Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Ritalin XL 10 mg modified-release hard capsules
Ritalin XL 20 mg modified-release hard capsules
Ritalin XL 30 mg modified-release hard capsules
Ritalin XL 40 mg modified-release hard capsules
Ritalin XL 60 mg modified-release hard capsules

(Methylphenidate hydrochloride)

UK Licence No: PL 00101/0973-0977

Novartis Pharmaceuticals UK Limited

LAY SUMMARY

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(Methylphenidate hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Ritalin XL 10 mg, 20 mg, 30 mg, 40 mg and 60 mg modified-release hard capsules (PL 00101/0973-0977). For ease of reading, the products will be referred to as 'Ritalin XL' or Ritalin XL hard capsules' in this lay summary. The summary explains how the applications for Ritalin XL hard capsules were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ritalin XL hard capsules.

For practical information about using Ritalin XL hard capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ritalin XL hard capsules and what are they used for?
Ritalin XL hard capsules are used to treat 'Attention Deficit Hyperactivity Disorder' (ADHD). These capsules are used:
• in children and young people between the ages of 6 and 18, and in adults.
• only after trying treatments which do not involve medicines, such as counselling and behavioural therapy and which have been insufficient.

Ritalin XL hard capsules are not for use as a treatment for ADHD in children under 6 years of age. It is not known if it is safe or of benefit in children under 6 years of age.

How do Ritalin XL hard capsules work?
Ritalin XL hard capsules contain the active substance methylphenidate hydrochloride, which is a psychostimulant that belongs to a group of medicines called centrally acting sympathomimetics. Ritalin XL improves 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.

Ritalin XL hard capsules are prescribed only by a specialist in behavioural disorders. This specialist will follow up the patient's further treatment. A thorough examination is necessary. If the patient is an adult and has not been treated before, the specialist will carry out tests to confirm that the adult patient has had ADHD since childhood. Using treatment programmes as well as medicine helps to manage ADHD.

About ADHD
Children and young people with ADHD find it:
• hard to sit still and
• hard to concentrate.

It is not their fault that they cannot do these things.

Many children and young people struggle to do these things. However, with ADHD they can cause problems with everyday life. Children and young people with ADHD may have difficulty learning and doing homework. They find it hard to behave well at home, at school or in other places.

Adults with ADHD often find it hard to concentrate. They often feel restless, impatient and inattentive. They may have difficulty organising their private life and work.

Not all patients with ADHD need to be treated with medicine.

ADHD does not affect intelligence.

How are Ritalin XL hard capsules used?
Ritalin XL is available as modified-release hard capsules and the capsules are taken by mouth (orally).

Ritalin XL can only be obtained with a prescription. The capsules should always be taken exactly as advised by the patient's doctor. The patient should check with the doctor or pharmacist if not sure.

The doctor will usually start treatment with a low dose and increase it gradually as required.
- Children/adolescents: the maximum daily dose is 60 mg. Ritalin XL is taken once daily in the morning in patients younger than 18.
- Adults: the maximum daily dose is 80 mg for adults.
  - If the patient has not taken Ritalin XL before, the doctor will start the patient's treatment with 20 mg, and will increase the dose gradually if required.
  - If the patient has been treated with Ritalin XL for ADHD during childhood, and have recently turned 18 years of age, the doctor can continue to prescribe the same dose. If the patient has been treated with Ritalin tablets during childhood, the patient's doctor will prescribe the equivalent dose of Ritalin XL
  - Ritalin XL is taken once daily usually in the morning with or without food in adults. The patient should not take his/her medicine too late in the day, in order to prevent sleep disturbance.
- • Ritalin XL can be taken with or without food
- • The capsule should be swallowed whole, with a drink of water.
- • The capsule should not be crushed, chewed or the contents divided.

If the patient is unable to swallow Ritalin XL, the contents of the capsule can be sprinkled on a small amount of food, as follows:
• Carefully opening the capsule and sprinkling the beads over a small amount of soft food (e.g. apple sauce, jam, spread, yoghurt)
• The food should not be warm because this could affect the special properties of the beads
The patient should immediately eat all of the drug/food mixture. The drug/food mixture should not be stored for future use.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Ritalin XL hard capsules have been shown in studies?
Clinical studies previously submitted for the approval of the Marketing Authorisation for Ritalin 10 mg tablets have been provided. In addition, further studies have been submitted to support these applications for methylphenidate hydrochloride as modified-release hard capsules indicated in the treatment of ADHD in children and young people between the ages of 6 and 18, and in adults.
These studies have shown that Ritalin XL hard capsules are effective in the proposed indications.

What are the possible side effects of Ritalin XL hard capsules?
Like all medicines, Ritalin XL hard capsules can cause side effects although not everybody gets them. Although some people get side effects, most people find that methylphenidate helps them.

Some side effects could be serious.

Common (affects less than 1 in 10 people) effects are:
• uneven heartbeat (palpitations)
• mood changes or mood swings or changes in personality

For the full list of all side effects reported with Ritalin XL hard capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Ritalin XL hard capsules approved?
It was concluded that, in accordance with EU requirements that, for Ritalin XL hard capsules, the benefits are greater than its risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Ritalin XL hard capsules?
A Risk Management Plan has been developed to ensure that Ritalin XL hard capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Ritalin XL hard capsules, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provided in the Ritalin XL product information, the RMP includes provision, via a website, of prescribing advice and educational materials for physicians to ensure the safe and effective use of Ritalin XL hard capsules.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Ritalin XL hard capsules
Marketing Authorisations were granted in the UK to Novartis Pharmaceuticals UK Limited on 20 December 2017.

The full PAR for Ritalin XL hard capsules follows this summary.

For more information about treatment with Ritalin XL hard capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2018.

SCIENTIFIC DISCUSSION

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Scientific Discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK considered that the applications for Ritalin XL 10 mg, 20 mg, 30 mg, 40 mg and 60 mg modified-release hard capsules (PL 00101/0973-0977) could be approved. The products may be referred to as 'Ritalin XL' or 'Ritalin XL hard capsules' in this scientific discussion.

Ritalin XL hard capsules are Prescription Only Medicines (POM) and are indicated as a part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient and in adults.

Special Diagnostic Considerations for ADHD in children

Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM criteria or the guidelines in ICD 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 symptoms.

Methylphenidate treatment is not indicated in all children with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity and the chronicity of the child's symptoms in relation to the child's age.

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 child's symptoms. The use of methylphenidate should always be according to the licensed indication and according to the prescribing/diagnostics guidelines.

Special Diagnostic Considerations for ADHD in adults

Treatment must be initiated and be under the supervision of a specialist in treatment of behavioural disorders. Diagnosis should be made according to DSM criteria or the guidelines in ICD and should be based on a complete history and evaluation of the patient. Adults with ADHD have symptom patterns characterized by restlessness, impatience, and inattentiveness. Symptoms such as hyperactivity tend to diminish with increasing age possibly due to adaptation, neurodevelopment and self-medication. Inattentive symptoms are more prominent and have a greater impact on adults with ADHD.

Diagnosis in adults should include a structured patient interview to determine current symptoms. The pre-existence of childhood ADHD is required and has to be determined retrospectively (by patients' records or if not available by appropriate and structured instruments/interviews). Diagnosis should not be made solely on the presence of one or more symptoms. The decision to use a stimulant in adults must be based on a very thorough assessment and diagnosis should include moderate or severe functional impairment in at least 2 settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

A comprehensive description of the indications and posology is provided in the Summary of Product Characteristics.

The applications for Ritalin XL hard capsules were submitted under Article 8.3 ('complete dossier', known active substance) of Directive 2001/83/EC, as amended. The applications are line extensions [of the immediate-release medicinal product Ritalin 10 mg tablets (PL 00101/0539), which was first authorised in the UK on 30 August 1988] for different strengths in a modified-release formulation (Ritalin XL 10 mg, 20 mg, 30 mg, 40 mg and 60 mg capsules).

In accordance with the pre-submission scientific advice meetings with the MHRA held on 05 September 2013 and with the MEB on 23-May-2013, the submission dossier contains two parts:

- A line extension supporting the use of once daily Ritalin XL as an alternative to twice daily dosing of Ritalin in the treatment of ADHD in children.
- Additional clinical data to support the extension of the indication of Ritalin XL to include the treatment of adults with ADHD.

The extension of the indication in adults was assessed in many EU member states as an informal work sharing procedure (DE/H/XXXX/WS/056). The UK was not involved as Ritalin LA was not approved in the UK. Nevertheless, the MHRA followed the principles of the work sharing procedure for the evaluation of the data supporting the adult indication. The MHRA is in possession of the assessment reports for this procedure and was an interested observer at discussions at CMDh in relation to the procedure.

The active substance, methylphenidate hydrochloride, is a racemic mixture containing d- and l-enantiomers, where the d-enantiomer is considered as the pharmacologically active enantiomer. Methylphenidate hydrochloride is a mild CNS stimulant with more prominent effects on mental than on motor activities. The mechanism of action of methylphenidate hydrochloride in ADHD is not completely understood but is thought to relate to increased availability of dopamine and norepinephrine by blocking reuptake of these monoamines into the presynaptic neuron and increasing their release into the extraneuronal space.

Since 2001, non-clinical study reports were submitted in support of Ritalin 10 mg immediate-release tablets when all methylphenidate products in the EU were the subject of an Article 31 referral of Directive 2001/83/EC in 2007. No additional non-clinical studies were conducted or required to support the registration of the new formulation and the adult ADHD indication.

In support of the applications, data from pharmacokinetic/pharmacodynamic studies and clinical and safety data were submitted. All key clinical pharmacology and clinical studies are declared to be GCP compliant.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder.

It was judged that the benefits of taking Ritalin XL hard capsules outweigh the risks.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Ritalin XL 10 mg is a hard gelatin capsule size 2, with a light brown opaque cap and a white opaque body, imprinted “NVR” radially in tan ink on the cap and “R10” in tan ink on the body, containing white to off-white beads roughly spherical in shape.

Ritalin XL 20 mg is a hard gelatin capsule size 2, white hard opaque gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R20” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

Ritalin XL 30 mg is a hard gelatin capsule size 2, yellow hard opaque gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R30” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

Ritalin XL 40 mg is a hard gelatin capsule size 1, light brown hard opaque gelatin capsule, imprinted with “NVR” in tan ink on the cap and “R40” in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

Ritalin XL 60 mg is a hard gelatin capsule size 00, with a light brown opaque gelatin cap and a yellow opaque body, imprinted with "NVR" radially in tan ink on the cap and "R60" in tan ink on the body, containing white to off-white beads that are roughly spherical in shape.

Each modified release hard capsule contains 10 mg, 20 mg, 30 mg, 40 mg, or 60 mg of methylphenidate hydrochloride, as the active substance. The products also contain pharmaceutical excipients in the capsule and capsule shell namely, ammonio methacrylate copolymer type B, methacrylic acid-methyl methacrylate copolymer (1:1), macrogol 6000, sugar spheres, talc, triethyl citrate, gelatin, titanium dioxide (E171), yellow iron oxide (E172; 10 mg, 30 mg, 40 mg and 60 mg capsules), black iron oxide (E172; 10 mg, 40 mg and 60 mg capsules only), red iron oxide (E172; 10 mg, 40 mg and 60 mg capsules only), and printing ink, tan; containing shellac (E904), titanium dioxide (CI 77891, E171), red iron oxide (CI 77491, E172) and yellow iron oxide (CI 77492, E172). Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in high-density polyethylene (HDPE) bottles, each with a child-resistant polypropylene (PP) with aluminium induction seal, in a pack size of 30 capsules.

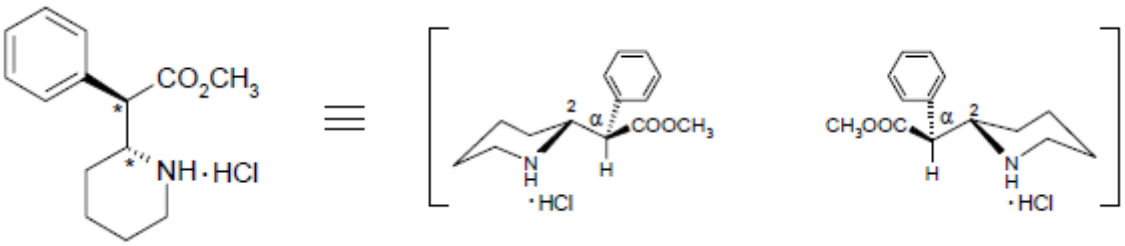
Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Methyphenidate hydrochloride

INN:	Methylphenidate
USAN, JAN:	Methylphenidate hydrochloride
Chemical name:	Methyl (2-RS)-2-phenyl-[(2-RS)-2-piperidyl]-acetate hydrochloride

Structure:



Molecular formula:	$C_{14}H_{20}ClNO_2$
M_r:	269.8
Appearance:	White, fine, crystalline powder
Solubility:	Freely soluble in water, 0.1 N HCl, chloroform and methanol; soluble in ethanol (95 per cent); slightly soluble in methylene chloride
Chirality	Methylphenidate hydrochloride contains two chiral centres. It is the racemate of the threo-form and is not optically active
Polymorphism	Methylphenidate hydrochloride does not exhibit polymorphism

Methylphenidate hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data, complying with the proposed specifications, are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, modified-release hard gelatin capsules, containing 10 mg, 20 mg, 30 mg, 40 mg or 60 mg methylphenidate hydrochloride, which produced a bimodal release of methylphenidate hydrochloride to mimic a twice daily administration of the immediate release formulation Ritalin 10 mg tablets (PL 00101/0539; Novartis Pharmaceuticals UK Limited). The bimodal profile was achieved through an immediate release of 50% of the dose (similar to Ritalin) with the remaining 50% dose release occurring approximately four hours after dosing. Suitable pharmaceutical development data have been provided for these applications.

With the exception of yellow iron oxide (E172), black iron oxide (E172) and red iron oxide (E172), all excipients comply with their respective European Pharmacopoeia monographs. Yellow red iron oxide

(E172), black iron oxide (E172) and red iron oxide (E172) are controlled to their respective National formulary specifications and are also in compliance with the current EU Directive concerning the use of colouring agents.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

These products do contain or consist of genetically modified organisms (GMO).

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of each strength of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product
The finished product specifications are acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 36 months for Ritalin XL 10 mg - 40 mg and 24 months for Ritalin XL 60mg, with special storage instructions of 'Do not store above 30°C' has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for these applications, from a quality point of view.

NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of methylphenidate hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The Applicant has provided suitable justification for non-submission of an updated non-clinical overview. The Applicant refers to the submission in support of Ritalin 10mg immediate-release tablets in the context of the Article 31 referral of Directive 2001/83/EC, as amended, for all methylphenidate containing products that was requested by the European Commission to the CHMP on 22 June 2007. No additional non-clinical studies were required to support the registration of the new formulation and the adult ADHD indication.

III.2 Pharmacology

No new data have been submitted and none are required for these applications. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics

No new data have been submitted and none are required for these applications. Refer to Section III.1, Introduction, above.

III.4 Toxicology

No new data have been submitted and none are required for these applications. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

The Applicant submitted a suitable [Phase I and II (Tier A)] Environmental Risk Assessment (ERA) for methylphenidate hydrochloride (MPH) to evaluate any potential risk of MPH use in adults and children to the environment.

In the first phase (Phase I) of the Environmental Risk Assessment, with the maximum methylphenidate hydrochloride daily dose of 80 mg and the default Fpen of 0.01, the predicted environmental concentration in surfacewater ($PEC_{surfacewater}$) value was calculated to be 0.4 µg/L. As a $PEC_{surfacewater}$ value of 0.4 µg/L exceeded the trigger value of 0.01 µg/L, the assessment proceeded to Phase II – Tier A.

The risk ratios derived from the Phase II - Tier A risk assessment for methylphenidate suggested that there is no significant risk for surface water, groundwater and sewage treatment plants. The highest risk ratio for methylphenidate of 0.0052 was found for the surface water compartment based on its toxicity on the green algae *Scenedesmus subspicatus*.

It is concluded that the use of Ritalin XL hard capsules is of negligible risk to the environment when used in accordance with the product information.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted, from a non-clinical point of view.

CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of methylphenidate hydrochloride (MPH) is well-known.

This section will address aspects relevant to the new prolonged release formulation.

In support of these line extension applications, the Applicant submitted pharmacokinetic/pharmacodynamic studies as well as efficacy and safety data, which are detailed in sections below.

IV.2 Pharmacokinetics

The name of the products Ritalin XL during the development program was Ritalin LA. The proposed products are referred to as 'Ritalin LA' in the studies detailed below.

Listing of PK studies for Ritalin LA

Study No.	Purpose & Design	Type of Control	Design, Dose/day	No. of Subjects[1]	Population
[Study RIT124D0001] (Protocol 01)	PK / tolerability	Ritalin tablets	Randomized, three period, three treatment, crossover study Ritalin IR (bid): 10 mg Modified release prototypes Elan 1 and Elan 2 (qd): 20 mg	9	Adult healthy volunteers
[Study RIT124D0002] (Protocol 02)	PK / PD profiles	Placebo	Double-blind, placebo controlled, randomized, five-treatment crossover study Formulation 1 (17.5 mg, 20 mg, 25 mg); Formulation 2 (20 mg) Modified release formulation or matching placebo administered once a day in Treatment Evaluation Period	34	Children with ADHD
[Study RIT124D0004] (Protocol 04)	Food interaction	None	Open-label, randomized, single-dose, three treatment crossover study Ritalin LA: 40 mg	20	Adult healthy volunteers
[Study RIT124D0006] (Protocol 06)	Relative bioavailability	Ritalin tablets	Open-label, randomized, single-dose, four-treatment, four-period crossover study Ritalin LA: 40 mg Ritalin IR: 2x20 mg	17	Adult healthy volunteers
[Study RIT124D0009] (Protocol 09)	Food interaction	None	Open-label, randomized, single-dose, four-treatment crossover study Ritalin bid: 10 mg Modified release prototypes Elan 1 and Elan 2 (qd): 20 mg	15	Adult volunteers

Bioavailability studies relative to other MPH products					
Study No.	**Purpose & Design**	**Type of Control**	**Dose/day**	**No. of Subjects**	**Population**
[Study RIT124DUS06]	Bioavailability study	Concerta	Open-label, single-center, randomized cross-over design Ritalin LA-20 mg Concerta-18 mg	20	Healthy adult (M/F) volunteers
[Study RIT124DDE02]	Bioequivalence study	Medikinet retard	Open label, single center, randomized, 4-treatment, 4-period single oral dose, cross-over design Ritalin LA: 40 mg Medikinet retard: 40 mg	28	Healthy adult (M) volunteers (18 to 30 years of age)
[RIT124E2101]	Bioavailability under fasted and fed (standard breakfast) conditions	Focalin XR Focalin	Open-label, single-dose, three-treatment, three-period, randomized crossover design Focalin XR: 20 mg Focalin: 2 X10 mg Ritalin LA: 40 mg	24	Healthy adult (M/F) volunteers (18-45 years of age)

Study RIT124D0001 (Protocol 01)
Comparison of bioavailability of two modified release MPH formulations relative to Ritalin 10 mg given twice in 4-hour intervals
This was an exploratory 3-way crossover study in 9 healthy male subjects comparing the bioavailability of two prototype modified release formulations of MPH at 20 mg dose (developed by Elan Pharmaceutical Technologies) relative to Ritalin 10 mg tablets given twice in 4 hour intervals under fasted conditions.

A: Single dose of Elan 1 – 20 mg MPH capsule (Eudragit S polymer coated beads)
B: Single dose of Elan 2 – 20 mg MPH capsule (Eudragit RS:L polymer combination coated beads)
C: Two doses of Ritalin tablet administered 4 h apart – 10 mg MPH tablet

Comments
Both Elan formulations retained the dual peak plasma concentration time profile, confirming dual release characteristics of both formulations, without loss of bioavailability. The Elan MPH capsule (Eudragit RS:L polymer combination coated beads) achieved a more clearly biphasic profile with an initial rise in plasma levels more similar to immediate release (IR) MPH.

Study RIT124D0004 (Protocol 04)
Effect of food on the pharmacokinetics of Ritalin LA
This was an open-label, randomized, single-dose, three-treatment crossover study with a 7-day washout period between treatments, in adult healthy volunteers. The study investigated the effect of a high-fat breakfast on the PK of Ritalin LA. As a secondary objective the PK of the Ritalin LA sprinkled on apple sauce was compared to Ritalin LA given fasted.

No dose dumping (i.e. release of the active drug substance at a too rapid rate) was observed in any group. PK results are presented in Table 2-3 and Table 2-4 below.

Table 2-3 Pharmacokinetic parameters of MPH following a single dose of Ritalin LA 40 mg under fasted and fed conditions

	Arithmetic Mean ± SD Coefficient of Variation (CV%) (Range)		
Parameter	**40mg (fed) [high fat breakfast] N = 18**	**40mg (fed) [applesauce] N = 17**	**40mg (fasted)**
AUC0-∞ (ng-h/mL)	111.33 ± 18.14 16.3 (89.58 – 159.90)	101.97 ± 20.56 20.20 (63.04 – 131.39)	105.72 ± 22.42 21.2 (72.93 – 162.47)
Cmax (ng/mL)	14.41 ± 3.68 25.6 (10.20 – 23.20)	14.49 ± 2.76 19.1 (10.50 – 19.80)	15.23 ± 2.45 16.1 (11.3 – 19.4)
Tmax* (h)	(0.5 – 10.0)	(1.0 – 6.0)	(1.0 – 6.0)

Table 2-4 Statistical evaluation of food-effect on MPH pharmacokinetics following a single dose of Ritalin LA 40mg

Parameter	Condition	N	p-value[1]	LS Mean Ratio[1]	90% C.I: for Ratio[1]
Cmax(abs) (ng/mL)	Breakfast Applesauce Fasted	16 16 16	0.10 0.27	0.9 0.93	(0.81, 1.00) (0.84, 1.04)
AUC0-∞ (ng-h/mL)	Breakfast Applesauce Fasted	16 16 16	0.22 0.29	1.05 0.95	(0.98, 1.13) (0.89, 1.03)

Parameter	Condition	N	Median	Median difference[2]	p-value[1]
tmax(abs) (h)	Breakfast Applesauce Fasted	16 16 16	3.0 5.3 4.8	0.0 0.0	0.90 0.83

[1]Comparison with fasted condition as the reference for subjects with complete data for all conditions.
[2]Median of the pairwise differences of each test condition vs. the reference.

Comments

It was concluded that co-administration of single oral dose of 40 mg Ritalin LA with either a high fat breakfast or apple sauce did not affect the overall rate and extent of absorption of dl-MPH compared to fasted condition. The SmPC recommendation that dosing either fed or fasted is supported.

Study RIT124D0009 (Protocol 09)

This was an exploratory open-label, randomized, single-dose, four- treatment crossover food interaction study in healthy adult volunteers to investigate the effect of a high fat meal on the bioavailability of the two prototype modified release Elan 1 and Elan 2 formulations MPH described above for protocol 01.

A: Single dose of Elan 1 – 20 mg MPH capsule under fasted state; (Eudragit S)
B: Single dose of Elan 1 – 20 mg MPH capsule under fed state; (Eudragit S)
C: Single dose of Elan 2 – 20 mg MPH capsule under fasted state; (Eudragit RS:L)
D: Single dose of Elan 2 – 20 mg MPH capsule under fed state; (Eudragit RS:L)

Fourteen subjects completed the study under fed and fasted conditions and were included in the analysis. The mean plasma concentration time profiles of both formulations under fasted and fed condition are presented in Figure 2-2 and Figure 2-3.

Figure 2-2 Mean plasma concentration time profile following single dose of 20 mg Elan 1 formulation (Lot No. RD089805; Eudragit S) under fasted (open circle) and fed state (open square)

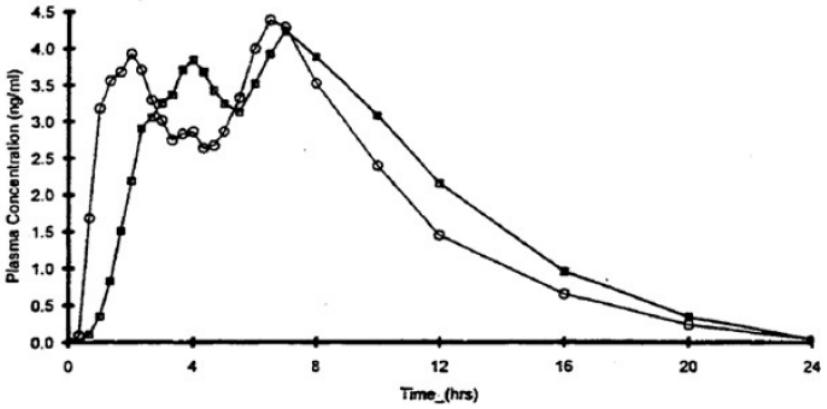
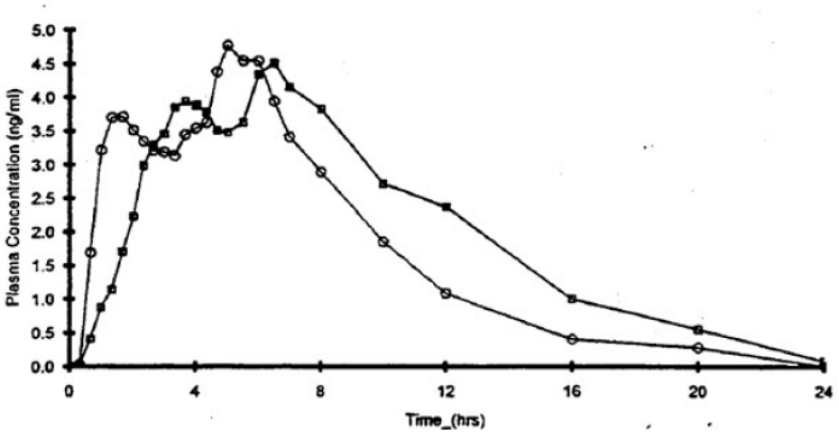


Figure 2-3 Mean plasma concentration time profile following single dose of 20 mg Elan 2 formulation (Lot No. RD089811; Eudragit RS:L) under fasted (open circle) and fed state (open square)



Both prototypes retained the bimodal profile under fed condition. The maximum concentrations (C_{max1} and C_{max2}) and AUC of Eudragit S formulations were similar for the fasting administration compared to the fed. The ratios of fed/fasted also indicated bioequivalence demonstrating that food had little impact on the exposure.

There were small increases (approximately 20%) in AUC_{all} and AUC_{inf} of the Eudragit RS: L formulation under fed state relative to fasted state. The ratio of fed/fasted in terms of C_{max2}, AUC_{all} and AUC_{inf} of Eudragit RS: L was outside the bioequivalence limits of 80 - 125%.

Table 2-5 Geometric mean and 90 percent CI of pharmacokinetic parameters of the two Elan formulations under fasted and fed condition

PK Parameter	ELan 1 (Eudragit S)			Elan 2 (Eudragit RS:L)		
	Fasted	Fed	90% CI Ratio	Fasted	Fed	90% CI Ratio
Cmax1	3.82	4.20	96-122	4.14	4.52	97-122
Cmax2	4.60	4.63	87-116	5.34	4.73	77-102
AUCall	38.62	41.99	99-118	37.32	45.21	11-132
AUCinf	40.18	43.10	98-117	39.13	46.86	110-131

The time to maximum concentration T_{max1} was delayed following administration of food (3.33± 0.69) compared to the fasted treatment (1.89 ± 0.55) for Eudragit S. T_{max1} was also longer when the Eudragit RS: L formulation was administered with food (3.42 ± 0.54) compared to the fasted treatment (2.13 ± 0.94). T_{max2} was similar following administration of food (2.50 ±1.32) compared to fasted administration (2.62 ± 0.80) for the Eudragit S prototype. However, Eudragit RS:L prototype showed a prolonged t_{max2}

(2.09 ± 1.08) compared to the fasted treatment (1.24 ± 0.67). This indicates an overall shift *in* the profile of Eudragit RS:L following administration of food in contrast to Eudragit S showing a shift in the first peak only.

Comments

The Applicant concluded that the dual peak plasma concentration time profile of IR Ritalin given twice daily with a 4h interval was retained for both modified release formulations (Eudragit S and Eudragit RS:L); this conclusion is endorsed. While food had no effect on the key PK parameters of the Eudragit S formulation, a small increase in $C_{max\ 2}$ and AUC was observed for the Eudragit RS:L formulation. This could have some effect on the pattern of symptom control during the day but is not a concern.

