CONCERTA. Treatment with CONCERTA was associated with a statistically significantly larger reduction from baseline in the AISRS total score compared with placebo beginning at Week 3 that was sustained through Week 6. At end point, 66% of subjects in the CONCERTA p21decrease in AISRS total score and a CGI-I rating of much or very much improved.
- A randomized, double-blind cross-over study compared flexible-dosing with CONCERTA or placebo for 4 weeks among 47 adults with ADHD. Approximately 40% of subjects had ADHD with significant emotional and oppositional symptoms. Treatment was initiated at a dose of 18 mg/day and was titrated to optimal response at 9-mg increments every 2-3 days to a maximum dose of 90 mg/day. At a mean dose of 64.0 mg/day, CONCERTA was superior to placebo for all clinical efficacy measures. Statistically significantly larger decreases from baseline to end point were seen with CONCERTA compared with placebo for the total ADHD-RS score (41% vs 14% decrease in score, respectively) and total Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS) (42% vs 13% decrease in score, respectively).
- In a randomized, double-blind study of 23 mother-child dyads, both diagnosed with ADHD, treatment with CONCERTA was shown to be associated with significant improvements in ADHD symptoms as well as in objective measures of parenting. In this study, all mothers participated in a 5-week double-blind titration phase; during this phase, dosing was started with placebo and adjusted upwards on a weekly basis to CONCERTA doses of 36, 54, 72, and 90 mg/day until subjects achieved an optimal response based on prespecified criteria. At the conclusion of the titration phase, subjects were randomly assigned to 2 weeks of treatment with placebo or their optimal dose of CONCERTA. At the end of the titration phase, statistically significant improvements from baseline (i.e., treatment during Week 1 of titration phase) relative to placebo were seen with CONCERTA (mean dose of 83.7 mg/day) for ADHD Hyperactivity/Impulsivity and Inattention subscale scores and for the CGI-S ratings compared with placebo. Mean scores on ADHD Inattention and Hyperactivity/Impulsivity subscales and CGI-S at the end of the randomized treatment phase of the study suggested that there were fewer symptoms among the 9 subjects who continued on CONCERTA relative to the 11 subjects who were switched to placebo. Measures of maternal involvement, poor monitoring/supervision, and inconsistent discipline at the end of the randomized treatment phase also showed positive treatment effect for CONCERTA.

Assessor's comments

The choice of end points appears appropriate in accordance with the CHMP Guideline on the Treatment of ADHD. CAARS was used in the studies submitted for atomoxetine which gained a similar indication. The validation of the AISRS is supported by other papers.

The primary endpoint was significantly positive for all the ITT analyses except for the 54mg dose in Study 3013. It should be noted that in this study the placebo response was greater. The magnitude of the response from baseline was -12.5 which is what would be expected if extrapolating from Study 3002 which showed changes from baseline of -11.5 for the 36mg dose and -13.7 for the 72mg dose. In addition 2 pre-specified sensitivity analyses (PP and Modified ITT were statistically significant). However, the robustness of these analyses is called in to question for the following reasons. In the LOCF analysis subjects were included as responders even when they had withdrawn due to an AE. The withdrawal rates in both placebo (30%) and active (40%) groups were high. The withdrawal rates and adherence were related to dose (non-compliance with study medication intake 8%, 22% and 25% for placebo and CONCERTA 54 mg and 72 mg groups, respectively).

Study 3002 was positive for the primary outcome for all 3 doses 18mg, 36mg and 72mg on ITT LOCF analysis. This result was supported by most ((CAARS inattention subscale, CAARS-S:S, CGI-S, CGI-I) but not all (Q-LES-Q and GAE) secondary endpoints. The CAARS hyperactivity subscale was only positive for 72mg but the lower doses showed a positive trend. SDS showed significant improvement in Studies 3002 for the 18mg and 72mg doses but not the 36mg dose (numerical improvement).

Study 02-159 was positive for the primary endpoint AISRS and supported by CGI-I, CAARS-S:S, Treatment Responder Rate, CGI-S and AIM-A but not the SDS Work Subscale.

Study 3013 was positive for the 72mg dose but not the 54mg dose for the primary endpoint (Total CAARS). The 72mg dose was supported by statistically significant improvements in the CAARS subscales, CGI-S, CGI-I, AIM-A [Performance, Living, Daily Life, Communication but not Symptoms on Daily Life or SDS. The secondary endpoints for the 54mg dose were mixed although all (including the primary endpoint) demonstrated positive trends.

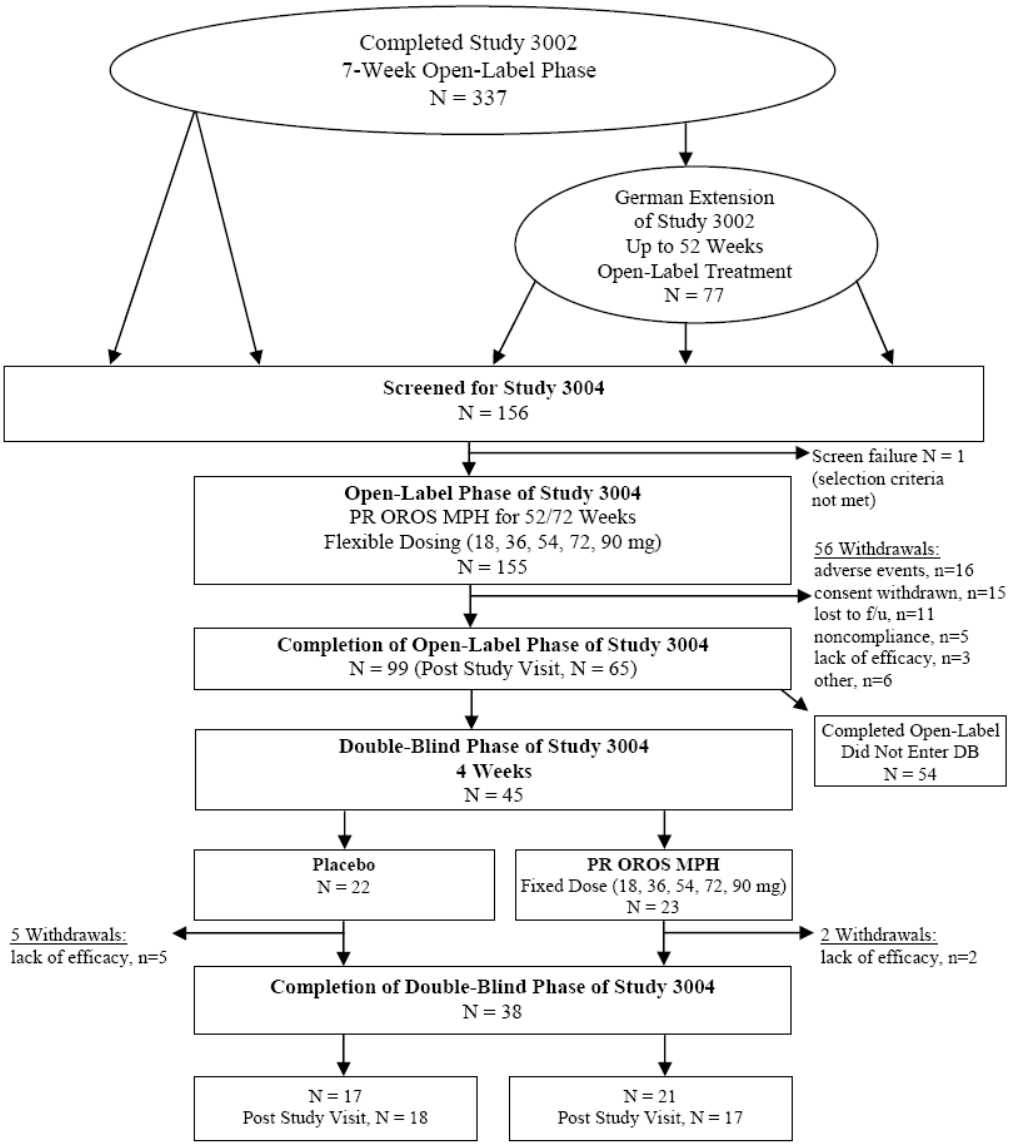
As presented the studies appear positive for short-term efficacy in the studied population but further analyses of the results is required treating all withdrawals as treatment failures before a firm conclusion can be drawn.

The subgroup analysis of primary interest is the one examining whether original diagnosis occurred before or after 18 years, since the indication sought is the in the former population. Less than 20% of the study group met this criterion. In Study 3002, treatment effect for those diagnosed <18 years compared to those diagnosed as adults was numerically greater for the 18mg and 36mg dose and identical for the 72mg dose. In Study 3013 treatment effect was greater in the <18 year population. This provides some reassurance that the data from patients diagnosed after the age of 18 may support the proposed indication, but it is of note that no statistical significance was observed in this subgroup, and there are still concerns regarding Study 02-259 where the opposite trend was observed.

There were heterogeneous results according to ADHD subtype between studies 3002 and 3013. No consistent effect in relation to age at recruitment or gender was seen.
BMI was positively correlated with effect size in Study 3002 but not Study 3013. Current Psychiatric morbidity and a history of Psychiatric Morbidity appeared to reduce the effect size (excluding the 72mg dose in Study 3013. No obvious pattern of differences was seen in whether the adult was MPH naïve or not.

Maintenance of effect – Subject disposition

(Study 3004: All Subjects/ Open-Label and Double-Blind Populations)

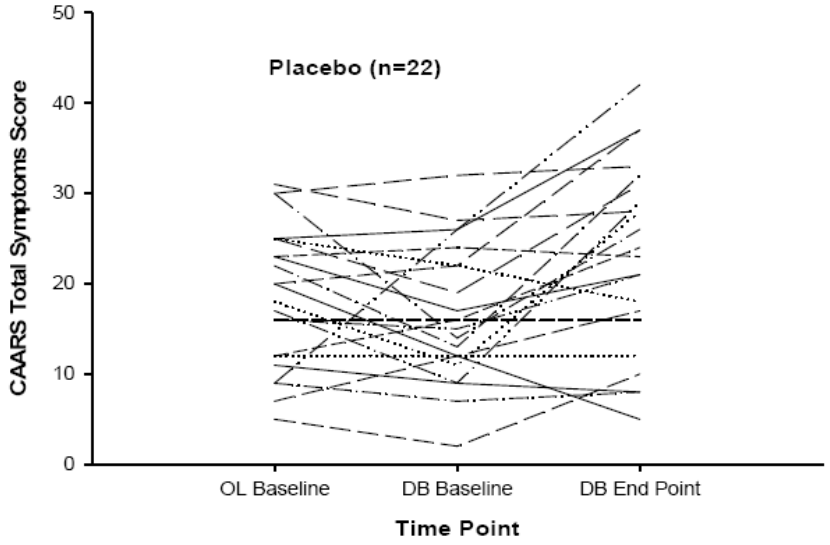


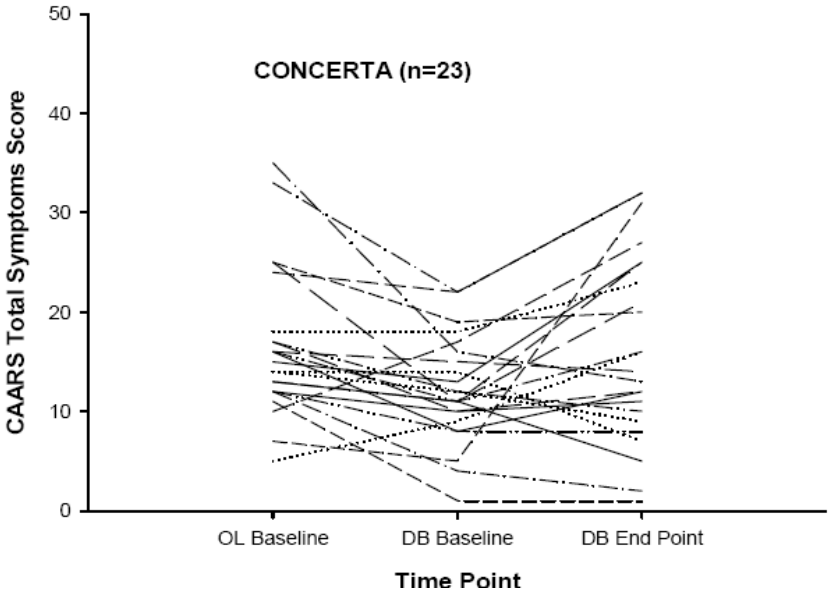
Results are shown below:

	Placebo (N=22)	PR OROS MPH (N=23)
Visit 7, baseline		
Mean (SD)	16.5 (7.49)	12.1 (5.34)
Median	15.5	11.0
Range	2 - 32	1 - 22
Endpoint		
Mean (SD)	23.0 (10.41)	16.2 (9.42)
Median	23.5	14.0
Range	5 - 42	1 - 32
Change from Baseline to Endpoint		
Mean (SD)	6.5 (7.82)	4.0 (7.61)
Median	5.5	2.0
Range	-7 - 20	-7 - 26
LS Means (p-value)[a]	2.89 (0.2586)	

[a] ANCOVA

Individual subject CAARS ADHD Symptom Total Score for the ITT double-blind population is stated below:





Maintenance of effect from published studies

Rösler M (2009), Fischer R, Ammer R, et al. A randomized, placebo-controlled, 24-week, study of low-dose extended-release methylphenidate in adults with attention-deficit/ hyperactivity disorder. Eur Arch Psychiatry Clin Neurosci 2009;259:120-9.

In one study, 359 adults with ADHD were randomly assigned to double-blind treatment with extended-release (ER) MPH (formulation consisting of 50% immediate release [IR] MPH and MPH ER) or placebo for 24 weeks. Treatment was initiated at a dose of 10 mg/day and titrated to optimal response up to 60 mg/day. The mean daily doses at Week 24 were 41.2 mg in the MPH ER group and 40.8 mg in the placebo group. Statistically significantly larger mean improvements from baseline to end point were seen in the MPH ER group compared with the placebo group on the mean WRAADDS score as well as on the CAARS ADHD symptoms total score. The response rate at end point was also significantly higher for the

MPH ER group (61%) than for the placebo group (42%); response was defined as a 30% or greater reduction in WRAADDS score.

In the second study, subjects who demonstrated a clinical response during an initial 6-week double-blind, placebo-controlled trial of MPH IR and placebo were enrolled in a double-blind maintenance study and continued on their same medication for an additional 6 months to assess stability of response. There was little change in the mean severity of ADHD symptoms from Week 0 to Week 24 of the maintenance phase for the MPH IR (n=59) or placebo (n=6) groups. However, a significantly higher percentage of subjects who continued on placebo (43%) compared with those maintained on MPH IR (15%) exhibited worsening of ADHD symptoms, defined as the loss of at least 25% of improvement on ADHD symptom rating scale.

Assessors' comments
No maintenance of effect has been demonstrated from the failed withdrawal Study 3004, which was probably under powered but the difference between placebo and Concerta is modest which may also explain the results. There is some evidence of maintenance of effect from the paper by Rosler. The second paper is available as a short extract only and cannot be assessed. In addition the robustness of the results from Study 3013 is also in question.

EFFICACY CONCLUSION
There are three randomised, double-blind studies, two in Europe and one in the US. The European studies both used fixed doses. The MAH are not applying to use the higher doses studied (90mg and 108mg) although they are proposing to increase the current approved dosage range to 72mg for the proposed adult population. There appears to be a dose related efficacy (and safety) effect. The population recruited to the studies was stated to be diagnosed in line with DSM IV criteria. However, the details around the characteristics of the populations and how they were deemed to be suitable for study entry are not included. This will require further scrutiny. There is an apparent contradiction when it is then stated that only a subgroup have had their ADHD diagnosed <18 years of age. This population formed less than 20% of the overall study population. There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. In addition there are 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 (excluding the 72mg dose in Study 3013). This weakens the external validity of the studies.

