CBG MEB

Public Assessment Report

Scientific discussion

Ritalin LA 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, modified-release capsules

(methylphenidate hydrochloride)

NL License RVG: 116377, 116379-116382

Date: 20 October 2016

This module reflects the scientific discussion for the approval of Ritalin LA 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, modified-release capsules. The marketing authorisation was granted on 30 August 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
ASRS	Adult Self-Report Scale
AUC	Area Under the Curve
b.i.d.	*bis in die*, twice a day administration
CAARS	Conners' Adult ADHD Rating Scale
CAARS-O:S	CAARS Observer Short Version
CADS	Conners' ADHD/DSM-IV Scale
CADS-P	Conners' ADHD/DSM-IV Scale for Parents
CADS-T	Conners' ADHD/DSM-IV Scale for Teachers
CASS	Conners-Wells Adolescent Self Report Scale
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CGI-I	Clinical Global Impression Improvement
CGI-S	Clinical Global Impression Severity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPRS	Conners' Parent Rating Scale
DR	Delayed Release
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference of Harmonisation
IR	Immediate Release
ITT	Intention to Treat
K_{ow}	Octanol-Water Partition Coefficient
LOCF	Last Observation Carried Forward
LS	Least Squares
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
MMRM	Mixed Model Repeated Measures
MSBP	Mean Systolic Blood Pressure
n	Number of patients
NICE	National Institute for Health and Care Excellence
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
PBT	Persistence, Bioaccumulation and Toxicity
PD	Pharmacodynamics
$PEC_{surface\ water}$	Predicted Environmental concentration in surface water
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PP	Per Protocol
q.d.	*quaque die,* once a day administration
RH	Relative Humidity
RMP	Risk Management Plan
RS	Rating Scale
SDS	Sheehan Disability Scale
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale
SmPC	Summary of Product Characteristics
SODAS	Spheroidal Oral Drug Absorption System
TEAE	Treatment-emergent Adverse Event
TSE	Transmissible Spongiform Encephalopathy
vPvB	Very persistent and very bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ritalin LA 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, modified-release capsules from Novartis Pharma B.V.

The product is indicated as 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.

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with Ritalin LA in adults is not appropriate.

A comprehensive description of the indications and posology is given in the SmPC.

This is a national application in accordance with article 8(3) of Directive 2001/83/EC. It concerns a line extension of Ritalin tablets 10 mg (NL License RVG 03957), which has been registered since 17 June 1982. The active substance is methylphenidate hydrochloride. It is developed as a new pharmaceutical form and new dosage strengths (10, 20, 30, 40 and 60 mg capsules). The modified-release capsules are designed to provide a bimodal release schedule that attempts to mimic that of b.i.d administration of Ritalin immediate-release tablets.

Ritalin LA uses Spheroidal Oral Drug Absorption System (SODAS) technology. The capsule is composed of nonpareil immediate- and extended-release beads with the delayed release mediated through a polymer coating. This formulation provides 50% immediate release beads and 50% extended release beads, resulting in a first peak at approximately two hours and a second peak at approximately six hours after administration.

In support of this application the MAH submitted data of pharmacokinetic/pharmacodynamic studies and clinical efficacy and safety data.

The MAH obtained scientific advice from the MEB in 2013 regarding the development programme. Scientific advice was also obtained from the German, Belgian and UK authorities.

Adults
Besides the indication in children and adolescents, the company also applied for an indication for ADHD treatment in adults. Based on the submitted data, this indication was however not granted. See section IV 'Clinical aspects' for the assessment of the presented results of safety and efficacy studies in adults. Ritalin LA is however authorised for continuation of treatment into adulthood for patients who were successfully treated in childhood/adolescence.

II. QUALITY ASPECTS

II.1 Introduction

Ritalin LA 10 mg is a hard gelatin capsule 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.
Ritalin LA 20 mg is a white hard opaque gelatin capsule, imprinted with "NVR" in tan ink on the cap and "R20" in tan ink on the body.
Ritalin LA 30 mg is a yellow hard opaque gelatin capsule, imprinted with "NVR" in tan ink on the cap and "R30" in tan ink on the body.
Ritalin LA 40 mg is a light brown hard opaque gelatin capsule, imprinted with "NVR" in tan ink on the cap and "R40" in tan ink on the body.
Ritalin LA 60 mg is 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.

The capsules contain a 50:50 mixture of white to off-white immediate release (IR) and delayed release (DR) beads that are roughly spherical in shape.

The capsules are packed in 90 cc and 175 cc square high density polyethylene (HDPE) bottles with 38 mm child resistant polypropylene (PP) closures with an aluminium induction seal.

The excipients are ammonio methacrylate copolymer, polyethylene glycol, sugar spheres, methacrylic acid copolymer type A, talc, triethyl citrate, gelatin, titanium dioxide (E171), iron oxide black and red (E172) (10, 40 and 60 mg), iron oxide yellow (10, 30, 40 and 60 mg), schellac (E904).

The five strengths are dose proportional; the formulation of Ritalin LA is the same, differing only in the quantity of beads.

II.2 Drug Substance

The active substance is methylphenidate hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white, fine, crystalline powder which is freely soluble in water. The drug substance corresponds to a racemate. The MAH indicated that no polymorphs have been reported. Particle size is controlled in the drug substance specification. Polymorphic form and particle size are less relevant as the drug substance is dissolved in water during the manufacturing process of the drug product.

Manufacturing process
The manufacturing process consists of six synthetic steps. The active substance was adequately characterized. Acceptable specifications were adopted for starting materials, solvents, and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph on methylphenidate hydrochloride with appropriate additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification were provided for three production scale batches.

Stability of drug substance
Stability data on the active substance were provided for three production scale batches stored at 25°C/60% RH (60, 36, and 24 months) and 40°C/75% RH (one batch for 60 months). No significant changes or trends were observed in the provided stability data. Based on the provided stability data, the proposed re-test period of two years is justified. The drug substance was shown to be photostable.
The temperature storage condition “Do not store above 25°C” is applied, although not necessary based on the data provided.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.
Aim of the formulation development was to develop a modified-release product which mimics dosing of two Ritalin immediate release tablets four hours apart. The modified-release pulse formulation was developed based on the SODAS (Spheroidal Oral Drug Absorption System) technology. Half of the dose is contained in immediate-release beads and half of the dose is contained in delayed-release beads. The release profile is achieved by film coating methylphenidate hydrochloride onto sugar spheres to produce immediate release beads. A portion of these immediate release beads are then coated with a polymeric film to effect the required delayed release or second pulse. The second pulse eliminates the need for a mid-day dose. A proportional amount of each type of beads based on assay values is encapsulated to produce 10 mg (5/5), 20 mg (10/10), 30 mg (15/15), 40 mg (20/20) and 60 mg (30/30) strengths.
The bead formulation allows sprinkling of the contents onto soft food. Moreover, the beads are less prone to dose dumping than a monolithic system. Dose dumping is however observed in *in vitro* dissolution studies in the presence of very high concentrations of ethanol. A corresponding warning has been included in the product information.

Dissolution profiles were similar for the different Ritalin LA strengths.
The MAH applied for a biowaiver for the 60 mg capsule. Clinical studies for this strength were carried out with 2 x 30 mg. Dissolution profiles of 2 x 30 mg and 1 x 60 mg are similar. Comparable dissolution of the immediate release beads and the delayed release beads has been demonstrated.

Manufacturing process
The manufacturing process consists of fluid bed coating of sugar spheres with IR coating solution following by drying and screening, fluid bed coating of part of the IR beads with DR coating solution followed by drying and screening, and encapsulation. The manufacturing process as such is considered a standard process. However, due to the modified-release component, the drug product is regarded as a specialised pharmaceutical dosage form for which production scale validation data should be provided.
The manufacturing process is adequately described including settings of critical process parameters.
The manufacturing of the IR and DR beads was successfully validated with three consecutive full scale batches of both types of beads. A bracketing approach was used for the encapsulation process. This is acceptable as the same beads are used for all strengths and the encapsulation process is a standard process. All predefined acceptance criteria were met.

Control of excipients
Apart from the capsule shells and iron oxides, all excipients comply with the Ph.Eur. The iron oxides comply with the National Formulary and Regulation 231/2002. The specifications of the excipients are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average capsule fill weight, identification, purity, residual solvents, assay, drug release and microbial enumeration. Apart from the fact that not all tests are carried out during stability studies, the release and shelf life specifications are identical. The drug product specification is acceptable.
Analytical methods were adequately described and validated. The method for assay and related substances was shown to be stability indicating. Batch analysis data of three commercial scale batches of each strength demonstrate compliance with the release specification.

Stability of drug product
Primary stability data on the product was provided on three pilot scale batches of the 10 mg, 20 mg, 30 mg, and 40 mg strength and three commercial scale batches of the 60 mg strength stored at 25°C/60% RH (lower strengths: 36 months, 60 mg strength: 18 months), 30°/65% RH (60 mg strength: 18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. Moreover, stability data was provided at other storage conditions which are relevant for other climatic zones and on annual stability batches. The batches were stored in high density polyethylene bottles with aluminium induction seal and child-resistant cap.
Out-of-specification results were seen for dissolution at 40°C/75% RH. No significant changes or trends were observed in the other parameters. Based on the provided stability data, the proposed shelf lives of 36 months for the lower strengths and 24 months for the 60 mg strength as well as the proposed storage conditions have been granted: “Do not store above 30°C. Keep the container tightly closed.” The drug product was shown to be photostable.
Stability of the drug product was demonstrated during three months storage at 25°C/60% RH and 30°C/75% RH in an open dish. An in-use shelf life in the SmPC is not necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is of bovine origin. Copies of valid TSE CEPs of the suppliers of gelatin have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Ritalin LA modified-release capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of methylphenidate are well known. It is widely used and its safety profile is well established. Overview based on literature review is, thus, appropriate.

The new dosage form is to be taken via the same route (oral) as the immediate release Ritalin tablet. The recommended dose for the paediatric population has not changed. Additional clinical data were provided regarding pharmacokinetics, efficacy and safety. Therefore it is not necessary to provide additional non-clinical data to support the new dosage form.

A new clinical development programme, including long-term follow-up, was carried out to support the extension of the indication for Ritalin from children to adults. The non-clinical data that would be more relevant to adults than children is repro-toxicity data. However, since the approved indication for Ritalin covers adolescents up to 17 years, repro-toxicity data have already been reviewed in the context of the Article 31 referral (2008) for methylphenidate and appropriate standard wording regarding fertility, pregnancy and lactation approved in all EU SmPCs for products that contain methylphenidate. Therefore, it is not necessary to provide additional non-clinical data to support the extension of the indication to include adults.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Substance (INN/Invented Name): Methylphenidate hydrochloride					
CAS-number: 298-59-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107				The study was not provided.
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	ion-corrected log D_{OW} = 0.97			not B
Persistence	DT50	7.0-8.3 hours			not P
Toxicity	NOEC	0.77 mg/L (for algae)			not T
PBT-statement	not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default	0.4	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Sludge Koc ads = 13 – 15 L/kg Sludge Kd ads = 4.2 – 5.1 L/kg Soil Koc ads = 134, 833, 2872 L/kg			
Ready Biodegradability Test	OECD 301				The study was not provided.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ = 7.0-8.3 h % shifting to sediment = 55.7-57.9			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Desmodesmus subspicatus*	OECD 201	NOEC	0.77	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	5.2	mg/L	
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	NOEC	3.3	mg/L	

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	326	mg/L	

Methylphenidate hydrochloride is not a PBT nor a vPvB substance.
Considering the above data, methylphenidate hydrochloride is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

This product is a line extension to the registered Ritalin immediate-release formulation. Reference is made to the preclinical data previously obtained. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required. An appropriate ERA has been provided, which demonstrated that a risk to the environment is not expected.

IV. CLINICAL ASPECTS

IV.1 Introduction

Methylphenidate is a well-known active substance with established efficacy and tolerability. In support of this line extension, the MAH submitted data of pharmacokinetic/pharmacodynamic studies as well as clinical efficacy and safety data. The Ritalin LA formulation was studied in children, adolescents and adults.