Study RIT124D0006 (D0006) (Protocol 06)

This was an open-label, randomised, single-dose, four-treatment, four-period, crossover study in adult healthy volunteers to evaluate the relative bioavailability of a single 40 mg dose of the Ritalin LA product proposed for marketing compared with IR Ritalin 20 mg twice a day (given four hours apart) in healthy adult subjects.

Table 2-6 Pharmacokinetic parameters of MPH following one single dose of Ritalin LA 40 mg and two 20 mg doses of Ritalin given four hours apart

	Arithmetic Mean ± SD Coefficient of Variation (CV%)	
Parameter	**Ritalin LA N = 17**	**Ritalin N = 16**
AUC0-t (ng.h/mL)	132.4 ± 47.7 (36)	133.9 ± 41.3 (30.9)
AUC0-∞ (ng-h/mL)	134.3 ± 48.8 (36.4)	136.0 ± 42.6 (31.4)
Cmax(abs) (ng/mL)	17.1 ± 6.2 (36.3)	19.5 ± 5.4 (27.4)
tmax(abs) (h)	5.1 ± 1.9 (37.6)	5.5 ± 0.97 (17.6)
FI(0-8)	0.81 ± 0.20 (24.6)	1.14 ± 0.16 (14.4)
Cmin (ng/mL)	9.1 ± 2.9 (32.2)	7.2 ± 1.9 (25.8)
C(8) (ng/mL)	10.8 ± 4.4 (40.9)	10.6 ± 3.1 (29.1)
t1/2 (h)	3.3 ± 0.54 (16.3)	3.3 ± 0.6 (18.1)
Frel (%)	97.0 ± 12.6 (13.0)	-
AUC0-4 (ng.h/mL)	37.0 ± 14.9 (40.2)	33.6 ± 10.8 (32.1)
Cmax(0-4) (ng/mL)	14.0 ± 5.5 (39.2)	13.2 ± 4.9 (37.6)
tmax(0-4) (h)	2.2 ± 1.1 (50.0)	1.7 ± 0.5 (28.0)
AUC4-8 (ng.h/mL)	49.4 ± 16.2 (32.9)	54.2 ± 14.9 (27.4)
Cmax(4-8) (ng/mL)	17.0 ± 6.4 (37.4)	19.5 ± 5.3 (27.4)
tmax(4-8) (h)	5.8 ± 1.0 (17.0)	5.7 ± 0.26 (4.5)

Ritalin LA produced mean plasma concentration-time profiles which were bimodal with two distinct peaks (Figure 2-4 below). Both the rate and the extent of absorption of MPH were similar for Ritalin LA

and Ritalin. Average AUC, C_{max} and t_{max} values were also comparable between Ritalin LA and Ritalin for the two intervals 0-4 hours and 4-8 hours after Ritalin LA dosing, respectively. Ritalin LA showed lower fluctuations in MPH plasma levels over an 8 hour interval (FI(0-8) = 0.81) compared to Ritalin (FI(0-8) = 1.14). The pharmacokinetic results for the two dosage forms are listed in Table 2-6 above.

The bioavailability of Ritalin LA capsules was similar to that of Ritalin immediate release tablets. There was lower fluctuation index in the 8 h time range post dose for the LA capsules, specifically much less of a trough (at about 5 hours for the IR product) and the second C_{max} was somewhat lower. These differences could have some implications for both efficacy and for dose related side effects. The initial rise in plasma levels after dosing was very similar for the two products. The decline in plasma levels from about 8 hours was also very similar to that for immediate release MPH so the two products seem likely to perform similarly in terms of evening / night-time symptom control and side effects.

Study RIT124DUS06 (DUS06)
Bioavailability of Concerta XL relative to Ritalin LA in healthy adult subjects
This was an open-label, single-centre, randomised cross-over, bioavailability study of two MPH modified-release formulations (Ritalin LA 20 mg and Concerta 18 mg) in 28 healthy subjects.

A summary of the pharmacokinetic parameters of the study are provided in Table 2-9 below.

Table 2-9 Pharmacokinetic parameters of d,l- MPH following the administration of Ritalin LA (20 mg) and Concerta (18 mg)

Parameter	Ritalin LA (20 mg) Mean (CV,%)	Range	Concerta (18 mg) Mean (CV,%)	Range	Dose-adjusted Mean*	Geometric Mean Ratio,% (C.I.)	P-value**
AUC 0-4 h [ng.hr/mL]	18.5 (43.8)	7.8-43.1	9.3 (50.5)	4.3-20.6	10.3	49.22 (45-53.7)	<0.001
AUC 0-t [ng.hr/mL]	75.0 (53.6)	30.7-192.8	61.6 (50.3)	30.7-141.7	68.4	83.8 (77.5-90.7)	<0.001
AUC 0-inf [ng.hr/mL]	78.7 (53.6)	34.5-204.4	66.9 (48.6)	40.2-154.5	74.3	87.6 (79.8-96.1)	0.024
Cmax 0-4 [ng/mL]	7.0 (47)	3.0-17	3.4 (44)	1.7-6.7	3.8	48 (44-52.5)	<0.001
Cmax [ng/mL]	9.9 (41.4)	4.7-20	5.9 (37.3)	3.4-11	6.5	60.8 (56-66)	<0.001
Tmax 0-4 [h]	2.1 (47.6)	0.9-4.0	3.3 (36.4)	0.9-4.0			0.007
Tmax 4-12 [h]	5.6 (8.9)	4.5-6.4	6.36 (18.9)	4.9-10			0.0208
Tmax [h]	5.5 (14.5)	3.0-6.4	6.0 (28.3)	0.9-10			0.086
T1/2 [h]	3.4 (23.5)	2.5-5.4	4.3 (34.9)	2.6-8.4			0.001

*Parameter values were adjusted to 20-mg dose assuming a linear kinetics.
**P-value is computed from the exact distribution of the Wilcoxon signed rank test on the original un-adjusted parameter values.

Ritalin LA exhibited a distinctly bimodal plasma concentration-time profile, with peaks at 2.1 and 5.6 hours post-dosing. Although the dose normalised AUC was similar for the two products, Ritalin LA exhibited faster initial absorption and reached approximately 2-fold higher peak plasma concentrations compared to Concerta. The mean peak plasma concentration of Ritalin LA at 5.6 hours (corresponding to the second peak) was 9.88 ng/mL compared to 5.87 ng/mL for Concerta at the same time point. Plasma concentrations were higher for Ritalin LA than for Concerta until approximately up to 8 hours

post dose. From about 10 hours post dose plasma concentrations were higher for Concerta than for Ritalin LA.

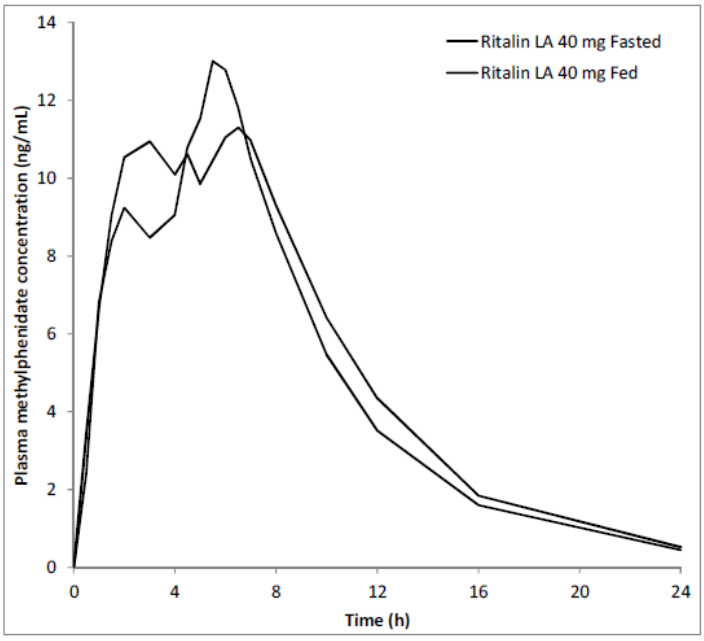
Comments
Although the dose adjusted extent of MPH absorption was similar, the PK profiles of the two products are quite different. Ritalin LA exhibited more rapid initial absorption and reached significantly higher peak plasma concentrations compared to Concerta.

The MAH states that "the concentration-time profile of Ritalin LA, when compared to Concerta more closely approximates a typical IR (immediate release) MPH dosing regimen". This is generally true although some patients treated with IR Ritalin have better symptom control with three times daily dosing, needing a small evening dose to prevent the treatment effect wearing off too early in the evening. Those patients may be better suited to the more prolonged PK profile of Concerta, as may patients who experience troublesome dose related (especially around C_{max}) side effects. Both twice daily IR Ritalin regimens and Concerta XL have been shown to be efficacious treatments for ADHD and the PK profiles would seem to suggest a useful difference in PK profiles of these two once daily products such that the one that best suits an individual patient can be selected.

Study RIT124DDE02 (DDE02)
Bioavailability of Medikinet Retard relative to Ritalin LA in healthy adult subjects)
This was an open-label, cross-over, randomized, four-treatment, four-period bioequivalence study in healthy male volunteers under fasted and fed conditions. All subjects received each of the following treatments once during the study according to a randomisation schedule:
• Treatment A: Ritalin LA 2x20 mg fasted
• Treatment B: Ritalin LA 2x20 mg fed
• Treatment C: Medikinet Retard 2x20 mg fasted
• Treatment D: Medikinet Retard 2x20 mg fed

The mean concentration time profile for Ritalin LA was bimodal with two distinct concentration peaks whereas Medikinet Retard showed a single peak plasma concentration time profile under fasting conditions while a bimodal profile was only evident under fed conditions.

Figure 2-9 **Plasma concentration time profile of Ritalin LA following 40 mg single dose administration under fasted and fed state**



The Applicant states that bioequivalence between Ritalin LA and Medikinet Retard in fasted state and equivalence of AUC in fed state were demonstrated. This conclusion cannot be fully endorsed, except to conclude equivalence for AUC of the two products. The mean MPH concentration-time profiles after administration of Ritalin LA and Medikinet Retard clearly showed that the two products have quite different PK profiles and they would not meet bioequivalence criteria for biphasic modified release products (there is no requirement in this case to show bioequivalence).

Table 2-10 **Geometric mean (percent CV) pharmacokinetic parameters for racemic dl-MPH after administration of 40 mg Ritalin LA (2 x 20 mg) and 40 mg Medikinet Retard (2 x 20 mg) to 27 healthy male subjects in fasted state**

Pharmacokinetic Parameter	Medikinet Retard (reference)		Ritalin LA (test)		point estimate	90 % CI
Cmax [ng/mL]	16.4	(29.8)	14.2	(22.6)	85.9	80.6-91.6
Tmax #[h]	3.0	(1.5-4.5)	5.5	(4.0-6.5)	--	--
AUClast [ng.h/mL]	108.2	(33.1)	108	(25.8)	--	--
AUC0-inf [ng.h/mL]	110	(33.2)	111	(25.9)	99.7	93.9-105.9
Cmax 0-4 [ng/mL]	15.9	(28.7)	9.5	(35.2)	--	--
Cmax 4-10 [ng/mL]	14.1	(31.8)	14.2	(22.6)	--	--
Tmax 0-4#[h]	3.0	(0.5-4.0)	2.0	(1.0-4.0)	--	--
Tmax 4-10# [h]	4.0	(4.0-4.5)	5.5	(4.0-6.5)	--	--
AUC 0-4 [ng.h/mL]	42.6	(34.1)	26.2	(33.3)	--	--
AUC 4-10 [ng.h/mL]	46.3	(37.1)	55.6	(23.9)	--	--
T1/2 [h]	3.87	(11.3)	3.76	(12.4)	--	--
MRT [h]	6.40	(9.3)	7.73	(8.4)	--	--

median (range)

Table 2-11 **Geometric mean (percent CV) pharmacokinetic parameters for racemic dl-MPH after administration of 40 mg Ritalin LA (2 x 20 mg) and 40 mg Medikinet Retard (2 x 20 mg) to 26 healthy male subjects after high fat breakfast**

Parameter	Medikinet Retard (reference)	Ritalin LA (test)	point estimate	90 % CI
Cmax [ng/mL]	18.8 (29.9)	12.8 (28.1)	68.6	63.3-74.3
Tmax #[h]	4.5 (1.5-5.5)	4.5 (1.0-8.0)	--	--
AUClast [ng.h/mL]	134 (26.4)	120 (25.5)	--	--
AUC0-inf [ng.h/mL]	137 (26.6)	123 (25.4)	89.8	85.7-94.0
Cmax 0-4 [ng/mL]	15.4 (38.5)	11.3 (31.6)	--	--
Cmax 4-10 [ng/mL]	17.5 (30.8)	12.3 (29.2)	--	--
Tmax 0-4#[h]	3.0 (1.5-4.0)	3.0 (1.0-4.0)	--	--
Tmax 4-10# [h]	4.75 (4.0-5.5)	6.25 (4.0-8.0)	--	--
AUC 0-4 [ng.h/mL]	39.5 (39.5)	31.8 (33.4)	--	--
AUC 4-10 [ng.h/mL]	65.4 (29.1)	55.8 (26.4)	--	--
T1/2 [h]	3.91 (12.7)	3.88 (9.6)	--	--
MRT [h]	7.11 (11.4)	7.91 (9.6)	--	--

median (range)

Study RIT124D0002 (D0002) (Protocol 02)

This was a double-blind, randomised, five-treatment crossover study of the pharmacodynamic and pharmacokinetic profiles of four formulation/dose variances of Ritalin modified release and placebo in ADHD children treated with Ritalin. The study was conducted in a laboratory classroom setting and compared SKAMP (Swanson, Kotkin, Agler, M-Flynn & Pelham) rating scale AUC of 4 new bimodal once daily formulations of Ritalin to placebo. The relative bioavailability of the new formulations was also compared to Ritalin tablets administered twice a day. The relationships between MPH plasma concentrations and pharmacodynamic (efficacy) variables (scores of the SKAMP and Math Test) were explored.

The plasma concentration versus time curves again showed a bimodal profile, with an initial peak in the morning and a second lower peak approximately four hours later (Figure 2-14). The bioavailability (AUC0-∞) of Ritalin LA was comparable to that of Ritalin 10 mg twice a day and Ritalin LA produced lower fluctuations in MPH plasma concentration over an 8-hour interval than IR Ritalin twice a day.

The analyses indicated an association between MPH plasma levels and SKAMP/Math Test scores. The graphical analyses suggested a positive correlation between MPH plasma concentration and improvement in SKAMP/Math Test scores. This is illustrated for the SKAMP-Attention scores in Figure 2-13, which also includes the placebo condition for comparison.

Figure 2-13 **Mean SKAMP-Attention scores[1] and MPH plasma concentration over time / Ritalin LA (RS:L) 20 mg versus placebo**

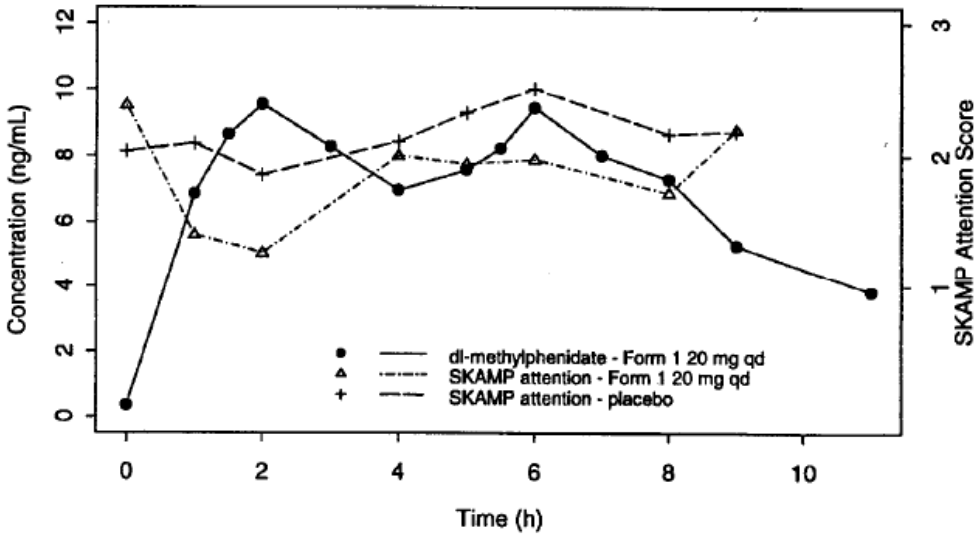


Figure 2-14 **Mean (plus minus SD) plasma concentration-time profiles of MPH following single dose of Ritalin LA (RS:L, Form 1) 20 mg and other formulation dose variants relative to two 10 mg doses of Ritalin tablets given four hours apart**

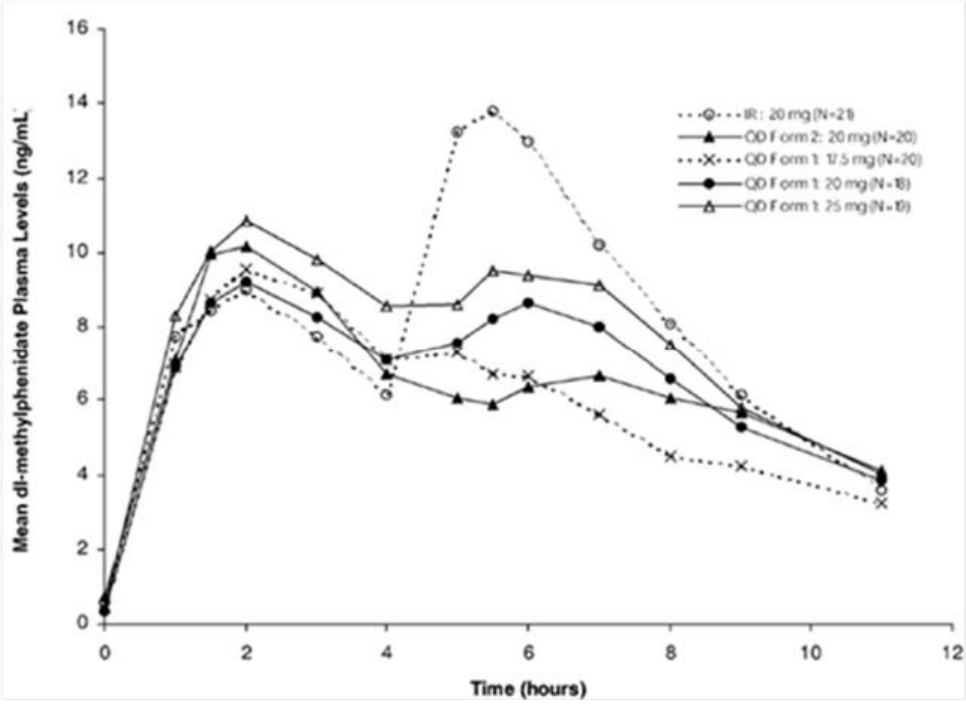


Table 2-16 Pharmacokinetic parameters of MPH following one single dose of Ritalin LA (RS:L) 20 mg and two 10 mg doses of Ritalin given four hours apart

	Arithmetic Mean ± SD Coefficient of Variation (CV%)	
Parameter	Ritalin LA (RS:L): 20mg N = 18	Ritalin:20mg N = 21
Cmax(abs) (ng/mL)	11.48 ± 5.81 (50.6)	15.49 ± 7.05 (45.5)
tmax(abs) (h)	3.53 ± 2.1 (58.8)	4.91 ± 1.77 (36.0)
AUC0-t (ng.h/mL)	74.53 ± 45.10 (60.5)	88.58 ± 42.02 (47.4)
Cmin (ng/mL)	6.33 ± 4.27 (67.4)	6.16 ± 3.14 (51.0)
Tmin (ng/mL)	4.36 ± 1.04 (23.9)	4.00 ± 0.00 (0)
FI(0-8)	0.86 ± 0.27 (31.9)	1.07 ± 0.28 (26.5)
Cmax(0-4) (ng/mL)	10.31 ± 5.10 (49.5)	10.41 ± 4.15 (39.9)
tmax(0-4) (h)	1.97 ± 0.76 (38.4)	1.88 ± 0.81 (42.8)
AUC0-4 (ng.h/mL)	28.38 ± 14.67 (51.7)	27.87 ± 11.00 (39.5)
Cmax(4-11) (ng/mL)	10.28 ± 5.91 (57.4)	15.29 ± 7.02 (45.9)
tmax(4-11) (h)	6.42 ± 1.65 (20)	5.57 ± 0.68 (12)
AUC4-11 (ng.h/mL)	46.14 ± 30.93 (67.0)	60.71 ± 35.88 (59.1)

The PK data are consistent with other studies. A discussion of the pharmacodynamics (PD) data and the PK/PD relationship is presented in the pharmacodynamics section of this report.

Comments

Although the dose adjusted extent of MPH absorption was similar for Ritalin LA and the equivalent dose of immediate release Ritalin dosed twice daily. The PK profiles of the two products / dose regimens show important similarities. Conventional prolonged release preparations of MPH are not in clinical use as they are considered to be less effective than their IR counterparts. Rapid initial absorption with an early high peak plasma concentration is believed to be necessary for optimal efficacy. This initial absorption phase is very similar for Ritalin LA and twice daily IR Ritalin. The lower peak to trough fluctuation and lower C_{max} for the second peak could be advantageous for consistent symptom control during the day and minimisation of dose related side effects that may occur around C_{max}. To conclude, the PK profile of Ritalin LA appears favourable.

Study RT124E2101 (E2101)

The relative bioavailability of Ritalin LA in comparison to Focalin XR was evaluated in this study. The plasma concentration-time profiles of Ritalin LA and Focalin XR were almost superimposable with similar maximum serum concentration after a single dose (C_{max}) and time to the maximum observed plasma concentration values. The ratios of geometric means for $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}4\ h)}$, $AUC_{(4\text{-}10\ h)}$, $AUC_{(0\text{-}inf)}$, C_{max}, $C_{max(0\text{-}4)}$, and $C_{max(4\text{-}10)}$ of d-MPH for the comparison between the two formulations ranged from 0.92 to 1.03, with all the 90% CI falling within bioequivalence range of (0.8, 1.25), indicating equivalent AUC between Focalin XR and Ritalin LA with respect to the active d-MPH. The

results of statistical comparison showed that average bioequivalence between Focalin XR and Ritalin LA has been established in this study.

Overall conclusions on pharmacokinetics of Ritalin LA

The PK characteristics of MPH are well established and the distribution, metabolism and elimination of MPH are not further evaluated in this report. The key PK characteristics specifically of Ritalin LA are summarised by the MAH as follows:

- MPH is rapidly absorbed following oral administration of Ritalin LA capsules producing bimodal plasma concentration-time profiles (two distinct peaks approximately four hours apart) [Study RIT124D0006]
- The average relative bioavailability of Ritalin LA ranges from 93-97% when compared with Ritalin tablets [Study RIT124D0006].
- Following a single 40 mg oral dose of Ritalin LA to healthy adults, the average terminal elimination half-life is 3.3 hours which is comparable to that observed following oral administration of Ritalin immediate release tablets [Study RIT124D0006].
- For similar total doses, lower fluctuations in plasma MPH levels are observed following Ritalin LA once-daily compared with Ritalin given bid [Study RIT124D0006].
- There is no food effect and no dose dumping when 40 mg Ritalin-LA is administered with either a high fat breakfast or apple sauce (up to two tablespoonfuls, 30 mL) compared to the fasted condition. Ritalin-LA can be given with or without food. For patients unable to swallow the capsule, the contents may be sprinkled onto soft food such as apple sauce and administered with it [Study RIT124D0004].
- The relative bioavailability of d-MPH is similar between Ritalin LA (40 mg single dose) and Focalin XR (20 mg single dose) products [RIT124E2101]. Focalin XR is the single isomer d-MPH product in a modified release formulation. It is marketed in the USA and Switzerland but not in the EU. Study RIT124E2101 was therefore not fully evaluated for this application.
- Ritalin LA (20 mg single dose) demonstrated rapid initial and subsequent absorption with substantially higher peak plasma concentrations for approximately up to 8 h post dose compared to Concerta (18 mg single dose) [Study RIT124DUS06].
- Ritalin LA (40 mg single dose) and Medikinet Retard (40 mg single dose) were bioequivalent under fasted conditions and AUC is equivalent under fed conditions [Study RIT124DDE02]
- Based on the cross-study comparison of the plasma concentration time profile of Ritalin (administered bid) and Ritalin LA, it can be concluded that equivalent proportional increase in the afternoon pulse is achieved with both formulations.

The dose adjusted extent of MPH absorption was similar for Ritalin LA and the equivalent dose of immediate release Ritalin dosed twice daily. The PK profiles of the two products / dose regimens show important similarities. Conventional prolonged release preparations of MPH are not in clinical use as they are considered to be less effective than their IR counterparts. Rapid initial absorption with an early high peak plasma concentration is believed to be necessary for optimal efficacy. This initial absorption phase is very similar for Ritalin LA and twice daily IR Ritalin. The lower peak to trough fluctuation and lower C_{max} for the second peak could be advantageous for consistent symptom control during the day and minimisation of dose related side effects that may occur around C_{max}. To conclude, the PK profile of Ritalin LA appears favourable.

IV.3 Pharmacodynamics

The mechanism of action of MPH in ADHD is not completely understood but is thought to relate to increased availability of dopamine and norepinephrine by blocking reuptake of these monoamines into the presynaptic neuron and increasing their release into the extraneuronal space. The l-isomer is thought to be pharmacologically inactive.

The pharmacodynamics effect of Ritalin-LA was evaluated in Study RIT124D0002, in children with ADHD aged 6-12 years. The pharmacokinetic data from this study are described above in Section IV2. Pharmacokinetics. The pharmacodynamic aspects are presented below.

Study RIT124D0002 (Children 6-12 years old)

Study D0002 was a US multicentre, double-blind, placebo-control, five-period, crossover study in a laboratory classroom setting. It evaluated the pharmacodynamic (efficacy) and pharmacokinetic (PK) profile of four formulation/dose variants of Ritalin LA (Formulation 1 (RS:L) / 17.5 mg, 20 mg, and 25 mg; Formulation 2 (S) / 20 mg) in 34 male and female children 6-12 years of age with ADHD.

Subjects were enrolled if they met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for ADHD (combined type) and had been treated with MPH for at least four weeks prior to enrolment. After a 1-week baseline phase during which the subjects received open-label Ritalin 10 mg twice a day, subjects were randomized into the treatment phase and received single doses of the four formulation/dose variants of Ritalin LA and placebo during five one-day treatment evaluation periods. On days between the treatment evaluation periods, subjects received open-label Ritalin at their usual regimen.

The efficacy assessments in Study D0002 were the SKAMP Rating Scale and Math Tests. The SKAMP Rating Scale is specifically designed for evaluations of ADHD behaviour in a laboratory classroom setting. It is used to generate scores on two behavioural subscales, "Attention" and "Deportment". The version of the scale used in Study D0002 consisted of 13 items (seven for Attention, six for Deportment). Each item was rated on a 7-point scale. The two subscale scores were derived from 20 minutes of direct observations of subject behaviour during eight class sessions scheduled throughout the evaluation periods. Paper and pencil Math Tests were administered to subjects during the class sessions to generate two scores: the number of problems attempted and the number of problems correctly answered.

The primary efficacy variable was the area under the curve (AUC) for the Attention factor scores of the SKAMP Rating Scale, obtained over the entire evaluation period (i.e. 0-9 hours post-dose).

Secondary efficacy variables were the AUC values for the SKAMP Attention factor scores analysed separately for the first and the second part of the evaluation period (i.e. 0-4 hours and 4-9 hours post-dose, respectively), the AUC values for the SKAMP Deportment factor scores (0-9, 0-4, and 4-9 hours post-dose), and the AUC values for the Math Test Attempted and Math Test Correct (number of problems attempted and number of problems correctly answered 0-9 hours post-dose, respectively).

All randomised subjects who received study medication and completed at least one post-baseline treatment evaluation (ITT population) were included in the data analyses.

Results

There was a statistically significant treatment effect ($p< 0.001$) in favour of Ritalin LA for the primary efficacy variable (SKAMP Attention AUC 0-9 hours) for all formulation/dose variants (Table 3-7). Superiority of Ritalin LA over placebo was also demonstrated for all secondary efficacy variables (AUC values for SKAMP and Math Test 0-9 hours post-dose) as well as for the first and second parts of the evaluation period, i.e. 0-4 hours post-dose and 4-9 hours post-dose.