The primary endpoint was significantly positive for all the ITT analyses except for the 54mg dose in Study 3013. It should be noted that in this study the placebo response was greater. The magnitude of the response from baseline was -12.5 which is what would be expected if extrapolating from Study 3002 which showed changes from baseline of -11.5 for the 36mg dose and -13.7 for the 72mg dose. In addition 2 pre-specified sensitivity analyses (PP and Modified ITT were statistically significant). However, the robustness of these analyses is called in to question for the following reasons. In the LOCF analysis subjects were included as responders even when they had withdrawn due to an AE. The withdrawal rates in both placebo (30%) and active (40%) groups were high. The withdrawal rates and adherence were related to dose (non-compliance with study medication intake 8%, 22% and 25% for placebo and CONCERTA 54 mg and 72 mg groups, respectively).

Study 3002 was positive for the primary outcome for all three doses 18mg, 36mg and 72mg on ITT LOCF analysis. This result was supported by most ((CAARS inattention subscale, CAARS-S:S, CGI-S, CGI-I) but not all (Q-LES-Q and GAE) secondary endpoints. The CAARS hyperactivity subscale was only positive for 72mg but the lower doses showed a

positive trend. SDS showed significant improvement in Studies 3002 for the 18mg and 72mg doses but not the 36mg dose (numerical improvement).

Study 02-159 was positive for the primary endpoint AISRS and supported by CGI-I, CAARS-S:S, Treatment Responder Rate, CGI-S and AIM-A but not the SDS Work Subscale.

Study 3013 was positive for the 72mg dose but not the 54mg dose for the primary endpoint (Total CAARS). The 72mg dose was supported by statistically significant improvements in the CAARS subscales, CGI-S, CGI-I, AIM-A [Performance, Living, Daily Life, Communication but not Symptoms on Daily Life or SDS. The secondary endpoints for the 54mg dose were mixed although all (including the primary endpoint) demonstrated positive trends.

As presented the studies appear positive for short-term efficacy in the studied population but further analyses of the results is required treating all withdrawals as treatment failures before a firm conclusion can be drawn.

There is some evidence of efficacy is available up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy from a published paper by Rossler 2009 but there is insufficient detail in the published paper to fully understand the population being studied.

Overall the evidence to support the proposed indication wording is considered weak.

Other Concerns
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.

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.

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.

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.

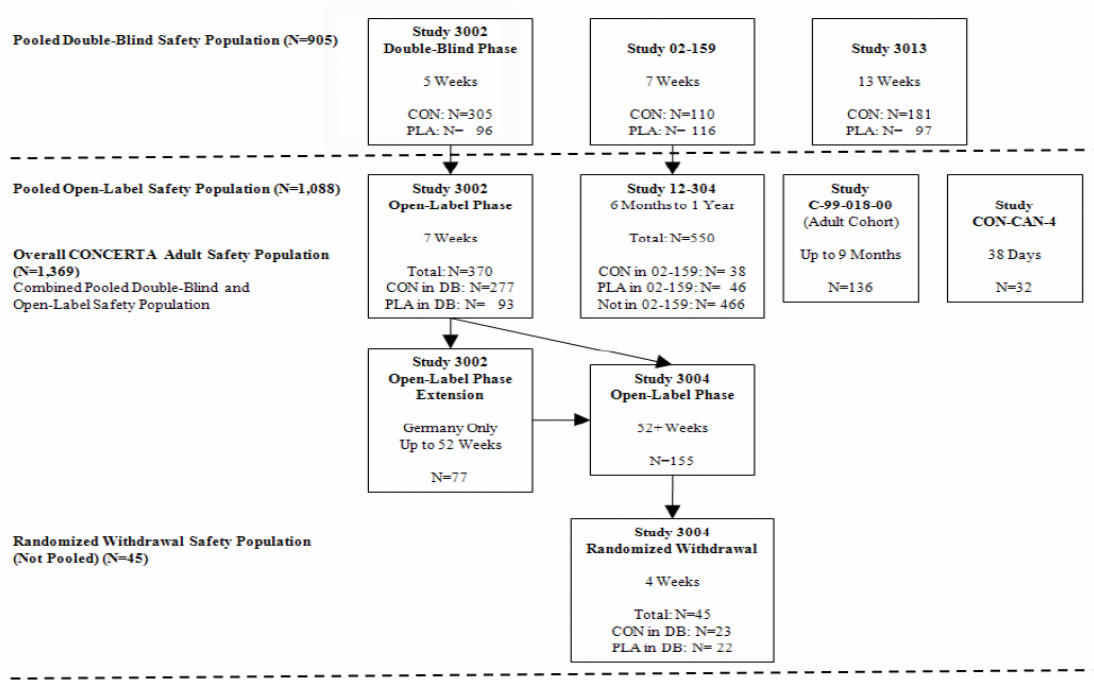
The applicant should investigate whether there is an interaction in any of the studies between age of diagnosis and age at enrolment in the study. If there is, the applicant should discuss further the apparent decrease in efficacy seen in younger patients in study 0159.

CLINICAL SAFETY

- Double-Blind Safety Analysis Set: Subjects from the double-blind portion of Study 3002 (3002 DB) and Studies 02-159 and 3013.
- Open-Label Safety Analysis Set: Subjects from the open-label portion of Study 3002 (3002 OL), the open-label portion of Study 3004 (3004 OL), and Studies 12-304, C-99-018-00, and CON-CAN-4.

- Overall CONCERTA Analysis Set: All subjects receiving CONCERTA from Studies 3002 DB, 02-159, 3013, 3002 OL, 3004 OL, 12-304, C-99-018-00, and CON-CAN-4. This population was only used to summarize overall demographics and exposure.

The disposition of patients in the double-blind and open-label studies using CONCERTA is presented below:



Patient exposure in the double-blind safety analysis set is presented below:

	----- ALL CONCERTA ---- (N=595)
Maximum dose, n (%)	
N	595
18 mg	101 (17.0)
36 mg	134 (22.5)
54 mg	106 (17.8)
72 mg	209 (35.1)
90 mg	16 (2.7)
108 mg	29 (4.9)
Maximum dose (days on drug)	
N	595
Mean (SD)	53.76 (24.180)
Median	54.00
Range	(18.0;108.0)
Length of time on maximum dose	
N	595
Mean (SD)	41.05 (26.757)
Median	35.00
Range	(1.0;106.0)
Final dose, n (%)	
N	595
18 mg	101 (17.0)
36 mg	138 (23.2)
54 mg	104 (17.5)
72 mg	213 (35.8)
90 mg	16 (2.7)
108 mg	23 (3.9)

Note: The lowest dose will be used in the analysis if a tie occurs.

Patient exposure in the open-label safety analysis set is presented below:

	--- ALL CONCERTA -- (N=1088)
Duration (days)	
N	1088
Category, n (%)	
1 - 30	142 (13.1)
31 - 60	274 (25.2)
61 - 90	45 (4.1)
91 - 180	130 (11.9)
181 - 270	189 (17.4)
271 - 360	137 (12.6)
> 360	171 (15.7)
Mean (SD)	197.82 (199.713)
Median	165.00
Range	(1.0;943.0)
Total Exposure (subject years)	589.3
At least 6 months, n (%)	
N	1088
Yes	497 (45.7)
No	591 (54.3)
At least 1 year, n (%)	
N	1088
Yes	171 (15.7)
No	917 (84.3)

Note: Subjects were allowed to change CONCERTA dose as needed clinically and may be counted in more than one dose group.
Note: 6 months is defined as 181 days.
Note: 1 year is defined as 361 days.
Note: Person Years of Exposure is the cumulative duration of exposure (days) for all subjects divided by 365.24.
rex02_tsub40b.rtf generated by rex02.sas.

Concomitant medication taken by at least 3% of subjects in one or more treatment groups for the double-blind safety analysis set

Table 12: Concomitant Medications Taken by ≥ 3% of Subjects in One or More Treatment Groups by Treatment Group - Double-Blind Safety Analysis Set
(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

Medication Name	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)	Total (N=905) n (%)
Total no. subjects WITH ANY CONCOMITANT MEDICATION	208 (67.3)	394 (66.1)	602 (66.5)
Acetylsalicylic acid	10 (3.2)	23 (3.9)	33 (3.6)
Ibuprofen	41 (13.3)	82 (13.8)	123 (13.6)
Loratadine	14 (4.5)	10 (1.7)	24 (2.7)
Multivitamins	19 (6.1)	19 (3.2)	38 (4.2)
Paracetamol	44 (14.2)	81 (13.6)	125 (13.8)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Includes all medications taken after the first dose of study medication.
rcm01_tsub32a.rtf generated by rcm01.sas.

Adverse events

Serious adverse events and deaths

A list of serious adverse events in the double-blind safety analysis set are presented below:

Evaluation	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Subjects with Adverse Events	213 (68.9)	491 (82.4)
Subjects with Serious Adverse Events	2 (0.6)	9 (1.5)
Subjects who discontinued due to Adverse Events	8 (2.6)	63 (10.6)
Deaths	0	0

Note: Percentages calculated with the number of subjects in each group as denominator.
rae01_tae01a.rtf generated by rae01.sas.

A list of serious adverse events in the open-label safety analysis set are presented below:

Evaluation	ALL CONCERTA (N=1088) n (%)
Subjects with Adverse Events	891 (81.9)
Subjects with Serious Adverse Events	26 (2.4)
Subjects who discontinued due to Adverse Events	147 (13.5)
Deaths	0

Note: Percentages calculated with the number of subjects in each group as denominator.
rae01_tae01b.rtf generated by rae01.sas.

There were no deaths. The number and percent of subjects with serious adverse events by MedDRA system organ class, preferred term and treatment group (double-blind safety set) are presented below:

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Total no. subjects WITH ADVERSE EVENTS	2 (0.6)	9 (1.5)
Gastrointestinal disorders	0	1 (0.2)
Abdominal pain	0	1 (0.2)
Nausea	0	1 (0.2)
Infections and infestations	1 (0.3)	0
Cholecystitis infective	1 (0.3)	0
Injury, poisoning and procedural complications	1 (0.3)	1 (0.2)
Concussion	0	1 (0.2)
Joint injury	1 (0.3)	0
Musculoskeletal and connective tissue disorders	0	1 (0.2)
Intervertebral disc protrusion	0	1 (0.2)
Nervous system disorders	0	2 (0.3)
Cerebrovascular accident	0	1 (0.2)
Migraine	0	1 (0.2)
Psychiatric disorders	0	3 (0.5)
Anxiety disorder	0	1 (0.2)
Depression	0	1 (0.2)
Suicidal ideation	0	1 (0.2)
Suicide attempt	0	1 (0.2)
Reproductive system and breast disorders	0	1 (0.2)
Ovarian cyst ruptured	0	1 (0.2)

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.
rae03_tae08a.rtf generated by rae03.sas.

Withdrawal Adverse Events

Study 3002

The treatment-emergent adverse events during the double-blind with action taken to permanently stop trial medication by at least two subjects is presented below:

(Study 42603ATT3002: *All Subjects / Double-Blind*)

Body System Preferred Term n (%)	Placebo (N=96)	PR OROS MPH 18 mg (N=101)	PR OROS MPH 36 mg (N=102)	PR OROS MPH 72 mg (N=102)	Overall (N=401)
Any AE in this category	**1 (1.0)**	**1 (1.0)**	**4[b] (3.9)**	**8 (7.8)**	**14 (3.5)**
Nervous System Disorders	**0**	**0**	**1 (1.0)**	**4 (3.9)**	**5 (1.2)**
Insomnia	0	0	0	2 (2.0)	2 (0.5)
Tremor	0	0	0	2 (2.0)	2 (0.5)
Psychiatric Disorders	**0**	**0**	**4 (3.9)**	**7 (6.9)**	**11 (2.7)**
Anxiety	0	0	1 (1.0)	3 (2.9)	4 (1.0)
Irritability	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Nervousness	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Restlessness	0	0	0	2 (2.0)	2 (0.5)
Vascular Disorders	**1 (1.0)**	**0**	**0**	**1 (1.0)**	**2 (0.5)**
Hypertension	1[a] (1.0)	0	0	1 (1.0)	2 (0.5)

[a] subject A11047 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.

[b] subject 10871 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.

Study 02-159

Dose	Withdrawal (%)	Dose Reduction (n)
36mg (n=110)	**4 (3.6%)**	**0**
54mg (n=78)	**7 (9.0%)**	**3 (3.8%)**
72mg (n=60)	**2 (3.3%)**	**3 (5%)**
90mg (n=45)	**1 (2.4%)**	**6 (13.3%)**
108mg (n=29)	**2 (6.7%)**	**5 (17.2%)**
Placebo (n=116)	**6 (5.2%)**	**5 (4.3%)**

Study 3013

The study completion/withdrawal information for the intent-to-treat population is presented below:

	Placebo (N = 97) n (%)	PR OROS MPH 54 mg/day (N = 90) n (%)	PR OROS MPH 72 mg/day (N = 92) n (%)	Total (N = 279) n (%)
Completed	68 (70.1)	55 (61.1)	55 (59.8)	178 (63.8)
Discontinued	29 (29.9)	35 (38.9)	37 (40.2)	101 (36.2)
Adverse event	2 (2.1)	15 (16.7)	19 (20.7)	36 (12.9)
Lack of efficacy	14 (14.4)	1 (1.1)	4 (4.3)	19 (6.8)
Non-compliance	3 (3.1)	5 (5.6)	5 (5.4)	13 (4.7)
Consent withdrawal	4 (4.1)	3 (3.3)	3 (3.3)	10 (3.6)
Loss to follow-up	5 (5.2)	2 (2.2)	0	7 (2.5)
Sponsor's decision	0	2 (2.2)	0	2 (0.7)
Ineligibility to continue the study	0	1 (1.1)	1 (1.1)	2 (0.7)
Other	1 (1.0)	6 (6.7)	5 (5.4)	12 (4.3)

N = number of subjects with data; n = number of subjects with observation

Assessor's Comments There is evidence of a greater risk of DAEs at higher doses of MPH particularly at the upper end of the doses studied.

Common Adverse Events

The number and percentage of adverse events at least 1% in either treatment group by MedDRA system organ class, preferred term and treatment group (double-blind safety set):

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Total no. subjects WITH ADVERSE EVENTS	213 (68.9)	491 (82.4)
Cardiac disorders	4 (1.3)	63 (10.6)
Palpitations	2 (0.6)	27 (4.5)
Tachycardia	0	36 (6.0)
Ear and labyrinth disorders	5 (1.6)	23 (3.9)
Vertigo	1 (0.3)	12 (2.0)
Eye disorders	8 (2.6)	34 (5.7)
Accommodation disorder	0	8 (1.3)
Vision blurred	3 (1.0)	8 (1.3)
Gastrointestinal disorders	65 (21.0)	206 (34.6)
Constipation	2 (0.6)	9 (1.5)
Dry mouth	11 (3.6)	90 (15.1)
Dyspepsia	6 (1.9)	12 (2.0)
Nausea	15 (4.9)	85 (14.3)
Vomiting	2 (0.6)	11 (1.8)
General disorders and administration site conditions	37 (12.0)	99 (16.6)
Asthenia	0	7 (1.2)
Fatigue	13 (4.2)	28 (4.7)
Irritability	9 (2.9)	31 (5.2)
Thirst	2 (0.6)	11 (1.8)
Infections and infestations	50 (16.2)	99 (16.6)
Sinusitis	3 (1.0)	8 (1.3)
Upper respiratory tract infection	3 (1.0)	10 (1.7)
Investigations	30 (9.7)	102 (17.1)
Alanine aminotransferase increased	0	6 (1.0)
Blood pressure increased	6 (1.9)	15 (2.5)
Heart rate increased	6 (1.9)	18 (3.0)

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.