IV.2 Pharmacokinetics

Part of the human pharmacokinetics (PK) is known from the marketed Ritalin IR 10 mg tablets. In order to evaluate the pharmacokinetics concerning absorption and bioavailability of methylphenidate hydrochloride from the LA formulation, 8 pharmacokinetic studies were submitted. Studies D0001, D0004, D0006, D0009, DDE02, DUS06 and E2101 were performed in healthy volunteers and study D0002 in children with ADHD aged 6-12.

Table 1. Design of the pharmacokinetic studies

Study	Purpose	Type of control	Design, Dose/day	No. of subjects	Population
D0001	PK/tolerability	Ritalin tablets	Randomized, 3 period, 3-treatment, crossover study Ritalin tablets (b.i.d.): 10 mg Modified release prototypes Elan 1 and Elan 2 (q.d.): 20 mg	9	Adult healthy volunteers
D0002	PK & PD profiles	Placebo	Double-blind, placebo controlled, randomized, 5-treatment crossover study Formulation 1 (17.5 mg, 20 mg, 25 mg) Formulation 2 (20 mg) Modified release	34	Children with ADHD

			formulation or matching placebo administered once a day in Treatment Evaluation Period		

Study	Purpose	Type of control	Design, Dose/day	No. of subjects	Population
D0004	Food interaction	None	Open-label, randomized, single dose, 3-treatment crossover study Ritalin LA: 40 mg	20	Adult healthy volunteers
D0006	Relative bioavailability	Ritalin tablets	Open-label, randomized, single-dose, 4-treatment, 4-period crossover study Ritalin LA: 40 mg Ritalin tablets: 2 x 20 mg	17	Adult healthy volunteers
D0009	Food interaction	None	Open-label, randomized, single-dose, 4-treatment crossover study Ritalin b.i.d.: 10 mg Modified release prototypes Elan 1 and Elan 2 (q.d.): 20 mg	15	Adult healthy volunteers
DDE02	Bioequivalence	Medikinet Retard	Open label, single center, randomized, 4-treatment, 4-period single oral dose, crossover design Ritalin LA: 40 mg Medikinet Retard: 40 mg	28	Adult healthy volunteers
DUS06	Bioequivalence	Concerta	Open-label, single-center, randomized crossover design Ritalin LA: 20 mg Concerta: 18 mg	20	Adult healthy volunteers
E2101	Bioequivalence	Focalin LA Focalin IR	Open-label, single-dose, 3-treatment, 3-period, randomized crossover design Focalin LA: 20 mg Focalin IR: 2 X 10 mg Ritalin LA: 40 mg	24	Adult healthy volunteers

Biowaiver

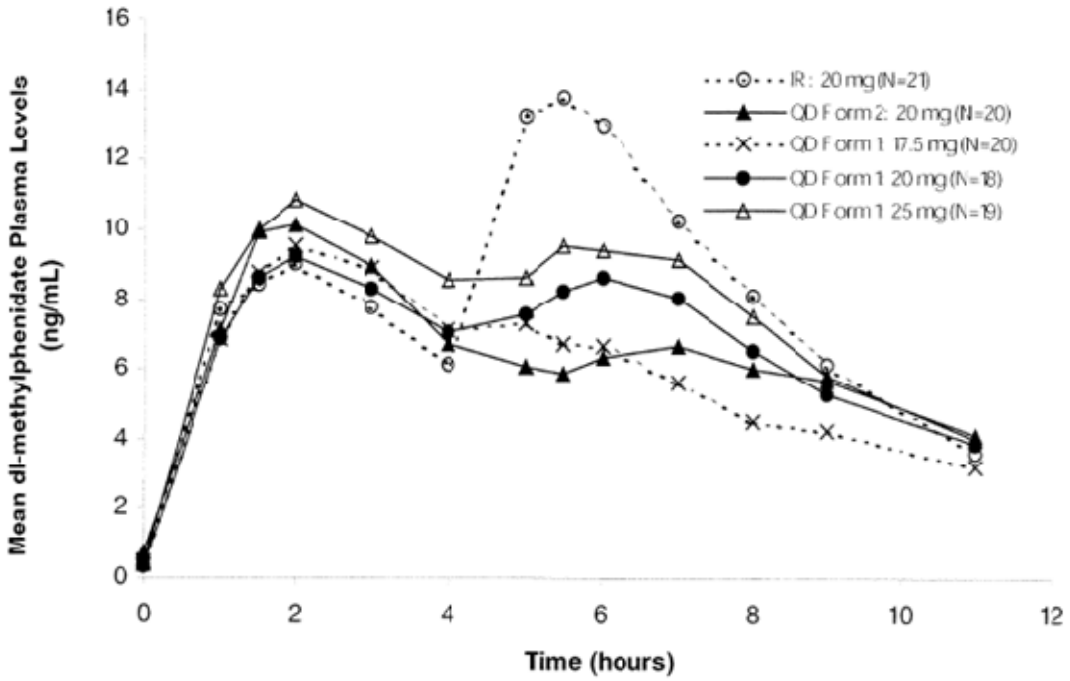
The application concerns 10, 20, 30, 40 and 60 mg Ritalin LA formulations. During development the pharmacokinetics of the 10, 20 and 40 mg dose have been characterized, the 30 mg, 50 mg and 60 mg doses have not been characterized. This is accepted, as the formulation of Ritalin LA is the same for all strengths (10, 20, 30, 40 and 60 mg) differing only in the quantity of beads. Dissolution profiles were similar for the different Ritalin LA strengths.

Summary of PK results

A single oral dose of a Ritalin LA capsule resulted in a bimodal methylphenidate concentration-time profile, with two distinct peaks approximately 4 hours apart. At a dose of 40 mg, the median t_{max} is 1.5 h under fasted conditions. The $C_{max0\text{-}4h}$ is ~13 ng/mL and $C_{max4\ 10h}$ is ~12 ng/mL.

Ritalin LA is bioequivalent to Ritalin IR, administered as two tablets 4 hours apart, with regard to the $AUC_{0\text{-}4h}$ and $C_{max0\text{-}4}$h. However, during the second part of the treatment (i.e. $AUC_{4\text{-}8h}$ and $C_{max4\text{-}8h}$) lower exposure to methylphenidate is obtained with the modified-release formulation, as compared to the IR tablet, with the 90% CI being outside the bioequivalence acceptance range (studies D0002 and D0006). The median $t_{max0\text{-}4h}$ and $t_{max4\text{-}t}$ were comparable between Ritalin LA and Ritalin IR b.i.d., i.e. 1.9 and 2.0 hours and 5.6 and 6.4 hours, respectively (see figure below).

Figure 1 Mean dl-methylphenidate concentrations versus time in children in Study D0002 comparing different modified-release formulations with 2 tablets of Ritalin IR 10 mg administered at t=0 and 4 hours; OD form 1 20 mg = Ritalin LA



The fluctuation index from 0-8 hours for methylphenidate following administration of the modified-release Ritalin capsule is smaller than the fluctuation index following administration of two Ritalin IR tablets given 4 hours apart.

C_{max} and $AUC_{0\text{-}t}$ of the two release profiles (0-4 h and 4-10h) are dose proportional over a dose range of 5 to 40 mg d-methylphenidate. Ritalin LA is composed of d- and l-methylphenidate in a 50:50 ratio. The pharmacodynamic activity of dl-methylphenidate resides entirely with the d-isomer and the bioavailability of l-methylphenidate is <10%. Overall, it can be concluded that Ritalin LA is dose-proportional over a dose range of 10 to 80 mg (dl-methylphenidate) and that d-methylphenidate is responsible for the efficacy and safety.

Food effects were investigated in studies D0004 (high fat breakfast, apple sauce and fasted conditions) and DDE02 (continental breakfast and fasted conditions). Following high-fat breakfast, the

majority of the subjects displayed bimodal plasma concentration versus time profiles for Ritalin LA. However, due to high inter-individual variability in $t_{max0-4h}$ and t_{max4-t}, it was not clear from the mean plasma concentration versus time profile. AUC_{4-8h} and $C_{max4-8h}$ following a high fat breakfast were lower (15-23%) as compared to fasting conditions. In addition, the median first t_{max} is shifted 1.5 hours (from 1.5 (1.0-2.0) to 3.0 (0.5-6.0)) and the median second t_{max} is shifted 2.5 hours (median (range) from 5.5 (4.5-6.0) to 8.0 (4-16)) compared to fasted conditions. No food effects were observed from intake with apple sauce compared to fasted conditions. Only slight effects on the $C_{max4-10h}$ (13%) and $t_{max4-10h}$ (shift from 4.0-6.5 hours to 4.0-8.0 hours) were observed after intake with a continental breakfast compared to fasted conditions (study DDE02). No effects were observed AUC_{0-4h}, AUC_{4-10h}, $t_{max0-4h}$ and $C_{max0-4h}$ following a continental breakfast. This indicates that a continental breakfast has only a slight effect on the second absorption phase of dl-methylphenidate. These observations however do not hamper the proposed recommendations regarding the food intake, i.e. regardless of food, as these were the conditions under which the product was administered in the pivotal phase III studies.

Relative bioavailability studies were performed for Ritalin LA compared to Medikinet, Concerta and Focalin LA.

Under fed conditions, Ritalin LA and Medikinet are bioequivalent based on the $AUC_{0-\infty}$ but not based on the C_{max}. In addition, $C_{max0-4h}$ and $C_{max4-10h}$ are higher for Medikinet than of Ritalin LA. Medikinet showed also superior efficacy compared to Ritalin LA.

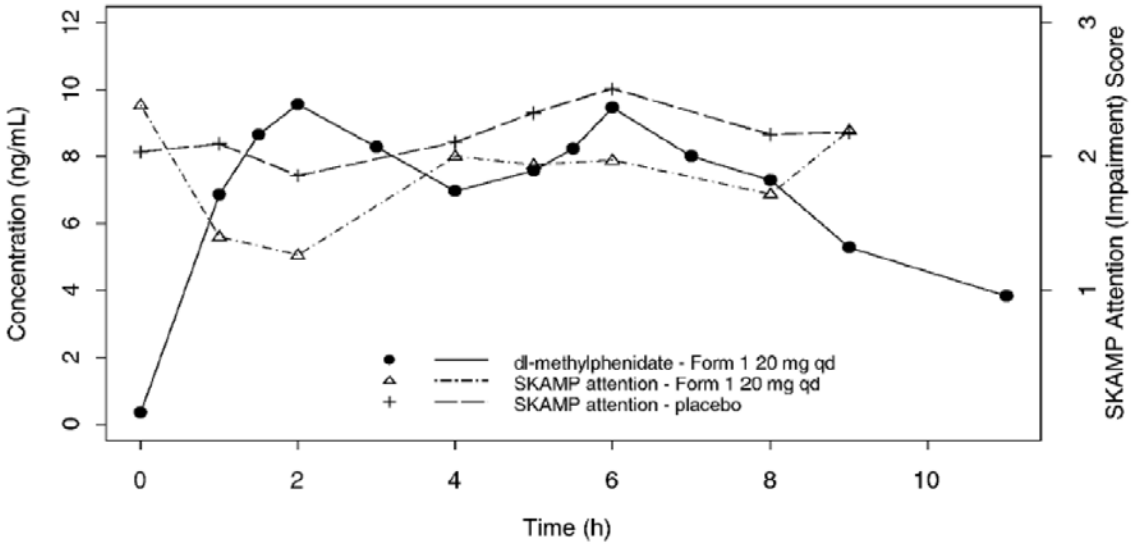
Ritalin LA and Concerta are also not bioequivalent and have very different plasma concentration time curves. The $C_{max0-4h}$ and $C_{max4-10h}$ of Ritalin LA are higher than that of Concerta. Ritalin LA showed superior efficacy compared to Concerta.

Ritalin LA and Focalin LA are bioequivalent. No clinical efficacy comparative study was performed for Ritalin LA and Focalin LA. Focalin LA is not registered for the EU market. Currently, it is only registered in the USA and Switzerland.