Table 3-7 Analyses of AUC for SKAMP and Math Test scores – Study D0002 (ITT population)

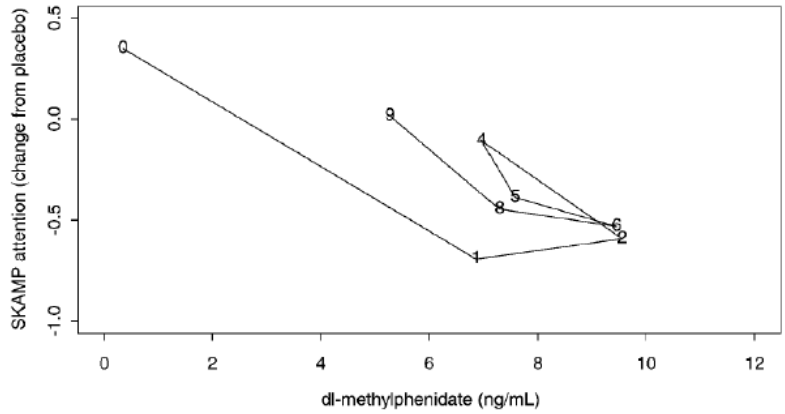
AUC Variable	Ritalin LA Formulation and strength				Control
	Form 1 17.5 mg	Form 1 20 mg	Form 1 25 mg	Form 2 20 mg	Placebo
Primary					
SKAMP-Attention (0-9 hr)					
Least squares mean	16.75	16.74	15.72	16.72	19.84
95% CI difference in LSM	(-4.57, -1.59)	(-4.58, -1.60)	(-5.57, -2.65)	(-4.60, -1.62)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
Secondary					
SKAMP-Attention (0-4 hr)					
Least square estimate	6.58	6.67	6.55	6.33	8.19
95% CI difference in LSM	(-2.32, -0.89)	(-2.23, -0.80)	(-2.34, -0.94)	(-2.57, -1.14)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Attention (4-9 hr)					
Least squares mean	10.17	10.07	9.17	10.39	11.64
95% CI difference in LSM	(-2.56, -0.37)	(-2.67, -0.47)	(-3.54, -1.39)	(-2.35, -0.15)	
p-value	**0.009***	**0.006***	**< 0.0001***	**0.026***	
SKAMP-Deportment (0-9 hr)					
Least squares mean	16.57	16.01	13.76	15.85	22.83
95% CI difference in LSM	(-8.54, -3.97)	(-9.11, -4.53)	(-11.31, -6.82)	(-9.27, -4.68)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Deportment (0-4 hr)					
Least squares mean	5.79	5.93	5.39	6.09	9.48
95% CI difference in LSM	(-4.98, -2.38)	(-4.85, -2.25)	(-5.36, -2.82)	(-4.69, -2.09)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Deportment (4-9 hr)					
Least squares mean	10.77	10.08	8.37	9.76	13.35
95% CI difference in LSM	(-4.12, -1.02)	(-4.82, -1.71)	(-6.49, -3.45)	(-5.13, -2.03)	
p-value	**0.001***	**< 0.001***	**< 0.001***	**< 0.001***	
Math Test Attempted (0-9 hr)					
Least squares mean	1172.44	1200.08	1183.71	1147.38	808.29
95% CI difference in LSM	(241.46, 486.63)	(268.68, 514.89)	(255.10, 495.73)	(216.01, 462.16)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
Math Test Correct (0-9 hr)					
Least squares mean	1134.59	1171.54	1150.27	1101.14	777.55
95% CI difference in LSM	(236.45, 477.64)	(272.99, 514.99)	(254.46, 490.99)	(202.62, 444.57)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	

All four formulation/dose variants of Ritalin LA were each associated with significantly better behavioural and cognitive responses relative to placebo over a nine-hour period, as measured by overall AUC for SKAMP Rating Scale and Math Test ($p < 0.001$). The analysis of secondary efficacy variables showed that this improvement was statistically significant during both the morning and the afternoon.

Pharmacokinetic/Pharmacodynamic (PK PD) relationship

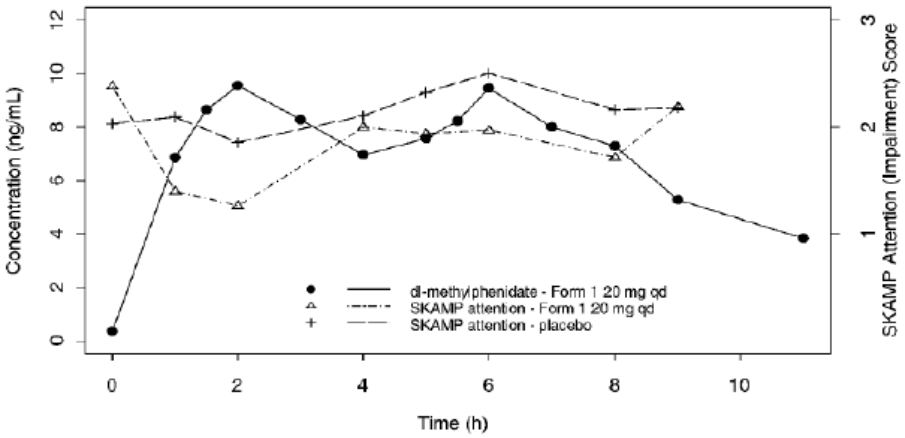
The data were explored for a relationship between PK and PD (efficacy). Analyses showed a significant association between exposure to MPH (AUC) and area-under- the effect curve values for the SKAMP and Math Test Scores. A trend was also seen of greater effect on PD scores being associated with higher MPH exposure. The relationships between mean plasma concentrations of MPH and three PD scores (SKAMP-Attention, SKAMP-Deportment, and Math Test-Correct) are explored graphically over time using two types of plots: (a) PK and PD versus time, and (b) PD versus plasma MPH concentration (hysteresis plots). These suggested that within treatments, there was a general trend toward a positive relationship between increasing dl-MPH concentration and improvement in PD scores compared to placebo (scores improved then deteriorated as plasma drug concentrations increased then decreased, respectively). This is illustrated below for the SKAMP-Attention scores (primary efficacy variable) by the PK and PD versus time plot (Figure 3-1), and by the PD vs plasma concentration plot (Figure 3-2).

Figure 3-1 PD (SKAMP Attention) vs concentration plot for Ritalin LA 20 mg FMI



Plotting symbols mark the time points (hour) of simultaneous PK and PD measurements.

Figure 3-2 PK and PD (SKAMP Attention) vs time for Ritalin LA 20 mg FMI



Comments

The MAH's conclusion that single doses of all four formulations/ dose variants of Ritalin LA were shown to be superior to placebo, in children with ADHD observed in a laboratory classroom, can be endorsed. The study provides useful preliminary evidence that the expected treatment effect is seen for both behavioural and cognitive domains in the morning and in the afternoon.

The finding of a positive correlation between MPH plasma concentration and improvement in SKAMP/Math Test scores is in line with expectations. The clinical effect of MPH (ADHD symptom control) is known to correlate directly with plasma levels so for example if plasma levels fall too much in the evening with a twice daily regimen (immediate release MPH) a small additional dose may be needed in the late afternoon to achieve symptom control for the full day.

Figure 3-2 PK and PD (SKAMP Attention) vs time for Ritalin LA 20 mg FMI

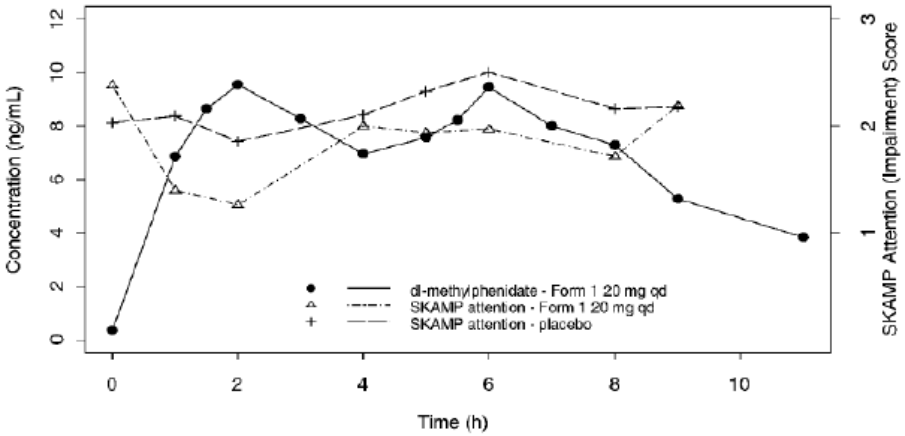


Table 3-7 Analyses of AUC for SKAMP and Math Test scores – Study D0002 (ITT population)

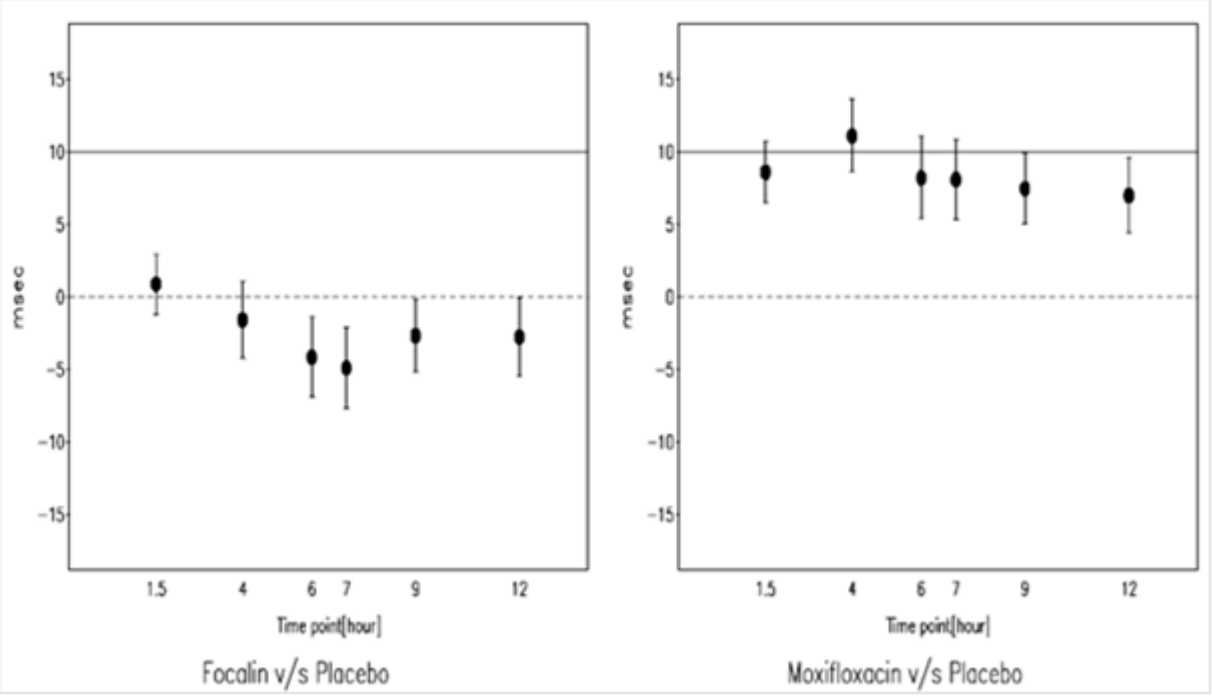
AUC Variable	Ritalin LA Formulation and strength				Control
	Form 1 17.5 mg	Form 1 20 mg	Form 1 25 mg	Form 2 20 mg	Placebo
Primary					
SKAMP-Attention (0-9 hr)					
Least squares mean	16.75	16.74	15.72	16.72	19.84
95% CI difference in LSM	(-4.57, -1.59)	(-4.58, -1.60)	(-5.57, -2.65)	(-4.60, -1.62)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
Secondary					
SKAMP-Attention (0-4 hr)					
Least square estimate	6.58	6.67	6.55	6.33	8.19
95% CI difference in LSM	(-2.32, -0.89)	(-2.23, -0.80)	(-2.34, -0.94)	(-2.57, -1.14)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Attention (4-9 hr)					
Least squares mean	10.17	10.07	9.17	10.39	11.64
95% CI difference in LSM	(-2.56, -0.37)	(-2.67, -0.47)	(-3.54, -1.39)	(-2.35, -0.15)	
p-value	**0.009***	**0.006***	**< 0.0001***	**0.026***	
SKAMP-Deportment (0-9 hr)					
Least squares mean	16.57	16.01	13.76	15.85	22.83
95% CI difference in LSM	(-8.54, -3.97)	(-9.11, -4.53)	(-11.31, -6.82)	(-9.27, -4.68)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Deportment (0-4 hr)					
Least squares mean	5.79	5.93	5.39	6.09	9.48
95% CI difference in LSM	(-4.98, -2.38)	(-4.85, -2.25)	(-5.36, -2.82)	(-4.69, -2.09)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
SKAMP-Deportment (4-9 hr)					
Least squares mean	10.77	10.08	8.37	9.76	13.35
95% CI difference in LSM	(-4.12, -1.02)	(-4.82, -1.71)	(-6.49, -3.45)	(-5.13, -2.03)	
p-value	**0.001***	**< 0.001***	**< 0.001***	**< 0.001***	
Math Test Attempted (0-9 hr)					
Least squares mean	1172.44	1200.08	1183.71	1147.38	808.29
95% CI difference in LSM	(241.46, 486.63)	(268.68, 514.89)	(255.10, 495.73)	(216.01, 462.16)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	
Math Test Correct (0-9 hr)					
Least squares mean	1134.59	1171.54	1150.27	1101.14	777.55
95% CI difference in LSM	(236.45, 477.64)	(272.99, 514.99)	(254.46, 490.99)	(202.62, 444.57)	
p-value	**< 0.001*** [1]	**< 0.001*** [2]	**< 0.001*** [1]	**< 0.001*** [2]	

The finding of a positive correlation between MPH plasma concentration and improvement in SKAMP/Math Test scores is in line with expectations. The clinical effect of MPH (ADHD symptom control) is known to correlate directly with plasma levels so for example if plasma levels fall too much in the evening with a twice daily regimen (immediate release MPH) a small additional dose may be needed in the late afternoon to achieve symptom control for the full day.

To further support the applications in the use of Ritalin XL in adults, the Applicant referred to a thorough QT-study (Study E2401). The results from Study E2401 are briefly described below.

Thorough QT-study: The effect of Focalin XR on the QT interval was evaluated in a double-blind, placebo- and open-label active (moxifloxacin)-controlled study following single doses of Focalin XR 40 mg in 75 adult healthy volunteers. ECGs were collected up to 12 h post-dose. Fridericia's method for heart rate correction was employed to derive the corrected QT interval (QTcF). The maximum mean prolongation of QTcF intervals was <5 ms, and the upper limit of the 90% confidence interval was below 10 ms for all time matched comparisons vs placebo. This was below the threshold of clinical concern and there was no evident-exposure response relationship.

Figure2-6 Focalin XR Thorough QT study: Treatment difference in QTcF change from mean baseline [msec] with 90% confidence intervals, for Focalin XR vs. placebo and for moxifloxacin vs. placebo (Study RIT124E2401)



IV.4 Clinical Efficacy

IV.4.1 Clinical efficacy (Paediatrics)

The paediatric clinical development programme consisted of six studies:

- Study RIT124D0007-a pivotal study in children aged 6-12 years with ADHD.
- Study RIT124DUS02 – a study in adolescent females aged 12-17 years with ADHD.
- Study RIT124D0002 -an exploratory study reported/detailed above in Section IV.2, Pharmacokinetics and Section IV.3 Pharmacodynamics of this scientific discussion.
- Studies RIT124DUS05, RIT124DUS07 and RIT124DDE01-Phase IV crossover studies providing comparative data between Ritalin LA and other marketed once daily methylphenidate products (Concerta XL and Medikinet retard); these studies are considered supportive.

Details of the studies are provided below.

Pivotal clinical study RIT124D0007 (D0007)

This was a multicentre, double-blind, placebo-control, parallel-group study in the usual school and home settings of children with ADHD. It evaluated the efficacy and safety of Ritalin LA at daily doses of up to 40 mg. Subjects were enrolled if they met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSMIV) criteria for ADHD (any type). Subjects could be either previously treated with methylphenidate or de novo.

Trial design

After a single-blind titration period of up to four weeks, during which the "optimal" dose (within the dose range 10-40 mg) for each subject was identified, subjects entered a one-week single-blind placebo-washout period. Subjects were then randomized to a double-blind treatment phase to receive their individually titrated dose (10, 20, 30 or 40 mg) of Ritalin LA or placebo for up to two weeks. Subjects who completed the double-blind treatment phase were allowed to enter a 12-week extension phase, during which they received Ritalin LA in an open-label fashion.

Efficacy measures

The efficacy assessments used were the:

- Conners ADHD DSM-IV Scale-teacher rated (CADS-T)
- Conners ADHD DSM-IV Scale-parent rated (CADS-P)
- Clinical Global Impression-Improvement (CGI-I) scales.

Both CADS-T and CADS-P include the DSM-IV total subscale (18 items), which is divided into the DSM-IV Inattentive subscale (9 items) and the DSM-IV Hyperactive-Impulsive subscale (9 items).

The CADS-T was completed by the teacher on a single day each week and covered an evaluation period of approximately one week. The CADS-P was completed by the parents on weekends. The CGI-I, a single-item investigator-rated assessment of a subject's global improvement, was completed twice during the Double-Blind Treatment Phase (after one week of double-blind treatment and at the final visit).

The primary efficacy endpoint was the change from baseline to final rating in the CADS- T total subscale score. Secondary efficacy endpoints were the changes from baseline in the scores of the CADS-T Inattentive and Hyperactive-Impulsive subscales, the changes from baseline in the subscale scores of the CADS-P, and the final rating by the investigator on the CGI-I at the end of the Double--Blind (DB) Treatment Phase (improvement compared with baseline).

All statistical analyses were performed with the ITT population using two approaches:

1. Last-observation-carried-forward (LOCF) analyses, which included all subjects who received double-blind study medication and from whom at least one post-randomization measurement was obtained.
2. Observed-cases (OC) analyses, which included only those subjects of the ITT population who had a final measurement at the end of the Double-Blind Treatment Phase.

Patient disposition

Approximately 76% of patients were male, 86% were Caucasian, the mean age was 9 years and the mean body weight was 35 kg. 75% of patients had a diagnosis of combined ADHD, 1.5% (2 patients) had the hyperactive/impulsive subtype and 19% had the inattentive subtype.

A total of 137 male and female children 6-12 years of age with ADHD were randomized into the double-blind treatment phase of the study and 130 (95%) completed the study. Seven (5.1%) patients discontinued during the double-blind Treatment, predominantly due to adverse events (2 Ritalin LA; 1 placebo) or unsatisfactory therapeutic effect (1 Ritalin LA; 1 placebo). The MAH reports that one subject discontinued prior to receiving double-blind study drug, so that the randomized population consisted of 136 subjects (65 Ritalin LA / 71 placebo), and two randomized subjects had no CADS-T

assessment after randomization. Thus, the MAH considers that the ITT population consisted of 134 subjects (63 Ritalin LA / 71 placebo).

Results

The tables below present the results of Study D0007 with respect to the primary and secondary outcome variables.

Table 4.1 Between-treatment comparison in CADS-T total score change from baseline-Study D0007 (ITT population LOCF)

	Ritalin LA N=63	Placebo N=71
Least squares mean	11.23	-3.06
95% CI difference in LSM[1]	(10.37, 18.22)	
p-value	**< 0.0001**	

[1] Treatment difference is calculated as Ritalin change minus placebo change
Results based om ANCOVA with treatment, center, and baseline score as explanatory variables

Table 4.2 Between-treatment comparison in CADS-T and CADS-P change from baseline-Study D0007 (ITT population LOCF)

	Ritalin LA N=63[1]	Placebo N=71[1]
CADS-T Subscale		
Inattentive		
Least squares mean	5.45	-1.50
95% CI difference in LSM[2]	(4.85, 9.05)	
p-value	**p< 0.0001**	
Hyperactive-Impulsive		
Least squares mean	5.76	-1.57
95% CI difference in LSM[2]	(5.27, 9.39)	
Treatment difference	**p< 0.0001**	
CADS-P Subscale		
Total		
Least squares mean	6.36	0.54
95% CI difference in LSM[2]	(1.86, 9.78)	
p-value	**p=0.0043**	
Inattentive		
Least squares mean	2.74	0.35
95% CI difference in LSM[2]	(0.36, 4.44)	
p-value	**p=0.0213**	
Hyperactive-Impulsive		
Least squares mean	3.62	0.20
95% CI difference in LSM[2]	(1.33, 5.50)	
p-value	**p=0.0015**	

[1] For CADS-P, one placebo subject was not included in the analyses due to missing any post-baseline CADS-P assessment.
[2] Treatment difference is calculated as Ritalin LA change minus placebo change
Results based om ANCOVA with treatment, center, and baseline score as explanatory variables

The results of the primary efficacy analysis in the LOCF population showed a significant treatment difference in favour of Ritalin LA for the mean change from baseline on the CADS-T total subscale (p< 0.0001). The analyses of the secondary efficacy variables, mean change from baseline on the CADS-T and CADS-P subscales and the final CGI-I rating also showed significant treatment differences in favour of Ritalin LA. Similar results were observed in the OC population for the primary and secondary efficacy analyses.

Of the 63 subjects in the Ritalin LA treatment group included in the LOCF analysis, 44 (69.8%) were rated "improved" on the CGI-I scale at the final visit, compared with 28/70 (40.0%) in the placebo group. The difference between the two treatment groups was statistically significant (p= 0.0009). The frequency distribution of CGI-I response categories at the final assessment also showed a significant treatment difference (p< 0.0001).

Comments
Study D0007 confirmed that Ritalin LA administered once daily at individually titrated doses (within the range 10-40 mg/day) was effective relative to placebo in controlling symptoms of ADHD in children in their normal routines at school and at home, and that the efficacy of Ritalin LA was consistently reflected in the assessments of teachers, parents, and investigators.

Study RIT124DUS02 (DUS02)
This was a 10-week multicentre, double-blind, randomised, placebo-controlled, crossover study to compare the efficacy of Ritalin LA 20 mg-60 mg/day to placebo in the symptomatic control of clinically confirmed ADHD in female adolescents (12-17 years of age). The duration of treatment included a 1-week screening period, two 4-week randomised treatment periods, and a 1-week placebo washout between the treatment periods.

A total of 109 female adolescents 12-17 years of age with ADHD were randomized and 83 (76%) completed the study. 10 patients discontinued for unsatisfactory therapeutic effect, 8 withdrew consent and 2 were withdrawn for an abnormal laboratory value.

The primary efficacy variable was the change in Conners Parent Rating Scale (CPRS) score from baseline to endpoint at the fourth week of treatment. Secondary efficacy variables were total scores on the Conners Wells Adolescent Self Report (CASS:S), the Piers Harris Children's Self Concept Scale (PHCSCS-2) and ratings on the Clinical Global Impression of Change (CGI-C) and the Clinical Global Impression of Severity (CGI-S).

76% of patients were Caucasian, the mean age was 13.8 years and the mean body weight was 58 kg. 55% of patients had a diagnosis of combined ADHD, 0.9% (1 patient) had the hyperactive/impulsive subtype and 44% had the inattentive subtype.

The primary efficacy analysis was performed on the difference between Ritalin LA versus placebo in mean changes in total scores on the CPRS from pre-treatment to the fourth week of treatment. The primary null hypothesis was that there was no difference between Ritalin LA and placebo in the change in the total score of CPRS from pre-treatment to the fourth week of treatment.

Least square means and 95% confidence intervals (CIs) were calculated for the change from pre-treatment in total scores on the CPRS for each treatment group. The difference between treatment changes (Ritalin LA - placebo) was analysed using a mixed effect model that included period and treatment as fixed effects and patient (sequence) as a random effect.

To determine whether any clinically significant change in pre-treatment scores had occurred between treatment periods 1 and 2, tests for carry-over were performed. Paired differences were formed by subtracting the treatment period 1 pre-treatment value from the treatment period 2 pre-treatment value (end of the washout period). If the p-value from this test was less than 0.05, the data were to be analysed for treatment period 1 only.

Secondary efficacy analyses included:
- Changes in total scores of CASS:S from pre-treatment to the fourth week of treatment (Ritalin LA - placebo)

- Changes in total scores of PHCSCS-2 from pre-treatment to the fourth week of treatment (Ritalin LA-placebo)
- CGI-C scores at subsequent visits after baseline
- CGI-S scores at pre-treatment of the period 1 and end of placebo washout period

Additional planned efficacy analyses included the correlation between the CPRS total score, the CASS:S total score, and the PHCSCS-2 total score at weeks 0, 2, 4, 5, 7 and 9. In addition, the difference in changes in total scores for the CPRS, CASS:S, and PHCSCS-2 between pre-treatment and the second week of treatment were compared using the methodology described for the analysis of the primary efficacy variable.

The statistical analyses for CASS:S and PHCSCS-2 were identical to those performed for the primary efficacy variable.

Results

Primary efficacy results

Statistically significant superiority of Ritalin LA over placebo was shown for the primary efficacy analysis (p< 0.001). The Least Squares (LS) Means (95% CI) for changes from baseline CPRS total scores to the end of the fourth week of treatment for Ritalin LA and placebo were -20.1 (95% CI: -22.8, -17.3) versus. -9.9 (95% CI; -12.8, -7.1), respectively (see Table 4.3 below). The LS Means difference between Ritalin LA and placebo was -10.1 (95% CI: -13.4, -6.9), which was statistically significant (p< 0.001).

Table 4.3 Change from pre-treatment CPRS total score – Study DUS02 (Efficacy population, LOCF)

	CPRS total score[1]	
	Ritalin LA	**Placebo**
	N = 102	**N = 99**
Pretreatment		
Mean (SD)	47.2 (14.3)	43.3 (16.3)
Median	48.5	44.0
Range	(12 – 81)	(4 – 77)
Change after fourth week of treatment (primary endpoint)		
Mean (SD)	-20 (13.8)	-9.7 (13.3)
LS Mean[2]	-20.1	-9.9
95% CI	(-22.8, -17.3)	(-12.8, -7.1)
LS Mean difference[3], [4]	-10.1	
95% CI	(-13.4, -6.9)	
p-value[4]	**< 0.001**	

[1] Possible total scores on the CPRS may range from 0 to 81, where a score of 0 indicates preferred behavior and a score of 81 indicates undesirable behavior.

[2] Missing efficacy scores at the fourth week of each treatment period are imputed using last-observation-carried-forward (LOCF) of non-missing scores at the second week of each treatment period.

[3] Treatment difference is calculated as Ritalin LA change - Placebo change.

[4] LS Means, confidence intervals, and p-values were produced using mixed model including period, sequence, and treatment as fixed effects, and subject as a random effect.

The efficacy population consisted of all randomized patients who had received at least one dose of study medication and had at least one primary efficacy assessment score during that treatment period.

Table 4.3 below presents the results of this study with respect to secondary endpoints (CPRS, CASS:S and PHCSCS-2 total scores).

The difference in change from pre-treatment to the end of the second week of treatment in CPRS total scores was statistically significant in favour of Ritalin LA (LS Mean treatment difference: -5.7; 95% CI: -8.8, -2.7; p< 0.001).

There was a statistically significant LS Mean difference (-1.9; 95% CI: -3.8, -0.1) in favour of Ritalin LA for changes in CASS:S total scores from pre-treatment at the end of the fourth week of treatment.

A small numerical between-treatment difference in favour of Ritalin LA was observed for changes in PHCSCS-2 total scores from pre-treatment to the end of the fourth week of treatment (Table 4.4).

By the end of the fourth week of treatment, CGI-C scores for Ritalin LA were very much improved in 14.4% or much improved in 37.1% compared with 1.1% and 16.1%, respectively for placebo.

Both treatment groups demonstrated similar responses according to the CGI-S scale at baseline and the end of week 5.

Table 4.4 Change from pre-treatment in secondary efficacy variables (CPRS, CASS:S and PHCSCS-2 total scores)-Study DUS02 (Efficacy population, LOCF)

	Ritalin LA N = 102		Placebo N = 99
CPRS total score[1]			
Change after second week of treatment			
Mean (SD)	-14.5 (14.1)		-8.7 (12.2)
LS mean[2]	-14.7		-8.9
95% CI	(-17.3, -12.0)		(-11.6, -6.2)
LS Means difference[3], [4]		-5.7	
95% CI		(-8.8, -2.7)	
p-value[4]		**< 0.001**	
CASS:S total score[1]			
Change after fourth week of treatment			
Mean (SD)	-11.5 (11.3)		-9.7 (12.0)
LS mean[2]	-11.6		-9.6
95% CI	(-13.9, -9.2)		(-12.0, -7.2)
LS Means difference[3], [4]		-1.9	
95% CI		(-3.8, -0.1)	
PHCSCS-2 Total Score[5]			
Change after fourth week of treatment			
Mean (SD)	5.8 (6.9)		5.2 (7.0)
LS mean[2]	5.8		5.3
95% CI	(4.4, 7.2)		(3.9, 6.8)
LS Means difference[3]		0.5	
95% CI		(-0.5, 1.5)	

[1] Possible total scores may range from 0 to 81, where a score of 0 indicates preferred behavior and a score of 81 indicates undesirable behavior.