(continued)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Investigations (continued)		
Weight decreased	11 (3.6)	52 (8.7)
Metabolism and nutrition disorders	30 (9.7)	180 (30.2)
Anorexia	4 (1.3)	25 (4.2)
Decreased appetite	19 (6.1)	148 (24.8)
Musculoskeletal and connective tissue disorders	33 (10.7)	61 (10.2)
Muscle spasms	1 (0.3)	6 (1.0)
Muscle tightness	0	8 (1.3)
Nervous system disorders	90 (29.1)	225 (37.8)
Dizziness	17 (5.5)	44 (7.4)
Headache	58 (18.8)	144 (24.2)
Paraesthesia	0	7 (1.2)
Tension headache	1 (0.3)	6 (1.0)
Tremor	2 (0.6)	20 (3.4)
Psychiatric disorders	62 (20.1)	236 (39.6)
Affect lability	2 (0.6)	8 (1.3)
Aggression	2 (0.6)	7 (1.2)
Agitation	2 (0.6)	19 (3.2)
Anxiety	9 (2.9)	50 (8.4)
Bruxism	2 (0.6)	9 (1.5)
Confusional state	1 (0.3)	6 (1.0)
Depressed mood	8 (2.6)	26 (4.4)
Depression	2 (0.6)	9 (1.5)
Initial insomnia	8 (2.6)	34 (5.7)
Insomnia	24 (7.8)	79 (13.3)
Libido decreased	2 (0.6)	8 (1.3)
Nervousness	2 (0.6)	14 (2.3)
Panic attack	1 (0.3)	8 (1.3)
Restlessness	0	24 (4.0)
Tension	1 (0.3)	8 (1.3)

See footnotes on the first page of the table.

(continued)

Body System Or Organ Class Dictionary-Derived Term	PLACEBO (N=309) n (%)	ALL CONCERTA (N=596) n (%)
Reproductive system and breast disorders	7 (2.3)	17 (2.9)
Erectile dysfunction	1 (0.3)	6 (1.0)
Respiratory, thoracic and mediastinal disorders	14 (4.5)	35 (5.9)
Cough	3 (1.0)	7 (1.2)
Dyspnoea	2 (0.6)	7 (1.2)
Oropharyngeal pain	4 (1.3)	9 (1.5)
Skin and subcutaneous tissue disorders	12 (3.9)	49 (8.2)
Hyperhidrosis	4 (1.3)	34 (5.7)
Vascular disorders	13 (4.2)	32 (5.4)
Hot flush	2 (0.6)	8 (1.3)
Hypertension	5 (1.6)	13 (2.2)

See footnotes on the first page of the table.

rae03_tae06a.rtf generated by rae03.sas.

Assessor's comments
The wide range of psychiatric adverse events is considered a cause for concern. Cardiovascular adverse events are very common but the number of individuals with recorded increases in heart rate and blood pressure are much lower from the AE data, this may relate to the study population and the protocol on treatment reduction and withdrawal.

Adverse events of Special Interest
The number and percentage of subjects with at least one adverse event considered of special interest by treatment group for the double-blind study (Overall Safety Analyses Set) is presented below:

Adverse Event Category 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.

Hypertension and Tachycardia There were more cases of hypertension and tachycardia reported on Concerta than placebo. Those who had BPs above 120/80 at baseline largely had BP reduction noted during the studies suggesting a 'white coat' effect. The analysis in those without hypertension at baseline (<140/80) was as follows:

Subjects must have had at least 2 post-baseline study visits; the development of hypertension was defined as either a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg at 2 or more post-baseline study visits.

Study 3002 CONCERTA 72 mg (8.9%), 36 mg (5.1%) 18mg (2.6%) placebo (6.8%)
In Study 02-159, CONCERTA compared with placebo (4% vs. 2%)
Study 3013 CONCERTA (72 mg, 18.9%; 54 mg, 14.5%) placebo (7.4%)

In 1.9% (n=26) in the Overall CONCERTA Safety Analysis Set the event resulted in the discontinuation of CONCERTA therapy. In 2/3 of cases the hypertension was said to have resolved.

Raynaud's
There was no signal.

Psychosis/mania
In all Concerta the incidence of psychosis/mania was 3.3%. In the double-blind studies, the likelihood of experiencing an adverse event coded to psychosis/mania adverse event category of special interest was higher on CONCERTA than on placebo (2.9% vs. 1.0%, odds ratio: 3.0). Events leading to discontinuation included Thinking abnormal (severe), Delusions of reference (severe), and Abnormal behavior (severe), and all of these events resolved following discontinuation.

Anorexia (and Weight)
For Studies 3002 and 3013, potentially clinically important decreases from baseline in body weight (≥7% of body weight) were observed for a higher percentage of CONCERTA versus placebo subjects (8.3% vs. 0.3%). There is some evidence that the rate of weight loss reduces after 6 months treatment.

Migraine
In the double-blind studies, the likelihood of experiencing an adverse event within the migraine adverse event category of special interest was not higher on CONCERTA (1.2%) than on placebo (1.9%) (odds ratio: 0.6). For one of these subjects, the event was serious, a computerized tomography (CT) scan revealed a slight expansion of the frontal horn of the right lateral ventricle with a probable lacunar infarct in the nucleus caudate. A specialist in neuroradiology judged the findings as an old lesion.

Repetitive behaviours
There was only one case, which consisted of repetitive lip biting. This resolved after 40 days without treatment discontinuation.

QT Prolongation
There were 4 cases in the Overall CONCERTA Safety Analysis Set, 0 in the double-blind and 1 in the placebo group. No case required treatment withdrawal.

Arrhythmias
Adverse events within the arrhythmias adverse event category of special interest were reported for 17.5% of adult subjects treated with CONCERTA across all clinical studies. Most of these adverse events were related to increased heart rate, with the most common arrhythmia-related adverse events in the Overall CONCERTA Safety Analysis Set being Tachycardia (n=80, 5.8%), Palpitations (n=79, 5.8%), and Heart rate increased (n=78, 5.7%). There were no reports of Ventricular fibrillation, Ventricular tachycardia, or Atrial fibrillation in any adult subject receiving CONCERTA. Arrhythmia-related adverse events led to discontinuation of CONCERTA therapy in 32 of the 1369 (2.3%) adults in the Overall CONCERTA Safety Analysis Set. In the Double-Blind Safety Analysis Set, the risk of experiencing an adverse event within the arrhythmias adverse event category of special interest was higher on CONCERTA (13.4%) than on placebo (3.6%) (odds ratio: 4.2)

CVD
Single case of cerebral infarction secondary to dissection in right posterior inferior cerebellar artery.

Aggression
For the Double-Blind Safety Analysis Set, 13 of the 596 subjects receiving CONCERTA (2.2%) were withdrawn for aggression-related adverse events (vs. none receiving placebo).

Hostility
In the Double-Blind Safety Analysis Set, three subjects receiving CONCERTA (0.5%) and no subject receiving placebo had an adverse events within the hostility adverse event category of special interest.

Depression
Approximately 20% of adult subjects in the Overall CONCERTA Safety Analysis Set reported an adverse events within the depression adverse event category of special interest (19.7%). In the Double-Blind Safety Analysis Set, the likelihood of experiencing an adverse events within the depression adverse event category of special interest was higher on CONCERTA (16.8%) than on placebo (10.4%) (odds ratio: 1.8 [CI 1.1-2.8]) .

In the Overall CONCERTA Safety Analysis Set, adverse events within the suicidality adverse event category of special interest were reported for 3 subjects (0.2%). 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

Tic/Tourettes/dystonias
In the double-blind studies, the likelihood of an adverse event within the tics/Tourette's syndrome/dystonias adverse event category of special interest was approximately 3-fold higher on CONCERTA (4.2%) than on placebo (1.3%) (odds ratio: 3.3)

Carcinogenicity
No signal was seen from the adult data.

Withdrawal reactions
No signal was seen from the small withdrawal study.

Assessor's comments
Adverse events related to arrthymia were due to sinus tachycardia related events (tachycardia, palpitations or heart rate increase) rather than any evidence of more malign arrythmias. These largely resolved 200/240, but required treatment withdrawal in 32 cases.

Safety in special populations
Summary of all adverse events by age at diagnosis of ADHD and treatment group are presented below for the double-blind safety analysis set:

(CONCERTA EU SCS: Double-Blind Safety Analysis Set)

	PLACEBO			ALL CONCERTA		
	Total	Age at Diagnosis of ADHD, n (%)		Total	Age at Diagnosis of ADHD, n (%)	
	(N=309)	<18 years	≥ 18 years	(N=596)	<18 years	≥ 18 years
Evaluation	n (%)	(N=39)	(N=205)	n (%)	(N=93)	(N=445)
Subjects with Adverse Events	213 (68.9)	28 (71.8)	145 (70.7)	491 (82.4)	71 (76.3)	370 (83.1)
Subjects with Serious Adverse Events	2 (0.6)	1 (2.6)	1 (0.5)	9 (1.5)	1 (1.1)	8 (1.8)
Subjects who discontinued due to Adverse Events	8 (2.6)	2 (5.1)	3 (1.5)	63 (10.6)	8 (8.6)	48 (10.8)
Deaths	0	0	0	0	0	0

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of age at diagnosis of ADHD sub-groups calculated with number of subjects per sub-group as denominator.
Note: Subjects with missing values for age at diagnosis of ADHD are included in the total column.
rae01 tae01g.rtf generated by rae01.sas.

Assessor's comments
There is a signal that individuals diagnosed after the age of 18 years' experience more adverse events and more serious (including withdrawal) adverse events on active treatment. This pattern is not observed in the placebo group. To explore this further it would be of interest to know the age of those individuals diagnosed with ADHD <18 years vs. those diagnosed as adults.

-

SAFETY CONCLUSION
The main new safety concern from the study data is around the frequency of psychiatric adverse events and that this is often de novo. Of note is the incidence of anxiety but also rates of depression and aggressive and hostile behaviour are raised. The latter adverse events, although occurring in a small proportion of individuals, is by its nature a particular cause for concern. There is a small signal of suicidality from the data. It is not clear if this has been analysed by Columbia Criteria with ideation removed as a pre-requisite.

The known cardiovascular adverse events are of particular concern in an adult population, potentially on long-term treatment. There is clear evidence from these studies of tachycardia and rises in BP. There is no discussion around what level of BP increase that could pose a risk to the individual and the data on sustained increases in BP have not been presented. The MAH will be asked for these data.

An observation study in the US (Vanderbilt Study) may provide more informative data in the future but currently the data are very limited and the studies do not provide robust information on individuals with cardiovascular co-morbidities.

Clinically important weight loss (>7%) has been demonstrated to be a common AE in an adult population.

RISK MANAGEMENT PLAN ASSESSMENT
In this version of the RMP, the MAH has proposed updates to the Core RMP (required by CHMP following the Article 31 referral for all methylphenidate products) to support a type II variation for a new indication for Concerta in treating adults with ADHD whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. Exposure, demographic, and important identified and potential risk data from double-blind and open-label clinical trials in adults with ADHD, and information from literature pertaining to adults with ADHD where applicable, were added to this RMP. I

Generally, there was a lack of adequate information on the epidemiology of ADHD in adults, specifically in the EU but also worldwide.

The Core important identified and potential risks for all methylphenidate products were reviewed for relevance in the adult ADHD population. A number of major risks were identified from the adult clinical trial data, which were either new, or were reported with a higher frequency category than in the paediatric population. Some of these should be categorised as important risks in the safety specification of the RMP for adults, these include: Anxiety/Anxiety disorders, depression, suicide-related events, aggression, agitation, mania/delusions, tics, cardiac arrhythmias, hypertension and clinically important changes in weight. The potential for other clinical significant adverse cardiovascular and cerebrovascular outcomes, as a consequence of effects on heart rate and blood pressure in adults, cannot be excluded and is considered a potential risk. These should be subject to proactive pharmacovigilance and risk minimisation measures.

Further analysis of the adult study data in relation to effects on diastolic and systolic blood pressure and heart rate should be requested, with the aim of characterising as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have experienced important changes.

In order to better understand the study population and its relationship to the target indicated adult population (in the RMP safety specification), the MAH should provide details of when the adult trial participants were initially diagnosed with ADHD, the pervasiveness and persistency, and severity of the symptoms over time, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical). The MAH should determine whether any of these factors have an impact on the safety or efficacy of Concerta in adults.

Important missing information in the Safety Specification should include: maintenance of the short-term effect in adults, long-term efficacy, effectiveness and safety (especially for key risks: cardiovascular risks, cerebrovascular risks and *de novo* or worsening of pre-existing psychiatric disorders including: mood disorders, depression, anxiety, agitation, suicide-

related events, psychosis /mania/delusion), safety & efficacy in new or continuing users of methylphenidate.

Because of the adult trial exclusion criteria, there is also important missing information from patients with a range of important cardiovascular, cerebrovascular neurological and psychiatric comorbidities, history of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, patients weighing < 45.4 KG.

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 in adults and the risk of diversion remain considerable. Measures proposed in the RMP to characterise the risks of off-label use and diversion and measures proposed to minimise them are considered inadequate and need to be addressed. Additionally, the MAH's proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow use in adults who have been diagnosed with ADHD at any age up to 18 years of age, which is not in line with current guidelines which state ADHD should be diagnosed before the age of 7.

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 MAH should submit proposals to further evaluate the risks in adults of suicidality and cerebrovascular disorders and the long-term effects on psychiatric outcomes.

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

The MAH should ensure that the risk minimisation measures 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.

The MAH should consider whether the current Core SmPC guidance and frequencies for neurological, psychiatric, weight and appetite monitoring are also appropriate for adults or whether they need to be modified.

Product information

Patient Information Leaflet and labelling are harmonised for this product.

Summary of Product Characteristics

Section 4.1

CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD). ***It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD***

diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.

Treatment must be under the supervision of a specialist in behavioural disorders ***in children or adults***. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising ***patients*** with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

CONCERTA XL treatment is not indicated in all patients with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the ***patient's*** symptoms ***with reference to the patient's age at diagnosis.***

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the ***patient's*** symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

Assessor's Comments
Section 4.1 As detailed in the efficacy conclusion the population proposed is wider than that described in DSM IV and should be tightly defined. Prescribing should be limited to experts in adult ADHD.

The inclusion of the posology for the 72 mg dose will be reviewed once the further analyses on the efficacy data are assessed. There does appear to be a dose response from the data submitted.

The wording regarding warnings for use in women of child-bearing age should be tightened. 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 the MAA should consider making the warning more prominent in this section of the SPC.

There is a lack of data addressing the optimal duration of treatment and this should be clearly stated in the posology and the need for regularly reviewing treatment continuation.

Patient Information Leaflet (PIL)
The proposed wording will need to be reviewed when the SmPC has been appropriately amended. Issues around the psychiatric adverse events and possibility of pregnancy will need to be addressed. These may more appropriately be done in a separate adult leaflet.

Educational tools for healthcare professionals (see RMP Assessment).

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The applicant has conducted 3 randomised, double-blind studies, 2 in Europe (Studies 3002 and 3013) and 1 in the US (Study 02-159). The European studies both used fixed doses. The MAH are not applying to use the higher doses studied in Study 02-159 (90mg and 108mg) although they are proposing to increase the current approved dosage range from 54mg to 72mg for the proposed adult population. There appears to be a dose related efficacy (and safety) effect. As presented, the studies are appear positive for short-term efficacy in the population studied but further analyses of the results is required treating missing data more conservatively. The current handling of the missing data is a Major Concern in the demonstration of short-term efficacy.

There is some evidence of efficacy is available up to 13 weeks but the long-term withdrawal study lacked sufficient power. There is some long-term efficacy from a published paper by Rossler 2009 but there is insufficient detail in the published paper to fully understand the population being studied.

The population recruited to the studies was stated to be diagnosed in line with DSM IV criteria. However, the details around the characteristics of the populations and how they were deemed to be suitable for study entry are not included. This will require further scrutiny. There is an apparent contradiction when it is then stated that only a subgroup have had their ADHD diagnosed <18 years of age. This population formed less than 20% of the overall study population. There is a major concern over the robustness of diagnosis of ADHD in the population recruited to the studies. In addition there are 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 (excluding the 72mg dose in Study 3013). This weakens the external validity of the studies.