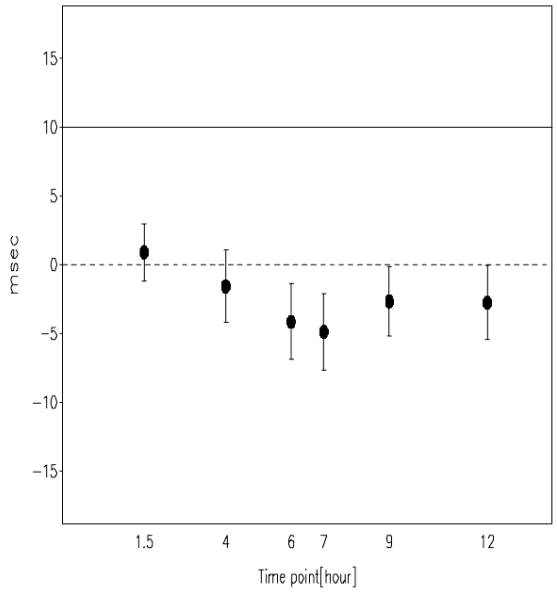
Further pharmacokinetics and interactions are conceivably the same as has been described for Ritalin IR tablets.

IV.3 Pharmacodynamics

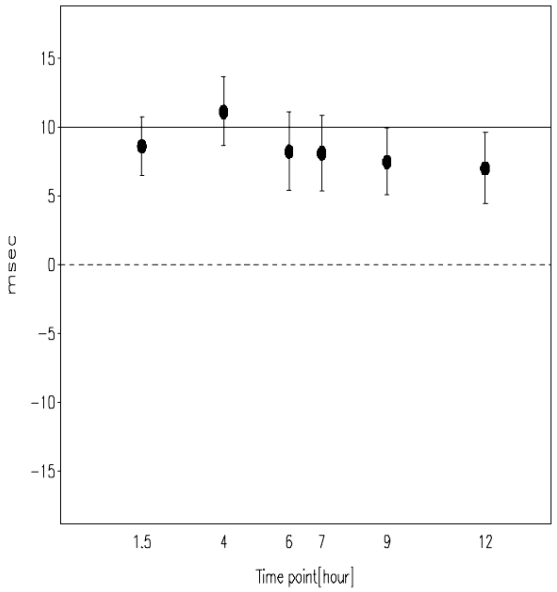
In a pharmacodynamic study in 34 ADHD children 6-12 years of age pre-treated with methylphenidate, a relationship was shown between plasma-concentration of methylphenidate in time after 20 mg Ritalin LA, and a rating-scale of cognitive performance ('SKAMP-attention'). See plot below:



In a thorough QT-study in 72 healthy adult volunteers effects (with 90%CIs) on the QT-interval (with Friderichia-correction) as compared to placebo of Focalin XR (the d-isomere of methylphenidate LA) 40 mg (stated to be equivalent to Ritalin LA 80 mg) were within the 10 msec safety margin, as opposed to the active comparator moxifloxacin. See figure below:



Focalin v/s Placebo



Moxifloxacin v/s Placebo

The PK-PD results in paediatric ADHD patients support an association between plasma-concentration of methylphenidate and improved cognitive performance.
Regarding PD-effects, i.e. central nervous system-effects such as cognitive performance, reference is made to PD results in children and adolescents and adult PK data.

IV.4 Clinical efficacy

IV.4.1 Children and adolescents

IV.4.1.1 Methodology

Six studies were conducted with a total of 517 children with ADHD aged 6 to 18 years. All studies were randomized, double blind and placebo controlled. One study had a parallel group design (study D0007) and the remaining 5 had a crossover design. Three of the studies had, in addition to placebo, an active control arm (2 Concerta and one Medikinet). Five of the studies were conducted in the US and Canada and one in Germany. One study included adolescents (adolescent girls) and the remaining 5 included only children.

Details of the design of the studies in paediatric patients are summarized below.

Table 2. Design of paediatric studies

Protocol Sites	**Design, population**	**N**	**Duration DB**	**Dosage**	**Primary endpoints**
D0007 US and Canada	- Parallel-group - Normal schools and home - children 6-12 with DSM IV ADHD -2 weeks titration methylphenidate IR	164 enrolled 137 randomised 130 completed 134 ITT (63 Ritalin LA, 71 placebo)	2 weeks	Individually titrated Ritalin LA (10-40 mg) or placebo	Change form baseline to 2 weeks on CADS-T

D0002 US	- 5-period crossover - laboratory classroom - Children 6-12 with DSM IV ADHD combined type already treated with methylphenidate IR	40 enrolled 34 randomized 34 completed	5 Saturdays: 4 Ritalin LA 1 placebo	Formulation 1 (RS:L) / 17.5 mg, 20 mg, and 25 mg; Formulation 2 (S) / 20 mg) In between: usual dose of methyl phenidate.	AUC for SKAMP and Math test over 9 hr period.
DUS02 US	- 2 period crossover - females adolescent 12-17 DSM IV ADHD -Patients treatment naïve and non-naive	109 randomised 83 completed	4 wk per period +1 wk placebo in between	Individually titrated Ritalin LA (20-60 mg) or placebo	Change form baseline to 4 weeks on CPRS total score
DUS05 US	-4 period crossover - laboratory classroom - Single blind - active control (Concerta) - children aged 6-12 DSM IV ADHD stabilised on 10 mg b.i.d. methylphenidate.	36 randomised 36 completed	4 x 1 day single dose Ritalin LA/Concerta/ placebo & 6 days of usual methylphenidate IR treatment in between	Ritalin LA 20 mg, Concerta 18/36 mg & placebo	AUC for SKAMP and Math test over 4 hr period. Superiority Ritalin LA 20 mg > Concerta 18mg
DUS07 US	- 5 period crossover - school setting - Single blind - active control (Concerta) - children aged 6-12 DSM IV ADHD stabilised on 20-40 mg methylphenidate.	54 randomised/ 53 completed	5 x 1 day single dose Ritalin LA/Concerta/ placebo & 6 days of usual methylphenidate IR treatment in between	Ritalin LA 20/40 mg, Concerta 18/36 mg, & placebo	AUC for SKAMP Attention ratings over 2 hr period. Superiority Ritalin LA 20 mg > Concerta 18mg
DDE01 Germany	- 3 period crossover - laboratory classroom - DB - active control (Medikinet	147 146 completed	3 x 1 week	Ritalin LA 20 mg, Medikinet Retard 20 mg, placebo	SKAMP Combined rating1.5, 3.0 and 4.5 hours after drug intake in a laboratory classroom

	Retard) - children aged 6-14 DSM IV ADHD stabilised on methylphenidate IR.				setting

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders 4th edition
CGI-I = Clinical Global Impression – Improvement Scale
CGI-S = Clinical Global Impression – Severity Scale
CPRS = Conners' Parent Rating Scale
SKAMP = Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale
CADS-P = Conners' ADHD/DSM-IV Scale for Parents
CADS-T = Conners 'ADHD/DSM-IV Scale for Teachers
DB = Double Blind

Study D0007
This was a multicenter, double blind, placebo controlled, parallel group study in the usual school and home setting of children with ADHD. After a titration period of 2-4 weeks with Ritalin IR (within the dose range of 10-40 mg), patients who responded (response was defined according to the investigator medical judgement) entered a one week, placebo washout period. Patients were then randomised to the double blind treatment phase of two weeks in which patients received their individually titrated dose of Ritalin LA or placebo.
The efficacy assessments used in this study was the Conners' ADHD/DSM-IV Scale for teachers (CADS-T) and parents (CADS-P) and the Clinical Global Impression - Improvement Scale (CGI-I) completed by the investigator. 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 patients' global improvement (from baseline, end of placebo washout period) was evaluated at the end of the double-blind treatment phase. The primary efficacy variable was the change from baseline of the CADS-T DSM-IV total scale score. Secondary efficacy variables were change from baseline in the CADS-P total score and the CADS-P and CADS-T Inattention and hyperactive/impulsive subscale scores and CGI-I ratings.

Instruments
The CADS (Conners' ADHD/DSM-IV Scale) consists of two versions: for parents and for teachers, respectively labelled as CADS-P and CADS-T. Each of these versions has 26 items divided into two sub-components: the ADHD Index (12 items) and the DSM-IV Symptoms subscale (18 items of which 4 are included in the ADHD Index therefore the scale consists of 26 and not 30 items). The DSM-IV symptoms subscale contains two scales: Inattentive (9 items) and Hyperactive-Impulsive (9 items). Each item can be scored 0 (if the symptom never or seldom occurs) to 3 (if the symptom occurs very often). Total scale scores range from 0 to the number of items on the scale multiplied by 3.

The psychometric properties of the scales were studied extensively and norms were developed. These studies indicate good internal consistency of the scales. The correlation between parents and teachers ratings were, however, low to moderate (r=0.46-0.49 for the ADHD Index and the DSM-IV Symptoms subscale respectively). The scales distinguish well between children with ADHD and children without a disorder. The ability of the scales to distinguish between ADHD and other disorders was not established. The scales were found to be sensitive to treatment effects.

Study D0002
This study was designed to evaluate the PD and PK profiles of four formulation variants of Ritalin LA: Formulation 1 (RS:L) 17.5 mg, 20 mg, and 25 mg and Formulation 2 (S) 20 mg. Subjects were male and female outpatients aged 6-12 years who met DSM-IV criteria for ADHD (combined type). Diagnosis was determined via a diagnostic interview (DISC interview - Diagnostic Interview Schedule for Children - Parent version, or a DICA interview - Diagnostic Interview for Children and Adolescents, both based on DSM-IV diagnostic criteria) that was administered to confirm a diagnosis of ADHD as well as the presence of any comorbid psychiatric disorders. Subjects were also required to have already been treated with methylphenidate (10 mg b.i.d) for at least four weeks at the time of enrolment. Required IQ was 80 or higher. Patients with comorbid chronic or severe somatic or psychiatric disorders requiring drug treatment other than methylphenidate were excluded.

After a one-week baseline phase during which patients received open-label methylphenidate 10 mg b.i.d., patients were randomly assigned to receive the four Ritalin LA formulations and placebo in one of 10 possible sequences (altogether there are 120 possible sequences but not all were used in this study). Double blind treatment and evaluations were conducted on five Saturdays in a laboratory classroom set up at each study centre where subjects underwent PD and PK evaluations over a course of eight classroom sessions in a total of an 11.5-hour day. During each treatment evaluation day patients received a single dose of Ritalin LA or placebo, which was administered in the morning of a treatment evaluation day. During the weekdays, between study days, patients received open-label methylphenidate at their usual regimen.

Instruments

Two efficacy measures were used in this study: the SKAMP rating scale and Math Tests. The SKAMP items were rated during 20 minutes of observation of patients during ten class sessions that were scheduled 0-9 hours post dose. The paper and pencil Math Tests were given to patients during the class sessions.

The SKAMP rating scale (named after Swanson, Kotkin, Agler, M-Flynn, and Pelham) was developed by Swanson (1992)[1], one of the two principal investigators on this study. It consists of 13 items, which are divided into 2 scales.

SKAMP Attention	SKAMP Deportment
1. Difficulty getting started on class assignments,	1. Problems in interactions with other children in the classroom,
2. Difficulty staying on task for a class period,	2. Problems in interactions with adult staff (teacher, aide),
3. Problems completing assignments	3. Difficulty remaining quiet according to classroom rules,
4. Problems performing accurate work,	4. Difficulty staying seated according to classroom rules,
5. Difficulty attending to an activity or discussion in class, and	5. Difficulty complying with usual requests or directions from teachers,
6. Difficulty in stopping and making transition to the next period	6. Difficulty following rules established for the school
7. Being careful and neat while writing,	

Each item is scored on a 7-point scale ranging from normal to severe. Hence, higher scores indicate more severe symptoms level. The SKAMP Attention subscale is the average of the 7 seven-point scaled items and the Deportment score of 6 seven-point scaled items.

Swanson also developed the paper and pencil Math Test. It consists of 100 math problems for which the subject is given a timed 10-minute period. Test difficulty can be altered for subjects at different skill levels by adjusting the number of digits being manipulated per calculation. The number of problems attempted and the number of problems correctly answered are generated as objective measures related to “academic productivity”.