[2] Missing efficacy scores at the fourth week of each treatment period are imputed using last-observation-carried-forward (LOCF) of non-missing scores at the second week of each treatment period.

[3] Treatment difference is calculated as Ritalin LA change - Placebo change.

[4] LS Means and confidence intervals produced using mixed model including period, sequence, and treatment as fixed effects, and subject as a random effect.

[5] Possible total scores on the PHCSCS-2 may range from 0 to 60, where a score of 0 indicates lowest possible self- concept, whereas a score of 60 indicates highest possible self-concept.

The efficacy population consisted of all randomized patients who had received at least one dose of study medication and had at least one primary efficacy assessment score during that treatment period.

Supportive study RIT124DUS05 (DUS05)

This was a patient and investigator blinded, single-centre, four-period, placebo-controlled cross-over study conducted in a laboratory classroom setting. The study compared the efficacy of single daily doses of Ritalin LA 20 mg to Concerta XL 18 mg, Concerta XL 36 mg and placebo during the 8-hour school day in male and female children aged 6 to 12 years with a DSM-IV diagnosis of ADHD. At enrolment, patients were stabilised on an equivalent dose of 10 mg twice a day administration of immediate release methylphenidate.

All personnel with the exception of the nurse dispensing the medication were blinded. The unblinded study nurse did not participate in any other study procedures. After completing a practice day, 34 patients were randomised into the treatment phase and received four single doses of Ritalin LA 20 mg, Concerta XL 18 mg, Concerta XL 36 mg and placebo during four one-day treatment evaluation periods. On days between the treatment evaluation periods (treatment periods where one week apart), patients resumed their regularly prescribed medication for the treatment of ADHD up until 24 hours prior to the next treatment period.

81% of patients were male, 36% were Caucasian and 28% black, the mean age was nine years and the mean body weight was 34 kg. All patients had a diagnosis of combined ADHD subtype. A total of 36 patients were randomised and all completed the study.

The efficacy assessments were based on the SKAMP rating scale and Math Tests. The primary efficacy variable was the AUC for change from pre-dose in SKAMP Attention subscale score computed for the first part of the evaluation period, i.e. 0-4 hours Superiority of 20 mg Ritalin LA over 18 mg Concerta was pre-defined as the primary hypothesis. The secondary efficacy variables were the AUC_{0-4h} for change from baseline on the SKAMP Deportment subscale, Math Test Attempted and Math Test Correct as well as the change from baseline in SKAMP Attention score, SKAMP Deportment score, Math Test Attempted and Math Test Correct scores at 0.5, 1 and 2 hour post-dose time points. In addition, the AUC_{0-4h} for change from baseline in SKAMP Combined score, and the AUC_{0-8h} for change from baseline in SKAMP Attention, SKAMP Deportment, SKAMP-Combined, Math Test Attempted and Math Test Correct were compared in exploratory analyses.

Results

Table 4.5 below presents the results of this study with respect to the primary endpoint, AUC change from pre-dose SKAMP Attention scores (Ritalin LA versus Concerta).

Table 4.5 AUC change from pre-dose SKAMP Attention scores (Ritalin LA versus Concerta)-Study DUS05 (Efficacy population)

	Treatment[1] Comparison		LS Means		LSM difference (95% CI)	P-Value[2]
Assessment Time period	**Test** N=36	**Ref.** N=36	**Test**	**Ref.**		
SKAMP Attention Change from pre-dose AUC (0-4h)	A	B	-2.481	-1.362	-1.119 (-2.019, -0.219)	**0.015**
	A	C	-2.481	-1.550	-0.932 (-0.179 [3])	**0.043**
	A	D	-2.481	1.240	-3.721 (-4.621, -2.821)	**< 0.001**

Note: Pair-wise comparisons are based on a mixed effect model with cohort, sequence, treatment, period, and cohort*treatment interaction as fixed effects, and subject (sequence) as random.

Ref.=reference

LSM= Least squares (LS) Mean. Treatment difference is calculated as Test AUC – Ref. AUC.

[1] Treatment: A=Ritalin LA 20mg, B=Concerta 18mg, C=Concerta 36mg, D=Placebo.

[2] P-values are 2-sided.

[3]For testing non-inferiority of treatment A vs. C, one-sided 95% upper confidence limit is provided.

Ritalin LA 20 mg produced statistically significantly greater improvement compared to Concerta 18 mg (p=0.015) and Concerta 36 mg (p=0.043) on AUC_{0-4h} for change from baseline in SKAMP-Attention ratings. Ritalin LA 20 mg was also statistically significantly superior to Concerta 18 mg in SKAMP Combined score (p< 0.001) up to 8 hours post-dose [AUC_{0-8h}].

The LS Means difference between Ritalin LA and placebo for change from baseline in SKAMP Attention score was statistically significant in favour of Ritalin LA at 0-4 hours [AUC_{0-4h}], 4-8 hours [AUC_{4-8h}] and 0-8 hours [AUC_{0-8h}] post-dose (p< 0.001). This superiority for Ritalin LA over placebo was also observed for SKAMP Deportment, SKAMP Combined, Math Test Correct, and Math Test Attempted at 0-4 hours, 4-8 hours and 0-8 post-dose (p< 0.001).

The LS Means difference in change from pre-dose SKAMP Attention score was numerically in favour of Ritalin LA 20 mg compared to Concerta 18 mg and 36 mg at 8 hours [AUC_{0-8h}] post-dose. (see Table 4.6 below).

Table 4.6 AUC change from pre-dose in secondary variables (Ritalin LA versus Concerta)-Study DUS05 (Efficacy population)

	Treatment[1] Comparison		LS Means		LSM difference[2] (95% CI)	P-Value[3]
Assessment	**Test**	**Ref.**	**Test**	**Ref.**		
Time period	N=36	N=36				
SKAMP Attention						
Change from pre-dose						
AUC (0-8h)	A	B	-4.481	-2.719	-1.763 (-3.698, 0.173)	0.074
	A	C	-4.481	-3.244	-1.237 (-0.382[4])	0.208
SKAMP Deportment						
Change from pre-dose						
AUC (0-4h)	A	B	-1.673	-0.277	-1.396 (-2.154, -0.638)	**< 0.001**
	A	C	-1.673	-0.549	-1.124 (-0.490[4])	**0.004**
AUC (0-8h)						
	A	B	-2.812	-0.828	-1.983 (-3.626, -0.341)	**0.018**
	A	C	-2.812	-1.338	-1.473 (-0.099[4])	0.078
SKAMP Combined						
Change from pre-dose						
AUC (0-4h)	A	B	-2.046	-0.778	-1.268 (-1.930, -0.606)	**< 0.001**
	A	C	-2.046	-1.011	-1.035 (-0.481[4])	**0.003**
AUC (0-8h)						
	A	B	-3.582	-1.701	-1.881 (-3.307, -0.456)	**0.010**
	A	C	-3.582	-2.218	-1.364 (-0.171[4])	0.061
Math Test Attempted						
Change from pre-dose						
AUC (0-4h)	A	B	112.25	62.08	50.17 (-3.30, 103.64)	0.066
	A	C	112.25	68.97	43.28 (-1.46 [5])	0.111
AUC (0-8h)						
	A	B	201.83	114.69	87.14 (-27.60, 201.88)	0.135
	A	C	201.83	136.99	64.84 (-31.18[5]))	0.265
Math Test Correct						
Change from pre-dose						
AUC (0-4h)	A	B	104.07	45.44	58.63 (7.04, 110.21)	**0.026**
	A	C	104.07	58.05	46.02 (2.85[5])	0.080
AUC (0-8h)						
	A	B	182.74	99.58	83.15 (-28.81, 195.11)	0.144
	A	C	182.74	116.72	66.02 (-27.68 [5])	0.245

Note: Pair-wise comparisons are based on a mixed effect model with cohort, sequence, treatment, period, and cohort*treatment interaction as fixed effects, and subject (sequence) as random.

Ref.= reference drug

[1] Treatment: A=Ritalin LA 20mg, B=Concerta 18mg, C=Concerta 36mg.

[2] Treatment difference is calculated as Ritalin LA change – reference drug change.

[3] P-values are 2-sided.

[4] For testing non-inferiority of treatment A vs. C, one-sided 95% upper confidence limit is provided.

[5] For testing non-inferiority of treatment A vs. C, one-sided 95% lower confidence limit is provided.

Statistically significantly greater improvement in SKAMP Deportment score was also observed at 0-4 hours [AUC_{0-4h}] post-dose for Ritalin LA compared to Concerta 18 mg and 36 mg and at 0-8 hours [AUC_{0-8h}] post-dose for Ritalin LA compared to Concerta 18 mg.

Greater improvement from baseline in SKAMP Combined score was observed for Ritalin LA than both Concerta dose strengths at 0-4 hours [AUC_{0-4h}] and 0-8 hours [AUC_{0-8h}] post-dose. Except for the difference at 0-8 hours [AUC_{0-8h}] post-dose between Ritalin LA and Concerta 36 mg, these differences were all statistically significant.

Ritalin LA was also significantly superior to Concerta 18 mg for Math Test Correct scores at 0-4 hours post-dose [AUC_{0-4h}] (p=0.026). Ritalin LA approaches statistical significance compared to Concerta 18 mg in Math Test Attempted (p=0.066) and showed better LS Means than Concerta 36 mg for Math Test Attempted and Correct scores.

Comment
The differences in the pharmacokinetic profiles of the two products are such that methylphenidate levels are rather higher in the 8 hours after dosing, and especially in the first 4 hours after dosing, for Ritalin LA in comparison to Concerta. However, this only covers half of a normal waking day (assuming 8 hours sleep period). As the therapeutic effect of methylphenidate is known to be directly related to plasma levels, the differences in clinical effects seen in this study merely reflect the pharmacokinetic differences. They do not imply overall clinical superiority of Ritalin LA over Concerta. In the late afternoon and evening symptom control is likely to be better with Concerta.

Supportive study RIT124DUS07 (DUS07)
This was a blinded (observer and patient), multi-centre, five-period, placebo-controlled cross-over study in a school setting of male and female children 6 to 12 years of age with a DSM-IV diagnosis of ADHD. It compared the efficacy of single daily doses of Ritalin LA 20 and 40 mg to Concerta 18 and 36 mg and placebo over a 12-hour period. Patients stabilised on an equivalent daily dose of 20 mg to 40 mg of methylphenidate for at least two weeks prior to study entry were enrolled.

All personnel with the exception of the nurse, pharmacist or physician dispensing the medication were blinded. The unblinded nurse, pharmacist or physician did not participate in any other study procedures.

After completing a practice day, 54 patients were randomised into the treatment phase and received five single doses of Ritalin LA 20 mg, Ritalin LA 40 mg, Concerta 18 mg, Concerta 36 mg and placebo during five one-day treatment evaluation periods. On days between the treatment evaluation periods, patients resumed their regularly prescribed medication for the treatment of ADHD up until 24 hours prior to the next treatment period.

The change from baseline in SKAMP Attention ratings was the primary efficacy variable. The primary analysis time point was the 2-hour post-dose. Superiority of 20 mg Ritalin LA over 18 mg Concerta was pre-defined as the primary hypothesis. Secondary efficacy variables included change from baseline in SKAMP Attention ratings (1, 3 and 4 hours post-dose), SKAMP Deportment and SKAMP combined ratings (1, 2, 3 and 4 hours post-dose) as well as Math Attempted scores and Math Correct scores (1, 2, 3 and 4 hours post-dose). Analysis of AUC 0-4h, 0-8hr, 8-12hr, and 0-12 hr was performed for each of these SKAMP and Math ratings.

63% of patients were male, 63% were Caucasian and 15% black, the mean age was 9.4 years and the mean body weight was 37 kg. 70% of patients had a diagnosis of combined ADHD, 2% (1 patient) had the hyperactive/impulsive subtype and 28% had the inattentive subtype.

A total of 54 patients were randomized and 53 completed the study (one withdrawal for “administrative problems).

Results

Ritalin LA 20 mg was statistically superior to placebo for all predefined primary and secondary efficacy variables ($p< 0.05$). A rapid onset of action (1 hour post-dose: LS Mean difference=-1.29, $p< 0.001$) and sustained efficacy over a 12-hour school day (AUC_{0-12h}: LSM difference= -10.88, $p< 0.001$). Similar results for the comparisons with placebo were observed for the Ritalin LA 40 mg treatment group.

Table 4.7 below presents the results of this study with respect to the primary endpoint, change from baseline in SKAMP Attention ratings 2 hours post-dose

Table 4.7 AUC change from pre-dose SKAMP Attention scores-Study DUS07 (Efficacy population)

Assessment Time point	Treatment[1] Comparison Test N=54)	Ref. (N=53)	LS Means Test	Reference	LSM difference (95% CI)	P-Value[2]
SKAMP Attention Change from pre-dose						
2 hours post-dose	A	C	-0.897	-0.689	-0.207 (-0.536, 0.121)	0.215
	B	C	-1-277	-0.689	-0.588 (-0.916, -0.259)	**0.001**
	B	D	-1-277	-0.415	-0.862 (-1.191, -0.534)	**< 0.001**
	A	D	-0.897	-0.415	-0.482 (-0.810, -0.153)	**0.004**
	A	E	-0.897	0.218	-1.114 (-1.443, -0.786)	**< 0.001**
	B	E	-1.277	0.218	-1.495 (-1.823, -1.166)	**< 0.001**

Note: Pair-wise comparisons are based on a mixed effect model with center, sequence, treatment and period as fixed effects, and subject (sequence) as random.

LSM difference is calculated as Test LSM – Ref. LSM

[1] Treatment: A=Ritalin LA 20mg, B=Ritalin 40 mg, C=Concerta 18mg, D=Concerta 36mg ,E=Placebo.

[2] All p-values are from t-tests with two-sided alternative performed at 5% level of significance.

At 2 hours post-dose, Ritalin LA 20 mg showed statistically significant greater improvement in the primary analysis of the SKAMP Attention score compared to Concerta 36 mg ($p=0.004$) and numerically greater improvement compared to Concerta 18 mg.

Results for the secondary efficacy variables are provided in Table 4.8 below. In the secondary efficacy analyses, Ritalin LA 40 mg was statistically superior to Concerta 18 and 36 mg on the SKAMP Attention score at hours 1, 2, 3 and 4 after dose administration. Ritalin LA 20 mg and 40 mg produced numerically greater improvement in SKAMP Deportment ratings, and Math Test Attempted and Correct scores up to 4 hours post-dose compared to Concerta 18 mg and Concert a 36 mg, although statistical significance was not reached.

Ritalin LA 20 mg did not consistently outperform Concerta 18 mg or 36 mg during the entire 12-hour post-dose period as assessed by AUC_{0-12h}. Ritalin LA 40 mg generally continued to outperform Concerta 18 mg and 36 mg up to 8 hours post-dose in terms of statistically significant change from baseline in SKAMP ratings (AUC_{0-8h}).

AUC change from baseline at 8-12 hours [AUC_{8-12h}] showed superiority of Concerta 18 or 36 mg over Ritalin LA. These between-treatment differences were statistically significant for the 18 mg and 36 mg

Concerta groups in SKAMP Deportment and SKAMP Combined scores and for the 36 mg Concerta group in Math Test Correct scores.

Table 4.8 AUC change from pre-dose in secondary efficacy variables (Ritalin LA versus Concerta) – Study DUS07 (Efficacy population)

	Treatment Comparison		LS Means			
Assessment	Test N=54	Ref. N=53	Test	Ref.	LSM difference[1] (95% CI)	P-Value[2]
Time period	Ritalin LA	Concerta				
SKAMP Attention						
Change from pre-dose						
AUC (0-4h)						
	20 mg	18 mg	-2.516	-1.672	-0.844 (-1.768, 0.080)	0.073
	20 mg	36 mg	-2.516	-1.435	-1.081(-2.003, -0.158)	**0.022**
	40 mg	36 mg	-3.716	-1.435	-2.281 (-3.204, -1.358)	**< 0.001**
AUC (0-8h)						
	20 mg	18 mg	-4.434	-3.405	-1.029 (-2.947, 0.889)	0.291
	20 mg	36 mg	-4.434	-3.300	-1.134 (-3.050, 0.782)	0.245
	40 mg	36 mg	-7.313	-3.300	-4.013 (-5.929, -2.097)	**< 0.001**
AUC (8-12h)						
	20 mg	18 mg	-0.396	-1.592	1.197 (-0.064, 2.458)	0.063
	20 mg	36 mg	-0.396	-1.469	1.074 (-0.186, 2.333)	0.094
	40 mg	36 mg	-2.016	-1.469	-0.547 (-1.807, 0.713)	0.393
AUC (0-12h)						
	20 mg	18 mg	-4.831	-4.994	0.163 (-2.793, 3.119)	0.913
	20 mg	36 mg	-4.831	-4.766	-0.064 (-3.018, 2.889)	0.966
	40 mg	36 mg	-9.330	-4.766	-4.564 (-7.517, -1.611)	**0.003**
SKAMP Deportment						
Change from pre-dose						
AUC (0-4h)						
	20 mg	18 mg	-1.520	-1.017	-0.503 (-1.576, 0.569)	0.356
	20 mg	36 mg	-1.520	-0.975	-0.545 (-1.616, 0.527)	0.317
	40 mg	36 mg	-3.185	-0.975	-2.210 (-3281, 1.139)	**< 0.001**
AUC (0-8h)						
	20 mg	18 mg	-2.492	-1.842	-0.650 (-2.867, 1.567)	0.564
	20 mg	36 mg	-2.492	-2.108	-0.383 (-2.598, 1.831)	0.733
	40 mg	36 mg	-6.404	-2.108	-4.296 (-6.511, -2.081)	**< 0.001**
AUC (8-12h)						
	20 mg	18 mg	0.749	-0.567	1.315 (0.032, 2.598)	**0.045**
	20 mg	36 mg	0.749	-0.705	1.453 (0.172, 2.735)	**0.026**
	40 mg	36 mg	-1.193	-0.705	-0.488 (-1.770, 0.793)	0.454
AUC (0-12h)						
	20 mg	18 mg	-1.758	-2.420	0.662 (-2.664, 3.988)	0.695
	20 mg	36 mg	-1.758	-2.825	1.067 (-2.255, 4.389)	0.527
	40 mg	36 mg	-7.612	-2.825	-4.787 (-8.109, -1.465)	**0.005**

Comment

The primary comparison of Ritalin LA to Concerta inherently favours the PK profile of Ritalin LA and do not imply overall clinical superiority of Ritalin LA. In the late afternoon and evening symptom control is expected to be better with Concerta and this is seen in the data from 8 to 12 hours.

There is trial personnel unblinding in this study, so measurement bias in relation to unblinding of Concerta cannot be ruled out.

Supportive study RIT124DDE01 (DDE01)

Study DDE01was a multicentre, double-blind, randomised, placebo and active-controlled three-period, crossover design in a laboratory classroom setting, comparing placebo, Ritalin LA (20 mg, once a day. and Medikinet retard (20 mg, once a day) under fed conditions. Male and female children 6-14 years of

age with a confirmed DSM-IV diagnosis of ADHD who were adequately controlled by immediate release MPH were enrolled.

The objectives of this study were to demonstrate superiority of Ritalin LA 20 mg to placebo and non-inferiority to Medikinet Retard 20 mg.

The study had a 4-week pre-randomisation phase and a 3-week crossover treatment phase. After completing a practice day, 147 patients were randomised to one of 6 treatment sequences. Patients were treated with placebo, Ritalin LA and Medikinet Retard, each for one week.

The primary efficacy variable was the mean of the first three SKAMP Combined ratings performed at 1.5, 3.0 and 4.5 hours after drug intake in a laboratory classroom setting. Secondary objectives included SKAMP ratings (Attention subscale, Deportment subscale and Combined score) at 1.5, 3.0, 4.5, 6.0, and 7.5 hours, SKAMP scores over all 5 ratings, over the first three individual time points and over the last two time-points. Other secondary efficacy assessments were mathematical performance tests (attempted and correct solutions) and the Nisonger Child Behaviour Rating Form.

The primary analysis was performed comparing treatments with respect to the primary efficacy variable in an ANOVA model with the factors centre, period, patient within centre, and treatment. Patients were fitted as a random effect; all other factors were treated as fixed. two-sided, 95% confidence intervals and p-values for the null hypothesis of no treatment difference were calculated for all treatment contrasts. For the comparison Ritalin LA 20 mg vs. Medikinet Retard 20 mg, an additional p-value is provided for the shifted null- hypothesis that the difference exceeds the non- inferiority margin in favour of Medikinet retard. Non-inferiority of Ritalin LA 20 mg vs. Medikinet retard 20 mg was claimed, if the upper limit of the confidence interval for the difference Ritalin LA – Medikinet Retard 20 mg was smaller than the non-inferiority margin (or, equivalently, if the p-value for the shifted null- hypothesis is significant). The significance level was 5% two-sided. A difference < 0.25 points on the normalized SKAMP scale was not regarded as clinically relevant. This margin was therefore used as delta for the non-inferiority comparison of Ritalin LA vs. Medikinet Retard.

81% of patients were male, 98% were Caucasian, the mean age was 10.2 years and the mean body weight was 37 kg. 55% of patients had a diagnosis of combined ADHD, 8% (1 patient) had the hyperactive/impulsive subtype and 37% had the inattentive subtype.

A total of 147 patients were randomized and 146 completed the study (one patient withdrew consent).

Results

In the primary efficacy analysis, SKAMP Combined score at 1.5 to 4.5 hours post-dose, Ritalin LA (LS Mean: 0.86) was significantly superior to placebo group (LS Mean:1.49; p< 0.0001). See Table 4.9 The MAH considers that the between-treatment group difference of 0.63 represents clinically significant superiority of Ritalin LA. Similarly, significant superiority of Ritalin LA vs. placebo (p< 0.0001) was demonstrated at 1.5 to 7.5 hours post-dose and 6.0 to 7.5 hours post-dose for the SKAMP Combined score, the SKAMP Attention subscale score, the SKAMP Deportment subscale score and for Math Test Correct and Attempted.

Table 4.9 Pre-dose SKAMP Combined scores (raw) – Study DDE01

Treatment group	Pre-dose SKAMP Combined score (raw)			
	Mean (SD)	Median	Min	Max
Ritalin LA 20 mg	1.16 (0.96)	1.00	0.000	4.25
Medikinet retard 20 mg	1.21(0.97)	1.00	0.000	3.75
Placebo	1.05 (0.91)	0.88	0.000	4.25

In the comparison of Ritalin LA vs Medikinet retard, all assessments at 1.5 to 4.5 hours, 1.5 to 7.5 hours and 6.0 to 7.5 hours post-dose showed a numerical or statistically significant between-treatment difference in favour of Medikinet Retard.

For the primary efficacy comparison, the lower 95% Confidence Limit for the observed difference between the two active treatments difference was -0.17 points on the normalized SKAMP scale. This is less than the difference of 0.25 points regarded as not clinically relevant and used as delta for the non-inferiority criteria for Ritalin LA versus Medikinet Retard.

Table 4.10 Study DDE01 - Summary of ANOVA on SKAMP Combined Scores over 1.5 to 4.5 hours in the double-blind phase (ITT and PP population)

Population	Treatment	Unadjusted means (SD)	LS Means	LSM difference[1] (95% CI)	P-value
ITT (n=147)	Ritalin LA	0.78 (0.75)	0.86	0.63 (0.53 , 0.74)	**< 0.0001**[2]
	Placebo	1.41 (1.04)	1.49		
PP (n=139)	Ritalin LA	0.76 (0.72)	0.85	-0.07 (-0.17 , 0.03)	0.0003[3]
	Medikinet retard	0.68 (0.71)	0.78		

Note: Pair-wise comparisons are based on a mixed effect model with center, period and treatment as fixed effects, and subject (center) as random factor.

Note: For ITT analysis missing values of the primary objective (SKAMP Combined - over 1.5 to 4.5 hours) were replaced by the worst value observed in another patient under the same treatment at the same assessment time.

ANOVA model to derive LS-means with variables center, patient within center, treatment, period.

[1] Least squares (LS) Mean difference is calculated relative to Ritalin LA, i.e., placebo mean minus Ritalin mean or Medikinet retard mean minus Ritalin LA mean

[2] (diff=0). From t-tests without shift with two-sided alternative performed at 5% level of significance (test for superiority)

[3] (diff=-0.25). One-sided p-value for the shifted hypothesis of non-inferiority of Ritalin LA compared to Medikinet retard.

Table 4.11 Study DDE01 - Summary of ANOVA on secondary efficacy variables (Ritalin versus Medikinet Retard) in the double-blind phase (ITT population)

Assessment Time period	Treatment	Unadjusted means (SD)	LS Means	LSM difference[1] (95% CI)		P-value[2]
SKAMP Attention						
Mean 1.5 to 4.5 hr.	Ritalin LA	0.78 (0.65)	0.81	-0.04	(-0.14 , 0.05)	0.3422
	Medikinet	0.72 (0.69)	0.77			
Mean 1.5 to 7.5 hr.	Ritalin LA	0.83 (0.66)	0.87	-0.08	(-0.16 , 0.00)	0.0587
	Medikinet	0.75 (0.65)	0.79			
Mean 6.0 to 7.5 hr.	Ritalin LA	0.91 (0.75)	0.96	-0.13	(-0.23, -0.02)	**0.0159**
	Medikinet	0.78 (0.68)	0.83			
SKAMP Deportment						
Mean 1.5 to 4.5 hr.	Ritalin LA	0.78 (1.00)	0.92	-0.09	(-0.23 , 0.04)	0.1842
	Medikinet	0.69 (0.94)	0.83			
Mean 1.5 to 7.5 hr.	Ritalin LA	0.88 (1.02)	1.03	-0.11	(-0.24 , 0.02)	0.1032
	Medikinet	0.77 (0.95)	0.92			
Mean 6.0 to 7.5 hr.	Ritalin LA	1.02 (1.16)	1.17	-0.13	(-0.31 , 0.04)	0.1399
	Medikinet	0.89 (1.11)	1.04			
SKAMP Combined						
Mean 1.5 to 7.5 hr.	Ritalin LA	0.85 (0.77)	0.95	-0.09	(-0.19 , -0.00]	**0.0476**
	Medikinet	0.76 (0.73)	0.86			
Mean 6.0 to 7.5 hr.	Ritalin LA	0.96 (0.86)	1.07	-0.13	(- 0.25 , -0.01)	**0.0360**
	Medikinet	0.83 (0.79)	0.94			
Math Test Attempted						
Mean 1.5 to 4.5 hr.	Ritalin LA	132.69 (52.45)	133.88	3.90	(-1.66 , 9.45)	0.1688
	Medikinet	137.22 (55.54)	137.77			
Mean 1.5 to 7.5 hr.	Ritalin LA	128.30 (51.00)	129.30	6.63	(1.43, -11.84)	**0.0127**
	Medikinet	135.33 (54.76)	135.93			
Mean 6.0 to 7.5 hr.	Ritalin LA	123.14 (52.09)	122.95	9.65	(3.49, 15.81)	**0.0023**
	Medikinet	131.91 (56.02)	132.59			
Math Test Correct						
Mean 1.5 to 4.5 hr.	Ritalin LA	128.52 (53.83)	128.85	3.62	(-1.9 , 9.14)	0.1973
	Medikinet	132.88 (56.85)	132.48			
Mean 1.5 to 7.5 hr.	Ritalin LA	124.34 (52.37)	124.55	6.45	(1.27, 11.64)	**0.0149**
	Medikinet	131.27 (56.12)	131.00			
Mean 6.0 to 7.5 hr.	Ritalin LA	119.45 (53.33)	117.77	9.68	(3.62, 15.57)	**0.0019**
	Medikinet	128.30 (57.21)	127.45			

Note: Pair-wise comparisons are based on a mixed effect model with center, period and treatment as fixed effects, and subject (center) as random factor.

ANOVA model to derive LS-means with variables center, patient within center, treatment, period.

[1] Least squares (LS) Mean difference is calculated as Medikinet mean minus Ritalin mean

[2] (diff=0). From t-tests without shift with two-sided alternative performed at 5% level of significance (test for superiority).

Overall conclusion on clinical efficacy (paediatrics)

The paediatric clinical efficacy data package shows efficacy of Ritalin LA that is consistent with the known efficacy of currently approved methylphenidate immediate release formulations such as IR Ritalin. However, none of the studies included immediate release methylphenidate as a comparator. In the absence of a direct comparison it is therefore not possible to conclude that Ritalin LA will be equivalent or non-inferior to IR Ritalin in terms of overall efficacy or in the profile of efficacy during the time course of the day.