Overall 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. Even then it is not clear if this sub-population adequately meets the DSM IV diagnostic criteria, as the MAH have not presented these data. Although, it should be noted that this sub-group analysis is from a group of positive efficacy studies rather than the more commonly seen manoeuvre of attempting to ‘save’ a negative study. This does lend more weight to the analysis.

There is a significant burden of adverse events from the studies. The psychiatric adverse events, particularly anxiety but also depression, aggression and hostile behaviour causes for concern. The latter AE, although occurring in a small proportion of individuals, is by its nature a cause may pose a clinical risk. There is a small signal of suicidality from the data. It is not clear if this has been analysed by Columbia Criteria with ideation removed as a pre-requisite. The MAH will be asked to address this.

There is clear evidence of the known risk of tachycardia and rise in BP. There is no discussion around what level of BP increase that could pose a risk to the individual and the data on sustained increases in BP have not been presented. The MAH will be asked for these data. Data from the pK Study 02-160 suggest dose dependent increases in HR and BP. The effect did not return to baseline between the dosing periods (3 days off medication). A clear presentation of baseline HR and BP for each treatment period should be presented from the pK study and similarly the individual patient data from the RCTS should be clearly presented for sustained HR and BP increases and whether these returned to normal after medication withdrawal.

An observation study in the US (Vanderbilt Study) may provide more informative data in the future but currently the data are very limited and the studies do not provide robust information on individuals with cardiovascular co-morbidities. The MAH will be asked about data from this study.

Clinically important weight loss (>7%) has been demonstrated to be a common AE in an adult population. Weight in adults should be monitored.

Many issues have arisen from the RMP assessment and these should be addressed. In particular the pD studies assessing the reward effect of Concerta show a clear effect in 'Light Drug Users'. Crushed Concerta delivers methylphenidate at a comparable rate and extent to IR MPH. It is assessed there is a significant abuse and diversion risk with Concerta.

The wording in the SmPC and PIL will require revision if the data are reviewed sufficiently robust after further scrutiny. The safety data from the studies should be added even if the indication is not approved.

V REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

Questions must be divided into "potential serious risks to public health" and/or "other concerns", which are defined as follow:

"Potential serious risks to public health", preclude a recommendation to the variation to the term of the marketing authorisation. In principle, one 'potential serious risk to public health' may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of the objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents

Ideally, the objection should include a clarification as to what kind of response/action by the MAH could be considered to solve the problem.

"Other concerns", may affect the proposed conditions to the variation to the terms of the marketing authorisation and product information.

V.1 Potential serious risks to public health

V.1.3 Clinical efficacy

1. 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 Rosser 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.

V.1.4 Clinical safety

The safety of Concerta in the proposed indication has not been adequately described (see safety concerns below).

V.2 Other concerns

V.2.2 Non clinical aspects

The non clinical concerns can be addressed through amending sections 4.6 and 5.3 of the SPC (see below).

V.2.3 Clinical efficacy

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

V.2.4 Clinical safety

7. 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.
   - For all studies increases in BP above 5mmHg and 10mmHg should also be presented as well as clinically significant sustained levels in HR.
   - Any cases where the HR or BP have not returned to baseline values after stopping Concerta should also be presented.
   - Additionally in Study 02-160 HR and BP did not return to baseline levels in between dosing periods, thus increases observed in HR and BP with higher doses may be less than if subjects had been monitored in a MPH naïve state. The baseline HR and BP for each treatment period and at study end should be presented for each subject. In addition, individual subject data for BP increases greater than 5mm Hg should be presented for each study period. There were 4 subjects who had ST changes during Tx. These were not described and could have been ST elevation or non-specific. In addition there were dysrhythmias observed in 3 subjects. Further scrutiny of these cases is warranted.

8. 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.

9. Further discussion on the implications of weight loss in adults.

10. Further discussion around the risk of 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).

11. 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.

V.2.5 Product information

12. 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.

13. 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.

14. 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.

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

16. The preclinical data should be addressed by adding to Section 4.6 as only 1 human case is currently described:

    In rats, methylphenidate-associated radioactivity was found in the milk at concentrations up to around 1.5 times that in the plasma.

    In addition the wording to Section 5.3 should be clarified as follows:

Pregnancy-embryonic/fetal development
Methylphenidate is not considered to be teratogenic in rats and rabbits. Fetal toxicity ***in the form of total litter loss*** was noted in rats at maternally toxic doses

RMP Concerns

The concerns raised from the RMP assessment should be addressed and in particular the following points answered:

17. 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.

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

Other RMP Points

The Risk Management Plan for Concerta in Adults should be revised based on the following points:

19. 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.

20. The following risks should be added to the adult RMP as important risks:

21. 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 Tourette's syndrome should be added to the Safety Specification as Important **Identified** Risks.

22. In relation to effects on diastolic and systolic blood pressure and heart rate in adults, the MAH should provide, for each time point, summary treatment group (by dose) data (including mean, SD, maximum and minimum) and summary change from baseline data (including mean, SD, maximum and minimum) together with individual patient data on which this is based for heart rate, systolic and/or diastolic blood pressure to describe the temporal relationship throughout the duration of all clinical trials. A table of data showing detailed data for patients where systolic and/or diastolic blood pressure increased ≥5 mmHG and significant changes in changes in heart rate should also be presented. The summary of the number and percentage of patients with an increase of at least 5 mmHg / significant changes in changes in heart rate should be included. Details of patient baseline characteristics (e.g. age, prior medications, prior illnesses, any other characteristics) should also be provided

23. An important aim of this analyses is to characterise as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have fallen into the category of concern (i.e. experienced changes of ≥5 mmHG, or important changes in pulse rate). Thus, the full temporal record of cardiovascular

outcomes in patients who at any time point have experienced a change in blood pressure of ≥5 mmHG or important changes in heart rate should be provided and included in the overall analysis.

24. The analysis must include a complete description of the hazard function over time for each patient who experienced a change in blood pressure of ≥5 mmHG or changes in pulse rate.

25. Description of the risks per 1,000 patients should be provided.

26. 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.

27. 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).

28. 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.

29. The MAH should provide a detailed analysis of all 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.

30. The MAH should include the following as Important Missing Information in the adult population, and provide study 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 section 5.1 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.

31. 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.

32. 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.

33. 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 (including whether diagnosis of ADHD in childhood was done retrospectively or during childhood) 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.

34. 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 minimisation 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 characterise the risk of diversion in all member states

35. 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.

36. 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.

37. 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.

38. 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.

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

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

41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

46. 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.

47. The MAH proposal to omit from the SPC, the requirement (including frequencies) for monitoring cardiovascular status (blood pressure and heart rate) in adults is not acceptable. Not acceptable. The current cardiovascular pre-treatment screening and ongoing monitoring requirements should also apply to the adult population and be included in the SPC, PIL and Educational Tools for HCPs and patients, or modified to be more appropriate for the adult population if necessary.

48. The MAH should provide a full review of the data used as a basis for the proposed addition of dyspnoea to the SPC as a side effect in adults. This should include a discussion of whether dyspnoea was a symptom of or associated with any respiratory, cardiovascular or other medical disorder.

49. 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.

ANNEX 1: RISK MANAGEMENT PLAN (RMP) ASSESSMENT REPORT

1.0 INTRODUCTION

Immediate-release (IR) methylphenidate formulations have a duration of effect of around 3-4 hours leading to the development of various formulations and delivery methods of extended/prolonged release methylphenidate products. The development of an extended-release formulation has been achieved by this MAH using OROS technology. Concerta (OROS methylphenidate) is a prolonged-release formulation with a duration of effect of 12 hours.

Based on the OROS technology, following oral administration, the drug overcoat dissolves providing an initial maximum drug concentration at about 1-2 hours. Delivery of the drug substance begins from the drug core when the volumetric expansion of the osmotic push layer begins to "push" the drug suspension through the orifice. Peak plasma concentrations are achieved at about 6 to 8 hours after which plasma levels of methylphenidate hydrochloride gradually decrease.

Previous Risk Management Plans (RMPs) for Concerta were limited to the paediatric population for the currently approved indication, with the exception of the post-marketing data and some of the referenced literature that included an adult population. RMP, Version 2, addressed the important core identified and potential risks for methylphenidate-containing products that were identified in the Rapporteur's previous Assessment Report dated 3 December 2008 that was related to the Article 31 Committee for Medicinal Products for Human Use (CHMP) referral procedure. Also, as part of the Article 31 referral, the additional Core pharmacovigilance and Core risk minimisation activities were specified by the CHMP for the EU marketing authorisation holders (MAHs) of methylphenidate-containing products for ADHD in the European Union (EU) including Novartis, Janssen-Cilag Ltd, Shire, Laboratorios Rubio and Medice.

This version of the Risk Management Plan (RMP, Version 3) principally proposes updates to support a type II variation for a new indication for the use of Concerta in treating adults with attention-deficit/hyperactivity disorder (ADHD) whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.

2.0 SAFETY SPECIFICATION

Non-clinical safety issues

The table below shows safety concerns identified in the Article 31 referral for which the sources of evidence that may impact benefit/risk arise partially from non-clinical data.

Table 1: Safety Concerns Not Adequately Addressed by Clinical Data or of Unknown Significance

SAFETY CONCERN (from nonclinical studies)	RELEVANCE TO HUMAN USAGE
Carcinogenicity	There is weak and insufficient evidence to conclude that methylphenidate is likely to be a human carcinogen. Initial data from ex vivo cytogenicity testing that suggested chromosomal abnormalities in children exposed to methylphenidate could not be replicated in 4 independent studies. The risk that CONCERTA is a causative agent for cancer in man is minimal.
Developmental toxicity	There is insufficient evidence to suggest a developmental risk to child or adolescent patient populations administered CONCERTA.
Cardiovascular toxicity	Other than the increase in blood pressure, there were no unexpected or statistically significant cardiovascular effects. No new pharmacologic effects were documented.

Summary of ongoing safety Concerns

The table below summarises the important identified and potential risk identified in the Article 31 Referral, for which there are specific pharmacovigilance activities (ongoing or proposed).

Table 23: Summary of On-Going Safety Concerns

Important identified risks	Hypertension Tachycardia Raynaud's phenomenon Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania Anorexia Decreased rate of growth
Important potential risks	Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias Sudden death Cerebrovascular disorders Aggression Hostility Depression Suicidality Tics/Tourette's syndrome/Dystonias Effect on final height Sexual maturation (delayed) Carcinogenicity Off-label use Diversion Withdrawal syndrome Drug abuse and Drug dependence Lymphocytic leukaemia Neonatal cardio-respiratory toxicity(neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth (via lactation)
Important missing information[a]	

[a] Long-term safety was identified as important missing information in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

The identified and potential risks presented in Version 1 of the RMP were determined by the CHMP as stated in the Second List of Outstanding Issues dated 30 May 2008. The identified and potential risks presented in Version 2 and in Version 3 (this document) were defined in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

Three new potential risks were identified in the Article 31 referral Rappourter/Co-Rapporteur Assessmen report Assessment Report: lymphocyticleukaemia, neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia, respiratory distress/apnoea), and neonatal effects on growth (via lactation). The Company also conducted a review of the risks for Concerta in adults with ADHD and has identified no new safety concerns beyond those presented in Section 1.5.2 of the RMP.

Details of Important Identified and Potential Risks

The MAH has evaluated the identified risks for methylphenidate-containing products and these are outline in **table 24 of the MAH submission** . No additional identified risks are proposed in relation to the new indication.

Of these risks, psychosis (of the combined Psychosis/Mania identified risk) and decreased rate of growth were not identified as adverse drug reactions (ADRs) for Concerta based on clinical studies and post-marketing surveillance. These identified risks are characterised in Tables 17.1 to 17.7 of the submitted RMP. Post-marketing data is only provided for those terms not identified as ADRs from the Concerta clinical trials database.

Of the potential risks outline in table 23, a causal relationship with Concerta was established for aggression, tics and depression. The potential risks are characterised in Tables 18.1 to 18.22 of the RMP. Post-marketing data is provided for those terms not identified as ADRs from the Concerta clinical trials database.

Assessor's comment

Important risks in the adult population identified from adult study data

The following are important risks in the adult population, mostly identified from adult trial data and should be included as important risks in the Safety specification for adults:

1. *Abuse potential, risk of abuse misuse, diversion (survey suggested diversion in about 44% of adults with ADHD and 29% used MPH inappropriately)*
2. *off-label use*
3. *cardiovascular risks (arrhythmias (OR:4.2), tachycardia [6% vs. 0%], hypertension, clinically important changes in: pulse, diastolic blood pressure [9.8% vs. 3.8%] and systolic blood pressure [7.8% vs. 6.1%])*
4. *potential for serious clinical cardiovascular outcomes*
5. *cerebrovascular risks*
6. *de-novo and worsening of psychiatric risks (including anxiety, panic attack, depression (OR: 1.8))*
7. *psychosis/mania (OR:3.0)*

8. *delusions*
9. *suicide-related events [3 events (0.2%) vs. o events]*
10. *mood disorders*
11. *tics (OR: 3.3)*
12. *dystonias*
13. *restlessness [4% vs. 0%]*
14. *aggression (OR: 2.3)*
15. *agitation*
16. *tension*
17. *irritability*
18. *anorexia (OR: 5.1)*
19. *decreased appetite*
20. *clinically significant decreased weight*
21. *abnormal liver enzymes/bilirubin*

These risks must be subject to adequate risk minimisation including information in the SPC and PIL, but also educational tools for HCPs, and patients.

*The following risks should be included as important **identified** risks in the safety specification, based on adult clinical trial data: aggression, agitation, restlessness, anxiety/anxiety disorders, suicide-related events, psychosis, mania/delusions, decreased appetite, decreased weight, cardiac arrhythmias, tics/worsening of tics.*

Important Missing Information

The Rapporteur's previous assessment report identified long-term safety as an area of important missing information. Long-term safety is listed in Table 23: Summary of Ongoing Safety Concerns. Also, routine and additional pharmacovigilance activities are listed for this concern in Part 2 of the RMP.

Assessor's comments

There is inadequate evidence of:

1. *Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risks including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis/mania/delusion)*
2. *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"*
3. *Long-term effectiveness (and efficacy).*
4. *Efficacy/safety in patients who have / have not used methylphenidate before*

There are no proposals to acquire any data on the long-term safety (and effectiveness) of Concerta in the adult population. The MAH should provide proposals to address this lack of data in the adult population

MAH view on Epidemiology of the Indication/Target Population

ADHD is one of the most common neurobehavioural disorders of childhood and can persist through adolescence and into adulthood. According to DSM-IV the prevalence of ADHD is estimated at 3% to 7% of school-age children. The reported rates vary

depending on the nature of the population sampled and the method of ascertainment. Data on prevalence in adolescence is limited. However, community samples of adolescents report prevalence estimates between 1.5% and 6% (Cuffe 2001). Published estimates of the prevalence of ADHD in adults vary, likely due to methodological and diagnostic differences between studies. In a prospective study of more than 11,000 individuals from 10 countries including the Americas and Europe, the prevalence of ADHD among adults was estimated to be 3.4% (Fayyad 2007).

According to DSM-IV-TR, ADHD is a developmental disorder that requires an onset of symptoms before age 7 years. After childhood, symptoms may persist into adolescence and adulthood, or they may ameliorate or disappear. The percentages in each group are not well established, but as many as 65% of children with ADHD will have ADHD or some residual symptoms of ADHD as adults.

In a study using data from the National Comorbidity Survey Replication (NCS-R), adult persistence of ADHD, defined as the conditional prevalence of clinician-assessed ADHD in adults among the 8.1% of NCS-R respondents classified as having had ADHD in childhood, was estimated to be 36.3% in the total sample. Persistence does not differ significantly by respondent sex, age, or race-ethnicity (Kessler 2005).