The primary efficacy variable was the area under the curve (AUC) for the SKAMP-attention scores obtained over the ten evaluations performed 0-9 hour post dose. AUC was calculated using the trapezoidal rule, i.e. slicing the area into vertical segments of trapezoidal form and calculating the total AUC by adding these segments together.

The comparisons between the two 20 mg variants of Ritalin LA (RS:L and S) with placebo were defined as the primary analysis. Hochberg’s Adjustment for multiple comparisons was applied only to this primary analysis but not to the comparison of the two other Ritalin LA doses (17.5 mg and 25 mg) with placebo.

Secondary efficacy variables were:

- The AUC values for the SKAMP-attention scores computed for the two parts of the evaluation period (i.e. 0-4 hours and 4-9 hours post-dose respectively)
- The AUC values for the SKAMP-deportment scores 0-9 and 4-9 hours post dose

[1] Swanson JM. School-based assessments and interventions for ADD students. Irvine, CA: KC publishing; 1992

- The AUC values for the Math Test scores 0-9 post dose.

Study DUS02
This was a 10-week multicenter, double-blind, randomized, placebo-controlled, crossover study. The primary objective was to compare the efficacy of Ritalin LA 20-60 mg/day to placebo in the symptomatic control of ADHD in female adolescents. The duration of treatment was 10 weeks, which included a 1-week screening period, two 4-week treatment periods, and a 1-week placebo washout period (between treatment periods). A total of 109 female adolescents 12-17 years of age with ADHD were randomized and 83 (76%) completed the study.

Instruments
The primary efficacy variable was the change in Conners' Parent Rating Scale (CPRS) score from pre-treatment to the fourth week of treatment. Secondary efficacy variables were total scores on the Conners-Wells Adolescent Self Report (CASS), and ratings on the Clinical Global Impression of Change (CGI-C) and the Clinical Global Impression of Severity (CGI-S).
The adolescent self-report form, the CASS, is appropriate for use with adolescents ages 12 through 17. The scales provide scores on several dimensions including an ADHD Index scale.

Study DUS05
This was an observer and patient blinded, single-center, four-period, placebo-controlled cross-over study conducted in a laboratory classroom setting. All personnel with the exception of the nurse dispensing the medication were blinded. The non-blinded study nurse did not participate in any other study procedures.
The study compared the efficacy of single daily doses of Ritalin LA 20 mg to Concerta 18 and 36 mg and placebo during an 8-hour school day in boys and girls with ADHD.
Patients aged 6 to 12 years with a DSM-IV diagnosis of ADHD and stabilized on an equivalent dose of 10 mg b.i.d. of immediate release methylphenidate were enrolled. After completing a practice day, 34 patients were randomized into the treatment phase and received four single doses of Ritalin LA 20 mg, Concerta 18 mg, Concerta 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.

Instruments
The efficacy assessments used were based on the SKAMP rating scale and Math Tests. The SKAMP Rating Scale was used to generate scores on two behavioural sub-scales, "Attention" and "Deportment". Scores on the two sub-scales were derived from 20 minutes of direct observations of subject behaviour during eight class sessions scheduled throughout the four treatment evaluation periods.
The Math Test was a paper and pencil test given to subjects during three class sessions to generate two scores: the number of problems attempted and the number of problems correctly answered.
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 $AUC_{0\text{-}4h}$ for change from pre-dose on the SKAMP Deportment subscale, Math Test Attempted and Math Test Correct as well as the change from pre-dose 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 $AUC_{0\text{-}4h}$ for change from pre-dose in SKAMP Combined score, and the $AUC_{0\text{-}8h}$ for change from pre-dose in SKAMP Attention, SKAMP Deportment, SKAMP-Combined, Math Test Attempted and Math Test Correct were compared in exploratory analyses.
Each efficacy variable was compared between treatments using an ANOVA model that includes sequence, treatment and period, and the random effects of subjects within sequences and within-subject errors.

Study DUS07
This was a blinded (observer and patient), multicenter, five-period, placebo-controlled cross-over study in a school setting of children with 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. Male and female patients 6 to 12 years of age with a DSM-IV diagnosis of ADHD of any diagnostic subtype (predominantly inattentive, hyperactive-impulsive or combined type) and stabilized on an equivalent daily dose of 20-

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 non-blinded study nurse, pharmacist or physician did not participate in any other study procedures. After completing a practice day, 54 patients were randomized 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.

Instruments
The efficacy assessments used were based on the SKAMP Rating Scale and Math Tests. The change from pre-dose in SKAMP Attention ratings was the primary efficacy variable in this study. 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 pre-dose 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, 0-8h, 8-12h, and 0-12 h was performed for each of these SKAMP and Math ratings.
Each efficacy variable was compared between treatments using an ANOVA model that includes the fixed effects of centre, sequence, treatment and period, and the random effects of subjects within sequences and within-subject errors.

Study DDE01
This was a multicenter, double-blind, randomized, placebo and active-controlled, three-period crossover design in a laboratory classroom setting, comparing placebo, Ritalin LA (20 mg, q.d.) and Medikinet Retard (20 mg, q.d.) under fed conditions. Male and female patients 6-14 years of age with a confirmed DSM-IV diagnosis of ADHD who were adequately controlled by immediate release methylphenidate were enrolled.
The study had a 4-week pre-randomization phase and a 3-week crossover treatment phase. After completing a practice day, 147 patients were randomized to one of 6 treatment sequences. Patients were treated with placebo, Ritalin LA and Medikinet, each for one week.
The primary objective of this study was to demonstrate the efficacy of Ritalin LA 20 mg in children with ADHD aged 6-14 by testing the hypothesis that Ritalin LA 20 mg is superior to placebo and is clinically not inferior to Medikinet Retard 20 mg.

Instruments
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 after drug intake, 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 Behavior Rating Form.

IV.4.1.2 Results

Patients disposition
All patients completed study D0002. In study D0007, a total of 7 (5.1%) patients discontinued during the double-blind treatment. The majority of discontinuations were due to adverse events (2 Ritalin LA; 1 placebo) or unsatisfactory therapeutic effect (1 Ritalin LA; 1 placebo).
No discontinuations due to adverse events were reported in any of the studies. In study DUS02, 23.9% of patients were permanently discontinued. The most frequent reason for discontinuation was ‘unsatisfactory therapeutic effect’, reported for 9.2% of patients. One patient was discontinued from study DUS07 due to administrative problems, and one patient in study DDE01 withdrew consent.

Demographic characteristics
Except for study DUS02 (in female adolescents) the majority of patients included in the studies were male (63%-80%) and except for study DUS05, the majority were Caucasian (63%-98%). Mean age was approximately 9-10 except for the adolescents study (mean age 14). Mean weight ranged

between 34kg and 38kg. The majority of patients in all studies had a diagnosis of combined ADHD. The mean age at onset of symptoms was similar across studies.

Study D0007
The results of study D0007 are summarised in the table below.

Table 3. Primary and secondary efficacy results for study D0007

	N	Baseline mean[a] (SD)	Change from baseline at week 5 (SD)	Difference between Ritalin LA and placebo (95% CI)
Primary outcome: CADS-T DSM-IV total subscale scores change from baseline				
Ritalin LA	62	27.2 (15.5)	11.2 (15.7)	14.3 (10.4 ↔ 18.2)
Placebo	70	28.3 (15.8)	-3.1 (10.6)	
Secondary outcomes				
CADS-T DSM-IV inattentive subscale scores change from baseline				
Ritalin LA	62	14.9 (8.4)	5.3 (8.3)	6.8 (4.4 ↔ 9.3)
Placebo	70	14.9 (7.9)	-1.5 (5.7)	
CADS-T DSM-IV hyperactive-impulsive subscale scores change from baseline				
Ritalin LA	62	12.3 (8.1)	5.4 (7.9)	6.7 (4.3 ↔ 9.1)
Placebo	70	13.4 (8.8)	-1.3 (5.9)	
CADS-P DSM-IV total subscale scores change from baseline				
Ritalin LA	63	27.5 (13.7)	6.3 (13.5)	5.8 (1.2 ↔ 10.4)
Placebo	70	27.6 (14.7)	0.5 (13.6)	
CADS-P DSM-IV inattentive subscale scores change from baseline				
Ritalin LA	63	15.0 (6.7)	2.8 (7.3)	2.6 (0.26 ↔ 4.94)
Placebo	70	14.7 (7.1)	0.2 (6.4)	
CADS-P DSM-IV hyperactive-impulsive subscale scores change from baseline				
Ritalin LA	63	12.5 (8.0)	3.5 (6.9)	3.2 (0.73 ↔ 5.67)
Placebo	70	12.9 (8.3)	0.3 (7.7)	
CGI scale final assessment				
		Improved[b] N (%)		
Ritalin LA	63	44 (69.8%)		29.8% (12.9% ↔ 44.4%)
Placebo	70	28 (40.0%)		
		Worsened[c] N (%)		
Ritalin LA	63	1 (1.6%)		-24.1% (-35.5% ↔ -13.0%)
Placebo	70	18 (25.8%)		

[a] baseline measurements were taken during the one week washout period
[b] Improved = very much improved, much improved, and minimally improved.
[c] Worsened = very much worse, much worse, and worse.

The mean scores on the CADS-T at baseline range between 27-28 (see table). Given the fact that this scale consists of 18 items, each of which can be scored between 0 (symptom not present) and 3 (symptom often present), the total score on this scale can range between 0 and 18x3=54. A total score

of 27 on the scale indicates that the mean score on each item is 1.5. This in turn implies a patient population that is medium severity.

The results for the primary efficacy analysis show a difference of 14.3 (10.4 , 18.2) points between the improvement in the Ritalin LA group and the improvement in the placebo group. This corresponds to a large effect size of 1.1.

The results from the secondary efficacy outcomes indicate that the improvement in the total score of the CADS-T is equally due to improvements in the inattentive subscale as to improvement in the hyperactive-impulsive subscale. Results with respect to the parent's version of this scale (the CADS-P) indicate that the magnitude of improvement at home as evaluated by parents is considerably smaller compared to the improvements as evaluated by teachers (effect size for parents rating is 0.43, which is considered a "medium" effect size).
Results with respect to the CGI assessments show considerable difference between the treatment groups in evaluated improvement as assessed by the investigator.

Study D0002
The table below presents the results of study D0002 with respect to the primary and secondary outcome variables. The two 20 mg doses variants of the primary analysis were statistically significantly different from placebo when the Hochberg procedure was applied to correct for multiple comparisons. The other two formulations (17.5 mg and 25 mg) were also significantly different from placebo at the 0.05 level, but no correction for multiple comparison was applied to these comparisons.

Table 4. Efficacy results for study D0002

Primary outcome **AUC of SKAMP attention scores 0-9 hours post dose**					
	Placebo (n=32)	**Form 1 17.5 mg** (n=34)	**Form 1 20 mg** (n=32+)	**Form 1 25 mg** (n=33)	**Form 2 20 mg** (n=34)
AUC	19.84	16.75	16.74	15.72	16.72
Δ treatment vs. placebo		-3.09	-3.10	-4.12	-3.12
95% CI		-4.57↔ -1.59	-4.58 ↔ -1.60	-5.57, ↔ -2.65	-4.60 ↔ -1.62
Secondary outcomes **AUC of SKAMP attention scores 4-9 hours post dose**					
AUC	11.64	10.17	10.07	9.17	10.39
Δ treatment vs. placebo		-1.47	-1.57	-2.47	-1.25
95% CI		-2.56 ↔ -0.37	-2.67 ↔ -0.47	-3.54 ↔ -1.39	-2.35 ↔ -0.15
AUC of SKAMP deportment scores 0-9 hours post dose					
AUC	22.83	16.57	16.01	13.76	15.85
Δ treatment vs. placebo		-6.26	-6.82	-9.07	-6.98
95% CI		-8.54 ↔ -3.97	-9.11 ↔ -4.53	-11.31 ↔ -6.82	-9.27 ↔ -4.68
4-9 hours post dose					
AUC	13.35	10.77	10.08	8.37	9.76
Δ treatment vs. placebo		-2,58	-3.27	-4.98	-3.59
95% CI		-4.12 ↔ -1.02	-4.82 ↔ -1.71	-6.49 ↔ -3.45	-5.13 ↔ -2.03
AUC Math test scores – number of problems correctly answered 0-9 hours post dose					
AUC	777.55	1134.59	1171.54	1150.27	1101.14
Δ treatment vs. placebo		357.04	393.99	372.72	323.59
95% CI		236.45 ↔ 477.64	272.99 ↔ 514.99	254.46 ↔ 490.99	202.62 ↔ 444.57

+ The report does not indicate why 32 rather than 34 patients were evaluated in the Form 1 20 mg and in the placebo conditions

A lower AUC for the SKAMP indicates better functioning compared to larger AUC and therefore a negative difference between active arm and placebo indicates superiority of the active arm over placebo.
The effect size for the primary endpoint varies between 0.5 and 0.7, depending on the dose. These are considered effects of "medium" size.
AUC for the 4-9 hours post dose showed a considerably (about 50%) smaller effect size.
All Ritalin q.d. doses have rapid onset of effect post dose but the effects diminish with time and approach that of placebo as time goes by, namely after 8 hours.