The CHMP Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr 1) states in respect of an application for a modified release formulation of a drug that is authorised as an immediate release formulation that "as the efficacy and safety of the immediate release product is known, the major issue would be to demonstrate that the new modified release formulation is as safe and effective as the existing formulation". It further states that comparative clinical studies "should be adequately designed and conducted to assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release formulation in comparison with the authorised immediate release formulation". Strictly speaking these requirements have not been met. However, this is not considered to preclude approval of the application for the following reasons:

1. Pharmacokinetic (PK) data show bioequivalence for AUC of Ritalin LA to twice daily Ritalin IR, and also a PK profile that, based on the known relationship between plasma levels and therapeutic effect, gives a high degree of confidence that broadly comparable efficacy is likely.
2. Superiority to Concerta XL was shown for the 0 – 8 hour time period during which plasma levels for Ritalin LA are somewhat higher than for Concerta XL. This does not imply overall better efficacy for Ritalin LA over the full day (and it is likely to be inferior in the late afternoon / evening) but this pattern of efficacy is at least as good as would be expected with IR Ritalin. The comparative data with other approved prolonged release MPH products provide highly relevant supporting data.
3. No single MPH product or regimen is optimal for all patients as they have different PK profiles, each of which can be expected to suit some patients more than others. This was clearly seen in the comparative studies with other approved prolonged release MPH products.
4. There are clear advantages of Ritalin LA over the corresponding immediate release Ritalin regimen, including avoiding the difficulties associated with having to take a dose of this controlled substance at school, and improving treatment adherence.
5. The efficacy data in adult patients (presented later in this report) add further supporting data of the overall clinical utility of Ritalin LA in the treatment of ADHD.

In conclusion, the efficacy of Ritalin LA has been adequately demonstrated in paediatric population.

IV.4.2 Clinical Efficacy (Adults)

The extension of the indication in adults was assessed in many EU Member States as an informal work sharing procedure (DE/H/XXXX/WS/056). The UK was not involved as Ritalin LA was not approved in the UK. Nevertheless, the MHR followed the principles of the work sharing procedure for the evaluation of the data supporting the adult indication. The MHRA is in possession of the assessment reports for this procedure and was an interested observer at discussions at CMDh in relation to the procedure. The intention of this UK national assessment is to adopt the harmonised product literature, updated for the adult indication but without further revision.

To support the applications for Ritalin XL in the indication for the treatment of ADHD in adults, the following were submitted:

1. A Phase III pivotal study (Study D2302) - is a combination of a 9 week, double-blind, randomized, placebo-controlled, parallel-group study to confirm the clinically effective and safe dose range of Ritalin LA in adults and a 6-month, double blind, randomized, withdrawal study to evaluate the maintenance of effect of Ritalin LA in adults. (The main focus of this submission is based on the efficacy and safety results from the Phase-III pivotal Study D2302),
2. An additional flexible dose extension study (D2302E1) of open-label treatment. 6 months efficacy and safety data is available; up to 12 months data will become available on completion of the extension study.
3. Additional supporting data, in the form of pharmacokinetic (PK) and clinical data from previous Focalin XR studies in the treatment of adults with ADHD and Ritalin LA studies in the treatment of children with ADHD.

Study D2302

Study D2302 is a combination of a 9-week, double-blind, randomized, placebo-controlled, parallel-group study to confirm the clinically effective and safe dose range of Ritalin LA in adults and a 6-month, double-blind, randomized, withdrawal study to evaluate the maintenance of effect of Ritalin LA in adults with ADHD. The study consisted of three periods: a dose range confirmation period (**Period 1**), a period in which patients are titrated to the individualized optimal dose of Ritalin LA (**Period 2**), and a withdrawal period (**Period 3**), in order to confirm dose range, establish safety and efficacy, and to evaluate maintenance of efficacy of Ritalin LA.

Table 4.12 Combined Short-term and Long-term Phase III Trial, Adults with ADHD, Study D2302, Ritalin LA vs. Placebo

Study	Study objectives	Patients randomized (completed)	Treatment duration/ study design	Treatment/ dose (mg)	Primary efficacy endpoints (two in Period 1 and one in Period 3)
Pivotal D2302 (Phase 3)	Efficacy, safety, and tolerability of Ritalin LA in adults (18-60 years) with ADHD	Period 1: 725 (584) Period 2*: 584 (489) Period 3 489 (235)	Period 1: 9 week (including a 3-week titration period and a 6-week fixed dose stage) Period 2: 5-week where patients re-titrated to their optimal dose of Ritalin LA Period 3: 6-month withdrawal period with optimal dose of Ritalin LA or Placebo	Ritalin LA (40, 60, or 80 mg/day) Placebo	Primary 1: Change of DSM-IV ADHD RS at week 9 Primary 2: Change of Sheehan Disabilty Scale at week 9 Primary 3: Percentage of treatment failures: defined as a DSM-IV ADHD RS total score during Period 3 which is at least a 30% worsening from Period 3 baseline (baseline 2) and a less than 30% remaining improvement from the Period 1 baseline (baseline 1)

Abbreviations: DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, ADHD=attention-deficit/hyperactivity disorder, and SDS= Sheehan Disability Scale
* Patients were not randomized into Period 2
Source: [Synopses of Individual Studies], [Tabular Listing of all Clinical Studies], [D2302-Table 10-1], [D2302-Table 10-2], and [D2302-Table 10-3]

Main inclusion criteria
- Male or female adults from 18-60 years of age
- Diagnosis of ADHD with confirmed childhood onset according to DSM-IV diagnostic criteria. ADHD was to be discriminated from disorders where inattention or other cognitive impairment was present and required treatment with medication, such as bipolar disorder, depression, anxiety, tension, agitation, aggressive behaviour, psychotic symptoms or suicidal tendency, and these active conditions were excluded from this study.

- DSM-IV ADHD RS total score greater than or equal to 30 at Screening and Baseline.
- Women of child-bearing potential, must have used an effective method of contraception during dosing of study treatment.

Dose
No dose-finding study has been done. Dose selection was based on clinical data from the Focalin XR studies in adults with ADHD.

Ritalin LA is a racemic mixture whereas Focalin XR is d-threo-methylphenidate. Based on the Study E2101, bioequivalence has been demonstrated between Ritalin LA 40 mg capsules (d,l-methylphenidate) and Focalin XR 20 mg capsules (d-threo-methylphenidate) [which is approved in USA], with regard to the d- methylphenidate. Therefore, 2-fold the effective dose of range of Focalin XR in adults were selected for the pivotal study with Ritalin LA.

All patients were assigned to one of the following 4 treatment arms in a ratio of 1:1:1:1: Ritalin LA 40, 60, or 80 mg or matching Placebo. The study consisted of three distinct periods:

Period 1: short-term phase (9 weeks, DB, PC; week 1 to 3 titration starting with 20 mg, then 6 weeks on fixed randomized dose (40, 60 or 80 mg) to confirm the effective dose range.
Period 2: a 5-week period during patients were re-titrated to their optimal dose of Ritalin LA (40, 60 or 80 mg); open-label.
Patients who did not respond to Ritalin during period 2 (less than 30% improvement in ADHD RS compared to baseline 1score (visit 1)) were discontinued from the study, i.e. these patients did not move on to period 3.
Period 3: 6-months, double-blind, PC, randomized (rd2), withdrawal period with optimal fixed dose of Ritalin LA (40, 60 or 80 mg) or Placebo to evaluate the maintenance of effect of Ritalin in adults with ADHD.

Primary Efficacy parameters
Three primary efficacy parameters were evaluated (two in Period 1= Short-term Period and one in Period 3= Long-term Period) for each administered dose, therefore corresponding to 7 statistical tests:

- **Primary 1**: Change from baseline 1 to week 9 (end of period 1) in the total score of the DSM-IV ADHD RS (Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) Attention Deficit Hyperactivity Disorder Response Scale); clinician rated; this is an 18-item scale based on the *DSM-IV-TR"* criteria for ADHD that provides a rating of the severity of symptoms. The first 9 items assess inattentive symptoms and the last 9 items assess hyperactive/ impulsive symptoms. The maximum score is 54 points.
- **Primary 2**: Change from baseline 1 to week 9 (end of period 1) in the Sheehan Disabilty Scale (functional outcome, self-reported). The Sheehan Disability Scale (SDS) assesses disability in three domains, work/school activities, family relationships, and social functioning. It is a self-report scale and is considered appropriate. On the SD, a higher score is indicative of more severe functional impairment; a decrease in score reflects a decrease in functional impairment. The total score ranges from 0-30.
- **Primary 3**: Percentage of treatment failures during Period 3 (long-term period/ withdrawal phase).

Initially, **'**Percentage of treatment failures', was predefined as at least a 30% worsening on ADHD RS from period 3 baseline (randomization 2) to end of period 3". Due to the forced withdrawal study design in Period 3, patients who met strict treatment failure criteria were discontinued from the study (and, thus for these patients, treatment failure status was missing). However, during the study, it became apparent the original protocol treatment failure criteria were overly strict, resulting in discontinuation of several patients who retained meaningful clinical benefit compared to their baseline 1 assessment. Therefore, the protocol was amended to change the treatment failure criterion to *"The percentage of treatment failures, defined as DSM-IV ADHD RS total score during Period 3 which is at least a 30% worsening from period 3 baseline (baseline 2) and a less than 30% remaining improvement from period 1 baseline (baseline 1)"*. The analysis was planned to be conducted within the framework of a logistic regression model using treatment, center as factors, and ADHD RS total score at baseline 1 and 2 as covariate.

Discontinuation of the patients from the study period 3 due to their treatment failure was done until the amendment of the treatment failure criterion came into force.

Key Secondary Efficacy Parameter

- CGI-I at week 9: Proportion of patients with clinical improvement (very much or much) on the Clinical Global Impression – Improvement Scale, defined by a score of 1 or 2 in the CGI-I scale. The CGI-I is a 7-point scale (1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; or 7= very much worse; clinician-rated in comparison to baseline).

Other Secondary Efficacy Parameters

- DSM-IV ADHD RS Inattention and Hyperactivity/Impulsivity subscores
- Sheehan Disability Scale (functional impairment): work/school life (1), family life (2), and social life (3) subscores
- CGI-I and CGI-S (Clinical Global Impression-Severity Scale). The CGI-S consists of seven ratings that range from 1 = "normal, not at all ill" to 7 = "most extremely ill"
- CAARS (Conner's Adult ADHD Rating Scale); observer scored; total score and e.g. Inattention/Memory problem, Hyperactivity/Impulsivityy, Impulsivity/Emotional lability, and Problems with self-concept subscores; Total ADHD Index (to distinguish ADHD adults from nonclinical adults), and Inconsistency Index (to identify random or careless responding); at screening, week 7, week 12, and week 19. The observer may be a family member, friend, or coworker but must not change during the study (Conners et al., 1999). The Observer Short Version (CAARS-O:S) was used. Per item a 4-point ordinal scale ranging from 0 (not at all, never) to 3 (very much, very frequently).
- ASRS (Adult Self-Report Scale)
  The World Health Organization's Adult Self-Report Scale (ASRS) (version 1.1) symptom checklist (Kessler et al., 2005) is a tool to screen for probable ADHD in adults. The ASRS checklist consists of 18 questions about frequency of inattention or hyperactivity symptoms over the last 6 months, which are rated from 0 ("Never") to 4 ("Very often").

Results

Short-term efficacy

Short term efficacy was analysed by change of DSM-IV ADHD RS (primary endpoint 1) and change of Sheehan Disability Scale score at week 9 (primary endpoint 2). The short-term period is Period 1 of the pivotal trial.

Primary endpoint 1: **DSM-IV ADHD RS at week 9**

Primary endpoint 1: The DSM-IV ADHD RS total scores in the three Ritalin LA dose levels had a significantly greater improvement from baseline in Period 1 (LS means 15.45, 14.71, and 16.36 points

for Ritalin LA 40, 60, and 80 mg, respectively; p<0.0001 compared to Placebo 9.35 points). See Table 4.13 below.

Table 4.13 Analysis of improvement from baseline 1 to end of Period 1 on DSM-IV ADHD RS total score by treatment / LOCF (Full Analysis Set for Period 1)—Primary endpoint 1

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit2(Baseline 1)	N	174	175	179	172
	Mean	**39.6**	**38.9**	**39.4**	**39.1**
	Median	39.0	38.0	40.0	38.0
	SD	6.19	5.57	5.55	5.95
	Min	30	30	29	21
	Max	54	54	53	54
Final visit*	N	160	155	156	161
	Mean	**23.7**	**24.0**	**22.5**	**29.5**
	Median	22.5	24.0	21.0	31.0
	SD	12.62	11.30	11.53	11.64
	Min	0	4	0	2
	Max	54	50	54	54
Improvement from baseline 1	N	160	155	156	161
	Mean	16.0	14.7	16.8	9.7
	SD	12.18	10.12	11.36	11.05
	LS mean	**15.45**	**14.71**	**16.36**	**9.35**
	LS mean difference from placebo(95% CI)	6.10(3.68, 8.53)	5.36(2.92, 7.79)	7.01(4.59, 9.42)	
	p-value**	<0.0001	<0.0001	<0.0001	
	significance level***	0.0167	0.0208	0.0313	

Abbreviations: CI = Confidence Interval; LOCF = Last observation carried forward
Improvement is a decrease and is calculated as baseline 1 - final visit value.
LS mean = Least squares mean changes from the Analysis of Covariance (ANCOVA) model with treatment group, centre as factors and baseline DSM-IV ADHD RS total score as covariate.
*LOCF using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1.
**Two-sided p-value based on the difference between each Ritalin LA group and Placebo.
***Significance level =the final two-sided level of significance(alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.
Source: [SCE-Table 3-9]

Primary endpoint 2: Sheehan Disability Score (Functional Impairment)

This primary efficacy endpoint was the change of SDS at week 9 compared to baseline as a measure of functional impairment. SDS total score improved in all three Ritalin LA dose levels significantly greater than Placebo (p-values were Ritalin LA 40 mg p=0.0003, 60 mg p=0.0176 and 80 mg p<0.0001, see Table 4.14 below).

Table 4.14 Improvement from baseline 1 to end of Period 1 on SDS total score by treatment / LOCF (Full Analysis Set for Period 1); study D2302

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit 2 (Baseline 1)	N	172	171	176	166
	Mean	20.7	19.2	19.6	19.9
	Median	21.0	20.0	20.0	20.0
	SD	5.77	6.14	5.88	5.17
	Min	1	0	0	2
	Max	30	30	30	30
Final visit*	N	151	149	149	154
	Mean	14.5	14.9	13.8	16.9
	Median	15.0	15.0	13.0	18.0
	SD	7.39	7.25	7.18	7.11
	Min	0	0	0	0
	Max	30	30	30	30
Improvement from baseline 1	N	151	146	148	152
	Mean	6.4	4.7	6.1	2.9
	SD	7.54	7.08	7.31	7.47
	LS mean	5.89	4.90	6.47	3.03
	LS mean difference from Placebo(95% CI)	2.86 (1.33, 4.39)	1.87 (0.33, 3.41)	3.44 (1.91, 4.97)	
	p-value**	0.0003	0.0176	<0.0001	
	significance level***	0.0167	0.0208	0.0313	

Source: [D2302-Table 11-5]
Improvement is a decrease and is calculated as baseline 1 - final visit value.
LS mean = Least squares mean changes from the Analysis of Covariance (ANCOVA) model with treatment group, center as factors and baseline SDS total score as covariate.

*LOCF using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1.

**Two-sided p-value based on the difference between each Ritalin LA group and Placebo.

***Significance level =the final two-sided level of significance (alpha) for the test following the extended gatekeeping procedure. Statistical significance is indicated if p < significance level.

In both Table 8 and Table 9, the maximum p-values of between treatment comparisons in the two tables were smaller than significance levels following the gate keeping procedure, both DSM-IV ADHD RS and SDS total score showed statistical significance in the composite hypothesis testing.

The positive results of the primary analysis for primary end points 1 and 2 were confirmed by Mixed Model Repeated Measures (MMRM) sensitivity analysis.

Secondary endpoints

≥30% improvement in DSM-IV ADHD RS total score: Period 1

'Responders' were defined as patients with equal to, or greater than, 30% improvement compared to the baseline 1 total score on the DSM-IV ADHD RS. At the end of Period 1, over three quarters of patients in all the Ritalin LA groups had at least 30% improvement in the DSM-IV ADHD RS total score during

Period 1 (75.8% for the 40 mg group; 80.5% for the 60 mg group; 81.0% for the 80 mg group) compared to 58.4% for the Placebo group; the difference compared to Placebo was statistically significant (p=0.0011 for the 40 mg Ritalin LA group, p<0.0001 for the 60 mg and 80 mg Ritalin LA groups) [SCE-Section 1.3].

Table 4.15 Responder Analysis

	Ritalin LA 40 mg	**Ritalin LA 60 mg**	**Ritalin LA 80 mg**	**Placebo**
Response (≥30% improvement in DSM-IV ADHD RS total score); short-term	75.8%	80.5%	81%	58.4%
p	0.0011	<0.0001	<0.0001	

Comment

The response analysis confirmed the positive results of both short term primary endpoints and similar and statistically significant efficacy was shown in all three Ritalin LA dose groups. 76%, 81% resp. 81% of the patients were responders compared to only 58% in the placebo group. This is considered to be clinically relevant.

CGI-I (Clinical Global Impression – Improvement Scale): Period 1

The proportion of patients who showed an improvement (a rating of 1 "very much improved" or 2 "much improved") on the clinician-rated CGI-I scale from baseline 1 to the end of Period 1 was presented. The three Ritalin LA doses had a significantly higher proportion of patients who showed improvement compared to placebo.

In the three Ritalin LA dose groups at week 9, a significantly higher proportion (56.3%, 54.8% and 57.1%) of the patients improved ("very much" or "much") compared to patients in the placebo group (31.7%). This is considered clinically relevant.

CGI-S (Clinical Global Impression – Severity Scale): Period 1

For the clinician-rated CGI-S, each Ritalin LA dose group was statistically significantly superior to Placebo in Periods 1 and 3**.**

Period 1 (short-term period): All three Ritalin LA doses had a significantly higher proportion of patients who showed improvement in CGI-S (71.3%, 73.7% and 74.2%) compared to Placebo (48.4%).

CAARS-O:S Subscores: Period 1

The three Ritalin LA doses had a statistically significant higher LS mean improvement in the CAARS-O:S subscores; Inattention/Memory Problems subscore, Hyperactivity/Restlessness subscore, Impulsivity/Emotional Lability subscore, Problems with Self-Concept subscore and CAARS-O:S ADHD Index by treatment.

Further Secondary endpoints during Period 1 (= short-term) and Period 3 (= long-term phase)

DSM-IV ADHD RS subscores:

Significant clinical efficacy was demonstrated at all three dose levels of Ritalin LA for both Inattention and Hyperactivity/Impulsivity subscores on the DSM-IV ADHD RS.

Period 1

Inattention subscore

For the DSM-IV ADHD RS inattention subscore, the three Ritalin LA dose levels had a significantly greater ($p<0.0001$ at all 3 doses) improvement from baseline (LS means were 8.29 points, 8.35 points, and 9.17 points for Ritalin LA 40, 60, and 80 mg respectively) compared to the Placebo group (4.83 points) in Period 1 [SCE-Section 3.2.1.2.2].

The three Ritalin LA dose levels had a significantly greater ($p<0.0001$ at all 3 doses) improvement from baseline (LS means were 8.29 points, 8.35 points, and 9.17 points for Ritalin LA 40, 60, and 80 mg respectively) compared to the Placebo group (4.83 points).

Hyperactivity/Impulsivity subscore

The analysis of improvement from baseline 1 to end of Period 1 on DSM-IV ADHD RS Hyperactivity/Impulsivity subscore for the three Ritalin LA doses had a significantly greater ($p<0.0001$ at the 40 mg dose, $p=0.0032$ at the 60 mg dose and $p<0.0001$ at the 80 mg dose) improvement from baseline (LS means were 7.12 points, 6.46 points and 7.23 points for Ritalin LA 40, 60, and 80 mg respectively) compared to the Placebo group (4.61 points) in Period 1 [SCE-Section 3.2.1.2.2.].

The three Ritalin LA doses had a significantly greater ($p<0.0001$ at the 40 mg dose, $p=0.0032$ at the 60 mg dose and $p<0.0001$ at the 80 mg dose) improvement from baseline (LS means were 7.12 points, 6.46 points and 7.23 points for Ritalin LA 40, 60, and 80 mg respectively) compared to the Placebo group (4.61 points).

Period 3

Inattention subscore

Final score change from baseline 2 for inattention subscore was statistically significantly lower in the All Ritalin LA group; and for each Ritalin LA dose group compared with Placebo (all $p<0.0001$). LS mean values were 0.84 (All Ritalin LA group), 0.38 (40 mg group), 1.33 (60 mg group), 0.75 (80 mg group), and 3.77 (Placebo group) [SCE-Section 3.2.1.4.1].

Similarly, final score improvement from baseline 1 for inattention subscore was statistically significant for the All Ritalin LA group; and for each Ritalin LA dose group compared with Placebo (all $p<0.0001$). LS mean values were 13.22 (All Ritalin LA group), 14.03 (40 mg group), 12.68 (60 mg group), 13.01 (80 mg group), and 9.87 (Placebo group).

The final score change from baseline 2 for inattention subscore was statistically significantly lower in the All Ritalin LA group; and for each Ritalin LA dose group compared with Placebo (all $p<0.0001$). LS mean values were 0.84 (All Ritalin LA group), 0.38 (40 mg group), 1.33 (60 mg group), 0.75 (80 mg group), and 3.77 (Placebo group).

Similarly, final score improvement from baseline 1 for inattention subscore was statistically significant for the All Ritalin LA group; and for each Ritalin LA dose group compared with Placebo (all $p<0.0001$). LS mean values were 13.22 (All Ritalin LA group), 14.03 (40 mg group), 12.68 (60 mg group), 13.01 (80 mg group), and 9.87 (Placebo group).

Hyperactivity/impulsivity subscore

Final score change from baseline 2 for hyperactivity/impulsivity subscore was statistically significantly lower compared with placebo, for the All Ritalin LA group ($p<0.0001$) and for each Ritalin LA dose group: 40 mg ($p<0.0001$), 60 mg ($p=0.0044$), 80 mg ($p<0.0001$). LS mean values were 0.46 (All Ritalin LA group), -0.08 (40 mg group), 0.98 (60 mg group), 0.39 (80 mg group), and 2.33 (Placebo group).

Similarly, final score improvement from baseline 1 for hyperactivity/impulsivity subscore was statistically significant for the All Ritalin LA group compared with Placebo ($p<0.0001$) and for each Ritalin LA dose group: 40 mg ($p<0.0001$), 60 mg ($p=0.0037$) and 80 mg ($p=0.0002$). LS mean values

were 10.98 (All Ritalin LA group), 11.73 (40 mg group), 10.37 (60 mg group), 10.95 (80 mg group), and 8.66 (Placebo group).

Comments
Significant clinical efficacy was demonstrated at all three dose levels of Ritalin LA for both Inattention and Hyperactivity/Impulsivity subscores on the DSM-IV ADHD RS for both short-term and long-term (when compared to baseline 1). Inattention seemed to improve a little bit better than Hyperactivity/Impulsivity. Nevertheless, the Applicant is asked to comment the results for the long-term phase when compared to baseline 2. The final score change from baseline 2 for both inattention and hyperactivity/impulsivity subscore was statistically significantly lower for each Ritalin LA dose group compared with Placebo.

Sheehan Disability Scale – Subscores: Period 1 (short-term phase)
In the Work disability subscore and Social life disability subscore each of the three Ritalin LA doses had a significantly greater improvement compared to the placebo group.

For the family life disability subscore the three Ritalin LA doses had a greater improvement from baseline than placebo (statistically significant at the 40 and 80 mg dose, but not statistically significant at the 60 mg dose.

Comment
Most of the Sheehan Disability Scale Subscores improved in all Ritalin LA dose groups.

The ASRS (Adult Self-Report Scale) is a patient self-report scale authorised by the WHO. On this scale a clear and significant improvement of the score was seen in all Ritalin LA dose groups (LS mean improvement 13.8, 13.1 resp. 15.9 points compared to placebo (6.8 points). Also' significant improvements were seen both on the Inattentive subscore and Hyperactive/ impulsive subscore; improvement seemed to be a little better on the Hyperactive/ impulsive subscore.

ASRS (Adult Self-Report Scale) – Period 1
The ASRS (Adult Self-Report Scale) is a patient self-report scale authorised by the World Health Organisation (WHO).

Analysis of improvement from baseline 1 to end of Period 1 on ASRS total score by treatment / LOCF (full analysis set for Period 1) is shown in Table 4.16. The three Ritalin LA doses had a significantly greater improvement in ASRS total score compared to Placebo. The LS mean improvement for the 40 mg, 60 mg resp. 80 mg Ritalin LA dose group was 13.8, 13.1 and.15.9 respectively; for Placebo the improvement was 6.8.

Table 4.16 ASRS total score at end of Period 1/ Last observation carried forward (Full Analysis Set for Period 1); Study D2302

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit 2 (Baseline 1)	N	174	173	179	172
	Mean	52.8	51.1	52.5	51.8
	Median	53.0	52.0	54.0	53.0
	SD	9.76	9.55	9.03	9.47
	Min	9	13	13	26
	Max	72	72	68	71

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Final visit*	N	154	151	151	159
	Mean	38.9	38.4	36.6	44.9
	Median	38.0	38.0	37.0	47.0
	SD	14.49	13.37	14.07	13.41
	Min	0	7	0	10
	Max	72	71	68	68
Improvement from baseline 1	N	154	150	151	159
	Mean	14.5	12.6	15.8	6.8
	SD	14.11	13.15	13.90	12.20
	LS mean	13.76	13.11	15.87	6.81
	LS mean difference from placebo (95% CI)	6.95 (4.04, 9.85)	6.30 (3.39, 9.21)	9.05 (6.17, 11.94)	
	p-value**	<0.0001	<0.0001	<0.0001	

Source: [D2302-Table 11-10]
Improvement is a decrease and is calculated as baseline 1 - final visit value.
LS mean = Least squares mean changes from the Analysis of Covariance (ANCOVA) model with treatment group, centre as factors and baseline as covariate.
*LOCF using the final visit for each patient with data in the 6-week fixed-dose phase of Period 1.
**Two-sided p-value based on the difference between each Ritalin LA group and Placebo. Statistical significance is indicated if $p < 0.05$

ASRS Subscores - Period 1

Inattentive subscore

The three Ritalin LA doses had a significantly greater improvement in ASRS inattentive subscore compared to Placebo. The LS mean improvement subscores for the 40 mg, 60 mg and 80 mg Ritalin LA dose group were 4.7 points, 4.6 points and 5.3 points respectively; the LS mean improvement subscore for the Placebo group was 2.2 points).

Hyperactive/ impulsive subscore

The three Ritalin LA doses had a significantly greater improvement in ASRS hyperactive/ impulsive subscore compared to Placebo. The LS mean improvement was 9.1 points for the 40 mg, 8.5 points for the 60 mg Ritalin and 10.6 points for the 80 mg Ritalin LA dose groups; The LS mean improvement score for the Placebo group was 4.6 points.

Conclusion on secondary endpoints

The results from analysis of the secondary endpoints generally provide consistent and persuasive support to the primary efficacy measures in establishing superiority of active treatment arms to placebo that is both statistically compelling and clinically relevant**.**

LONG-TERM EFFICACY

Primary Endpoint 3: Treatment failures – Period 3 (long-term phase)

At the re-randomisation to Period 3 of the pivotal adult study 2302, all patients had been treated with their optimal dose (40, 60 or 80mg Ritalin LA) during Period 2 and had a significant improvement (of at least 30% on DSM-IV ADHD RS compared to study entry - baseline 1).

The aim of the evaluations during Period 3 was to measure the maintenance of effect and disease control for a duration of 6 months or to the point at which the patient met treatment failure status/early discontinuation. This was measured by the percentage of treatment failures in the Ritalin LA vs Placebo group at the end of a 6-month treatment withdrawal period (=at the end of Period 3), according to DSM-IV ADHD RS scores.

Long-term efficacy Treatment failures (Period 3, randomised withdrawal phase):

Treatment failure according to Amendment 4 was defined as a DSM-IV ADHD RS total score during Period 3 which is at least a 30% worsening from Period 3 baseline (baseline 2) and a less than 30% remaining improvement from the Period 1 baseline (baseline 1).