The MAH described in Table 21 of the RMP, the important co-morbidities in patients with ADHD, where possible, in adults as well as children & adolescents.

Assessor's comment

The MAH should provide details of when the adult trial participants were diagnosed with ADHD. It is important to know when the initial diagnosis was made, what the pervasiveness and persistent, and severity of the symptoms were, over time, as well as other factors such as the diagnosis and range/severity/pervasiveness/persistence of symptoms at baseline in adulthood, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical).

- *The MAH should provide details of whether the trial participants were benefiting from methylphenidate or any other drug therapy for ADHD during childhood and adolescence, and whether this had any bearing on the safety or efficacy in adulthood.*

- *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.*

Section 1.7.1.5 of the RMP indicates that "as many as 65% of children with ADHD will have ADHD or some residual symptoms of ADHD as adults". This is not referenced, and is a very vague statement. It highlights concerns regarding the poor characterisation of the target population and the great potential for off-label use in patients who are not indicated for Concerta treatment as adults (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 outside of a comprehensive treatment programme etc). The MAH should describe their proposals to reduce these risks.

Section 1.7.1.5 then goes on to describe findings of a study using data from the National Comorbidity Survey Replication, describing the "adults persistence of ADHD" in respondents having had ADHD in childhood as about 36%. This in contrast with the statement above that 65% of children with ADHD will have ADHD or residual symptoms as adults ADHD, again highlighting the poor characterisation of ADHD in adults. 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 risk of Concerta use in adults who are not indicated for Concerta therapy.*

In November 2009, PhVWP concluded that none of the important positive findings regarding the risk of carcinogenicity with methylphenidate, such as those resulting from the El-Zein study in 2004, have been independently reproduced to date. Despite a few other unresolved positive or equivocal findings, the majority of the studies conducted to date do not indicate a genotoxic potential for MPH. Based on an evaluation of all relevant data from all sources, including the new study data submitted as a follow-up measure to the Article 31 referral, it was be concluded that there is no strong evidence of a genotoxic or carcinogenic potential for methylphenidate. Carcinogenicity should remain in the Core table of Risks and subject to routine pharmacovigilance in the Pharmacovigilance Plan of the Core RMP for methylphenidate.

Post-marketing exposure

The table below shows the post-marketing (non-study) exposure to Concerta, by age group.

Table 14: Postmarketing (Nonstudy) Exposure by Age Group (IMS MIDAS, January 2003 Through June 2009)

Age groups (years)	EU (G4) (5,080 Rx)[a]	Total (29,406 Rx)[a]
<6	0.4%	2%
6-20	94.0%	85%
21-65	5.4%	10%
>65	0.1%	0%
Age not specified	0.1%	3%

[a] (000)
EU (G4) = France (launch = May 2004), Germany (launch = January 2003), Spain (launch = April 2004), and UK (launch = March 2002)
Rx = prescription

Assessor's comment

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 good quality post-marketing / spontaneous data on the key risks in adults.

Regulatory Action Taken
On 23 July 2007, the CHMP initiated an Article 31 referral procedure for all MAHs of methylphenidate-containing products. This was due to concerns about cardiovascular adverse events including sudden death, cerebrovascular disorders, and psychiatric disorders. Following discussions between the CHMP and MAHs, a final opinion was issued on 22 January 2009; the Rapporteur's (MHRA) final Assessment Report was issued on 3 December 2008. The CHMP concluded that there was no need for a restriction on the use of methylphenidate-containing products, but that new recommendations on pre-treatment screening and ongoing monitoring of patients were required in the prescribing information. A number of post-referral commitments for the MAHs of methylphenidate-containing products were also adopted by the CHMP (provided in this section). The CHMP opinion was ratified by the European Commission
(EC) on 27 May 2009

This RMP updates the 23 November 2009 Concerta Paediatric EU RMP and takes into account changes proposed to support the additional indication for use in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. The following pharmacovigilance and risk minimisation actions are currently in progress by the Company in order to fulfil the conditions of its Marketing Authorisations as adopted by the CHMP (Annex IV of the EC decision; Annex 4).

Cytogenicity
The reports of Studies CRIT124D2201 (An open-label, behavioural treatment controlled evaluation of the effects of extended-release methylphenidate [Ritalin LA] on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder) (published by Tucker 2009) and NCT 00341029 (Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall) (published by Witt 2008) submitted by one of the MAHs were evaluated by the MAHs of methylphenidate-containing products and the findings were submitted to the MHRA and CHMP members for assessment on 30 March 2009. These findings, in addition to those of Walitza (2007 and 2009) and Ponsa (2009), concluded that methylphenidate does not pose a mutagenic and/or carcinogenic risk associated with cytogenetic damages to exposed humans. The studies mentioned in this paragraph are described in Section 1.1.1.1.2 in greater detail. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

Product Information - SmPC
As of the preparation of this RMP update, the Company has submitted updated product information in EU Member States to align with the core SmPC text ratified by the CHMP (refer to Annex III of the EC decision, Annex 4).

Product Information - Package Leaflet
The Company (with the other MAHs) has revised and user tested the core Patient Information Leaflet (PIL) text provided in Annex III of the EC decision (Annex 4). As of the preparation of this RMP update, the results of the user testing have been filed with EU Health Authorities for assessment.

Suicidality
The Company (with the other MAHs) has completed its investigation of the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of data from placebo-controlled studies available to the MAHs. This was submitted to MHRA on 31 July 2009. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

Long-Term Safety
The Company (with the other MAHs) has submitted a detailed feasibility assessment for a scientifically valid, well designed and suitably powered long-term safety study to examine specific endpoints for adverse cognitive and psychiatric outcomes. As of the preparation of this RMP update, the MHRA/CHMP assessment is ongoing.

Drug Utilisation
The Company (with the other MAHs) will provide all available retrospective drug utilisation data using health-related electronic databases in all Member States where methylphenidate is commercially available, to allow an evaluation of changes in usage over time. An evaluation of methylphenidate usage in 2008 will be submitted for assessment in December 2009.

Educational Tools
The Company (with the other MAHs) will submit fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklist) which will contain all of the important information from the Clinical Particulars section of the core SmPC for assessment. As of the preparation of this RMP update, these materials are being finalised in preparation for submission in December 2009 as part of the PSUR work-sharing procedure.

PSUR Work-Sharing
At the request of the EU Member States, the Company (with the other MAHs) will harmonise the PSUR reporting schedule for methylphenidate-containing products.

Assessor's overall comments:

Anxiety/Anxiety disorders

Adult studies have identified anxiety as a very common risk in adults (the risk is common in children & adolescents from pooled MAH studies and post-marketing data), and is one the most frequent reasons for withdrawal or dose reduction in adult studies. This is a major concern for the benefit/risk in this proposed variation. The risk of anxiety/anxiety disorders should be added to the Safety Specification (table of risks) as an ***Important Identified Risk****.*

Depression and Aggression

Following evaluation of the adult clinical trial data, depression and aggression should be changed from important potential risks to important ***identified*** *risks.*

Analysis of study data on cardiovascular effects

In relation to diastolic and systolic blood pressure and heart rate in adults, the MAH should provide, for each time point, summary treatment group (by dose) data (including mean, SD, maximum and minimum) and summary change from baseline data (including mean, SD, maximum and minimum) together with individual patient data on which this is based for heart rate, systolic and/or diastolic blood pressure to describe the temporal relationship throughout the duration of all clinical trials. A table of data showing detailed data for patients where systolic and/or diastolic blood pressure increased ≥5 mmHG and significant changes in changes in heart rate should also be presented.

The summary of the number and percentage of patients with an increase of at least 5 mmHg / significant changes in changes in heart rate should be included. Details of patient baseline characteristics (e.g. age, prior medications, prior illnesses, any other characteristics) should also be provided.
An important aim of this analyses is to characterise as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have fallen into the category of concern (i.e. experienced changes of ≥5 mmHG, or important changes in pulse rate). Thus, the full temporal record of cardiovascular outcomes in patients who at any time point have experienced a change in blood pressure of ≥5 mmHG /important changes in heart rate should be provided and included in the overall analysis.

- *The analysis must include a complete description of the hazard function over time for each patient who experienced a change in blood pressure of ≥5 mmHG or changes in pulse rate.*
- *A description of the risks per 1,000 patients should be provided.*

Dose-dependency of adverse effects

There is evidence to indicate that many of the important neurological, psychiatric and cardiovascular risks in adults treated with Concerta are dose-dependent.

- *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.*

Trial subjects with residual adverse effects (important risk of special interest)

In a proportion of trial subjects who experienced adverse effects of special interest, the adverse effect did not resolve without residual effects (including hypertension, tachycardia, psychosis/mania, arrhythmias, aggression, depression, tics).

- *The MAH should provide a detailed analysis of 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 factor, and discuss whether further pharmacovigilance activities or risk minimisation is required for any risks with persistent effects.*

Adverse effects (safety specification of RMP and SPC section 4.8)

Adverse events from adult clinical trials that were newly identified or identified as being associated with a higher reporting frequency than those identified from child/adolescent trials and post-marketing data, which may also be of particular concern for the benefit/risk are:

- *Anxiety*
- *Depressed mood*
- *Panic attack*
- *Delusion*
- *Mania*
- *Cerebrovascular accident*
- *Irritability*
- *Restlessness*
- *Tension*
- *Dyspnoea*
- *Confusional state*
- *Fatigue, Lethargy*
- *Feeling jittery*
- *Decreased appetite*
- *Initial insomnia*
- *Apathy*

Off-label use

The MAH has summarised the important potential risk of off-label use in table 18.16 of the Safety Specification. It is clear from this summary that the prevalence for off-label use, particularly in adults, is poorly understood.

- *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.*

Diagnosis in the target population (see also proposed SPC wording)

The MAH proposed wording for section 4.1 and 4.2 (and 4.4.) of the Concerta SPC is not in line with diagnostic criteria for ADHD (ICD-10 or DSM-IV). The proposed wording implies that it can be used in patients whose diagnosis was established before the age of 18. However, diagnostic criteria in ICD-10 states that "onset of disorder should be no later than 7 years" and DSM-IV states that ADHD symptoms that cause impairment should be present before 7 years of age. The proposed wording will allow potentially inappropriate use in adults who have been diagnosed with ADHD at any age up to 18 years of age, or who may have partial symptoms and not full ADHD.

- *The MAH should propose alternative wording that complies with diagnostic guidelines in DSM-IV and ICD-10 and also ensure that the wording does not allow use of Concerta to treat partial symptoms (i.e. not full ADHD) in adults.*
- *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.*

Diversion

The MAH has cited a small study in adults in Canada, where 44% of subjects admitted to diverting methylphenidate, primarily by giving it away. As the MAH states in table 18.17 regarding the preventability of the risk of diversion, that from a review of public information sources, it appears that there are currently no databases in place at an EU or national Member State level to directly monitor pharmaceutical product diversion in the EU. Methylphenidate is a controlled substance, distribution, prescription, and dispensing is restricted by national laws. However, these restrictions are unlikely to be adequate in preventing diversion by the individuals prescribed Concerta.

The MAH mention that the maintenance of records in some Member States of the supply of methylphenidate to the patients may provide an opportunity for measuring the possibility of product diversion. The extent to which this record keeping is electronic or centrally organised within each Member State is likely to vary. The MAH does not propose any measures to study this issue nor to minimise the risk beyond a statement in the SPC advising that patients should be monitored for the risk of diversion.

The limited evidence on the extent of this risk indicates that it is likely to be important, potentially common and may have a significant public health impact.

- *The MAH must propose methods to measure the risk of diversion in adults in all Member States and also propose risk minimisation measures including, but not limited to SPC and PIL wording, as these alone are likely to have a limited impact, especially on diversion by individual users.*

Use in pregnancy & lactation / neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia; respiratory distress; apnoea) / neonatal effects of growth

The SWP and CHMP reviewed all relevant data on use in pregnancy and lactation during the Article 31(2) referral for all methylphenidate-containing medicinal products. As a result, the contraindication was removed and replaced with information and advice in section 4.6 and 5.3 of the core SPC reflecting the evidence, in line with current guidelines.

Section 4.6 stating that methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy. Section 4.6 also states that methylphenidate has been found in breast-milk and mentions a report of decreased weight in an infant, whose mother was exposed to methylphenidate, with a positive dechallenge, and concludes that a risk to the suckling child cannot be excluded. A statement regarding studies in animals that have shown evidence of reproductive toxicity at maternally toxic doses is provided in Sections 4.6 and 5.3 of the SPC. Section 4.6 of the SPC also states that "cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."

It is likely that the number of patients of child-bearing age will increase if Concerta is used in adults, thus it is important to ensure that the information and guidance on safety and use in pregnancy/lactation in the SPC is adhered to.

- *The MAH should include this information in the Educational tools for HCPs and patients.*

The two potential risks of neonatal cardio-respiratory toxicity and effects on neonatal growth were identified from review of post-marketing data during the Article 31 referral, and included in the Core RMP as potential risks. The MAH suggest that these risks are specific to the child population. However 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 are breast-feeding and be exposed to Concerta will increase.

- *The risks of neonatal cardio-respiratory toxicity and effects on neonatal growth should be considered a potential risk for both neonates receiving methylphenidate and women who are pregnant or breast-feeding.*

Evidence in Hyperactive-Impulsive subtype of ADHD

The adult trials contained very few subjects with the Hyperactive-Impulsive subtype of ADHD. Most subjects were categorised as having combined type (about 70%) and the rest had the Inattentive-subtype.

- *The MAH should discuss the impact of this on the validity of the proposed indication.*

3.0 PHARMACOVIGILANCE PLAN

Routine pharmacovigilance

The MAH described their methodology for their proposed routine pharmacovigilance practices, including real-time review of single cases, scheduled reviews of aggregate data, aggregate reviews at pre-specified intervals to identify safety signals related to product quality and manufacturing, data mining of regulatory databases (such as FDA AERS,WHO Vigibase), including medically confirmed and unconfirmed reports.

The MAH has provided a summary of their pharmacovigilance action plan for each of the safety concerns and detailed their action plan for each of the specific concerns identified in the Article 31 Referral in **table 25 of their submission**. A summary of their action plan, from Table 24 of the MAH submission, is presented below:

Table 24: Summary of Safety Concerns and Planned Pharmacovigilance Actions

Safety Concern	Planned Action
Important Identified Risks	
Hypertension Tachycardia	• Routine pharmacovigilance • Follow up on FDA pharmacoepidemiologic study (ongoing)[a]
Raynaud's phenomenon Hallucinations (auditory, skin sensation, visual disturbance) Psychosis/Mania Anorexia	• Ongoing monitoring with routine pharmacovigilance practices as described in Section 2.1. No additional surveillance activities are needed at this time to monitor risk (see Section 3).
Decreased rate of growth	• Routine pharmacovigilance • Follow up MTA Study (ongoing)[a] • Investigator-initiated study in adolescents (ongoing)[a]
Important Potential Risks	
Migraine Repetitive behaviours QT prolongation Cyanosis Arrhythmias Aggression Hostility Depression Tics/Tourette's syndrome/Dystonias Withdrawal syndrome Lymphocytic leukaemia Neonatal cardio-respiratory toxicity(neonatal/foetal tachycardia, respiratory distress/apnoea) Neonatal effects on growth (via lactation)	• Ongoing monitoring with routine pharmacovigilance practices as described in Section 2.1. No additional surveillance activities are needed at this time to monitor risk (see Section 3).
Sudden death Cerebrovascular disorders	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for sudden death and Cerebrovascular disorders through the use of a questionnaire) (ongoing)[a] • Follow up on FDA pharmacoepidemiologic study (ongoing)[a]
Suicidality	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for suicidality through the use of a questionnaire) (ongoing)[a] • Determine the feasibility of a meta-analysis of the risk of suicidality (feasibility report submitted to MHRA for assessment on 31 July 2009)[a]
Effect on final height	• Routine pharmacovigilance • Follow up MTA Study (ongoing)[a]
Sexual maturation (delayed)	• Routine pharmacovigilance • Investigator-initiated study in adolescents (ongoing)[a] • Follow up MTA Study (ongoing)[a]

(Continued)

Table 24: Summary of Safety Concerns and Planned Pharmacovigilance Actions (Continued)

Carcinogenicity	• Routine pharmacovigilance • Enhanced pharmacovigilance (additional surveillance for carcinogenicity through the use of a questionnaire) (ongoing)[a] • Evaluation of cytogenicity studies (CRIT124D2201 and NCT00341029) submitted to the MHRA and CHMP members by a MAH on behalf of all MAHs of methylphenidate-containing products on 30 March 2009.
Off-label use	• Routine pharmacovigilance • IMS prescription data drug utilisation survey (DUS) (ongoing)[a]
Diversion	• Routine pharmacovigilance • Monitoring supply of controlled substances follows National regulations [a]
Drug abuse and Drug dependence	• Routine pharmacovigilance
Important missing information	
Long-term safety[b]	• Routine pharmacovigilance was described in Section 2.1. • Determine the feasibility of a long-term safety study with outcomes for adverse cognitive and psychiatric effects in corporation with other MAHs (ongoing)

[a] See Section 2.3 for further information.
[b] Identified in the Rapporteur's (MHRA) Assessment Report dated 3 December 2008.