The SKAMP deportment scores initially improve with time and reach the best point at 2 hours post dose, from which point they start to slowly worsen. At 6 and 8 hours post dose the 20 and 25 mg dose reach another improvement, but this is not as pronounced as the improvement at 2 hours post dose. At 9 hours post dose the baseline level is almost reached.

Results with respect to the Math test indicate that the AUC for the number of problems correctly answered (see table above) and number of problems attempted (not shown) are significantly larger for all Ritalin LA doses compared to placebo. The advantage is booked early during the observation period (0-4 hours after administration) and diminishes with time. However, as the IR product was not included as an active control arm in this study, a direct comparison of efficacy over time is not possible.

Study DUS02
The table below presents the results of this study (crossover study in adolescent girls) with respect to the primary endpoint (Conners' Parent Rating Scale (CPRS)). The Least Squares (LS) Means (95% CI) for changes from pre-treatment in 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) vs. -9.9 (95% CI; -12.8, -7.1), respectively. 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) and corresponds to an effect size of 0.8 which is considered a large effect size.

Table 5. Efficacy results for study DUS02: Change from pre-treatment CPRS total score (ITT with LOCF)

	CPRS total score[1]	
	Ritalin LA N = 102	**Placebo 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.

Secondary efficacy results
The difference in change from pre-treatment to the end of the second week of treatment in CPRS total scores was smaller than at the end of week 4 but still statistically significant in favour of Ritalin LA (LS Mean treatment difference:-5.7; 95% CI: -8.8, -2.7; p< 0.001).
The change in Conners-Wells Adolescent Self Report (CASS) total scores from pre-treatment to the end of the fourth week of treatment was small. However, it reached statistical significance (Mean difference (-1.9; 95% CI: -3.8,-0.1) in favour of Ritalin LA.
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.

It was shown that the SKAMP attention score became worse with time in the placebo treated patients. In the Ritalin LA treated patients, the scores initially improve with time and then start to slowly attenuate.

The LS Means differences in change from pre-dose in SKAMP Attention scores to 4 hours post-dose were statistically significant in favour of Ritalin LA 20 mg compared to Concerta 18 mg (p=0.015), Concerta 36 mg (p=0.043) and placebo (p<0.001).

Ritalin LA vs. placebo
The LS Mean difference between Ritalin LA and placebo for change from pre-dose in SKAMP Attention score was statistically significant in favour of Ritalin LA at 0-4 hours (primary endpoint) as well as at 4-8 hours and 0-8 hours.
This superiority for Ritalin LA over placebo was also observed in SKAMP Deportment, SKAMP Combined, Math Test Correct, and Math Test Attempted at 0-4 hours, 4-8 hours and 0-8 post-dose.

Ritalin LA vs. Concerta
Ritalin LA was not statistically better than Concerta on SKAMP attention during the entire assessment period (0-8 hours post dose). With respect to SKAMP Deportment, Ritalin LA was statistically significantly better than Concerta (both doses) at the 0-4 post dose time frame, but only significantly better than Concerta 18 mg at the 0-8 hours time frame.
Ritalin LA was also not statistically significant better than Concerta on the Math Test, except for the comparison of Ritalin LA vs. Concerta 18 mg in the 0-4 hours time frame on the Math Test Correct.

Study DUS07
Table 6 below presents the results of the change from pre-dose in attention scores for hours 1-4 in study DUS07. Note that a negative change score indicates improvement.

Table 6. Efficacy results for study DUS07: SKAMP Attention Scores - AUC change from pre-dose to hours 1-4

	Comparison		Adjusted LS Means		Difference of LS Means (SE)	P-Value
Parameter	Test (N=54)	Ref. (N=53)	Test (SE)	Ref. (SE)		
1.0 hour, change	A (54)	C (53)	-0.603 (0.133)	-0.300 (0.134)	-0.303 (0.173)	0.081
	B (54)	C (53)	-0.823 (0.133)	-0.300 (0.134)	-0.523 (0.172)	0.003
	B (54)	D (53)	-0.823 (0.133)	-0.284 (0.134)	-0.539 (0.172)	0.002
	A (54)	D (53)	-0.603 (0.133)	-0.284 (0.134)	-0.320 (0.172)	0.065
2.0 hour, change	**A (54)**	**C (53)**	**-0.897 (0.124)**	**-0.689 (0.125)**	**-0.207 (0.167)**	**0.215**
	B (54)	**C (53)**	**-1.277 (0.124)**	**-0.689 (0.125)**	**-0.588 (0.167)**	**0.001**
	B (54)	**D (53)**	**-1.277 (0.124)**	**-0.415 (0.125)**	**-0.862 (0.167)**	**<0.001**
	A (54)	**D (53)**	**-0.897 (0.124)**	**-0.415 (0.125)**	**-0.482 (0.167)**	**0.004**
3.0 hour, change	A (54)	C (53)	-0.685 (0.111)	-0.523 (0.112)	-0.162 (0.156)	0.300
	B (54)	C (53)	-1.173 (0.111)	-0.523 (0.112)	-0.650 (0.156)	<0.001
	B (54)	D (53)	-1.173 (0.111)	-0.406 (0.112)	-0.767 (0.156)	<0.001
	A (54)	D (53)	-0.685 (0.111)	-0.406 (0.112)	-0.279 (0.156)	0.074
4.0 hour, change	A (54)	C (53)	-0.681 (0.117)	-0.443 (0.118)	-0.238 (0.160)	0.138
	B (54)	C (53)	-0.902 (0.117)	-0.443 (0.118)	-0.459 (0.160)	0.005
	B (54)	D (53)	-0.902 (0.117)	-0.557 (0.118)	-0.345 (0.160)	0.032
	A (54)	D (53)	-0.681 (0.117)	-0.557 (0.118)	-0.124 (0.160)	0.440

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.

A=Ritalin LA® 20 mg capsule, B=Ritalin LA® 40 mg capsule, C=Concerta® 18 mg tablet, D=Concerta® 36 mg tablet, E=Placebo.

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

The table shows that for the primary endpoint (2 hours post dose) Ritalin LA 20 mg was not significantly better than Concerta 18 mg statistically, but it was significantly better than Concerta 36 mg. Ritalin LA 40 mg had a statistically significant greater improvement in attention from pre-dose as compared to Concerta both 18 and 36 mg, at the 2 hour time point. For all other time points, Ritalin 20 mg was not statistically better than the 2 doses of Concerta while Ritalin LA 40 mg was.
All treatment groups were statistically superior to placebo.

The SKAMP Attention Scores AUC change from pre-dose to hours 6-12 shows that that for the 6 and 8 hours post-dose Ritalin LA 20 mg was not statistically significantly worse than Concerta 18 mg or 36 mg but was significantly better than placebo while Ritalin LA 40 mg was statistically significant better than both doses of Concerta and better than placebo. Both doses of Concerta were also significantly better than placebo at that time point (6h).

At 10h post dose, Ritalin LA and Concerta (all doses) did not differ from each other and both were significantly better that placebo. At 12h both doses of Concerta were significantly better than Ritalin LA 20 mg.

It can be seen that efficacy of Ritalin LA starts to diminish at 2h post-dose (20 mg) and at 6h post-dose (40 mg). However, the comparison with Concerta suggests that the 40 mg Ritalin LA is superior to Concerta up to and including 8h post-dose. Ritalin LA 20 mg is generally not statistically significant superior to Concerta (except at 2h post-dose) but also not inferior to Concerta except for at 12h post-dose.

Study DDE01
The table below presents the results of the study with respect to the primary (in bold) and secondary outcome variables.

Table 7. Efficacy results for study DDE01: Summary of ANOVA on SKAMP Combined Scores (ITT or PP population)

Visit	Popu-lation	Unadjusted means		Adjusted LS Means		Difference of LS Means (95% CI, 2-tail)	P-Value (diff=0) †
		Test	Ref.	Test	Ref.		
pre-dose	ITT	R (1.16)	P (1.09)	n.a.	n.a.	n.a.	n.a.
	PP	R (1.16)	M (1.21)	n.a.	n.a.	n.a.	n.a.
	ITT	M (1.21)	P (1.09)	n.a.	n.a.	n.a.	n.a.
1.5 hours	ITT	R (0.82)	P (1.25)	0.90	1.33	0.43 [0.31 ; 0.55]	<.0001
	PP	R (0.80)	M (0.75)	0.88	0.83	-0.05 [-0.18 ; 0.07]	0.4074
	ITT	M (0.78)	P (1.25)	0.86	1.33	0.47 [0.35 ; 0.59]	<.0001
3.0 hours	ITT	R (0.67)	P (1.36)	0.76	1.45	0.69 [0.57 ; 0.81]	<.0001
	PP	R (0.64)	M (0.59)	0.74	0.69	-0.05 [-0.17 ; 0.08]	0.4418
	ITT	M (0.61)	P (1.36)	0.71	1.45	0.74 [0.62 ; 0.96]	<.0001
4.5 hours	ITT	R (0.85)	P (1.51)	0.95	1.62	0.66 [0.54 ; 0.79]	<.0001
	PP	R (0.82)	M (0.70)	0.94	0.82	-0.12 [-0.25 ; 0.01]	0.0668
	ITT	M (0.72)	P (1.51)	0.93	1.62	0.78 [0.66 ; 0.91]	<.0001
6.0 hours	ITT	R (0.95)	P (1.38)	1.05	1.50	0.45 [0.32 ; 0.59]	<.0001
	PP	R (0.94)	M (0.79)	1.05	0.90	-0.15 [-0.29 ; -0.01]	0.0332
	ITT	M (0.81)	P (1.38)	0.90	1.50	0.60 [0.46 ; 0.74]	<.0001
7.5 hours	ITT	R (0.95)	P (1.38)	1.11	1.56	0.45 [0.32 ; 0.58]	<.0001
	PP	R (0.94)	M (0.84)	1.09	0.96	-0.13 [-0.27 ; 0.01]	0.0606
	ITT	M (0.86)	P (1.38)	0.97	1.56	0.59 [0.46 ; 0.72]	<.0001
Mean 1.5 to 4.5 hours	**ITT**	**R (0.78)**	**P (1.41)**	**0.86**	**1.49**	**0.63 [0.53 ; 0.74]**	**<.0001**
	PP	**R (0.76)**	**M (0.68)**	**0.85**	**0.78**	**-0.07 [-0.17 ; 0.03]**	**0.1476**
	ITT	**M (0.73)**	**P (1.41)**	**0.81**	**1.49**	**0.68 [0.58 ; 0.79]**	**<.0001**
p (diff=-0.25) ‡	**PP**	**R (0.76)**	**M (0.68)**			**p=0.0003**	
Mean 1.5 to 7.5 hours	ITT	R (0.85)	P (1.40)	0.95	1.50	0.55 [0.46 ; 0.64]	<.0001
	PP	R (0.83)	M (0.74)	0.94	0.84	-0.10 [-0.19 ; -0.00]	0.0469
	ITT	M (0.76)	P (1.40)	0.86	1.50	0.64 [0.55 ; 0.74]	<.0001
Mean 6.0 to 7.5 hours	ITT	R (0.96)	P (1.38)	1.07	1.52	0.45 [0.33 ; 0.58]	<.0001
	PP	R (0.95)	M (0.82)	1.06	0.93	-0.13 [-0.26 ; -0.01]	0.0392
	ITT	M (0.83)	P (1.38)	0.94	1.52	0.58 [0.46 ; 0.71]	<.0001

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.
R=Ritalin LA® 20 mg, M=Medikinet® ret. 20 mg, P=Placebo.
ANOVA model to derive LS-means with variables center, patient within center, treatment, period.
† All p-values (diff = 0) are from t-tests without shift with two-sided alternative performed at 5% level of significance (test for superiority)
‡: P-value (diff = -0.25) is the one-sided p-value for the shifted hypothesis of non-inferiority of Ritalin® compared to Medikinet®.