A statistically significantly smaller proportion of patients in the All Ritalin LA group (21.3%) compared with the Placebo group (49.6%) had a treatment failure. The odds ratio of 0.3 for Ritalin LA versus Placebo suggested that the odds of failure were 3 times greater for Placebo than in the All Ritalin LA group (odds ratio: 0.3, 95% CI: 0.2, 0.4).

For the different Ritalin LA dose groups the results were as follows: Statistically significantly smaller proportions of patients in each Ritalin LA dose group: 40 mg (18 patients, 16.4%), 60 mg (34 patients, 26.6%) and 80 mg (23 patients, 20.2%), had treatment failure when compared with placebo (57 patients, 49.6%).

The results based on the original definition for treatment failure in the protocol are in line with the amended ones. The sensitivity analyses (in regard to missing treatment failure status and the original treatment failure definition) show that the Primary Endpoint analysis in results in Period 3 are robust. Long-term efficacy has been sufficiently demonstrated.

<u>Sensitivity analyses in regard to Primary Endpoint 3</u>

To assess the robustness of the Period 3 primary analysis results to potential violations of the underlying missing at random assumption applied in the multiple imputation method, two sensitivity analyses were performed on the percentage of treatment failures in the Full Analysis Set (FAS) during Period 3]. The findings for both sensitivity analyses were similar to those reported above – a statistically significantly smaller proportion of patients in the All Ritalin LA group compared with the Placebo group had treatment failure ($p<0.0001$) in both sensitivity analyses. The OR of 0.3 for Ritalin LA versus Placebo suggested that the odds of failure were 3 times greater for Placebo than in the All Ritalin LA group (OR: 0.3, 95% CI: 0.2, 0.5) in both sensitivity analyses.

<u>Time to treatment failure</u>

The distributions of time to treatment failure was statistically significantly different for the All Ritalin LA group compared with the Placebo group (Chi square = 39.403, $p<0.0001$). At Visit 15/ Week 20, the proportion of All Ritalin LA patients having treatment failure had increased to 18.6%; the proportion of patients in the Placebo group at this time having treatment failure was much higher at 48.8%. The proportion of patients having met treatment failure criteria in the two groups stabilized at Visit 16/ Week 24 and Visit 17/ Week 28 (21.05 % and 22.27% in the All Ritalin LA group and 50.0% and 52.33% in the Placebo group). It can be concluded therefore that most discontinuations due to treatment failure had occurred by Visit 15/ Week 20, which was within 6 weeks of treatment in Period 3.

Secondary Analyses – Period 3 (long-term phase)
DSM-IV ADHD RS - Period 3
Change from baseline 2 to end of Period 3: Final score change from baseline 2 was statistically significantly lower for each Ritalin LA dose group compared with Placebo (see Table 12 below). LS mean value changes 0.40 (40 mg group), 2.41 (60 mg group), 1.16 (80 mg group) and 6.30 (Placebo group). These results indicated that patients treated with Ritalin LA maintained the disease control during 6 months while the placebo patients worsened.

Change from baseline 1 to end of Period 3, DSM-IV ADHD RS total score
Final score improvement from baseline 1 was statistically significant compared with Placebo for all 3 Ritalin LA groups .LS mean values were 25.79 (40 mg group), 23.09 (60 mg group), 23.88 (80 mg group), and 18.48 (Placebo group). Full Analysis Set.

Final score change from baseline 2: Similarly, the change from baseline 2 was statistically significantly lower for each Ritalin LA dose group compared with Placebo. LS mean value changes were 0.40 (40 mg group), 2.41 (60 mg group), 1.16 (80 mg group) and 6.30 (Placebo group).

DSM-IV ADHD RS total subscale scores - Period 3
Inattention subscale
Final score change from baseline 2 for inattention subscore was statistically significantly lower for each Ritalin LA dose group compared with Placebo. LS mean values were, 0.38 (40 mg group), 1.33 (60 mg group), 0.75 (80 mg group), and 3.77 (Placebo group).

Similarly, final score improvement from baseline 1 for inattention subscore was statistically significant for each Ritalin LA dose group compared with Placebo. LS mean values were 14.03 (40 mg group), 12.68 (60 mg group), 13.01 (80 mg group), and 9.87 (Placebo group).

Hyperactivity/impulsivity subscale
Final score change from baseline 2 for hyperactivity/impulsivity subscore was statistically significantly lower compared with placebo, for each Ritalin LA dose group. LS mean values were -0.08 (40 mg group), 0.98 (60 mg group), 0.39 (80 mg group), and 2.33 (Placebo group).

Similarly, final score improvement from baseline 1 for hyperactivity/impulsivity subscore was statistically significant for each Ritalin LA dose group. LS mean values were 11.73 (40 mg group), 10.37 (60 mg group), 10.95 (80 mg group), and 8.66 (Placebo group).

Sheehan Disability Scale (SDS) - Period 3
Final score change from baseline 2 was statistically significantly lower for each Ritalin LA dose group compared with Placebo. LS mean values were 1.30 (40 mg group), 1.86 (60 mg group), 2.82 (80 mg group), and 5.48 (Placebo group).

Table 4.17 Change of SDS total score from baseline 2 to end of Period 3 / LOCF/Multiple Imputation (Full Analysis Set for Period 3); Study D2302

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit 13 (Baseline 2)	N	110	128	112	350	115
	Mean	8.7	9.8	11.2	9.9	9.3
	Median	9.0	9.0	10.0	9.0	9.0
	SD	5.34	6.38	6.40	6.14	5.66
	Min	0	0	0	0	0
	Max	21	30	25	30	29
Final visit	N	100	118	103	321	102
	Mean	10.8	11.9	13.2	12.0	14.3
	Median	11.0	11.0	13.0	11.0	14.5
	SD	7.03	7.11	6.60	6.97	7.97
	Min	0	0	0	0	0
	Max	30	30	30	30	28
Final score change from baseline 2	N	100	118	101	319	102
	Mean	2.1	2.3	2.0	2.1	5.0
	SD	6.34	7.19	6.81	6.79	8.15
	LS mean *	1.30	1.86	2.82	1.98	5.48
	LS mean difference from placebo (95% CI) *	-4.18 (-6.03,-2.33)	-3.62 (-5.38,-1.85)	-2.66 (-4.56,-0.77)	-3.52 (-5.03,-2.02)	
	p-value**	<0.0001	<0.0001	0.0058	<0.0001	

Source: [D2302-Table 11-15]
Final visit only includes non-missing end visit values.
Change from baseline is calculated as final visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) SDS total score as covariate.
Final visit only includes non-missing end visit values
* For missing SDS total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing SDS total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

Change from baseline 1 to end of Period 3; SDS total score

Final score improvement from baseline 1 was statistically significantly higher for each Ritalin LA dose group compared with Placebo. LS mean values were 9.8 (40 mg group), 8.8 (60 mg group), 7.6 (80 mg group) and 5.1 (Placebo group).

CGI-I (Clinical Global Impression – Improvement Scale) – Period 3

Maintenance of effect between baseline 2 and end of Period 3: The proportion of patients who maintained disease control during Period 3 according to CGI-I scores of 'no change', 'minimally improved', 'much improved' and 'very much improved' was 86.7% in the All Ritalin LA group compared to 74.5% in Placebo. More patients in the All Ritalin LA group experienced improvement on CGI-I (scores of 'minimally improved', 'much improved' and 'very much improved'; 71.5%) than in the Placebo group (50.0%).

The proportion of patients with worsening on the CGI-I scale from baseline 2 to the end of Period 3 was significantly smaller in the All Ritalin LA group (24 patients, 7.3%; p=0.0005) compared to Placebo (21 patients, 19.4%).

Comment
The Applicant commented that the results of CGI-I in Period 3 should be interpreted with caution as later on in the study it was discovered that for 62.6% of the patients, the clinicians used the incorrect baseline for Period 3 (Visit 2 instead of Visit 13) due to misunderstanding/ misinterpretation for the CGI-I score assessment for Period 3.

CGI-S (Clinical Global Impression – Severity Scale) - Period 3
The proportion of patients who maintained disease control during Period 3 (CGI-S score maintained or improved from baseline 2 to end of Period 3) was 62.3% in All Ritalin LA group compared to 34.5% of patients in the Placebo.

Compared to Placebo (65.5%), a statistically significantly smaller proportion of patients in each Ritalin LA dose group: 40 mg (38.2%; p<0.0001), 60 mg (41.7%; p=0.0001), 80 mg (32.7%; p<0.0001) had worsening in CGI-S score from baseline 2 to end of Period 3

Improvement from baseline 1 to end of Period 3, CGI-S:
A statistically significantly higher proportion of patients in each Ritalin LA dose group: 40 mg (46.1%), 60 mg (45.0%) and 80 mg (52.3%) had improvement in CGI-S score from baseline 1 to end of Period 3, compared to Placebo (33 patients, 30.0%), The odds of improvement in CGI-S score in the All Ritalin LA group was more than three times higher than in the Placebo group (OR: 3.63, 95% CI: 2.19, 6.01).

CAARS (Conner's Adult ADHD Rating Scale) – Period 3
Final score change from baseline 2 was statistically significantly lower for each Ritalin LA dose group except for 80 mg (p=0.086) when compared with Placebo (see Table 4.18). LS mean values were, -2.89 (40 mg group), 1.49 (60 mg group), 2.86 (80 mg group) and 6.40 (Placebo group).

Table 4.18 Change of CAARS-O:S total score from baseline 2 to end of Period 3 / LOCF/Multiple Imputation (Full Analysis Set for Period 3); Study D2302

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit13 (Baseline 2)	N	109	126	113	348	115
	Mean	28.6	29.6	34.3	30.8	33.3
	Median	28.0	28.0	33.0	30.0	33.0
	SD	12.73	12.54	14.60	13.49	13.19
	Min	0	8	2	0	7
	Max	58	64	73	73	73
Final visit	N	76	92	83	251	78
	Mean	26.0	30.7	34.5	30.6	36.2
	Median	25.0	29.0	34.0	29.0	34.0
	SD	13.39	14.08	14.62	14.41	14.82
	Min	0	6	0	0	0
	Max	63	62	75	75	73
Final score change from baseline 2	N	76	92	83	251	78
	Mean	-2.7	1.7	-0.2	-0.3	2.9
	SD	11.74	12.00	14.23	12.78	15.26
	LS mean *	-2.89	1.49	2.86	0.53	6.40
	LS mean difference from placebo (95% CI) *	-9.29 (-13.4,-5.18)	-4.91 (-8.85,-0.97)	-3.54 (-7.58, 0.49)	-5.86 (-9.29,-2.44)	
	p-value**	<0.0001	0.0147	0.0855	0.0008	

Source: [D2302-Table 11-17]
Final visit only includes non-missing end visit values.
Worsening is an increase and is calculated as final visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) total score as covariate.
* For missing total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

Change from baseline 1 and 2 to end of Period 3, CAARS-O:S total score

Analysis of change from baseline 1 and 2 to end of Period 3 on CAARS-O:S total score in the FAS is summarised in. Final score improvement from baseline 1 was statistically significant for each Ritalin LA dose group except for 80 mg (p=0.82) when compared with Placebo. LS mean values were 20.28 (40 mg group), 15.90 (60 mg group), 12.96 (80 mg group), and 8.97 (Placebo group).

Comment

As mentioned in the short-term efficacy analysis the CAARS data in this study may not have been as reliable as other rating scales as revealed by the Inconsistency Index and therefore the results for the CAARS should be interpreted with caution.

ASRS (Adult Self-Report Scale) – Period 3

Change from baseline 2 to end of Period 3: Final score change of ASRS from baseline 2 was statistically significantly lower for the for each Ritalin LA dose group compared with Placebo. LS mean values were 1.66 (40 mg group), 2.80 (60 mg group), 3.24 (80 mg group) and 8.98 (Placebo group).

Table 4.19 Change of ASRS total score from baseline 2 to end of Period 3 / LOCF/Multiple Imputation (Full Analysis Set for Period 3); Study D2302

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	All Ritalin LA	Placebo
Visit13 (Baseline 2)	N	110	128	113	351	115
	Mean	26.8	28.0	30.6	28.5	29.2
	Median	27.0	27.0	30.0	28.0	30.0
	SD	13.21	11.02	11.34	11.91	12.07
	Min	0	1	0	0	2
	Max	72	56	52	72	59
Final visit	N	99	119	105	323	103
	Mean	29.9	31.9	33.3	31.8	36.9
	Median	29.0	30.0	34.0	30.0	38.0
	SD	14.95	12.58	13.03	13.52	14.23
	Min	0	0	0	0	0
	Max	72	69	72	72	68
Final score change from baseline 2	N	99	119	105	323	103
	Mean	3.0	3.8	3.0	3.3	8.0
	SD	12.64	12.66	11.54	12.27	16.39
	LS mean *	1.66	2.80	3.24	2.57	8.98
	LS mean difference from placebo (95% CI) *	-7.31 (-10.9,-3.76)	-6.18 (-9.55,-2.81)	-5.74 (-9.35,-2.13)	-6.41 (-9.30,-3.53)	
	p-value**	<0.0001	0.0003	0.0018	<0.0001	

Source: [D2302-Table 11-18]
Final visit only includes non-missing end visit values.
Change from baseline is calculated as final visit value – baseline 2 value.
Analysis of Covariance (ANCOVA) model is used with treatment group, center as factors and baseline (Period 3) total score as covariate.
Final visit only includes non-missing end visit values.
* For missing total score at week 40, last available post-baseline score at early discontinuation is carried forward. If no post-baseline score is available, missing total scores at week 40 are imputed based on the Multiple Imputation approach within each treatment arm.
** Based on comparison between Ritalin LA and Placebo.

Change from baseline 1 to end of Period 3, Adult Self-Report Scale
Final score improvement from baseline 1 was statistically significant for each Ritalin LA dose group compared with Placebo. LS mean values were 23.12 (40 mg group), 20.21 (60 mg group), 19.90 (80 mg group) and 13.68 (Placebo group).

ASRS Subscale scores - Period 3
Positive results in regard to long-term effects were obtained both for the Inattentive subscale Hyperactive/impulsive subscale of the Adult Self-Report Scale.

Final score change from baseline 2 for both the ASRS Inattentive subscale score and Hyperactive/impulsive subscale score was statistically significantly lower for each Ritalin LA dose group compared with Placebo.

Similarly, final score improvement from baseline 1 for both ASRS subscales was statistically significant for each Ritalin LA dose group compared with Placebo.

Comment
Long-term efficacy: In the pivotal study the maintenance of effect was measured by the percentage of Ritalin LA vs. Placebo treatment failures at the end of a 6-month treatment withdrawal period, according to DSM-IV ADHD RS scores (Primary Endpoint 3). Statistically significantly smaller proportions of patients in each Ritalin LA dose group: 40 mg (16.4%), 60 mg (26.6%) and 80 mg (20.2%), had treatment failure when compared to those treated with Placebo (49.6%) in the 6-month treatment withdrawal period. The OR of 0.3 for Ritalin LA versus Placebo suggested that the odds of failure were 3 times greater for Placebo than in the All Ritalin LA group. The lower treatment failure rate compared to placebo is considered clinically relevant, but validity of the results might be questioned, as for 29.5% of the patients in the All Ritalin LA group and 25.2% in the placebo group the treatment failure status is missing (as already discussed above this is a consequence of the change of the primary long-term efficacy parameter). However, the provided sensitivity analysis (answer to question 6 "Long-term efficacy – Missing treatment failure status primary endpoint 3) yielded robust results for different assumed missing mechanisms (MAR, MNAR, worst-case imputation) and different populations. Additionally, the analysis of the original failure definition delivered consistent results. Thus, long-term efficacy has been shown.

The long-term effect of Ritalin LA was further supported by significantly smaller changes from Period 3 baseline (baseline 2) to end of Period 3 in all secondary long-term efficacy assessments (DSM-IV ADHD RS, Sheehan Disability Scale, CGI-I, CGI-S, CAARS and ASRS [Adult Self-Report Scale]). Nevertheless, as mentioned the CAARS data (short-terms as well long-term) and the CGI-I long-term data in this study have impaired validity due to study conduct issues

Subgroup analyses
The requested sub-analyses show that both females and males had a statistically better improvement of DSM-IV ADHD RS compared to placebo in all Ritalin dose groups. For men, best numerical improvement of the score was achieved with Ritalin LA 80 mg, whereas for women best improvement was reached in the lowest dose group Ritalin LA 40 mg.

Subgroup analyses of DSM-IV ADHD RS by age were heterogeneous: In the age group 18-30 years a statistically better improvement compared to placebo was achieved in all dose groups whereas in the age of 31-40 years in none of the dose groups. In patients of 41-50 years only with the lowest and highest Ritalin dose resp. in those of 51-60 years only with the lowest Ritalin dose a statistically significant improvement compared to placebo was achieved.

Subgroup analysis for SDS (Sheehan Disability Score) revealed similar results: Both females and males had a statistically better improvement of SDS compared to placebo in all Ritalin dose groups, apart from females in middle dose group.

Subgroup analyses of SDS by age again were heterogeneous: In the age group 18-30 years a statistically better improvement compared to placebo was achieved in all dose groups whereas in the age of 31-40 years in none of the dose groups. In patients of 41-50 years resp. 51-60 years only with the lowest Ritalin dose a statistically significant improvement of SDS compared to placebo was achieved.

It is acknowledged that the study was not powered to estimate significant differences between subgroups based on gender and age. The results according to age were heterogeneous. In the age group 31-40 years, no significant improvement of neither ADHD RS nor SDS with Ritalin compared to placebo was achieved.

Dose-Response Effects
In the Ritalin LA pivotal adult study, a clinically effective dose range of 40-80 mg MPH daily was measured by the change from baseline to the end of a 9-week, fixed-dose treatment period in DSM-IV ADHD RS total score, and by improvement in functional impairment as measured by change from baseline in total score on the SDS.

This was confirmed by the efficacy results from the pivotal study which suggested that flexible dosing is required to individualize the dose based on patient's needs. After a 5-week dose optimization period which allowed titration to each patient's individual optimal dose, similar numbers of patients were found to be treated optimally with each of the 3 doses tested (Ritalin LA 40, 60 or 80 mg).

Daily doses over 80 mg are not recommended, since 80 mg was the highest dose studied in study D2302.

Blood level-response effects: The exposure response relationship was not specifically evaluated in the pivotal study.

The results from the pivotal study also provide evidence that for adults the initial MPH dose of 20 mg can be followed by weekly titration of 20 mg to reach individual optimal dose. The practice of starting MPH treatment at a low dose, and titrating up to a dose effective for the individual patient, is well established in paediatric patients.

Clinical studies in special populations
Specific subgroup analyses of patients with hepatic or renal impairment in the targeted population were not evaluated as no new issues were identified

IV.5 Clinical Safety
The safety profile of MPH in the treatment of children and adolescents with ADHD is well established.

The PK profile of the new Ritalin LA product does not give any reason to think that there might be safety issues additional to those known for the immediate release product. Peak plasma levels are lower and peak to trough fluctuation is reduced, so safety and tolerability should if anything be improved. The only potential new safety issue would be dose dumping of MPH from the prolonged release part of the formulation. There was no evidence of this from the pharmaceutical or PK data but this is the main assessment issue for the Ritalin LA clinical safety data.

The evidence of the safety for Ritalin LA is supported by the clinical studies discussed above, a number of other clinical studies and post marketing data. The safety data submitted to support use of the proposed formulation in the paediatric and adult population in the treatment of ADHD is discussed below

IV.5.1 Clinical Safety (Paediatrics/Children and Adolescents)
The safety data generated from the studies presented in the clinical pharmacology and clinical efficacy sections of this report were submitted to support the applications. The safety population was defined in

each study as all subjects randomised/enrolled, who received study medication. For the purposes of analysis and data presentation, the following safety analysis populations were defined in this submission:

- Dataset A: Safety population of controlled multiple-dose paediatric Ritalin LA studies
- Dataset B: Safety population of all Ritalin LA paediatric studies
- Dataset C: Safety population of controlled single-dose Ritalin LA paediatric studies

A description of each dataset is provided below in Table 5-1.

Table 5-1 Population groupings and safety assessments in pooled datasets

Pooled Dataset	Analysis population	Studies	Pooled Treatment groups
Dataset A	Safety population of controlled multiple dose pediatric Ritalin LA trials	D0007, DUS02, DDE01	1. All Ritalin LA: N=314 2. Placebo: N=318 3. Active control: N=146
Dataset B	Safety population of all pediatric Ritalin LA studies	D0002, D0007, D0007E1, DUS02, DUS05, DUS07, DDE01, D2201	1. All Ritalin LA: N=587 2. Placebo: N=439 3. Active control: N=235
Dataset C	Safety population of controlled single-dose pediatric Ritalin LA trials	D0002, DUS05, DUS07	1. Ritalin LA 17.5mg: N=34 2. Ritalin LA 20mg: N=124 3. Ritalin LA 25mg: N=33 4. Ritalin LA 40mg: N=54 5. All Ritalin LA: N=124 6. Active control (Concerta) 18 mg: N=89 7. Active control (Concerta) 36 mg: N=89 8. Placebo: N=121

This report focuses on the safety population of controlled, multiple-dose studies (Dataset A) because this population includes controlled studies with similar designs and durations of exposure and allows for clear comparisons with placebo.

Mean exposure to study drug was similar amongst the Ritalin LA and placebo groups (14.8 days and 14.5 days respectively). The overall time that subjects were exposed to Ritalin LA, placebo and active control was 4660 days (12.8 years), 4592 days (12.6 years) and 1022 days (2.8 years) respectively. In the context of the well-established safety profile of MPH in the treatment of children and adolescents with ADHD, the extent of exposure to Ritalin LA was considered sufficient for an adequate assessment of safety.

Adverse events (AEs)

A higher incidence of adverse events was observed in the all Ritalin LA group (42.0%) compared to placebo (35.2%) and active control (30.1%) groups. The most commonly affected system organ classes (SOCs) (≥ 5% in any treatment group) were Nervous system disorders, Gastrointestinal disorders, Infections and infestations, Metabolism and nutrition disorders, Psychiatric disorders and General disorders and administration site conditions.

The frequency of adverse events in the safety population, Dataset A is given in the table below. The most frequently reported AEs were headache and decreased appetite. Headache was reported in similar percentages of patients in the Ritalin LA and placebo groups (11.8% and 10.1 %, respectively); whereas, the incidence of decreased appetite was considerably higher in the Ritalin LA group (9.6%) compared to the placebo group (1.6%) or active control group (4.1%). The incidence rates of abdominal pain upper, nausea or vomiting were below 5.0% in all treatment groups, although considerably higher in the Ritalin LA group (4.8%, 3.8% and 3.2%, respectively) than in the placebo group (2.8%, 1.3% and 1.3%, respectively) or active control group (each 2.1%).

Table 5-2 Adverse events (AEs) by preferred term regardless of relationship to treatment (at least 2% in any group) (Safety population- controlled, multiple dose studies)

Preferred term	All Ritalin LA N=314 n (%)	Placebo N=318 n (%)	Active Control N=146 n (%)
Number of patients with any AE	132(42.0)	112(35.2)	44(30.1)
Headache	37(11.8)	32(10.1)	11(7.5)
Decreased appetite	30(9.6)	5(1.6)	6(4.1)
Abdominal pain upper	15(4.8)	9(2.8)	3(2.1)
Nasopharyngitis	13(4.1)	15(4.7)	8(5.5)
Nausea	12(3.8)	4(1.3)	3(2.1)
Vomiting	10(3.2)	4(1.3)	3(2.1)
Insomnia	8(2.5)	4(1.3)	3(2.1)
Upper respiratory tract infection	8(2.5)	8(2.5)	0
Dysmenorrhoea	7(2.2)	0	0
Cough	4(1.3)	3(0.9)	5(3.4)
Abdominal pain	3(1.0)	3(0.9)	5(3.4)

Analysis Dataset A: Safety population of studies, D0007 (DB), DUS02, DDE01
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category.
Preferred terms are sorted by descending order of incidence in the All Ritalin LA group.

In Dataset A, a higher incidence of AEs suspected to be study drug related was observed in the Ritalin LA group (24.8%) compared to placebo (17.6%) and active control (16.4%) groups. The AEs reported as 'suspected', the affected SOCs and the distribution of these events over the 3 treatment groups in Dataset B were similar to that reported in Dataset A.

Serious adverse events (SAEs) and deaths
No deaths were reported in any of the paediatric studies comprising this submission. In Dataset A (controlled, multiple–dose studies), the incidence of SAEs in controlled, multiple dose studies was low with 2 (0.6%) patients reporting events in the Ritalin LA group (1 patient with an appendicitis and 1 patients with depression), 1 (0.3%) patient in the placebo group (intentional self-injury) and none in the active control group. One additional SAE in the Ritalin LA group was reported in Dataset B (abdominal pain). No SAEs were reported in the Dataset C (controlled single-dose studies).

Laboratory findings
No new findings or unexpected differences between treatment groups were observed in the Ritalin LA paediatric population studied with regard to laboratory tests.

ECGs, vital signs, body weight, and physical examinations
The incidence rates of clinically notable changes in vital signs or weight in all 3 datasets were low, with no clinically meaningful differences between treatment groups. Since only 2 of the paediatric Ritalin LA studies presented post-baseline ECG data (Studies DUS02 and D2201), no pooled presentations of ECG data were produced. A review of the results from the individual studies showed no clinically relevant abnormalities.

Safety in special populations
Analysis of subgroups of patients with AEs, SAEs, AEs leading to discontinuation by SOC and preferred term showed no potential differences in the safety profile of Ritalin LA relating to gender, age or race.

Discontinuation due to AEs
In Dataset A, only one AE (depression), reported in the Ritalin LA group, led to discontinuation. In Dataset B (all studies), AEs leading to discontinuation were reported only in the Ritalin LA group (1.2%). The affected SOCs were: Psychiatric disorders (0.7%), Nervous system disorders (0.3%) and General disorders and administration site conditions (0.2%). Except for 2 (0.3%) patients reporting an

AE of anger, all AEs leading to discontinuation were single-patient events; these included fatigue, lethargy, migraine, anxiety, depressed mood, depression and hypomania. No AEs led to study drug discontinuation in Dataset C.

Post marketing experience
For all Ritalin formulations (Ritalin LA, Ritalin tablets and Ritalin SR), a total of 18,932 case reports that reported 42,807 adverse events (AEs) were received cumulatively in relation to the use of Ritalin in age groups, including adults (18 – 69 years old) and children (< 18 years old). Of these 18,932 cases, 3,884 were reported in adults, 9,894 were reported in children, 265 were reported in the elderly (> 69) and 4,889 were reported in patients with unknown age.

The relative frequency of all adult AEs compared to the cumulative total of all AEs in the Novartis safety database for all Ritalin formulations (Ritalin, Ritalin LA and Ritalin SR) is 25% (10640/ 42807), while that for all AEs in children is 53% (22569/ 42807).

To compare the safety profile (AE distribution) of Ritalin LA with Ritalin in children and adolescents, the frequency of AEs by SOC for Ritalin and Ritalin LA were calculated by dividing the number of AEs reported in each SOC by the total number of AEs reported for all SOCs in patients treated with Ritalin or Ritalin LA. Overall, the analysis of adverse event case reports in the Novartis safety database for children and adolescents treated with Ritalin compared to children and adolescents treated with Ritalin LA, showed that the safety profile of Ritalin is similar to that of Ritalin LA in this age group.

Overall conclusions on clinical safety (Paediatric)
No additional safety or tolerability issues for the LA formulation have been identified, either in the clinical trial programme or from post marketing data.

No unexpected AEs were reported and no new safety signals emerged from the analysis of AEs, AEs leading to discontinuation, or SAEs. Overall, the safety results from the studies comprising this submission were consistent with the known safety profile of Ritalin LA, Ritalin tablets and MPH.

No potential differences in the safety profile of Ritalin LA based on gender, age or race were observed.

No new findings or unexpected differences between treatment groups were observed in the Ritalin LA paediatric population studied with regard to laboratory tests, ECGs or vital signs.

Analysis of post-marketing adverse events reported in the Novartis safety database show that incidence rates of AEs by SOC are very similar for children and adolescents treated with Ritalin immediate-release tablets or Ritalin LA.

IV.5.2 Clinical Safety (Adult)
The adverse event (A)E profile for the Ritalin LA adult population with ADHD was as expected and was consistent with the known AE profile as described in previous reports from paediatric patients with ADHD treated with Ritalin LA.