Assessor's comment

The MAH has provided details of their proposed routine pharmacovigilance practices, which appear adequate.

Diversion

- *There are no proposals from the MAH to measure or monitor the risk of diversion beyond routine pharmacovigilance. Table 24 of the RMP states that for the risk of diversion, "monitoring supply of controlled substances follows National regulations". The MAH should clarify what this means and how it relates to their activities to characterise the risk of diversion in all Member States.*
- *The MAH must propose methods to measure the risk of diversion in adults in all Member States and also propose risk minimisation measures including, but not limited to, SPC and PIL wording, as these alone are likely to have a limited effect.*

Hepatic disorders

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

Summary of outstanding actions, including milestones (of the Core RMP)

The present list of actions, based on requirements following the Article 31 referral (for the childhood and adolescent ADHD indication), are summarised below.

Table 26: Present List of Actions to be Completed (Ongoing and Planned) With Milestones and Timelines

Actions[a]	Milestones/ Exposure[b]	Milestones/ Calendar Time[b]	Status
Enhanced pharmacovigilance through the use of a questionnaire			Ongoing
Follow-up FDA pharmacoepidemiologic study			Ongoing
Follow-up MTA Study			Ongoing
Investigator-initiated/Smoking cessation study in adolescents			Ongoing
Meta-analysis of the risk of suicidality (feasibility report)		31 Jul 2009	Submitted
Evaluation of cytogenicity studies (CRIT124D2201 and NCT00341029)		30 Mar 2009	Submitted
Drug utilisation analysis based on IMS prescription data	2008 Data	Q4 09	Ongoing
Long-term safety study (feasibility report)		Q3 09	Submitted

[a] The identified and/or potential risks for which these actions are ongoing or proposed are listed in Table 25 (links actions with applicable risks). Long-term safety was identified by the CHMP as important missing information.
[b] If not listed, milestones to be determined.

Assessor's comments:

The following points are subject to ongoing assessment in the context of the child/adolescent ADHD Core RMP but the first two may not be relevant to the target adult population.

1) **Feasibility of a proposed meta-analysis of the collaborating MAHs' pooled data on suicidality**
2) **The collaborating MAHs' feasibility statement on studying long-term effects of MPH on psychiatric outcomes/cognition**
3) **Risk of cardiovascular disorders, cerebrovascular disorders, sudden death: follow-up of FDA/AHRQ/Vanderbilt University pharmacoepidemiological study**

- *The MAH should submit proposals to further evaluate the risk of suicidality and the long-term effects of Concerta in adults.*

The results of the ongoing FDA pharmacoepidemiological study may provide useful data on the cardiovascular and cerebrovascular risks in adults exposed to ADHD medications, including methylphenidate.

- *The MAH should provide an evaluation of the results of the ongoing FDA/AHRQ/Vanderbilt University study as soon as the results are available and propose regulatory action in the context of the target adult population.*

Patients excluded from adult trials

There is missing information from patients with a range if important cardiovascular, cerebrovascular neurological and psychiatric co-morbidities, history of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, weight below 45.4 KG.

- *The MAH should discuss the impact of these exclusions on the safe and effective use of Concerta in the proposed target adult population and discuss what risk minimisation measures or further studies are required.*

Use in pregnancy & lactation / neonatal cardio-respiratory toxicity (neonatal/fetal tachycardia; respiratory distress; apnoea) / neonatal effects of growth / Signal for Spina bifida / neural tube defect

During the Article 31 Referral the Safety Working Party of CHMP reviewed all data relating to safety in pregnancy and lactation from all MAHs, and noted that there were a few weak cases of spinda bifida/neural tube defect in humans and one rabbit study which showed cases in treated subjects, but not statistically higher than controls. The SWP recommended that more information should be obtained on this signal, and that the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) may have relevant data.

- *Given the predicted wider exposure of Concerta in the adult population the MAH should commit to capturing and evaluating relevant data on pregnancy outcomes, specifically a pregnancy registry should be considered.*
- *As previously recommended the MAH should also obtain and evaluate data on these issues from the WHO Collaborating Centre for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) and any other relevant sources.*

Drug utilisation studies

MAHs must provide utilisation data for all Member States where their product is used. 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. The method for each member state can be decided at a national level to ensure it is suitable for capturing the required data.

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.

- *Collaboration with specialist treatment centres for adults with ADHD should be considered in the proposals.*

- *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.*

Important missing information on long term: safety (especially for key risks), effectiveness, maintenance of (short-term) effects

- *The MAH has not proposed any proactive pharmacovigilance (studies) to address these issues, which should be rectified.*

4.0 RISK MINIMISATION PLAN

SPC and additional measures

The MAH believes that the current contraindications, warnings and precautions within the proposed harmonised EU SPC for Concerta adequately inform prescribers and patients about the benefit-risk of Concerta.

In addition, the MAH has not identified any evidence to support new risks associated with Concerta that necessitates new risk minimisation activities. However, the CHMP requested in the Article 31 referral that MAHs of methylphenidate produce a risk minimisation tool (an education tool).

Proposed SPC

The MAH proposed an SPC with revisions to support the Type II variation for use of Concerta in adults. The ADR section in the current Core SPC, Section 4.8, is based on the assessment by the major EU MAHs of methylphenidate-containing products of their individual paediatric clinical databases and/or post-marketing pharmacovigilance information.

The MAH state that incorporation of newly identified ADRs from the adult Concerta clinical database into a single table would require implementation in the SPCs of all methylphenidate containing products, as the current table is part of the core SPC of methylphenidate-containing products for the treatment of ADHD (in children). To maintain transparency of the current core SPC ADR table, the MAH proposes to add a new table with 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 ADR table in the SPC or are reported more frequency than in the current ADR table on the basis of adult clinical study data. It is not the intention of the MAH to position the newly identified ADRs as relevant for adults only. An introductory sentence to this additional ADR table is proposed:

"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."

Assessor's comments:

It is recommended that "or in a higher frequency category than the paediatric" is replaced with " or reported more frequently than in the paediatric".

Additional Risk Minimisation measures

Educational materials are in development as part of the Article 31 referral commitments, to help physicians use methylphenidate in children and adolescents according to the guidance given in the EU harmonised prescribing information. The CHMP requests that all MAHs of methylphenidate produce the following risk minimisation tools with information from the Clinical Particulars section of the agreed upon SPC (based on the child/adolescent ADHD indication).

• Physician's guide to prescribing, and
• Checklists for actions before prescribing and for ongoing monitoring for prescribers and, if possible, caregivers.

The Company in coordination with 4 of the other largest MAHs holders of methylphenidate (Novartis, Shire, Medice, and Laboratorios Rubio) are working to produce such an educational programme. It has been agreed that it would be appropriate for the MAHs to work with an independent group to produce the educational tool. In this way, the educational tools will be applicable to all methylphenidate products, rather than company or brand specific.

Table 28 in the MAH submission provides information on the proposed educational tools (specific to the child/adolescent ADHD indication).

The Company will also review the educational materials developed for children and adolescents following approval of wording for an indication for continued treatment of adults with ADHD within the SPC; this review and any applicable educational materials would be independent of the other MAHs of methylphenidate-containing products for the treatment of ADHD due to the revised wording within the Concerta label only.

Risk Minimisation measures / Educational Tools specifically for the Adult ADHD population

The MAH (with other MAHs for methylphenidate products in the EU) will submit fully harmonised risk minimisation tools (physician's guide to prescribing and prescriber's checklist) which will contain all of the important information from the Clinical Particulars section of the core SPC for assessment.

As of the preparation of this RMP update, these materials are being finalised in preparation for submission as part of the PSUR work-sharing procedure.

Assessor's comments:

Risk Minimisation measures / Educational Tools specifically for the adult ADHD population

- *Educational tools (for HCPs) as proposed in the Core RMP for the childhood and adolescence ADHD indication, should be modified to be specific for the adult population, and include issues that are of particular concern in the adult population.*
- *Risk minimisation measures are also important for **patients**, and the MAH should provide educational tools similar to those proposed for HCPs in the childhood and adolescence ADHD indication, specifically for adult patients.*

Anxiety/anxiety disorders, aggression, depression and suicide-related events

- *Adult studies have identified anxiety as a very common risk in adults and is a major concern for the benefit/risk in this proposed variation. The risk of anxiety/anxiety disorders should be added to the Safety Specification (table of risks) as an **Important Identified Risk**. The MAH should propose proactive measures to minimise this risk.*
- *The risk of aggression, depression and suicide-related events should also be added to the Safety Specification (table of risks) as an **Important Identified Risk**.*
- *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 the MAH should consider making the warning more prominent in this section of the SPC.*

Use in pregnancy & lactation/neonatal cardio-respiratory toxicity (neonatal/foetal tachycardia; respiratory distress; apnoea) /neonatal effects of growth

Section 4.6 states that methylphenidate has been found in breast-milk and mentions a report of decreased weight in an infant, whose mother was exposed to methylphenidate, with a positive dechallenge, and concludes that a risk to the suckling child cannot be excluded. A statement regarding studies in animals that have shown evidence of reproductive toxicity at maternally toxic doses is provided in Sections 4.6 and 5.3 of the SPC. Section 4.6 of the SPC also states that "cases of neonatal cardio-respiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports."

- *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 including these in educational tools for HCPs treating adult female patients and for the patients themselves.*

Specialist initiation and prescribing

The MAH should ensure that the risk minimisation measures (including but not limited to the SPC, PIL and educational tools for HCPs and patients) are adequate in ensuring : that specialists in adult ADHD are responsible for prescribing Concerta in adults; the correct and appropriate diagnosis of Adult ADHD; 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; regular evaluation of the need for continuing treatment and the maintenance of effect in adults.

Important missing information on long term: safety (especially for key risks), effectiveness, maintenance of (short-term) effects &
Evidence of maintenance of effect beyond short-term use

- *The MAH must ensure the SPC (section 4), PIL and educational tools for HCPs, and for carers adequately address the lack of evidence on long-term safety, effectiveness and maintenance of short-term effects of Concerta in the adult population.*

Specialist initiation and prescribing

- *The MAH should give further consideration to what risk minimisation measures (including the SPC and PIL and educational tools) are needed to ensure correct and appropriate diagnosis, pre-treatment screening, initiation of prescribing and review of the need for ongoing treatment by specialists.*

Use of 'Concerta' vs 'methylphenidate' in SPC

- *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.*

Determining long-term usefulness

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

Pre-treatment screening

- *The MAH should consider whether any further modifications required to the pre-treatment screening advice in the Core SPC, in order to be more appropriate for the Adult ADHD population.*

Ongoing monitoring (in SPC and Educational Tools)
Cardiovascular

- *The MAH are proposing to omit from the SPC, the requirement and frequencies for monitoring cardiovascular status (blood pressure and heart rate) in adults. This is not acceptable. The current cardiovascular monitoring requirements should also apply to the adult population and be included in the Educational Tools for HCPs and patients.*

Effects on weight and appetite

- *Regular monitoring for changes to weight and appetite are currently is required for children & adolescents, but the MAH propose to omit this requirement for adults. Given the evidence for anorexia, decreased appetite and clinically important weight loss in adults, this is not appropriate and 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.*

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

Maintenance of effect

- *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". There is no adequate evidence that it has been partially established, 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.*

Possible Adverse effects (Section 4.8 of the proposed SPC)

- *Adverse events from adult clinical trials that were newly identified or identified as being of a higher frequency than those identified form child/adolescent trials and post-marketing data, which may be of particular concern for the benefit/risk (in addition to the important risks identified from child/adolescent trials and all post-marketing data) are:*

Anxiety
Depressed mood
Panic attack
Delusion
Mania
Cerebrovascular accident
Irritability
Restlessness
Tension

Dyspnoea
Confusional state
Fatigue, Lethargy
Feeling jittery
Decreased appetite
Initial insomnia
Apathy

- *The proposed wording in section 4.8 of the SPC is acceptable.*

AUDIT TOOLS

- *MAH needs to 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.*

5.0 OVERVIEW

In this version of the RMP, the MAH has proposed updates to the Core RMP (required by CHMP following the Article 31 referral for all methylphenidate products) to support a type II variation for a new indication for Concerta in treating adults with ADHD whose diagnosis was established before the age of 18 years and whose symptoms persist into adulthood. Exposure, demographic, and important identified and potential risk data from double-blind and open-label clinical trials in adults with ADHD, and information from literature pertaining to adults with ADHD where applicable, were added to this RMP. I

Generally, there was a lack of adequate information on the epidemiology of ADHD in adults, specifically in the EU but also worldwide.

The Core important identified and potential risks for all methylphenidate products were reviewed for relevance in the adult ADHD population. A number of major risks were identified from the adult clinical trial data, which were either new, or were reported with a higher frequency category than in the paediatric population. Some of these should be categorised as important risks in the safety specification of the RMP for adults, these include: Anxiety/Anxiety disorders, depression, suicide-related events, aggression, agitation, mania/delusions, tics, cardiac arrhythmias, hypertension and clinically important changes in weight. The potential for other clinical significant adverse cardiovascular and cerebrovascular outcomes, as a consequence of effects on heart rate and blood pressure in adults, cannot be excluded and is considered a potential risk. These should be subject to proactive pharmacovigilance and risk minimisation measures.

Further analysis of the adult study data in relation to effects on diastolic and systolic blood pressure and heart rate should be requested, with the aim of characterising as fully as possible, the patterns of change in blood pressure and heart rate over time in patients who at any time point have experienced important changes.

In order to better understand the study population and its relationship to the target indicated adult population (in the RMP safety specification), the MAH should provide details of when the adult trial participants were initially diagnosed with ADHD, the pervasiveness and persistency, and severity of the symptoms over time, and details of prior/existing treatments (both pharmaceutical and non-pharmaceutical). The MAH should determine whether any of these factors have an impact on the safety or efficacy of Concerta in adults.

Important missing information in the Safety Specification should include: maintenance of the short-term effect in adults, long-term efficacy, effectiveness and safety (especially for key risks: cardiovascular risks, cerebrovascular risks and *de novo* or worsening of pre-existing psychiatric disorders including: mood disorders, depression, anxiety, agitation, suicide-related events, psychosis /mania/delusion), safety & efficacy in new or continuing users of methylphenidate.

Because of the adult trial exclusion criteria, there is also important missing information from patients with a range of important cardiovascular, cerebrovascular neurological and psychiatric comorbidities, history of abuse/misuse/SUD, liver or renal insufficiency, and in some studies, from patients with other past or current non-

drug treatments, known non-responders to methylphenidate (or other ADHD drugs), recent users of methylphenidate, patients weighing < 45.4 KG.