The results of the primary efficacy endpoint show that Ritalin LA is significantly better than placebo (p<.0001) and that the difference between the two active treatments as well as its confidence interval did not exceed the predefined non-inferiority margin of 0.25 points (point estimate: d=-0.07 in favour of Medikinet Retard (95% confidence interval (-0.17; +0.03)) suggesting that the difference between Ritalin LA and Medikinet Retard is not clinically relevant. Medikinet Retard was superior to placebo (p<.0001).

Results at later time points, i.e. 4.5h post-dose and later, show that Ritalin LA can be considered inferior to Medikinet Retard.

IV.4.2 Adults

IV.4.2.1 Methodology

One pivotal study was carried out in adults, i.e. a short-term study, followed by a dose optimization phase and subsequently a long-term randomised withdrawal study in responders.

Table 8. Design of the Ritalin LA pivotal placebo-controlled Study D2302

Study	Study objectives	Patients randomized (completed)	Treatment duration/ study design	Treatment/ dose (mg)	Primary efficacy endpoints
Pivotal D2302 (Phase III)	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)	3 Periods: Controlled periods are Periods 1 and 3 **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 from baseline to the end of the Period 1 treatment (Week 9) in the total score of the DSM-IV ADHD RS **Primary 2:** Change from baseline to end of Period 1 treatment (Week 9) in the SDS total score **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, SDS= Sheehan Disability Scale
* Patients were not randomized into Period 2

Design
The study consisted of three periods: a dose ranging short-term study (Period 1), a period in which patients were titrated to an individualized optimal dose of Ritalin LA (Period 2), and a long-term randomised withdrawal period (Period 3) in which patients who improved by more than 30% on the DSM-IV ADHD RS compared to the baseline were assigned to either their optimal dose from period 2 or to placebo at a ratio of 3:1.

Inclusion criteria
The study population consisted of male and female patients (18-60 years old) with a diagnosis of ADHD, all types, with a confirmed childhood onset according to DSM-IV diagnostic criteria. DSM-IV ADHD RS total score had to be ≥30 at screening and baseline. In addition, according to the ADHD 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.

Dose
Dose selection for adults in the pivotal study was based on the pharmacokinetic and clinical data for Focalin XR. The rationale was that the pharmacological activity of Ritalin LA (i.e. racemic mixture of l- and d-isomer) resides almost entirely in the d-isomer of methylphenidate, and that a dose of Ritalin LA

2-fold that of Focalin XR (only d-isomer) provides similar pharmacological effects. Since clinical studies with Focalin XR showed that doses of 20, 30, and 40 mg/day are safe and effective in adults with ADHD, 2-fold that of the effective dose range of Focalin XR in adults were selected for the pivotal study with Ritalin LA, i.e. doses of 40, 60 and 80 mg. Patients were assigned to one of these doses or placebo in a ratio of 1:1:1:1. The first 4 weeks of the study were used for dose escalation starting with a dose of 20 mg and escalating by 20 mg a week.

Endpoints

The co-primary endpoints in Period 1 of this study were change from Baseline 1 in the DSM-IV Attention-Deficit/Hyperactivity Disorder Rating Scale (DSM-IV ADHD RS) and the Sheehan Disability Scale (SDS) which were selected to tap effects on ADHD symptoms and on functioning, respectively. Secondary endpoints included Clinical Global Impression Improvement (CGI-I), Clinical Global Impression Severity (CGI-S), Conner's Adult ADHD Rating Scale (CAARS), and Adult Self-Report Scale (ASRS).

The primary endpoint in the maintenance of effect phase was percentage of treatment failures in patients treated with Ritalin LA versus placebo, with treatment failure defined as a deterioration of ≥ 30% from period 3 baseline DSM-IV ADHD RS total score and a less than 30% remaining improvement from the Period 1 baseline.

Statistical methods

For the analysis of the short-term study, change from baseline to the end of the study (Week 9) in the total score of the DSM-IV ADHD RS was analyzed using analysis of covariance (ANCOVA) model with treatment group and centre as factors, and baseline DSM-IV ADHD RS total score as covariate. The same method was used for the SDS change scores.

For the analysis of the randomized withdrawal study proportion of treatment failures were analyzed using a logistic-regression model with treatment as factor and DSM-IV ADHD RS total score at baseline 1 and baseline 2 as covariates.

Control over the overall type I error

For the primary and key secondary variables a total of 10 hypotheses were tested. The natural hierarchy of the endpoints is as follows:

Primary 1 (change from baseline to the end of Period 1 in the total score of the DSM-IV ADHD RS) and Primary 2 (change from baseline to end of Period 1 treatment in the SDS total score) were of equal importance and both were required to be significant at a particular dose to claim efficacy for that dose.

Primary 3 (percentage of treatment failures at the end of Period 3) was next in the hierarchy, followed by the key secondary (proportion of patients with clinical improvement on the CGI-I scale at the end of Period 1).

GCP compliance

All data for the 22 patients randomized at one of the sites were removed from the efficacy analysis due to serious non-compliance with International Conference On Harmonization (ICH)-GCP at the site. The results in the excluded site were similar to the rest of the study.

Conduct of the study

Change in the definition of treatment failure during the randomized withdrawal phase

Initially, patients were to be discontinued from the randomized withdrawal study if they had ≥ 30% worsening on the DSM-IV ADHD RS from Period 3 baseline. However, some of these patients retained a clinically meaningful improvement compared to their Period 1 baseline at the entry of the study. This problem was initially noted by individual investigators expressing concern that they were required per protocol to discontinue patients who still showed significant therapeutic effect despite slight worsening from the Period 3 baseline. For example, a patient with a period 3 baseline score of 20 required a 6 point worsening in their DSM-IV ADHD RS to achieve a 30% worsening and therefore qualify as a treatment failure, or a patients with a baseline score of 6 required a worsening of only 2 points to achieve a 30% worsening and qualify as a treatment failure. Therefore, the protocol was amended to change the definition of treatment failure (leading to discontinuation in Period 3) to require that patients must meet both of two criteria: 1) a ≥ 30% worsening from Period 3 baseline on the DSM-IV ADHD RS score and 2) a < 30% remaining improvement from the Period 1 baseline score on the DSM-IV ADHD RS.

Some patients left the study under the original definition who would not have done so under the revised definition. Before the revised treatment failure definition was in place, 43.7% of the Ritalin LA and 59.3% of the placebo patients would have been considered as treatment failures. After the treatment failure definition was revised (to be more clinically meaningful), 16.1% of patients treated with Ritalin LA met the treatment failure criteria vs 41.5% of those treated with placebo. The number of patients meeting the amended treatment failure definition compared to the original treatment failure definition was lower in both groups, but represented a greater drop in patients treated with Ritalin LA.

IV.4.2.2 Results

Patients disposition
Table 9 below presents patients disposition in the short-term study.

Table 9. Patient disposition for Period 1 (All patients)

Disposition/reason	Ritalin LA 40 mg N=181 n (%)	Ritalin LA 60 mg N=182 n (%)	Ritalin LA 80 mg N=181 n (%)	All Ritalin LA N=544 n (%)	Placebo N=181 n (%)	All N=725 n (%)
Screened	NA	NA	NA	NA	NA	863
Randomized	181	182	181	544	181	725
Completed all Period 1 visits	156 (86.2)	147 (80.8)	145 (80.1)	448 (82.4)	155 (85.6)	603 (83.2)
Completed and Entered Period 2	152 (84.0)	141 (77.5)	138 (76.2)	431 (79.2)	153 (84.5)	584 (80.6)
Discontinued						
Total	29 (16.0)	41 (22.5)	43 (23.8)	113 (20.8)	28 (15.5)	141 (19.4)
Adverse Event(s)	13 (7.2)	18 (9.9)	26 (14.4)	57 (10.5)	3 (1.7)	60 (8.3)
Unsatisfactory therapeutic effect	2 (1.1)	2 (1.1)	4 (2.2)	8 (1.5)	11 (6.1)	19 (2.6)
Patient withdrew consent	5 (2.8)	8 (4.4)	6 (3.3)	19 (3.5)	7 (3.9)	26 (3.6)
Lost to follow-up	4 (2.2)	6 (3.3)	3 (1.7)	13 (2.4)	4 (2.2)	17 (2.3)
Administrative problems	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.4)	2 (1.1)	4 (0.6)
Protocol deviation	5 (2.8)	6 (3.3)	3 (1.7)	14 (2.6)	1 (0.6)	15 (2.1)

Denominator used in the percentage calculations: randomized patients.
NA=not applicable

More than 80% of patients in all treatment groups completed the study. The rate of discontinuation due to AEs was highest in Ritalin LA 80 mg (14.4%) and lowest in placebo (1.7%).

Period 2
By the end of Period 2, the 5-week optimal dose period, patients were required to meet at least 30% improvement in DSM-IV ADHD RS in order to qualify for re-randomization into Period 3 (the randomised withdrawal study). Among the 489 patients (83.7%) who completed this period and entered Period 3, 152 patients were on Ritalin LA 40 mg; 177 were on Ritalin LA 60 mg; and 160 on Ritalin LA 80 mg. These patients were then randomised to either continue on their dose of Ritalin LA or placebo.

Long-term randomised withdrawal study (period 3)
Patients disposition in the withdrawal study is presented in the table below.

Table 10. Patient disposition for Period 3 (Randomized withdrawal phase).

Disposition/reason	Ritalin LA 40 mg N=114 n (%)	Ritalin LA 60 mg N=132 n (%)	Ritalin LA 80 mg N=120 n (%)	All Ritalin LA N=366 n (%)	Placebo N=123 n (%)	All N=489 n (%)
Randomized in Period 1*	181	182	181	544	181	725
Completed Period 1*	156	147	145	448	155	603
Completed Period 2*	141	132	125	398	139	537
Randomized at end of Period 2	114	132	120	366	123	489
Completed	60 (52.6)	63 (47.7)	70 (58.3)	193 (52.7)	42 (34.1)	235 (48.1)
Discontinued						
Total	54 (47.4)	69 (52.3)	50 (41.7)	173 (47.3)	81 (65.9)	254 (51.9)
Adverse Event (s)	5 (4.4)	11 (8.3)	6 (5.0)	22 (6.0)	5 (4.1)	27 (5.5)
Abnormal laboratory value (s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.2)
Abnormal test procedure result (s)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)	0 (0.0)	1 (0.2)
Unsatisfactory therapeutic effect	28 (24.6)	42 (31.8)	29 (24.2)	99 (27.0)	62 (50.4)	161 (32.9)
Patient's condition no longer requires study drug	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Patient withdrew consent	12 (10.5)	6 (4.5)	4 (3.3)	22 (6.0)	3 (2.4)	25 (5.1)
Lost to follow-up	3 (2.6)	4 (3.0)	6 (5.0)	13 (3.6)	3 (2.4)	16 (3.3)
Administrative problems	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.3)	0 (0.0)	1 (0.2)
Protocol deviation	5 (4.4)	6 (4.5)	3 (2.5)	14 (3.8)	7 (5.7)	21 (4.3)

* Randomized set for Period 1.
Denominator used in the percentage calculations: randomized patients in Period 3.