The key safety population comprised of subjects from the follow studies:
- Ritalin LA adult pivotal study (D3202)
- Ritalin LA adult extension study (D3202E1)

Supportive trials safety population comprised of subjects from the following studies:
- Ritalin LA paediatric studies
- Focalin XR adult studies (only approved in USA): controlled multiple-dose trials

Ritalin LA adult pivotal study (D3202)

The key safety population from pivotal Study D2302 consisted of 3 distinct periods. Safety Analysis Sets were defined for each period 1 to 3. Each Safety Analysis Set consisted of all patients who received at least one dose of study drug in the particular period.

- **Safety analysis set for Period 1** – consisted of all treated patients, who were assigned to the dose they received within the randomized doses, Ritalin LA 40, 60, 80 mg, or Placebo (N=722).
- **Safety analysis set for Period 2** – included all treated patients, who were assigned to Ritalin LA 40, 60 or 80 mg in Period 2 (N=580).
- **Safety analysis set for Period 3** – consisted of all treated patients, who were assigned to the treatment they received; Ritalin LA 40, 60, 80 mg, or Placebo (N=482).

The assessment of the side-effect profile of Period 1 only was straight forward, as assessment of the following periods was limited by some selection of the patients due to side-effects.

The mean age was approximately 35 years (age range: 18 to 60 years) in patients treated with Ritalin LA (in Period 1 of the pivotal study). Caucasian patients accounted for the majority (88.2%) of the study population treated with Ritalin LA in Period 1 followed by Other (5.3%), Asian (3.1%), and Black (2.9%) patients. A slightly larger percentage of the patients were male (54.5% vs 45.5%).

Patient exposure

Period 1: During Period 1 (the 9-week, double-blind, placebo-controlled short-term phase of the study), the number of patients with cumulative exposure of >56 days in the All Ritalin LA and Placebo groups was 81.5% and 85.0%, respectively.

Period 2: The median duration of exposure in Period 2 was 35.0 days, which also was the expected duration of the period. The majority of patients completed >28 days in Period 2 (91.9%).

Period 3*:* (Randomised withdrawal phase until week 40). The median duration of therapy for the Ritalin LA 40 mg, Ritalin LA 60 mg, Ritalin LA 80 mg, All Ritalin LA, and Placebo patients was 174.0, 158.0, 180.5, 175.0, and 43.0 days, respectively.

Over the entire study: Total exposure was almost 5 times higher in patients treated with Ritalin LA 261.3 patient-years (95449 patient-days) vs those patients treated with Placebo, 57.5 patient-years (20992 patient-days). A total of 226 patients (32.5%) and 23 patients (8.4%) of the patients treated with Ritalin LA and Placebo, respectively were exposed for 6 months.

Results

- (Period 1 (9 weeks short-term phase)

  The overall incidence of AEs reported by patients in Period 1 was higher in the Ritalin LA groups and slightly increasing by dose (72.8%, Ritalin LA 40 mg; 74.0%, Ritalin LA 60 mg; 75.1%, Ritalin LA 80 mg) compared to Placebo (60.0%).

  The most notable differences between the All Ritalin LA group and Placebo group were the higher incidence of gastrointestinal disorders (primarily dry mouth and nausea): 36.2% versus 16.1%;metabolism and nutrition disorders (primarily decreased appetite): 25.5% versus 7.2%; psychiatric disorders (primarily insomnia, anxiety, and initial insomnia; 34.7% versus 13.9%; cardiac disorders (primarily palpitations): 11.6% versus 0.6%; and nervous system disorders (primarily headache and dizziness): 32.1% versus 25.0%. See Table 5-3 below.

Table 5-3 Number (%) of patients with AEs during Period 1 by System Organ Class (Safety Analysis Set for Period 1) – Study D2302

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Primary system organ class										
Any primary system organ class	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Blood and Lymphatic System Disorders	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)	0	(0.0)
Cardiac Disorders	15	(8.3)	24	(13.3)	24	(13.3)	63	(11.6)	1	(0.6)
Ear and Labyrinth Disorders	5	(2.8)	7	(3.9)	8	(4.4)	20	(3.7)	4	(2.2)
Endocrine Disorders	1	(0.6)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
Eye Disorders	4	(2.2)	5	(2.8)	6	(3.3)	15	(2.8)	4	(2.2)
Gastrointestinal Disorders	67	(37.2)	61	(33.7)	68	(37.6)	196	(36.2)	29	(16.1)
General Disorders and Administration Site Condition	30	(16.7)	33	(18.2)	33	(18.2)	96	(17.7)	27	(15.0)
Immune System Disorders	1	(0.6)	0	(0.0)	2	(1.1)	3	(0.6)	0	(0.0)
Infections and Infestations	42	(23.3)	28	(15.5)	34	(18.8)	104	(19.2)	40	(22.2)
Injury, Poisoning and Procedural Complications	6	(3.3)	5	(2.8)	6	(3.3)	17	(3.1)	2	(1.1)
Investigations	12	(6.7)	10	(5.5)	24	(13.3)	46	(8.5)	6	(3.3)
Metabolism and Nutrition Disorders	40	(22.2)	49	(27.1)	49	(27.1)	138	(25.5)	13	(7.2)
Musculoskeletal and Connective Tissue Disorders	10	(5.6)	12	(6.6)	10	(5.5)	32	(5.9)	11	(6.1)
Nervous System Disorders	63	(35.0)	59	(32.6)	52	(28.7)	174	(32.1)	45	(25.0)
Psychiatric Disorders	58	(32.2)	63	(34.8)	67	(37.0)	188	(34.7)	25	(13.9)
Renal and Urinary Disorders	1	(0.6)	2	(1.1)	2	(1.1)	5	(0.9)	0	(0.0)
Reproductive System and Breast Disorders	3	(1.7)	5	(2.8)	6	(3.3)	14	(2.6)	2	(1.1)
Respiratory, Thoracic and Mediastinal Disorders	6	(3.3)	8	(4.4)	12	(6.6)	26	(4.8)	4	(2.2)
Skin and Subcutaneous Tissue Disorders	16	(8.9)	18	(9.9)	21	(11.6)	55	(10.1)	11	(6.1)
Vascular Disorders	6	(3.3)	6	(3.3)	5	(2.8)	17	(3.1)	1	(0.6)

Source: [D2302-Table 12-8]

Overall in Period 1, similar incidence of AEs was observed in all of the Ritalin LA dose groups and the incidence was lower in Placebo compared to Ritalin LA-treated groups (See table 5-4 below). The most frequently reported AEs in the Ritalin LA groups were decreased appetite, headache, and dry mouth:

Table 1-4 Number (%) of patients with most frequent AEs during Period 1 by Preferred Term (>=5% for any group) (Safety Analysis Set for Period 1) – Study D2302

	Ritalin LA 40 mg N=180 n(%)		Ritalin LA 60 mg N=181 n(%)		Ritalin LA 80 mg N=181 n(%)		All Ritalin LA N=542 n(%)		Placebo N=180 n(%)	
Total no. of patients with AEs	**131**	**(72.8)**	**134**	**(74.0)**	**136**	**(75.1)**	**401**	**(74.0)**	**108**	**(60.0)**
Decreased appetite	39	(21.7)	49	(27.1)	48	(26.5)	136	(25.1)	8	(4.4)
Headache	39	(21.7)	42	(23.2)	30	(16.6)	111	(20.5)	30	(16.7)
Dry mouth	34	(18.9)	39	(21.5)	37	(20.4)	110	(20.3)	4	(2.2)
Nausea	15	(8.3)	20	(11.0)	23	(12.7)	58	(10.7)	9	(5.0)
Nasopharyngitis	22	(12.2)	15	(8.3)	17	(9.4)	54	(10.0)	17	(9.4)
Insomnia	13	(7.2)	18	(9.9)	13	(7.2)	44	(8.1)	7	(3.9)
Hyperhidrosis	12	(6.7)	14	(7.7)	17	(9.4)	43	(7.9)	5	(2.8)
Palpitations	8	(4.4)	15	(8.3)	16	(8.8)	39	(7.2)	1	(0.6)
Fatigue	11	(6.1)	16	(8.8)	11	(6.1)	38	(7.0)	11	(6.1)
Dizziness	12	(6.7)	9	(5.0)	11	(6.1)	32	(5.9)	5	(2.8)
Irritability	11	(6.1)	12	(6.6)	9	(5.0)	32	(5.9)	8	(4.4)
Anxiety	8	(4.4)	11	(6.1)	10	(5.5)	29	(5.4)	1	(0.6)
Initial insomnia	9	(5.0)	4	(2.2)	15	(8.3)	28	(5.2)	2	(1.1)
Restlessness	9	(5.0)	10	(5.5)	7	(3.9)	26	(4.8)	5	(2.8)
Tachycardia	6	(3.3)	10	(5.5)	10	(5.5)	26	(4.8)	0	(0.0)
Abdominal pain upper	6	(3.3)	3	(1.7)	13	(7.2)	22	(4.1)	7	(3.9)
Diarrhoea	4	(2.2)	4	(2.2)	9	(5.0)	17	(3.1)	12	(6.7)

Source: [SCS-Table 2-2]

- **Period 2** (5-weeks titration phase)

In Period 2, the overall incidence of AEs in the All Ritalin LA group was 65.2%. The most commonly affected SOCs were similar to those reported in Period 1.

- **Period 3** (randomized withdrawal phase until week 40)

In Period 3, the overall incidence of AEs was higher in the Ritalin LA treated groups (56.6% in Ritalin LA 40 mg, 57.7% in Ritalin LA 60 mg, 49.2% in Ritalin LA 80 mg) compared to Placebo (36.4%) (Table 5-5 below), however dose-dependency was not seen. Overall, comparable incidences of AEs were observed in all of the Ritalin LA dose groups. The most frequently reported AEs were nasopharyngitis and headache.

It is noted that fewer patients in Period 3 treated with Ritalin LA reported AEs than those treated with Ritalin LA in Period 1; however, this observation is limited by possible selection mechanisms.

Table 5-5 Number (%) of patients with AEs during Period 3 by System Organ Class, (Safety Analysis Set for Period 3) – Study D2302

	Ritalin LA 40 mg N=113 n(%)		Ritalin LA 60 mg N=130 n(%)		Ritalin LA 80 mg N=118 n(%)		All Ritalin LA N=361 n(%)		Placebo N=121 n(%)	
Primary system organ class										
Any primary system organ class	**64**	**(56.6)**	**75**	**(57.7)**	**58**	**(49.2)**	**197**	**(54.6)**	**44**	**(36.4)**
Blood and Lymphatic System Disorders	1	(0.9)	2	(1.5)	0	(0.0)	3	(0.8)	0	(0.0)
Cardiac Disorders	5	(4.4)	2	(1.5)	7	(5.9)	14	(3.9)	2	(1.7)
Congenital, Familial and Genetic Disorders	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)
Ear and Labyrinth Disorders	2	(1.8)	1	(0.8)	1	(0.8)	4	(1.1)	1	(0.8)
Endocrine Disorders	0	(0.0)	1	(0.8)	0	(0.0)	1	(0.3)	0	(0.0)
Eye Disorders	2	(1.8)	4	(3.1)	3	(2.5)	9	(2.5)	0	(0.0)
Gastrointestinal Disorders	13	(11.5)	15	(11.5)	16	(13.6)	44	(12.2)	6	(5.0)
General Disorders and Administration Site Condition	6	(5.3)	8	(6.2)	3	(2.5)	17	(4.7)	7	(5.8)
Hepatobiliary Disorders	0	(0.0)	0	(0.0)	1	(0.8)	1	(0.3)	0	(0.0)
Immune System Disorders	1	(0.9)	0	(0.0)	1	(0.8)	2	(0.6)	0	(0.0)
Infections and Infestations	28	(24.8)	27	(20.8)	26	(22.0)	81	(22.4)	18	(14.9)
Injury, Poisoning and Procedural Complications	5	(4.4)	8	(6.2)	4	(3.4)	17	(4.7)	3	(2.5)
Investigations	4	(3.5)	4	(3.1)	4	(3.4)	12	(3.3)	4	(3.3)
Metabolism and Nutrition Disorders	4	(3.5)	6	(4.6)	4	(3.4)	14	(3.9)	2	(1.7)
Musculoskeletal and Connective Tissue Disorders	11	(9.7)	9	(6.9)	8	(6.8)	28	(7.8)	9	(7.4)
Nervous System Disorders	14	(12.4)	21	(16.2)	12	(10.2)	47	(13.0)	12	(9.9)
Psychiatric Disorders	12	(10.6)	15	(11.5)	14	(11.9)	41	(11.4)	12	(9.9)
Renal and Urinary Disorders	0	(0.0)	1	(0.8)	3	(2.5)	4	(1.1)	0	(0.0)
Reproductive System and Breast Disorders	4	(3.5)	0	(0.0)	0	(0.0)	4	(1.1)	1	(0.8)
Respiratory, Thoracic and Mediastinal Disorders	5	(4.4)	5	(3.8)	5	(4.2)	15	(4.2)	3	(2.5)
Skin and Subcutaneous Tissue Disorders	6	(5.3)	4	(3.1)	2	(1.7)	12	(3.3)	2	(1.7)
Vascular Disorders	2	(1.8)	3	(2.3)	3	(2.5)	8	(2.2)	1	(0.8)

Source: [D2302-Table 12-12]

Adverse events of special interest

- **<u>Cardiac Disorders</u>**: During Period 1 palpitations occurred in 4.4%, 8.3% and 8.8% (Ritalin LA 40, 60 mg and 80 mg, respectively) of the patients compared to placebo (0.6%). Tachycardia occurred in 3.3%, 5.5% and 5.5% (Ritalin LA 40 mg, 60 mg and 80 mg, respectively) of the patients compared to placebo (0%). Both palpitations and tachycardia increased by dose. Also, blood pressure increased during Period 1 in 2.2%, 0% and 4.4% (Ritalin LA 40 mg, 60 mg and 80 mg respectively of the patients compared to placebo (0.6%). These side effects and especially tachycardia further increased during Period 3 (long-term treatment). Increase of heart rate and blood pressure are known effects of methylphenidate.

  Data from adult ADHD study (D2302) are in line with cardiovascular safety data from paediatric studies.

During short-term treatment (at the end of week 9) mean change in the All Ritalin LA group was an increase of 1.7 mmHg and 1.5 mmHg in systolic and diastolic BP respectively in comparison to a decrease of 1.5 mmHg and 1 mmHg in systolic and diastolic BP in the placebo group. Mean change in heart rate in the All Ritalin LA group was an increase of 6.1bpm in comparison to decrease of 0.6bpm in placebo group (Table 5-6 below).

Table 5-6 Systolic blood pressure shift table from baseline 1 to end value during entire study by Ritalin LA exposure (Study D2302 Safety analysis set)

			End value (mmHg)			
		Baseline 1	<=120	>120-140	>140-160	>160
Exposure		n (%)	n (%)	n (%)	n (%)	n (%)
> 31 weeks (N=187)	<=120	93 (52.2)	59 (33.1)	33 (18.5)	1 (0.6)	0
	>120-140	74 (41.6)	21 (11.8)	46 (25.8)	7 (3.9)	0
	>140-160	11 (6.2)	1 (0.6)	8 (4.5)	2 (1.1)	0
	>160	0	0	0	0	0
	Total	178 (100.0)	81 (45.5)	87 (48.9)	10 (5.6)	0
>14-31 weeks (N=204)	<=120	113 (58.9)	71 (37.0)	40 (20.8)	2 (1.0)	0
	>120-140	69 (35.9)	19 (9.9)	39 (20.3)	10 (5.2)	1 (0.5)
	>140-160	10 (5.2)	0	7 (3.6)	2 (1.0)	1 (0.5)
	>160	0	0	0	0	0
	Total	192 (100.0)	90 (46.9)	86 (44.8)	14 (7.3)	2 (1.0)

Source: Table Q20-4

Safety analysis set consists of all treated patients who were assigned to the treatment in each period.

Percentage have been calculated from number of evaluable patients

Long-term treatment: The mean change in systolic, diastolic blood pressure and heart rate over the 40 week study duration (baseline 1 to the end of period 3) was 2.7 mmHg, 1.9 mmHg and 4 beats per minute (bpm) in All Ritalin LA group as compared to -1.0 mmHg, -0.3 mmHg and -1.7 bpm in the placebo group.4.

According to these data, blood pressure and heart rate changes observed in the adult study are in line with the expectations from the existing paediatric data.

The pivotal study did not show any consistent trend for drug induced increases in QTcF. However, there was a small decrease in mean QTcF from baseline 1 to end of period 2 and period 3. It was noted that there were no changes from baseline in QTcF that exceeded the thresholds for particular concern of 60 msec and no QTcF values that exceeded 500 msec.

- **Weight loss**: During short-term treatment Ritalin LA treated patients showed weight loss (3% compared to 1.1% with placebo). A clinically notable decrease in weight (≥ 7% from baseline) was observed in 36 (7.3%) patients in the Ritalin LA group during Period 2. Weight decrease during long-term treatment was relevant, in the All Ritalin LA group 16.9% of the patients compared to 2.7% in the placebo group had a weight decrease ≥ 7% compared to their baseline Period 1 value.

- **Psychiatric Disorders**: The most frequent psychiatric AE during Period 1 were sleep disorders (plus insomnia and initial insomnia), anxiety and restlessness. In Period 1 depression was noted in 2.4% of the All Ritalin Group compared to 0.6% in the placebo group. Insomnia/initial insomnia/sleep disorder increased with long-term treatment > 12 months. The incidence of depressed mood slightly increased over time (4.8% for the periods of <2 months, 4.5% for >6 months and 6.6% >12 months) whereas depression decreased over time (0% in > 12 months). Also, the frequency of anxiety decreased by long-term exposure.
- In Period 3 (long-term treatment) one patient in the Ritalin 80 mg group developed paranoia and one patient attempted suicide compared to none in the placebo group. The suicide attempt was not suspected as being drug-related.

- **Gender:** A slightly higher incidence of AEs was observed in females (84.4%, All Ritalin LA and 53.7%, Placebo) vs males (79.0%, All Ritalin LA and 50.6%, in Placebo) during the entire study; however, in general, a similar safety profile was demonstrated for males and females. The mean doses of Ritalin LA received by female and male patients during Periods 1, 2, and 3 were 0.85 to 0.86 mg/kg/day and 0.71 to 0.77 mg/kg/day, respectively.

- **SAE**: Frequencies of SAE were low and similar in the Ritalin LA and placebo groups (1.3% versus. 1.5%) (See table below). No deaths were reported during the study period; however, one death (by rupture of an aortic aneurysm) was reported during the 30-day follow up period after discontinuation from the study in the Ritalin LA group. No SAEs were suspected to be related to the study drug.

Table 5-7 Number (%) of patients with SAEs (Safety Analysis Set for Period 1) – Study D2302

	All Ritalin LA N=695 n (%)		Placebo N=275 n (%)	
Total no. of patients with AEs	**566**	**(81.4)**	**143**	**(52.0)**
Serious AEs or significant AEs				
Death	0		0	
SAE(s)	9	(1.3)	4	(1.5)
Discontinued due to SAE(s)	2	(0.3)	1	(0.4)

Source: [D2302-Table 12-24]

- **Pregnancies**-Two patients became pregnant while in the study. One patient was treated with Ritalin LA 60 mg in Period 1 was found to be pregnant in Period 2 resulting in discontinuation from the study. The pregnancy outcome was a delivery of a healthy baby. Another patient was treated with 2 days of Ritalin LA 40 mg treatment in Period 1 before discontinuing due to pregnancy and later experienced a spontaneous abortion at 12 weeks (no histopathological investigation performed).
- **Laboratory findings**-The occurrence of clinically notable hematology or clinical chemistry value abnormalities was low. There were no clinically meaningful changes in hematology or clinical chemistry results during any period and no clinically meaningful differences between Ritalin LA and placebo groups were seen.

- **Discontinuation due to AE -** The proportion of AEs leading to discontinuation by Preferred Term was higher in Ritalin LA groups compared to Placebo in Period 1 and 3 (11.3% vs. 2.2% resp. 5.0% vs. 3.3%).

The most affected SOC (≥ 5%) during the entire study periods was Psychiatric disorders (primarily anxiety).

- **Withdrawal/Rebound -** The patients who were assigned to Placebo in Period 3 were suddenly discontinued from treatment with Ritalin LA 40 mg, 60 mg and 80 mg but they did not experience increased signs of withdrawal and rebound compared to patients who continued on Ritalin LA treatment during Period 3. At Week 0-2, placebo patients had fewer AEs (53; 17.2%) compared to Ritalin LA patients (17; 13.2%). In fact, during Week 2-6, slightly fewer patients in Placebo group had AEs. The frequency of AEs possibly associated with withdrawal and rebound symptoms was very low and similar in both groups.

Ritalin LA adult extension study (D3202E1)

Ritalin LA adult extension study (D3202E1) was a 6-months open label extension to Core study D2302 with Ritalin LA 40, 60 and 80 mg (N=299) in the treatment of adult ADHD patients with child-onset ADHD.

Table 5-8 Core and extension Ritalin LA studies in adults

Study and purpose	Randomized / enrolled patients (completed)	Study design details
Core **Study D2302**: Efficacy and safety of Ritalin LA in adult ADHD patients with childhood-onset ADHD.	**Period 1**: 725 (584) **Period 2**: 584 (489) **Period 3**: 489 (235)	40-week, randomized, double-blind, placebo-controlled study to evaluate Ritalin LA (40, 60, or 80 mg/day) vs. Placebo. Treatment periods included: pre-randomization period, Period 1 (3 weeks titration followed by 6 weeks fixed-dose), Period 2 (5 weeks optimal dose), and Period 3 (6-months withdrawal).
Extension Study RIT124D2302E1: Long-term efficacy and safety of Ritalin LA in adult ADHD patients with childhood-onset ADHD.	298 (262)**	A 6-month, open-label extension to Core Study with Ritalin LA in the treatment of adult ADHD patients with childhood-onset ADHD.

Abbreviations: ADHD=attention deficit hyperactivity disorder
** One additional patient (Patient D2302E1-0504-00019) entered the extension, but did not receive a single dose of the study medication, and was subsequently excluded from the All-extension-patients population.
Source: [Clinical Overview dated 27-Nov-2012][Study D2302E1 Table 10-1]

In the Extension Study all patients, initially received Ritalin LA 20 mg and were then titrated to their optimal dose Ritalin LA 40 mg-80 mg (n=298).

The overall incidence of patients with AEs occurring during the treatment with Ritalin LA was increased with exposure time (≤ 2 months 72.4%, > 6 months 85.3%, and > 12 months 88.2%). (See Table 5.9 below).

Overall, the long-term safety profile of Ritalin LA in this Extension study was generally comparable to the safety seen following short term use of Ritalin LA in adults. Nevertheless, the frequency of several AE increased with long-term exposure. Decreased weight occurred in 0.7% (≤ 2 months), 5.6% (> 6 months) and 7.4% (> 12 months) of the patients.

Insomnia/initial insomnia/sleep disorder increased with long-term treatment > 12 months. Incidence of depressed mood slightly increased over time (4.8% for the periods of <2 months, 4.5% for >6 months and 6.6% >12 months) whereas depression decreased over time (0% in > 12 months).

Also, the frequency of anxiety decreased by long-term exposure.

Table 5-9 Number (%) of patients with adverse events starting in periods where maximum continuous exposure achieved by primary system organ class and maximum continuous exposure (Safety analysis set in Period 1)

	Ritalin LA maximum continuous exposure					
Primary System Organ Class	≤ 2 months N=145 n (%)		> 6 months N=354 n (%)		> 12 months N=136 n (%)	
Any primary system organ class	**105**	**(72.4)**	**302**	**(85.3)**	**120**	**(88.2)**
Blood and Lymphatic System Disorders	0	(0.0)	5	(1.4)	1	(0.7)
Cardiac Disorders	16	(11.0)	62	(17.5)	24	(17.6)
Congenital, Familial and Genetic Disorders	0	(0.0)	0	(0.0)	0	(0.0)
Ear and Labyrinth Disorders	7	(4.8)	21	(5.9)	6	(4.4)
Endocrine Disorders	0	(0.0)	2	(0.6)	0	(0.0)
Eye Disorders	4	(2.8)	20	(5.6)	8	(5.9)
Gastrointestinal Disorders	40	(27.6)	153	(43.2)	70	(51.5)
General Disorders and Administration Site Condition	20	(13.8)	86	(24.3)	37	(27.2)
Hepatobiliary Disorders	0	(0.0)	0	(0.0)	0	(0.0)
Immune System Disorders	0	(0.0)	10	(2.8)	6	(4.4)
Infections and Infestations	21	(14.5)	188	(53.1)	86	(63.2)
Injury, Poisoning and Procedural Complications	1	(0.7)	35	(9.9)	17	(12.5)
Investigations	9	(6.2)	42	(11.9)	19	(14.0)
Metabolism and Nutrition Disorders	24	(16.6)	102	(28.8)	47	(34.6)
Musculoskeletal and Connective Tissue Disorders	4	(2.8)	62	(17.5)	29	(21.3)
Neoplasms Benign, malignant & Unspecified (Incl Cysts & Polyps)	0	(0.0)	1	(0.3)	1	(0.7)
Nervous System Disorders	56	(38.6)	154	(43.5)	62	(45.6)
Psychiatric Disorders	64	(44.1)	147	(41.5)	55	(40.4)
Renal and Urinary Disorders	3	(2.1)	9	(2.5)	3	(2.2)
Reproductive System and Breast Disorders	2	(1.4)	19	(5.4)	6	(4.4)
Respiratory, Thoracic and Mediastinal Disorders	9	(6.2)	43	(12.1)	21	(15.4)
Skin and Subcutaneous Tissue Disorders	15	(10.3)	47	(13.3)	23	(16.9)
Surgical and Medical Procedures	0	(0.0)	1	(0.3)	1	(0.7)
Vascular Disorders	8	(5.5)	19	(5.4)	9	(6.6)

Primary system organ classes are presented alphabetically.
A patient with multiple occurrences of an AE under one treatment is counted only once in AE category for that treatment.
A patient with multiple adverse events within a primary system organ class is counted only once.
Total N treated Ritalin LA in any period through the core and extension study is 695.

Source: [Study D2302E1-Table 14.3.1-1.1f]

Taken together depression and depressed mood did not increase with long-term exposure.

The incidence of tachycardia and palpitations slightly increased with long-term exposure (tachycardia: 4.8% with exposure < 2 months and 6.6% with exposure > 12 months; palpitations 6.9% with exposure < 2 months and 9.6% with exposure > 12 months).

Also, the incidence of high blood pressure slightly increased with long-term exposure; from 2.1% with exposure < 2 months to 5.1% with exposure > 12 months.

Mean change in heart rate slightly increased from 2.4 bpm (exposure < 2 months) to 4.9 resp. 4.8 bpm (exposure > 6 months resp. exposure > 12 months).

These findings are expected for methylphenidate and do not seem worse than in children/adolescents.

No new or unexpected safety concerns were observed over the 6-month duration of the Extension study.

No death was reported during Period 3 of the core study or during this extension study.

The overall rates of SAEs starting in Period 3 and the extension were low (0.7% in AEP) with a total of 2 patients in the > 60 mg mean daily dose Ritalin LA group reporting SAEs: 1 patient experienced exostosis and another patient reported Non-Hodgkin's lymphoma as well as pancreatitis during the course of the extension. None of the 3 SAEs was suspected to be study drug related by the investigator (and assessor).

Out of 208 patients experiencing AEs during the extension, overall 7 patients were discontinued prematurely due to an AE, 5 patients in the ≤ 40 mg mean daily dose group and 1 patient each in the >40-60 mg and the >60 mg dose groups. All of these AEs that caused premature discontinuation from the study occurred as single events (each one event of anxiety, depersonalization, dizziness, dysphoria, hypertension, impulsive behavior, irritability, migraine, restlessness, sleep disorder, tension.

Safety in special populations

Period 1:

Subgroup analysis of AEs by gender and age group revealed no clinically meaningful differences in the incidence of AEs during Period 1 Overall, a higher incidence of AEs was observed in females (77.1% All Ritalin LA and 64.6% Placebo) compared to males (71.3% All Ritalin LA and 56.4% Placebo); The mean weight corrected dose was higher in females (All Ritalin LA, 0.85 mg/kg/day) compared to males (All Ritalin LA, 0.71 mg/kg/day).

Period 2:

No clinically meaningful differences were observed when analyzing AEs by gender or age during Period 2.

Period 3:

Subgroup analysis of AEs by gender and age revealed no overall clinically meaningful gender or age-related differences between the groups. A higher incidence of AEs was observed in females (58.0% in All Ritalin LA group) compared to males (51.8% in All Ritalin LA group).

Corresponding numbers in the Placebo group were 40.0% in males and 31.4% in females. The mean weight-corrected dose was higher in females (All Ritalin LA, 0.86 mg/kg) compared to males (All Ritalin LA: 0.77 mg/kg).