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 in adults and the risk of diversion remain considerable. Measures proposed in the RMP to characterise the risks of off-label use and diversion and measures proposed to minimise them are considered inadequate and need to be addressed. Additionally, the MAH's proposed wording for sections 4.1, 4.2 and 4.4 of the SPC will allow use in adults who have been diagnosed with ADHD at any age up to 18 years of age, which is not in line with current guidelines which state ADHD should be diagnosed before the age of 7.

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 MAH should submit proposals to further evaluate the long-term effects on psychiatric outcomes, the risks of suicidality and of cerebrovascular disorders, in Adults.

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

The MAH should ensure that the risk minimisation measures 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.

The MAH should consider whether the current Core SPC guidance and frequencies for neurological, psychiatric, weight and appetite monitoring are also appropriate for adults or whether they need to be modified.

6.0 LIST OF QUESTIONS ON THE PROPOSED ADULT RMP

The Risk Management Plan for Concerta in Adults should be revised based on the following points:

1. 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.

2. 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.

3. 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.

4. 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).

5. 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.

6. The MAH should provide a detailed analysis of the 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.

7. 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:
   - Long-term safety (especially for key risks: cardiovascular, cerebrovascular, psychiatric risksincluding: 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.

- 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".
- Long-term effectiveness (and efficacy).
- Efficacy/safety in patients who have/have not used methylphenidate before.

8. 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.

9. 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.

10. 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.

11. 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 minimisation 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 characterise the risk of diversion in all member states

12. 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.

13. 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.

14. 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.

15. 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.

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

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

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

FINAL VARIATION ASSESSMENT REPORT

Our Reference:	PL 00242/0400 - 0088
Product:	Concerta® XL 18mg Prolonged-Release Tablets
Marketing Authorisation Holder:	Janssen-Cilag Limited
Active Ingredient(s):	Methylphenidate hydrochloride
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Complex
EU Procedure Number (if applicable):	UK/H/0544/001/II/056

Reason:
To add the treatment of ADHD in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood, at doses ranging from 18 mg to 72 mg per day as a new clinical indication. Sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the SPC have been updated.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 93231 and covers the following submissions PL 00242/0374 - 0088, PL 00242/0373 - 0085, PL 00242/0400 - 0042.

Supporting Evidence
See PVAR which is imported separately for the full assessment.

Evaluation
Not approvable with major efficacy and safety concerns. See EAG and CHM advice in Appendix 1 and CMS comments Appendix 2.

RFI Response

Major Objections
1. 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).**

Addressed in sections 2.3-2.7. Points 2.4-2.7 are considered addressed by the further analysis and withdrawal of the indication. Point 2.3 is considered partially resolved. There are two outstanding efficacy issues relating to the proposed SmPC wording which could be addressed through different wording to Sections 4.2 and 5.1 of the SmPC as detailed in the Conclusion to this report. **Point partially resolved.**

- **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.

Not addressed as MAH are no longer applying for previously proposed indication.
Point resolved through removal of proposed indication.

- **Long-term efficacy. The withdrawal study failed to demonstrate efficacy. The published paper by Rosser 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.**

Not addressed as MAH are no longer applying for previously proposed indication.
Point resolved through removal of proposed indication.

2. 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).

Addressed in sections 2.8-2.12 and 2.25. These are partially addressed see below.

Other Efficacy Concerns
3. 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.

The applicant has clarified how the missing data was handled in the trials, and has provided a more conservative analysis as requested. Although the applicant was asked to use Dunnett's test to control for multiple doses, the applicant has instead chosen to use the Sidak test. This is acceptable.

The applicant has also clarified how many patients had missing data per arm as requested. For study 3002, statistical significance of all doses compared to placebo has been maintained, but with a much weaker statistical evidence of efficacy, and with much smaller point estimates. For example, taking the 72 mg dose, the initial (incorrect) analysis had a point estimate for efficacy of 59.6%, with placebo having a 27.4% rate, the difference being 32.2%.

When missing data is imputed as failure which is appropriately conservative, the point estimates are now 26.0 and 50.0 respectively, the difference being 24%. It is clear that the magnitude of the efficacy is being driven by the method used to handle the missing data and additionally that the use of LOCF is not appropriately conservative and could bias in favour of active treatment.

For Study 02-159, the requested analysis yields a p-value of 0.055 at the 2-week time-point, marginally failing to reach statistical significance. In the strictest interpretation this could be seen as a failed trial.

For Study 3013 the 13-week time point data is mixed. The initial treatment differences between active and placebo were 10.2% and 18.7% for the 54 mg and 72 mg doses respectively (with only the 72 mg dose being significant, p=0.0098). When using the more appropriate missing as failure analysis, these point estimates become 11.6% and 13.8% respectively, with neither attaining anything near to significance (p=0.274 and p=0.198 respectively). This is clearly a failed trial.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The proposed wording in section 5.1 of the SmPC states that "Generally, efficacy of CONCERTA XL was demonstrated in a dose range of 18 to 72 mg/day." The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1. The following wording is considered to reflect the data more appropriately:

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. *Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage the range of 18 to 72mg/day but this has not been consistently shown beyond 5 weeks.*
Point partially addressed.

4. 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.

The applicant has provided the requested analysis. It is noted that a larger proportion of patients who dropped out on active were considered 'responders' in the initial analysis, which helps to clarify the results seen in Question 3 and discussed there.
The point is considered resolved as the MAH has withdrawn the proposed indication.

5. 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.

The applicant has provided the requested analyses. It is of note that in general the response rate is higher in Concerta than in placebo. It is also of note that although the numbers are small there seems to be a better maintenance of response (proportion of

patients who initially respond who remain responders at the final visit) in the placebo group. Although interesting, it is not considered that this data is conclusive due to the numbers involved.
The point is considered resolved as the MAH has withdrawn the proposed indication.

6. 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.

The applicant has provided the requested analyses that provide the reassurance that any efficacy is not driven by a *post hoc* inclusion in the statistical model. Although a missing as failure rather than an LOCF model would have been preferred, it is unlikely that further re-analyses would change the interpretation.
The point is resolved.

7. 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.

The applicant has again presented the requested analysis, with a clear visual differentiation of the patient population into early and late diagnosis, and an appropriate age classification of <7, 7-18 and >18. Balance across all arms of the trials was achieved and there is no evidence that there is an interaction. Accordingly no discussion of this effect (as there is no evidence that there is one) is required.
Point Resolved

Safety Concerns
8. 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.

The MAH have responded by considering:

- The level of response that poses a risk in adults
- Presentation of Clinical Data relating to vital signs increases.

8.1 Level of response that poses a risk in adults
GU et al High BP and CV MR among US adults: III National Health and Nutrition Examination Survey
NHANES III study (1988-1994) in adults compared CV mortality sik between hypertensives, prehypertensives to normotensives. Individuals with a mean systolic BP120 mm Hg and a mean diastolic BP80 mm Hg were classified as having normal BP. Individuals with a mean systolic BP between 120 and 139 mm Hg or a mean diastolic BP between 80 and 89 mm Hg were classified as having prehypertension. Individuals with a mean systolic BP > 140 mm Hg or a mean diastolic BP > 90 mmHg were classified as having hypertension. Compared with normotension, the relative risks of CVD mortality were 1.23 (95% confidence interval [95% CI] 0.85–

1.79,) for prehypertension, 1.64 (95% CI 1.11–2.41) for hypertension,1.74 (95% CI 1.28–2.49,) for uncontrolled hypertension, and 1.15 (95% CI 0.79–1.80) for controlled hypertension..

Menotti The role of a baseline casual blood pressure measurement and of blood pressure changes in middle age in prediction of cardiovascular and all-cause mortality occurring late in life: a cross-cultural comparison among the European cohorts of the Seven Countries Study
The effect of a 20mmHG increase in systolic BP could be detected on CV MR in subsequent decades with increases of 10mmHG having an impact on all deaths:

The relative risk for 20 mmHg of SBP (and its 95% confidence intervals) in predicting CVD deaths was 1.65 (1.54–1.77) for the first 10-year block; 1.33 (1.24–1.42) for the second block; and 1.22 (1.13–1.31) for the last 10-year block. The corresponding levels of ALL deaths were 1.41 (1.34–1.49), 1.26 (1.19–1.32) and 1.11 (1.05–1.17). Changes in SBP during 10 years (˜-SBP) added predictive power to baseline measurements in a direct and significant way, with a relative risk for a change of 10 mmHg of 1.14(1.10–1.17) for CVD deaths and 1.11 (1.09–1.13) for ALL deaths.

Tverdal 2008 Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379 843 men and women aged 40–45 years
A prospective study of participants in cardiovascular surveys that were carried out in 1985–1999 and covered men and women aged 40–45 years in all counties except the capital, Oslo. In total, 180 353 men and 199 490 women aged 40–45 years without cardiovascular history or diabetes accrued 4 775 683 years of follow-up. There was a positive and graded association between heart rate and mortality from all causes, as well as between heart rate and deaths from cardiovascular disease (CVD), ischaemic heart disease, and stroke. However, these associations were greatly reduced when we adjusted for the main risk factors of disease. The hazard ratios for any death were reduced from 3.14 to 1.82 for men (95% CI, 1.62–2.04) and from 2.14 to 1.37 for women (95% CI, 1.19–1.59), when we compared 95 b.p.m. with 65 b.p.m. The corresponding figures for CVD were a reduction 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 conclude that a raise in pulse rate is likely to be a marker rather than an independent risk factor for cardiovascular disease.

Assessor' comments However there are others that consider raised pulse rate as a marker for increased sympathetic activity which is known to cause harm e.g Palatini in a review article refers to the association with increases risk of insulin resistance (Palatini P Heart rate as a cardiovascular risk factor: do women differ from men? Ann Med 2001;33:213-221).

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 , Study 02-159 and the pooled open-label studies . The studies are presented in this fashion since the former had postural readings and the latter just sitting observations. The percentage of subjects in each treatment group experienced sustained elevated blood pressure was numerically higher for methylphenidate in both analyses: pooled Studies 3002 DB and 3013 (6.1%

placebo, 7.8% MPH) and Study 02-159 (0.0% placebo, 1.1% MPH). For the pooled open-label studies, 4.7% of the subjects experienced sustained elevated blood pressure. For sustained elevated pulse over 100 there were no cases in pooled Studies 3002 DB and 3013, for Study 02-159 (0% placebo, 1.1% MPH). In the OL studies 0.4% (n=975) had a sustained increase in pulse >100bpm.

Number (and percent) of subjects with increase greater than 5mmHg at any post baseline blood pressure measurement for Studies 3002 DB and 3013 are presented below:

	-- 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.

Number (and percent) of subjects with increase greater than 5mmHg at any post baseline blood pressure measurement for Study 02-159 are presented below:

	-- 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.

Number (and percent) of subjects with increase greater than 10mmHg at any post baseline blood pressure measurement for Studies 3002 DB and 3013 are presented below:

	-- 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.

Number (and percent) of subjects with increase greater than 10mmHg at any post baseline blood pressure measurement for Study 02-159 are presented below:

	-- 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.

Number (and percent) of subjects presenting at least one treatment-emergent post baseline potentially clinically important blood pressure measurement in patients with a medical history of hypertension for Studies 3002 DB and 3013 are presented below:

	-- 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.

Number (and percent) of subjects presenting at least one treatment-emergent post baseline potentially clinically important blood pressure measurement in patients with a medical history of hypertension for Study 02-159 are presented below:

	-- 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.

Potentially clinically important (PCI) rises (defined as >140/90) did not show a signal but the denominators are very small. This is not surprising considering the entry criteria and age of population studied.

Assessor's comments

Data from longitudinal studies in the medical literature appear to show that rises in 10mmHG are associated with increase of all cause mortality. Increases in pulse rate were also associated with an increase in MR but largely disappeared when controlled by disease process in one analysis by Tverdal. This is not reassuring since this may be

the mechanism through which diseases such as DM cause an increased an increased cardiovascular disease risk.

From the MPH data there is a signal in terms of an increase in those experiencing a raised BP >5mmHG or 10mmHg systolic. Interestingly in those with a diagnosis of hypertension these patients experienced less variability in their BP measurements than those on placebo, implying that treatment prevents transient rises in BP. It would have been more helpful to interpret the significance of the signal of transient rises in BP on MPH by a further analysis comparing those with a consistently raised systolic/diastolic pressure of 5mmHg/10mg Hg over baseline rather than just single measurements. The MAH also presented data from RCT and OL studies on numbers of subjects have at least 1 reading of >130 or >85 including subgroup analyses with those with baseline hypertension and prehypertension. The numbers were very small and as stated previously it is difficult to interpret the significance of isolate readings. There is a signal from the RCTs that there are more elevations in systolic and diastolic BP in subjects on MPH compared to placebo but this is based on any reading post-baseline rather than consistent elevation.

Form the previously submitted data there is a signal that sustained elevations of BP SBP ≥140 mmHg and/or DBP ≥90 mmHg occur more frequently with subjects on MPH: pooled Studies 3002 DB and 3013 (6.1% placebo, 7.8% MPH) and Study 02-159 (0.0% placebo, 1.1% MPH). For the pooled open-label studies, 4.7% of the subjects experienced sustained elevated blood pressure. For sustained elevated pulse over 100 there were no cases in pooled Studies 3002 DB and 3013, for Study 02-159 (0% placebo, 1.1% MPH). In the OL studies 0.4% (n=975) had a sustained increase in pulse >100bpm.

Monitoring is already in section 4.4 of the SmPC and continued monitoring will part of the PSURs. **Point resolved.**

9. 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.**

Suicidality

There was no validated instrument used in the studies to assess suicidal ideation. There are 3 cases of suicidal ideation reported (1 subject in Study 3013 and 2 in OL Study 12-304) one of which was associated with a suicide attempt. The narratives have been provided. On case was associated with depression treated with venlafaxine and deemed possibly related to study medication. The individual had a history of a previous suicide attempt. The second case (Subject A10056, a 29-year-old woman, in Study 3013) had a history of MDD but had been asymptomatic for a year. Anxiety, irritability and panic attacks were reported on starting the medication. These increased in severity when the study medication was increased, suicidal ideation was noted on 15th April which culminated in a hospital admission with an overdose 5 days later. The study medication had not been stopped despite the increased in symptoms with an

increase in dose and suicidal ideation being noted at the last visit. This is a cause of concern regarding this subject's management within the study. The MAH will be asked to clarify the management of this case. The third case had been on MPH for over 1 year and on a stable dose for more than 6 months. The depression and suicidal ideation were in relation to recurrence of her breast cancer.

Output DAE19D13: Number and Percent of Subjects With an Adverse Event of Special Interest: Aggression
by Seriousness, Severity, Outcome and Treatment Group - Double-Blind and Overall CONCERTA Analysis Sets.

	DOUBLE-BLIND		
Identified Risk: Aggression*	(PLACEBO N=309)	(CONCERTA N=596)	OVERALL CONCERTA (N=1369)
Frequency**			
N (%)	17 (5.5)	71 (11.9)	202 (14.8)
Odds Ratio		2.3	
95% confidence interval***		1.3 to 4.3	
Seriousness/outcomes****			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	13	30
Resolved/Recovered/Recovered From AE	16	65	169
Recovered With Residual Effects	0	0	0
Continuing/Not Yet Recovered	1	6	33
Severity****			
Mild	10	31	91
Moderate	5	30	92
Severe	2	10	19

* MedDRA preferred terms searched for this risk are provided in Annex 4
** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Aggression; The subject is counted only once regardless of the number of events or the number of occurrences.
*** The 2-sided exact 95% CI in odds ratio is of Concerta to the comparator.
**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

Output DAE19D13: Number and Percent of Subjects With an Adverse Event of Special Interest: Aggression
by Seriousness, Severity, Outcome and Treatment Group - Double-Blind and Overall CONCERTA Analysis Sets.