Patients treated with Ritalin LA had a higher completion rate compared to patients treated with placebo in the randomised withdrawal study. The most common reason for discontinuation in all treatment groups was unsatisfactory therapeutic effect as defined in the protocol. This was expected and is attributable to the fact that patients who met criteria for unsatisfactory response were discontinued from the study. The proportion of patients who discontinued due to AEs in the All Ritalin LA group (6.0%) was higher compared to the placebo group (4.1%). Among the Ritalin LA dose groups the incidences of discontinuation due to AEs was not dose related i.e. highest with the 60 mg dose group (8.3%) compared to the 40 mg (4.4%) and 80 mg (5.0%) dose groups.

Demographic and baseline variables

Short-term study
Patient demographics and background characteristics were similar across all treatment groups. For all groups, a higher percentage of males were enrolled (54.5% overall). Most of the patients were Caucasian (89.5%) with a mean weight of 77 kg and mean age 35.4 years.

Overall, the treatment groups were similar with respect to background disease characteristics. The investigator most commonly rated patient's global severity as "markedly ill" in each treatment group (as rated on the CGI-S at baseline). In addition, the patients median selfrating of baseline ADHD symptoms was within +/−1 point on the 72 point ASRS across groups. Finally, the patient's close observer median rating was within +/− 2 points on the 78 point CAARS-O:S scale in each group. The DMS-IV ADHD RS mean total scores at baseline 1 were 39.6, 39.1, 39.3, 39.3, and 39.0 in the Ritalin LA 40 mg, 60 mg, 80 mg, All Ritalin LA, and placebo groups, respectively. The SDS mean total scores were 20.7, 19.4 and 19.7 in the Ritalin LA 40, 60, and 80 mg groups and 19.9 in All Ritalin LA and placebo groups.
The majority of patients had at least one past or current medical condition, which was expected for this adult population (75.4% "All Ritalin LA" vs 77.9% placebo). The most frequently reported past or current medical conditions were primarily in the system-organ classes of surgical and medical procedures (primarily tonsillectomy and appendectomy: 24.8% vs 32.0%, respectively), psychiatric disorders (primarily depression: 21.5% vs 22.7%), immune system disorders (primarily seasonal allergy: 22.1% vs 16.0%), nervous system disorders (primarily headache and migraine: 19.7% vs 14.9%), and gastrointestinal disorders (primarily gastro-oesophageal reflux disease and dyspepsia: 9.4% All Ritalin LA vs 13.8% placebo).

Long-term randomised withdrawal study

The baseline demographics and background characteristics of the patients in the randomised withdrawal study show no differences from baseline of the short-term study in terms of demographics and disease characteristics. Overall, the combined Ritalin LA and placebo groups were similar with respect to background disease characteristics at the baseline of the randomised withdrawal phase. The Ritalin LA 80 mg group had the highest (worst) DSM-IV ADHD RS and SDS total scores at baseline compared to the remaining groups. The DMS-IV ADHD RS mean total scores at baseline were 12.1, 12.9, 14.6, 13.2, and 13.7 in the Ritalin LA 40 mg, 60 mg, 80 mg, All Ritalin LA, and placebo groups, respectively. The SDS mean total scores were 8.6, 9.8, 11.2, 9.9, and 9.7 in the Ritalin LA groups 40 mg, 60 mg, 80 mg, All Ritalin LA, and placebo groups. Similar trends were noted for the other scales and subscores.

With respect to medical history and current medical conditions, as noted in the short-term study, the majority of patients had at least one past or current medical condition, which was expected for this adult population (77.3% “All Ritalin LA” vs 68.3% placebo). The most frequently reported past or current medical conditions were primarily in the system-organ classes of surgical and medical procedures (primarily tonsillectomy and appendectomy: 47.0% “All Ritalin LA” vs 42.3% placebo), immune system disorders (primarily seasonal allergy: 27.6% “All Ritalin LA” vs 35.0% placebo), psychiatric disorders (primarily depression: 26.0% “All Ritalin LA” vs 31.7% placebo), nervous system disorders (primarily headache and migraine: 24.0% “All Ritalin LA” vs 18.7% placebo), and gastrointestinal disorders (primarily gastroesophageal reflux disease and dyspepsia: 13.9% “All Ritalin LA” vs 10.6% placebo).

Efficacy results

Short-term study

Primary efficacy

Primary efficacy results for the short-term study for the 2 co-primary endpoints are presented in tables 11 (ADHD-RS) and 12 (SDS).

Table 11. Analysis of improvement from baseline 1 to end of Period 1 on DSM-IV ADHD RS total score by treatment/LOCF (Full Analysis Set)

	Statistics	Ritalin LA 40 mg	Ritalin LA 60 mg	Ritalin LA 80 mg	Placebo
Visit 2 (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	

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 DSM-IV ADHD RS total score as covariate.
CI = Confidence Interval, LOCF = Last observation carried forward
*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.

Table 12. Analysis of improvement from baseline 1 to end of Period 1 on SDS total score by treatment/LOCF (Full Analysis Set)

	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	

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.

As the tables indicate, the maximum p-values of the two tables are smaller than significance levels following the gate-keeping procedure. Hence, both DSM-IV ADHD RS and SDS total score showed statistical significance in the composite hypothesis testing.
Analyses of the per-protocol population and sensitivity analyses with MMRM also produced statistically significant results.

Secondary efficacy results
Statistically significant efficacy was demonstrated at all three dose levels of Ritalin LA for both Inattention and Hyperactivity/Impulsivity sub-scores on the DSM-IV ADHD RS.
Similarly, statistically significant efficacy was demonstrated in improvement for all 3 areas of function (work, social and family life) as shown by SDS sub scores improvement, except for the effect of the 60 mg group on family life, which did not reach statistical significance (p=0.16).

The improvement from baseline to end of the short-term study in underproductive days in the SDS scale was 1.5 days for all Ritalin LA group and 0.8 days for the placebo group.
All three Ritalin LA doses had a significantly higher proportion of patients who showed improvement in CGI-S (p-value<0.0001, for all 3 doses) compared to placebo.
For the CAARS Observer Short Version (CAARS-O:S) improvement from baseline to the end of the study in total score showed that the three Ritalin LA doses had a significantly greater improvement in

LS mean compared to placebo (p=0.0008 at the 40 mg dose, p=0.0014 at the 60 mg dose and p=0.0001 at the 80 mg dose).
For the ASRS total score improvement from baseline to the end of the study showed that the three Ritalin LA doses had a significantly higher proportion of patients who showed improvement in ASRS total score (p-value<0.0001, for all 3 doses) compared to placebo.

Long-term randomised withdrawal study
For the analysis with imputation, a statistically significantly smaller proportion of patients (p<0.0001) in the Ritalin LA group (75 patients, 21.3%) compared with the placebo group (57 patients, 49.6%) had treatment failure. The difference between the two groups is 28.3% (95%CI: 21.3%, 50.0). For the analysis without imputation, the difference between the groups is 26.7% (95%CI: 16.8%, 43.5%).

To assess the robustness of the primary analysis results to potential violations of the underlying 'missing at random' assumption, 2 methods of multiple imputation were applied using different rules for imputing the missing. The results of the analyses for the 2 sensitivity analyses were similar to those reported above. The odds of a treatment failure in the All Ritalin LA group was approximately three times lower than in the placebo group (OR: 0.3, 95% CI: 0.2, 0.5) in both sensitivity analyses.

Analysis of the primary endpoint by dose showed that the percentage of treatment failures was statistically significantly smaller in each Ritalin LA dose group: 40 mg (18 patients, 16.4%; p<0.0001), 60 mg (34 patients, 26.6%; p=0.0008) and 80 mg (23 patients, 20.2%; p<0.0001) compared with placebo (57 patients, 49.6%). The odds of a treatment failure in each Ritalin LA dose group compared to placebo was: 40 mg (OR: 0.2, 95% CI: 0.1, 0.4), 60 mg (OR: 0.4, 95% CI: 0.2, 0.7) and 80 mg (OR: 0.3, 95% CI: 0.1, 0.5).

Secondary efficacy results
Statistically significantly fewer patients in the All Ritalin LA group (51.1%) and in the Ritalin LA dose groups (47.9%, 58.0% and 46.5% in the 40 mg, 60 mg and 80 mg groups respectively) had a ≥30% worsening from baseline during the randomised withdrawal study compared with placebo (68.6%).
Statistically significantly fewer patients in the All Ritalin LA group (72 patients, 28.9%; p=0.0006) and in all three individual Ritalin LA dose groups had a <30% remaining improvement from baseline during the randomised withdrawal study compared with placebo (53 patients, 60.9%).

IV.5 Clinical safety

IV.5.1 Safety in children and adolescents

Adverse events (AEs) in paediatric patients in the submitted studies were generally in accordance with the known safety profile of methylphenidate-containing products. In male paediatric patients, exposure of 13-17 year olds to Ritalin LA in the context of the submitted studies was very limited, restricting interpretation of controlled safety data that were gathered in this age group. However, the MAH has indicated that the safety profile in this group was similar to other groups which was confirmed by post-marketing data. Most frequent treatment emergent adverse effects were decreased appetite (9.6%, placebo: 1.6%), upper abdominal pain (4.8%, placebo: 2.8%), nausea (3.8%, placebo 1.3%), vomiting (3.2%, placebo 1.3%), insomnia (2.5%, placebo: 1.3%) and dysmenorrhoea (2.2%, placebo: 0%).
Psychiatric AEs including insomnia emerging during treatment were not infrequent, occurring in 12.3% of paediatric patients (placebo: 4.8%, active control: 3.4%). This also included irritability (2.4%, placebo: 0.2%, active control: 0%).

IV.5.2 Safety in adult patients

Limited data were submitted regarding exposure of adult patients to Ritalin LA in clinical studies. In particular no data were submitted regarding elderly patients (i.e. >60 years of age). Regarding patients aged 51-60 years of age a total of 41 were exposed to Ritalin LA, of whom only 13 patients used a 80 mg dose and only 22 patients were included in the extension study. ADHD in adults should be regarded to be a chronic disorder (i.e. persisting from childhood onwards) that may hence in some cases even persist into old age. Although little data were presented to assess safety in (older) adults, it was shown that similar proportions of treatment-emergent adverse events (TEAEs) for separate adult age-groups, resolving that concern.

There were no deaths in the adult study, but one patient died due to rupture of aortic aneurism 20 days after study completion. This event was assessed as probably unrelated.

Psychiatric TEAEs
Psychiatric TEAEs were notably more common in adults as compared to children and adolescents, occurring in 64 of the n=145 (44.1%) adults exposed for <2 months duration. Insomnia occurred in 11.1% of all treated adult patients (placebo: 3.3%), anxiety in 7.2% (placebo: 1.1%), and irritability in 7.2% (placebo: 3.3%). Some of these AEs appear to increase in the course of (long-term) treatment. As an example, irritability occurred in 3.4% of patients exposed <2 months, but in 9.6% of patients exposed >12 months. However, it was adequately demonstrated that these differences were cumulative, while occurrence of *de novo* TEAEs did not increase with longer exposure. Discontinuations due to (any) psychiatric AE occurred in 6.7% of patients included in the controlled Focalin XR-study, but discontinuations due to (any) psychiatric AE in the adult Ritalin LA studies were not specified. As psychiatric co-morbidity is common in adult ADHD patients in clinical practice, worsening of those symptoms may reduce possible treatment benefits regarding ADHD symptoms or even cause mental state to deteriorate despite possible benefits. The MAH confirmed the high risk of psychiatric TEAEs in adults, and even higher risk in adult patients with psychiatric co-morbidity at baseline.