Supportive trials safety population

- Ritalin LA paediatric
- Focalin XR adult studies (only approved in USA): controlled multiple-dose trials

The Ritalin LA paediatric data presentation focuses on the safety population of the controlled multiple-dose pediatric Ritalin LA trials (Studies D0007, DUS02, and DDE01), since this population includes controlled studies with similar designs and durations of exposure.

Similarly, the Focalin XR discussion focuses on the controlled multiple-dose adult Focalin XR population (Study E2302) since this is a placebo-controlled study with similar duration of exposure in the treatment groups and was basis for approval in adults with ADHD in USA.

Post-marketing data

Ritalin formulations (Ritalin, Ritalin LA, and Ritalin SR) are currently approved for the treatment of ADHD in children 6 years old or older. In addition, Ritalin and Ritalin SR are also approved for narcolepsy in adults. Methylphenidate is also approved for treatment of narcolepsy for both adults and children.

Post-marketing data in adults are only available for Ritalin and Ritalin SR in narcolepsy, thus these data are not strictly transferable to adults with ADHD. The mean dose applied in narcolepsy is 20 mg to 30mg MPH/ day and therefore lower than the mean dose applied in adult ADHD. The maximum dose in both indications is 80 mg/day. The total incidence for cardiac disorder in the Post-marketing data in adults was slightly higher compared to in children (4.1% vs. 2.6%). Incidence of psychiatric disorders was similar in adults compared to children (21.5% vs. 22.5%). It must be borne in mind, however, that both populations "narcolepsy" and "ADHD" are very different and differ also, for example in their risk to develop psychiatric side-effects.

For all Ritalin formulations (Ritalin LA, Ritalin tablets and Ritalin SR), a total of 15371 case reports that reported 32863 adverse events (AEs) were received cumulatively in relation to the use of Ritalin in age groups, including adults (18 – 69 years old) and children (<18 years old). Of these 15371 cases, 3220 were reported in adults, 8012 were reported in children, 235 were reported in the elderly (>69) and 3904 were reported in patients with unknown age.

The relative frequency of all adult AEs compared to the cumulative total of all AEs in the Novartis safety database for all Ritalin formulations (Ritalin, Ritalin LA and Ritalin SR) is 26% (8426/32863), while that for all AEs in children is 52% (17017/32863). Those for all elderly and all unknown age groups are 2% (612/32863) and 21% (6808/32863), respectively.

To compare the safety profile (AE distribution) in adults with that in children, the frequency of AEs per SOC in adults and children were calculated by dividing the number of AEs per SOC within each respective age group by the total number of AEs reported for that age group.

Overall conclusions on clinical safety (Adults)
Ritalin LA was found to be effective and safe in the short- and long-term treatment of ADHD in adults, in a dose range including 40 mg-80 mg daily. Only few unlabeled adverse events were observed. The adverse effect profile of Ritalin LA in the treatment of adults with ADHD during short and long-term treatment seemed to be similar to that previously observed in the treatment of children with ADHD.

IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ritalin XL.

A summary of safety concerns is listed in the table below:

Table: Summary of safety concerns

Important identified risks	Hypertension Tachycardia Raynaud's phenomenon Psychosis/mania Hallucinations Anorexia Decreased rate of growth Aggression Depression
Important potential risks	QT prolongation Arrhythmias Ischemic cardiac events Cyanosis Sudden death Cerebrovascular disorders Hostility Suicidality Repetitive behaviors Migraine Tics/Tourette's syndrome/dystonias Effect on final height Sexual maturation (delayed) Drug abuse and drug dependence Withdrawal syndrome Diversion Off-label use Carcinogenicity Lymphocytic leukemia Neonatal cardio-respiratory toxicity Effects on neonatal growth Cardiomyopathy
Missing information	None

Routine and additional pharmacovigilance activities are planned for all safety concerns which are considered acceptable.

A summary of routine and additional risk minimisation activities planned for all safety concerns are detailed in the table below.

Summary table of risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
High blood pressure (Hypertension)	SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC: Interactions (Sec 4.5) SmPC: Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Fast heart rate (Tachycardia)	SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Blocked blood flow to fingers or toes (Raynaud's phenomenon)	SmPC: Undesirable Effects (Sec 4.8)	Routine risk minimization is considered sufficient at this time.
Abnormal condition of the mind/abnormal mood (Psychosis/mania)	SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Hallucinations	SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Decreased appetite (Anorexia)	SmPC: Posology/Admin (Sec 4.2) SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Decreased rate of growth	SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Aggression	SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) except hostility and dystonia	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Depression	SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Important potential risks		
Increased time between heart beats (QT prolongation)	This potential risk is not listed in the SmPC.	Routine risk minimization is considered sufficient at this time.
Abnormal heart rate (Arrhythmias)	SmPC: Contraindications (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Heart problems caused by decreased blood flow (Ischemic cardiac events)	SmPC: Contraindications (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Skin having a blue tinge due to decreased oxygen in the blood (Cyanosis)	This potential risk is not listed in the SmPC.	Routine risk minimization is considered sufficient at this time.
Sudden death	SmPC: Contraindications (Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC: Interactions (Sec 4.5) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Decreased blood flow to the	SmPC: Contraindications	A website for physicians to learn about

Safety concern	Routine risk minimization measures	Additional risk minimization measures
brain (Cerebrovascular disorders)	(Sec 4.3) SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Hostility	SmPC: Warnings (Sec 4.4)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Having suicidal thoughts (Suicidality)	SmPC: Contraindication (Sec 4.3) SmPC: Warning (Sec 4.4) SmPC Undesirable Effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Repetitive behaviors	SmPC: Undesirable effects (Sec 4.8)	Routine risk minimization is considered sufficient at this time.
Migraine	SmPC: Undesirable effects (Sec 4.8)	Routine risk minimization is considered sufficient at this time.
Repetitive, involuntary movements (Tics/Tourette's syndrome/dystonias)	SmPC: Warnings (Sec 4.4) SmPC Undesirable Effects (Sec 4.8) except dystonia	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Effect on final height	SmPC: Posology/Admin (Sec 4.2) SmPC: Warnings (Sec 4.4)	Routine risk minimization is considered sufficient at this time.
Sexual maturation (delayed)	This potential risk is not listed in the SmPC.	Routine risk minimization is considered sufficient at this time.
Drug abuse	SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Drug dependence	SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4) SmPC: Undesirable effects (Sec 4.8)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Symptoms after stopping the medication (Withdrawal syndrome)	SmPC: Warning (Sec 4.4)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Use of the medication for recreational purposes (Diversion)	SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4)	A website for physicians to learn about the correct way to prescribe MPH, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Using the medication for something other than what it was intended for (Off-label use)	SmPC: Posology/Admin (Sec 4.2) SmPC: Warning (Sec 4.4)	A website for physicians to learn about the correct way to prescribe MPHe, which is the main active ingredient in Ritalin. This website will also have educational materials to inform physicians on the best way to monitor their patients currently on Ritalin.
Cancer (Carcinogenicity)	SmPC: Preclinical safety data (Sec 5.3)	Routine risk minimization is considered sufficient at this time.
Cancer in the blood stream (Lymphocytic leukemia)	This potential risk is not listed in the SmPC.	Routine risk minimization is considered sufficient at this time.
Newborn heart or lung problems (Neonatal cardio-respiratory toxicity)	SmPC: Warning (Sec 4.6)	Routine risk minimization is considered sufficient at this time.
Newborn effect on growth (Effects on neonatal growth)	SmPC: Warning (Sec 4.6)	Routine risk minimization is considered sufficient at this time.
Cardiomyopathy	This potential risk is not listed in the SmPC.	Routine risk minimization is considered sufficient at this time.
Missing information		
None	NA	NA

IV.7 Discussion of the clinical aspects

Ritalin XL was found to be effective and safe in the short- and long-term treatment of ADHD in i) children over 6 years and ii) adults in a dose range including 40 mg to 80 mg daily. It is recommended that Marketing Authorisations are granted, from a clinical point of view.

IV. USER CONSULTATION

User testing of the text and layout common to all package leaflets of methylphenidate products in EU was performed in 2009 following the referral under Article 31 of Council Directive 2001/83/EC triggered by the European Commission in 2007. The results have been submitted to the MHRA and have been approved.

The proposed changes to the package leaflet related to the extension of the indication to the adult population are considered not to be significant and will not impact understanding of the information by the patients or their care givers. Therefore, no additional consultation with target patient group was considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified.

It is agreed that the effectiveness and safety of Ritalin XL have been established in the short and long-term treatment of ADHD in i) children aged 6 years of age and over and (ii) in adults in the proposed daily dose ranges.

The benefit/risk assessment is considered to be positive.

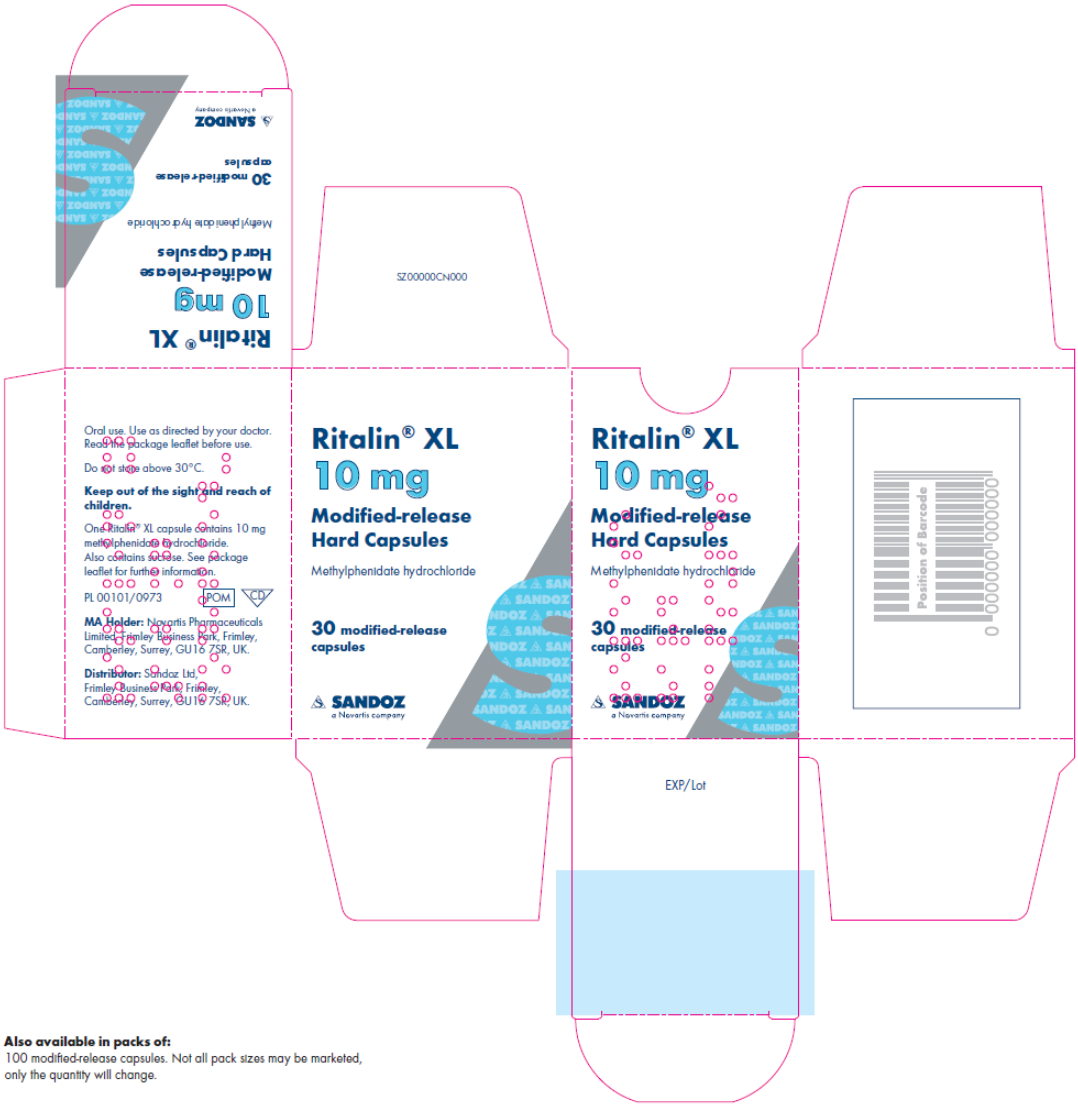
The grant of Marketing Authorisations is, therefore, recommended.

The product information for methylphenidate-containing products is harmonised across the EU. This harmonisation should be maintained for Ritalin LA. The additional information for the indication in adults, adopted following the work-sharing procedure, is satisfactory. The dose advice is appropriately supported by the data. The MAH is requested to include the UK in any future work-sharing procedures, in order to maintain the current harmonisation.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

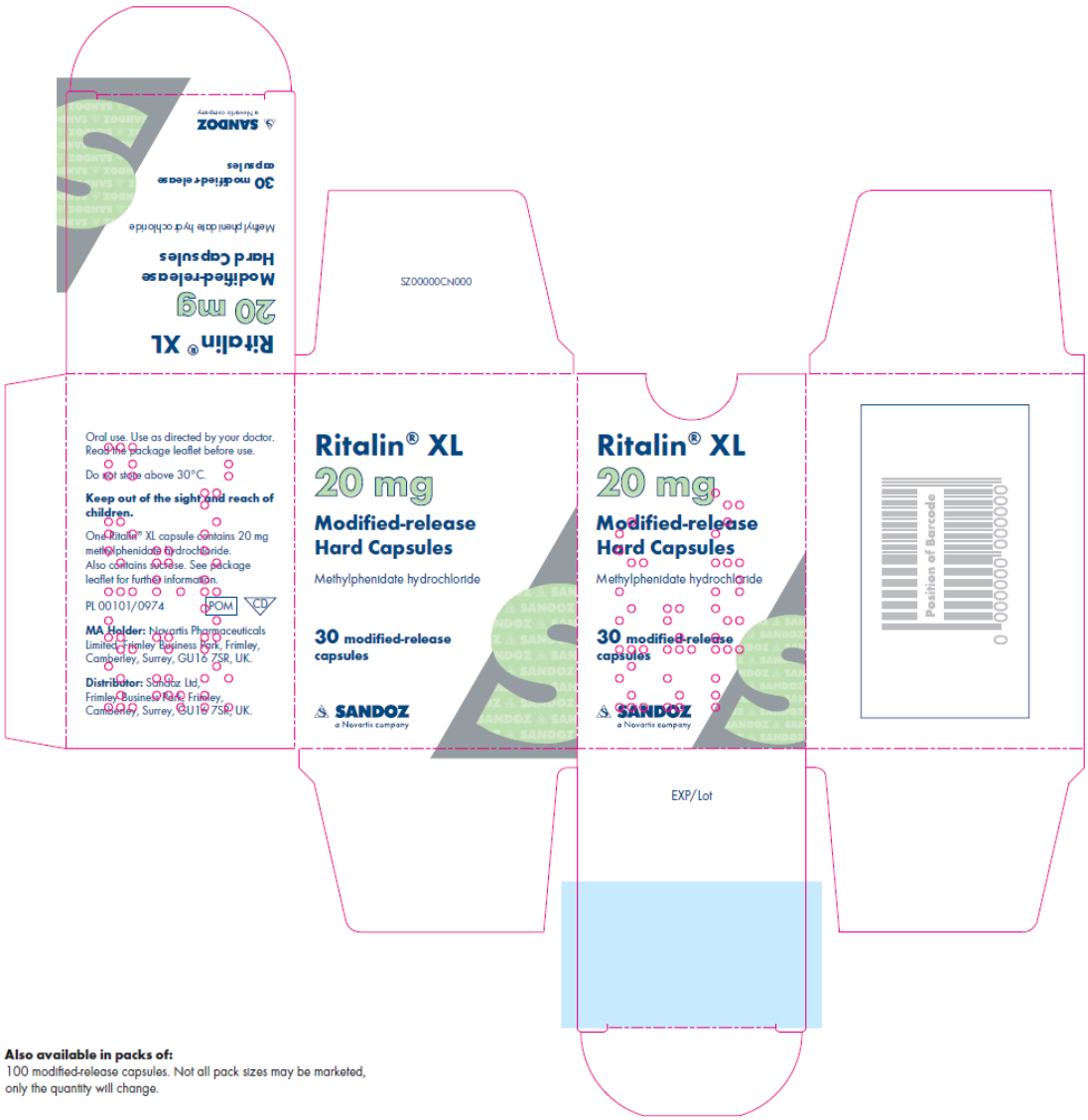
In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL is available on the MHRA website. The current labelling is provided below.

Ritalin XL 10 mg modified-release hard capsules



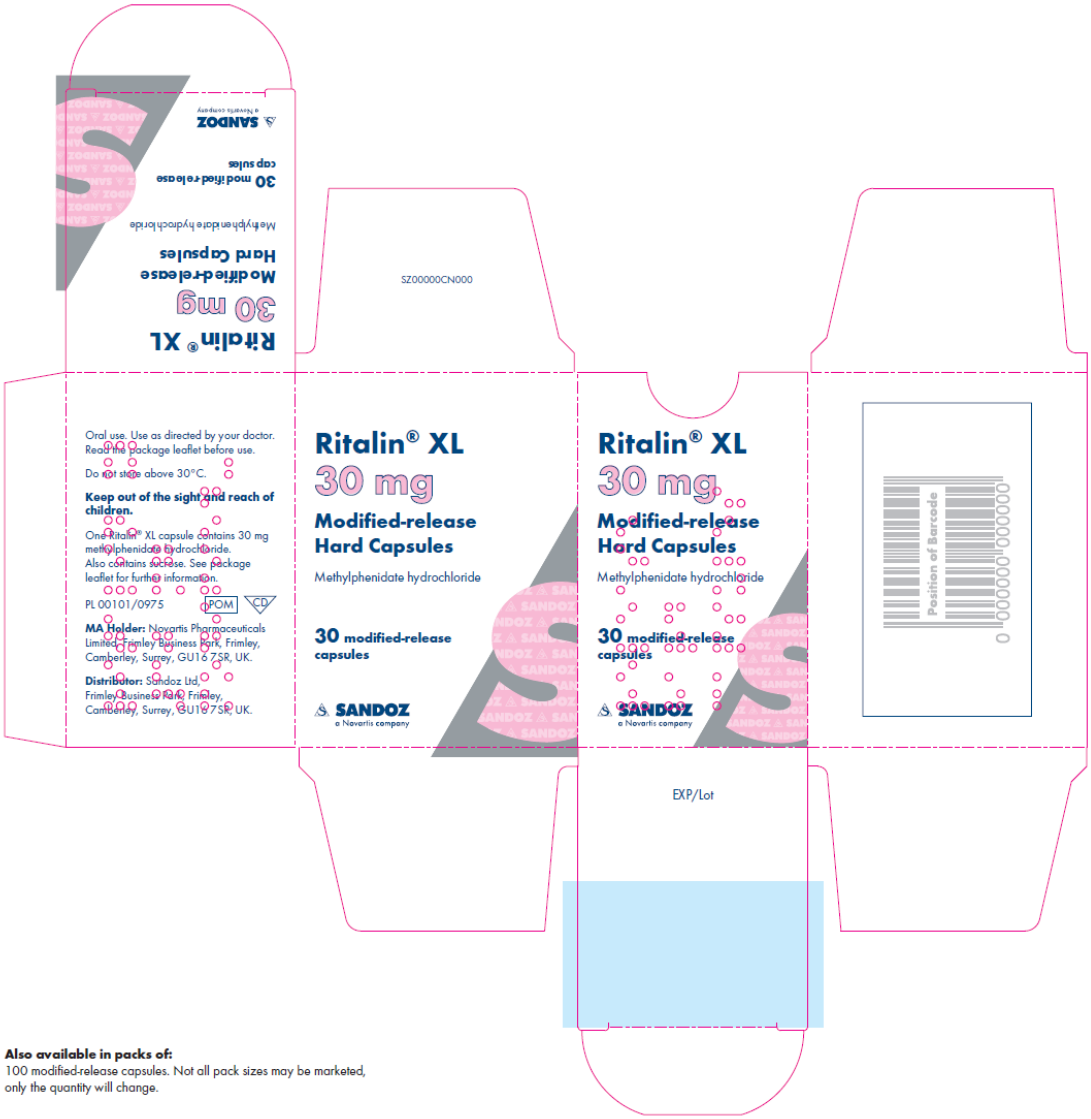
Also available in packs of:
100 modified-release capsules. Not all pack sizes may be marketed, only the quantity will change.

Ritalin XL 20 mg modified-release hard capsules



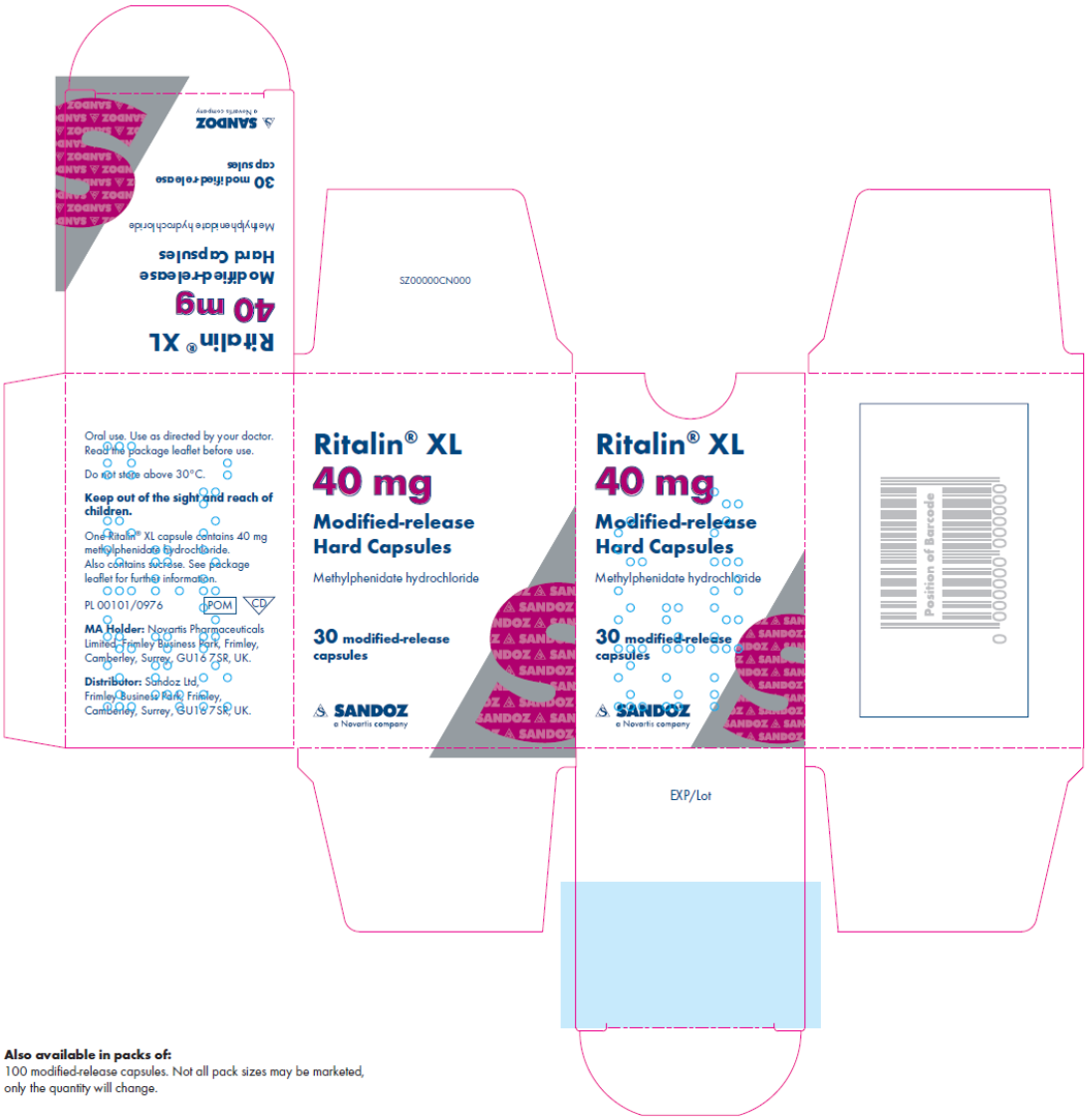
Also available in packs of:
100 modified-release capsules. Not all pack sizes may be marketed, only the quantity will change.

Ritalin XL 30 mg modified-release hard capsules



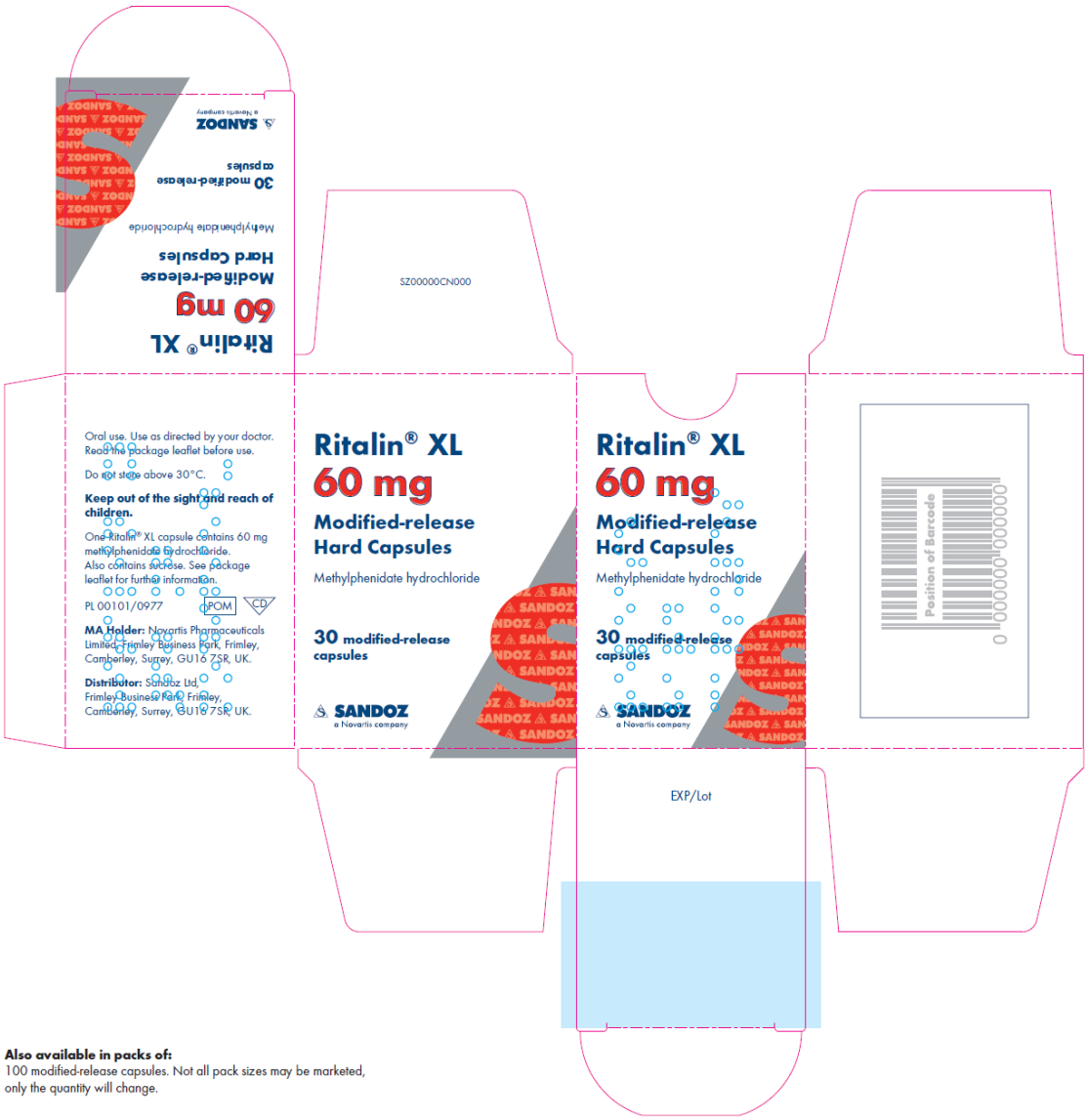
Also available in packs of:
100 modified-release capsules. Not all pack sizes may be marketed, only the quantity will change.

Ritalin XL 40 mg modified-release hard capsules



Also available in packs of:
100 modified-release capsules. Not all pack sizes may be marketed, only the quantity will change.

Ritalin XL 60 mg modified-release hard capsules



Also available in packs of:
100 modified-release capsules. Not all pack sizes may be marketed, only the quantity will change.

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)