	DOUBLE-BLIND		
Identified Risk: Aggression*	(PLACEBO N=309)	(CONCERTA N=596)	OVERALL CONCERTA (N=1369)
Frequency**			
N (%)	17 (5.5)	71 (11.9)	202 (14.8)
Odds Ratio		2.3	
95% confidence interval***		1.3 to 4.3	
Seriousness/outcomes****			
Resulted in Death	0	0	0
Was Serious	0	0	0
Discontinued Treatment	0	13	30
Resolved/Recovered/Recovered From AE	16	65	169
Recovered With Residual Effects	0	0	0
Continuing/Not Yet Recovered	1	6	33
Severity****			
Mild	10	31	91
Moderate	5	30	92
Severe	2	10	19

* MedDRA preferred terms searched for this risk are provided in Annex 4
** Includes all subjects who had one or more occurrences of an adverse event that coded to the MedDRA preferred terms grouped under Aggression; The subject is counted only once regardless of the number of events or the number of occurrences.
*** The 2-sided exact 95% CI in odds ratio is of Concerta to the comparator.
**** Each subject is counted once for Death (if any event caused death), Serious (if any event was serious), Discontinued (if any event led to discontinuation), Outcome categories (last occurrence of event and if more than one least resolved), and Severity (most severe).

Assessor's comments

Psychiatric adverse events: subjects demonstrating suicidal ideation (2) or behaviour (1 attempted suicide) were few (n=3 0.2.%). The MAH have not made an attempt to analyse any cases of potential self-harm.

Aggression.
There is a clear signal around aggression with an OR 2.3 no CI included (MPH 11.9% and Placebo 5.5%). Additional medication was seldom used to control the aggression (6/273 occasions). Over 10% of aggressive episodes were considered as serious in the DB studies. During the double-blind studies, 13 of the 596 subjects receiving MPH (2.2%) were withdrawn for aggression-related adverse events (vs.0% receiving placebo). This is already has a SmPC warning. These should be monitored in future PSURs.

The MAH will be asked further details on the handling of Subject A10056, a 29-year-old woman, in Study 3013.

Point resolved.

10. Further discussion on the implications of weight loss in adults.
The MAH presented data according to BMI categories of Underweight, Normal, Overweight and Obese weight loss occurred in these groups (MPH vs placebo) 1 (7.7%) vs 0%, 17 (7.1%) vs 0 (0%), 33 (16.2%) vs 3 (2.9%) and 21 (19.1%) vs 5 (6.5%) respectively lost at least 7% of their BMI. In the Open Label studies 1.7% had to have their medication adjusted due to weight loss. There is a lack of detail over when the majority of the weight loss occurred and the trajectory of the change.

Assessor's comments
As expected those on methylphenidate lost more weight than on placebo with 0.7% requiring withdrawal from the study. The majority of the subjects losing weight were in the overweight or obese groups but this is a cause of concern fro those in the underweight and lower ends of the normal weight groups. Only 3 subjects switched status from normal weight to underweight though. There should be wording in section 4.4 requiring weight to be monitored in patients who have stopped growing in they have a low BMI.
Point not resolved.

11. 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).

The MAH state that although the crushed Concerta AUC was equivalent to Ritalin the Cmax and AUC 0-2 hrs was less for the crushed Concerta, thus reducing the abuse potential. No figures were quoted in the response document to support these statements but these were supplied in the original application. They also comment on the fashion that MPH induces dopamine release is less likely to induce abuse as it is slow tonic firing not fast, phasic firing. It is assessed that although the figures adjusted for dose are slightly lower for crushed Concerta than Ritalin the difference is relatively small and that crushing Concerta increases the rate of absorption as measured by AUC0-2 and Cmax in comparison to intact Concerta. The abuse potential for crushed Concerta is likely to be similar to the IR formulation of MPH.

This point is considered resolved with the removal of the proposed indication. **Point resolved.**

12. 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.

The MAH refer to the work done for the Article 31 referral 27/5/09. **Point resolved.**

Product Information
13. 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.

The MAH have not addressed this as they are no longer applying for an indication. The SmPC has instructions to monitor these in all patients receiving Concerta. **Point resolved.**

14. 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.

The MAH have not addressed this as they are no longer applying for an indication. **Point resolved.**

15. 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.

The MAH have not addressed this as they are no longer applying for an indication. This needs to be stated for the proposed continuance of therapy, see proposed wording for section 4.2 below. **Point not resolved.**

16. 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.

The MAH have not addressed this as they are no longer applying for an indication. **Point not resolved.**

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

The MAH have not addressed this as they are no longer applying for an indication. These will be presented in future PSURs. Monitoring weight at those at risk has been dealt with above. **Point resolved.**

RMP Concerns
The MAH have not addressed the majority of these points as they are no longer applying for an indication or they are being addressed through the PSUR work sharing procedure UK/H/PSUR/0068/002. All points are considered resolved as far as this assessment is concerned. **Points resolved.**

The concerns raised from the RMP assessment should be addressed and in particular the following points answered:
18. 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. A similar request was received under the PSUR work sharing and a response is currently being assessed.

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

Other RMP Points
The Risk Management Plan for Concerta in Adults should be revised based on the following points:
20. 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.

21. 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.

22. 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.

23. 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).

24. 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.

25. The MAH should provide a detailed analysis of the 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.

Three case of serious unresolved adverse events were presented. Two were psychiatric related which will be captured in future PSURs and the third was a recurrence of breast cancer which is unlikely to be related to study medication. This should be addressed through future PSURs. **Point resolved.**

26. 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.
27. 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.

28. 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.

29. 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.

30. 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 minimisation 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 characterise the risk of diversion in all member states

31. 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.

32. 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.

33. 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.

34. 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, comorbidities, 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.

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

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

37. 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.

38. The MAH should ensure that the risk minimisation measures (including but not limited to the SmPC, 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.

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

40. 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.

41. 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.

42. 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.

43. 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.

CMS Comments

DAY 85 COMMENTS BY CMS
POTENTIAL SERIOUS RISK TO PUBLIC HEALTH
2.4 Part IV/Module 5 – Clinical
Some of the main concerns are:
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)

Assessor's comments
The robustness of the diagnosis, the weak external validity of the studies has been addressed by the MAH amending their proposed wording for the SmPC. They are no

longer claiming an adult indication but one of continued treatment in some cases as follows:
The missing has been handled as treatment failure no which reduces the size of the efficacy. Please see response 3.

The safety concerns have been addressed above.

DAY 85 COMMENTS BY CMS
Although we think there is an unmet need for an approved psychostimulant drug for treatment of adult ADHD 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.

Assessor's comments
The further analyses demonstrate only borderline efficacy and further long-term data has not been forthcoming, thus a new indication cannot be supported on this data. The MAH have dropped their proposed new claim for section 4.1 but have proposed an amended wording for section 4.2. This is assessed as not approvable but alternative wording by the RMS is proposed. Please see conclusion below.

DAY 85 COMMENTS BY CMS
Environmental Impact / Environmental risk assessment
Non-clinical aspects
This Type II Variation is to apply for an additional therapeutic indication of Methylphenidate 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 comments:
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 Methylphenidate hydrochloride. It is well known that

Methylphenidate 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 Methylphenidate only will result in a higher log Pow.

Assessor's comments
As a new indication is no longer being proposed and thus no significant increase in usage, an environmental assessment is no longer required.

COMMENTS FROM CMS
Support PVAR.

Assessor's comments

Please see the full response assessment and conclusion.

DAY 55 COMMENTS
"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."

Assessor's comments
The MAH are no longer applying for a new indication. The further analyses do not support this. The new proposed wording for section 4.2 is not assessed as adequately supported and different wording is proposed. Please see the conclusion below.

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 transfer 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 questionable: 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.

- Safety

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).

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

-

Assessor's comments The MAH have removed their proposed indication addressing the above points since the further analyses do not robustly support the previously proposed indication. Please see above.

Overall Conclusion

Efficacy

The more conservative analyses of the data submitted in this response demonstrate for study 3002, statistical significance of all doses compared to placebo has been maintained, but with a much weaker statistical evidence of efficacy, and with much smaller point estimates. For example, taking the 72 mg dose, the initial (incorrect) analysis had a point estimate for efficacy of 59.6%, with placebo having a 27.4% rate, the difference being 32.2%. When missing data is imputed as failure which is appropriately conservative, the point estimates are now 26.0 and 50.0 respectively, the difference being 24%. It is clear that the magnitude of the efficacy is being driven by the method used to handle the missing data and additionally that the use of LOCF is not appropriately conservative and could bias in favour of active treatment.

For Study 02-159, the requested analysis yields a p-value of 0.055 at the 2-week time-point, marginally failing to reach statistical significance. In the strictest interpretation this could be seen as a failed trial.

For Study 3013 the 13-week time point data is mixed. The initial treatment differences between active and placebo were 10.2% and 18.7% for the 54 mg and 72 mg doses respectively (with only the 72 mg dose being significant, p=0.0098). When using the more appropriate missing as failure analysis, these point estimates become 11.6% and 13.8% respectively, with neither attaining anything near to significance (p=0.274 and p=0.198 respectively). This is clearly a failed trial.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1 (see below).

Safety
Cardiovascular concerns Data from longitudinal studies appears to show that raises in 10mmHg increases the risk of all cause mortality. Increases in pulse rate were also associated with an increase in MR but largely disappeared when controlled by disease process. This is not reassuring since this may be the mechanism through which DM. There is a signal in terms of an increase in those experiencing a raised BP >5mmHG or 10mmHg systolic. Interestingly in those with a diagnosis of hypertension these patients experienced less variability in their BP measurements than those on placebo, implying that treatment prevents transient rises in BP. The MAH also presented data from RCT and OL studies on numbers of subjects have at least 1 reading of >130 or >85. There is a signal from the RCTs.

Psychiatric adverse events: subjects demonstrating suicidal ideation (2) or behaviour (1 attempted suicide) were few (n=3 0.2.%). The MAH have not made an attempt to analyse any cases of potential self-harm. **Aggression.** There is a clear signal around aggression with an OR 2.3 no CI included (CONCERTA 11.9% and Placebo 5.5%). This is already has an SmPC warning.

Weight loss: There is a clear signal for weight loss, whilst this may not be over concern in those who are overweight or obese it is a concern at low BMIs.

The reanalysis of the data which treats missing subjects as failures has produced short-term efficacy results that have borderline significance. When this is taken in the context that this was a retrospective subgroup analysis of the data and with the lack of long-term efficacy the previously proposed indication is not approvable. The MAH have recognised this and proposed new wording for the SmPC:

The following wording is viewed as more appropriate:
Adults
If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these adults should be reviewed regularly and undertaken not less frequently than 2 years.

Safety and efficacy have not been established for the initiation of treatment in adults or the routine continuation of treatment beyond the age of 18 years of age.

The other references to continued treatment in sections 4.2 and 4.4 are not required and should be removed.

A separate table for adults in Section 4.8 is not acceptable. Where an AE is more common/less common an asterisk and relevant footnote can be made. AE only occurring in adults can be added making this clear by use of asterisks and footnote.

Section 5.1
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.

The totality of the data is therefore weak, with one successful, one borderline failure and one clearly failed trial. One key difference is of course that the efficacy measurements were taken at different time points. It is also of note that the point estimates are always positive and broadly favours Concerta, although they are not as impressive as the initial analysis suggested. The MAH has withdrawn the proposed indication but still wish to add a claim in Section 5.1 which has not been clearly substantiated. The only study that has shown robust efficacy is the 5 week study with the longer term 7 and 13 week failing to consistently demonstrate this. Although numerically the point estimates were all positive this is not assessed as robust enough data to support the claim made in section 5.1 (see below).

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. *Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage the range of 18 to 72mg/day but this has not been consistently shown beyond 5 weeks.*

The PIL: the proposed change to the section 'what this medicine is for' is acceptable. The AEs should be amalgamated with the main section as per the SmPC.

The Variation is considered approvable provided the SmPC and PIL are amended as indicated above.

RECOMMENDATION

Based on the review of the data on safety and efficacy the RMS considers that the variation application UK/H/0544/001/II/056 for Concerta (Methylphenidate MR), for the continuation of treatment in ***adults with ADHD***, for the following proposed changes to section 4.2:

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 (see section 4.4 and section 5.1).

is approvable.

The CMS are referred to this additional FVAR dealing with the comments received and the amended wording for the SmPC which addresses the comments received.

ASSESSMENT OF DAY115 COMMENTS AND RESPONSES

1 Summary

The Day 115 Responses form the CMS from NL, FR, ES, NO and IT all support the conclusion of the FVAR. There were further comments on the precise wording of the SmPC and RMP from NL, NO and FR. It is proposed that these comments are addressed as follows:

Section 4.2
Both NL and FR support the CHMP wording previously used for atomoxetine. FR raises the concern of how the MAH will ensure that a given adult who is prescribed MPH had been treated with the drug during childhood or adolescence and benefited from it. The RMS has similar concerns which were behind the new proposed wording which emphasised the need for a withdrawal before assuming continued benefit of therapy.

The RMS proposes the following to address these issues:

The harmonised wording is used in **Section 4.2** as follows:

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 in adults is not appropriate.

A cross-reference is added to the above statement to Section 4.4 and 5.1:

Section 4.4
Use in Adults
Safety and efficacy have not been established for the initiation of treatment in adults or the routine continuation of treatment beyond 18 years of age. If treatment withdrawal has not been successful when an adolescent has reached 18 years of age continued treatment into adulthood may be necessary. The need for further treatment of these adults should be reviewed regularly and undertaken annually.

In addition there are safety points raised by FR and NL which the MAH have addressed (please see following assessment of the DAY 115 Response). Comments have also been addressed from NO.

Section 5.1

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. Some short-term efficacy has been demonstrated for CONCERTA XL in a dosage range of 18 to 72 mg/day, but this has not been consistently shown beyond 5 weeks. In one study, in which response was defined as at least a 30% reduction from baseline in CAARS ADHD Symptoms total score at Week 5 (endpoint) and analysed assuming subjects with missing data at their final visit were non-responders, a significantly higher proportion of patients responded to treatment with CONCERTA XL at doses of 18, 36, or 72 mg/day compared to placebo. In the two other studies, when analysed assuming subjects with missing data at their final visit were non-responders, there were numerical advantages for CONCERTA XL compared to placebo but a statistically significant difference in the proportion of patients meeting predefined response criteria was not demonstrated between CONCERTA XL and placebo.

Conclusion
The variation is recommended for approval.

Date 24/4/11

APPENDIX 1

E. CHM ADVICE

	ADVICE
DATE OF MEETING :	12 July 2010
REFERENCE NUMBER(S) :	PL 00242/0373-085 PL 00242/0372 & 0374 and 0400
COMPANY :	Janssen-Cilag Ltd
PRODUCT :	Concerta XL 18,27,36 & 56mg prolonged release tablets
ACTIVE CONSTITUENT :	Methylphenidate hydrochloride
THERAPEUTIC CLASS :	Psycho analeptic, psychostimulant & nootropics, centrally acting sympathomimetics: ATC code: N06BA04
KEY WORDS :	

The Expert Advisory Group advise that the proposed indication:

> CONCERTA XL is indicated as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD***). It may be used when remedial measures alone prove insufficient*** in children aged 6 years of age and over ***as well as in adults whose ADHD diagnosis was established before the age of 18 years and whose symptoms persist into adulthood.***

is not approvable unless the major objections and other concerns raised below are adequately addressed.

Major Objections

1. **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 Rosser 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.

2. **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).

Other Efficacy Concerns

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

Safety Concerns

8. 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.

9. 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.

10. Further discussion on the implications of weight loss in adults.

11. 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).

12. 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.

Product Information

13. 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.

14. 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.

15. 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.

16. 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.

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

RMP Concerns

The concerns raised from the RMP assessment should be addressed and in particular the following points answered:

18. 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.

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

20.