Regarding risk for psychiatric AEs, the MAH indicated that: 'psychiatric co-morbidity was not an absolute exclusion criterion for the core/extension study.' It was reported that 21.5% of all enrolled methylphenidate-treated patients had a history of psychiatric disorder at enrolment, and 7.2% had active psychiatric disorder. However, in the Clinical Study Report the following exclusion criterion is listed:
'Any psychiatric condition, including anxiety, tension, agitation, aggressive behaviour, psychotic symptoms, suicidal tendency, that required treatment with medication or that, in the judgment of the investigator, may have interfered with study participation and/or study assessments'.
This text indicates that not only psychiatric disorders, but also single psychiatric symptoms (e.g. 'anxiety') or emotional states (e.g. 'tension') outside psychiatric disorders could be ground for exclusion. Additionally, there is an exclusion criterion regarding family history of Tourette's syndrome, as well as an exclusion criterion regarding patients who were receiving any psychotropic medications. Two further exclusion criteria included receiving any psychological of behavioural therapies within one to three months. Therefore it is concluded that a psychiatrically relatively healthy patient population was studied. The majority of patients (i.e. 92.8%) were 'pure ADHD', probably as a result of the elaborate exclusion criteria. The MAH, referring to Spencer et al (2007)[2], acknowledged that in clinical practice: 'the very high level of associated psychiatric comorbidity puts those with "pure" ADHD (i.e., ADHD only) in a distinct minority'.
The MAH proposed to list a number of psychiatric diagnoses as contra-indications in the SmPC, but it remains unclear to which extent those diagnoses correspond to the single psychiatric symptoms and emotional states that were ground for exclusion from the study. In clinical practice, given the limited proposed psychiatric contra-indications and expected difficulty to implement those contra-indications, the proportion of patients with psychiatric co-morbidity who are likely to be treated with Ritalin LA may be substantially larger as compared to the proportion in the pivotal adult study, while in that study it was shown that patients with psychiatric co-morbidity at baseline had more psychiatric TEAEs as compared to patients without psychiatric co-morbidity at baseline. Hence in clinical practice, the proportion of patients with psychiatric TEAEs will probably be substantially higher and TEAEs may be more severe as compared to those encountered in adult study D2302.

The MAH referred to a number of published studies that are claimed to support psychiatric safety of methylphenidate use in adults. However, all but one of these studies (Adler et al 2011[3]) report only on children and/or adolescents. Adler et al reported that 20.7% of all treated adult patients experienced insomnia, 13.8% anxiety and 10.0% irritability. Regarding the 'psychiatric AEs of special interest' in that study, mania occurred in 3 patients, aggression in 2 patients and a further 2 patients developed paranoia. Though no placebo-group was studied, these data confirm a high risk of *de novo* psychiatric adversity in adults treated using methylphenidate, and also a risk of serious psychiatric TEAEs

[2] Spencer TJ, Adler LA, McGough JJ, et al (2007) Efficacy and safety of dexmethyphenidate extended-release capsules in adults with ADHD. Biol Psychiatry; 61:1380–1387
[3] Adler L, Orman C, Starr L et al (2011) Long-Term Safety of OROS Methylphenidate in Adults With Attention-Deficit/Hyperactivity Disorder. An Open-Label, Dose-Titration, 1-Year Study. J Clin Psychpharmacol 201; 31:108-114.

including psychosis, reiterating the unfavourable psychiatric safety profile as compared to use in children and adolescents.
It is concluded that the elaborate psychiatric exclusion criteria implemented for the adult study effectively prevented large numbers of serious psychiatric TEAEs, but milder psychiatric TEAEs were numerous, and in clinical practice feasibility of implementing these exclusion criteria through contra-indications is questioned.

Regarding a possible relationship with dose, in period 1 of the adult study the proportion of patients with psychiatric TEAEs was similar in the 40 mg, 60 mg and the 80 mg dose-group (i.e. 33.8%, 39.1%, and 36.0% respectively for common psychiatric TEAEs only). Hence it is concluded that limiting dose recommendations to a maximum of 60 mg in adults will not solve this safety problem.

Cardiovascular safety
The MAH was requested to discuss the consequences of persistent rise in heart rate and blood pressure for risk of cardiomyopathy in adult ADHD patients treated for prolonged periods as is anticipated regarding chronicity of the disorder.

Data regarding the effects of long-term exposure of adults to increased blood pressure is considered limited. In the submitted data in adults mean increase of systolic blood pressure as compared to baseline in the highest dose group (80 mg) was 3.6 mmHg and the end of period 3 and 4.4 mmHg at the end of the extension study, in accordance with Adler et al (2011) who found mean change from baseline of 4.5 mmHg at month 7.

The increase of mean systolic blood pressure (MSBP, in mmHg) appears dose-related in the adult study regarding change of MSBP between visit 2 and visit 20:

Methylphenidate Dose	MSBP visit 2	MSBP visit 20	MSBP change
40 mg	117.6	119.4	1.8
60 mg	119.9	120.7	0.8
80 mg	122.6	126.3	3.7

The MSBP increase appears to be limited to the highest dose group (80 mg). However the highest dose has been stated by the MAH to be indispensable to enable individual dose-titration for best efficacy. Therefore efficacious treatment of adults is concluded to increase the risk of elevated systolic blood pressure for a prolonged time-span, and to hence increase cardiovascular risk.

The report by Habel et al (2011)[4] on the adult data in the FDA/AHRQ/VanderBilt University epidemiological study including cardiovascular outcome, provides only limited reassurance, as exposure in that study was limited to median 1.3 years (interquartile range 0.6 – 2.6 years per person). The negative findings by Habel et al should probably be attributed to limited duration of exposure and to healthy user bias. Other studies that are referred to by the MAH, including Rosler et al (2009)[5], Buitelaar et al (2012)[6], and Adler et al (2011) suffer similar limitation of duration of exposure, varying from 24-52 weeks. Cooper et al (2011)[7] included only children and young adults up to 24 years of age. Olfsen et al (2012)[8] included only children and young adults up to 21 years of age.

[4] Habel et al, 2011. ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults. JAMA;306(24):2673-2683
[5] Rosler M, Fischer R, Ammer R, Ose C, Retz W (2009)] A randomized, placebo-controlled, 24 week, study of low dose extended release methylphenidate in adults with attention deficit/hyperactivity disorder. European Archives of Psychiatry and Clinical Neuroscience; 259 (2):120-129
[6] Buitelaar J, Montgomery S, van Zwieten Boot BJ et al (2003. Attention deficit hyperactivity disorder: guidelines for investigating efficacy of pharmacological intervention. European Neuropsychopharmacology; 13: 297–304.
[7] Cooper WO, Habel LA, Sox CM, et al (2011) ADHD drugs and serious cardiovascular events in children and young adults. N Engl. J Med; 365:1896-1904.
[8] Olfson M, Huang C, Gerhard T (2012) Stimulants and Cardiovascular Events in Youth With Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatr 51(2):147-56

In addition, the randomised withdrawal study indicates that discontinuation of treatment may induce relapse or recurrence of symptoms. Therefore treatment may typically require prolonged exposure, which can be expected to increase risk of cardiomyopathy associated cardiac failure.

IV.6 Risk Management Plan

In 2009 the CHMP performed an Article 31 Referral regarding all methylphenidate containing medicinal products because of concerns over the safety of methylphenidate products particular the risk of cardiovascular and cerebrovascular disorders. The CHMP recommended that risk management programs be put in place to monitor the safety of methylphenidate-containing medicines and minimise any possible long-term risks of their use.

The MAH has submitted a risk management plan, 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 LA. The important identified and potential risks are listed in the table below.

Table 13. Summary table of safety concerns as approved in RMP

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 behaviours • 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

*Additional risk minimisation measures in place

Additional risk minimisation measures have been laid down based upon the Article 31 referral, including educational tools in the form of checklists for actions before prescribing, dispensing or administering methylphenidate and for ongoing monitoring of (paediatric) patients on methylphenidate. This educational material can be found on http://www.methylphenidate-guide.eu/nl/welcome.php.

IV.7 Discussion on the clinical aspects

Pharmacokinetics

Methylphenidate is subject to first-pass metabolism, resulting in a relatively low systemic availability of approximately 30% upon oral administration of d-methylphenidate and only 5% of l-methylphenidate. The volume of distribution of methylphenidate is approximately 13.1 L/kg. Methylphenidate is subject to extensive and rapid metabolism. The most important metabolite is alpha-fenyl-2-piperidinic acid. Although plasma levels of the metabolite are maximally 30 to 50-fold higher than that of methylphenidate, most of the activity seems to be caused by the parent compound. The $t_{½}$ of alpha-fenyl-2-piperidinic acid is approximately 4 hours, whereas the $t_{½}$ of methylphenidate itself is 2 hours. Most of the dose is excreted as metabolite via the urine, and only 1-3% via the feces. Pharmacokinetics of methylphenidate in ADHD patients and healthy volunteers following administration of Ritalin LA modified-release capsules were comparable. In addition, there are no gender-related differences in the pharmacokinetics of methylphenidate.

Clinical efficacy

Children and adolescents

Altogether 6 clinical randomised trials were conducted in children and adolescents with ADHD (n=517). All studies were randomized, double blind and placebo controlled. One study had a parallel group design (study D0007) and the remaining 5 had a crossover design. Three of the studies had, in addition to placebo, an active control arm (2 Concerta and one Medikinet). Five of the studies were conducted in the US and Canada, and one in Germany. One study included adolescents (adolescent girls) and the remaining 5 included only children.

The results of the studies showed that Ritalin LA 20-40 mg was efficacious compared to placebo, with effect sizes ranging between medium (0.3-0.8) and large (>0.8) for the primary endpoints. Efficacy of methylphenidate in general is well known.

The controlled release aspect was not assessed as a primary endpoint. It was not studied whether the extended release product has an advantage over, or is at least equivalent to the well-known and widely used IR formulation applied as a b.i.d administration, which Ritalin LA q.d. is intended to mimic. As no studies included a Ritalin IR arm as an active control, it is necessary to revert to PK information relevant to this issue regarding time-concentration relationship. PK study 2101 indicates that the second plasma concentration-peak of Focalin IR (which is administered b.i.d.) is higher as compared to the second peak of Focalin LA and Ritalin LA (q.d.). This suggests that efficacy of Ritalin LA later in the day is inferior to that of Ritalin IR with a b.i.d administration. The clinical data from the laboratory classrooms also suggest that the efficacy of Ritalin LA is at its highest around 2-4 hours post-administration and that it diminishes considerably in the afternoon (4-8 hours post administration). Hence switching from Ritalin IR to Ritalin LA reduces afternoon efficacy.

Additional evidence from PK studies that compare Ritalin LA to Concerta and to Medikinet Retard indicate that the second peak of Ritalin LA is higher as compared to that of Concerta and lower as compared to that of Medikinet Retard. The clinical data from the laboratory classroom studies provide some clinical corroboration for these PK findings. Specifically, study DUS07 suggests that Ritalin LA 40 mg is superior to Concerta up to and including 8 hours post-dose and that Ritalin LA 20 mg is numerically - but not statistically - better than Concerta up to 10 hours post administration. The results of study DDE01 suggest that Ritalin LA is inferior to Medikinet Retard starting at 4.5 hours post dose.

Overall, based on the studies comparing Ritalin LA to Concerta and Medikinet Retard, as well as data from PK studies, Ritalin LA at equivalent doses may be superior to Concerta and non-inferior to Medikinet Retard.

All but one study were carried out in children and the one study in adolescents included only girls, while ADHD is predominately a disorder in male patients. The MAH adequately addressed this concern, demonstrating that there is no systematic difference in efficacy between the genders and hence the efficacy that was demonstrated in female adolescents can be extrapolated to male adolescents.

The MAH was also requested to clarify some issues with respect to study D0002: the study report does not provide a rationale for the choice of the comparisons between the two 20 mg variants of Ritalin LA (RS: L and S) with placebo as the primary ones. The MAH indicated that the results of study D0002 showed that the plasma concentration time profiles at all the strengths retained dual peak profile, and demonstrated similar pharmacokinetics and pharmacodynamics profile, without considerable difference. Hence to maintain consistency with the total dose of immediate release Ritalin tablets, the RS:L formulation at 20 mg dose strength was selected as formulation to be equivalent to Ritalin 10 mg given b.i.d. (total dose of 20 mg).

Adults

The evidence for efficacy of Ritalin LA in adults comes from a study which consisted of a short-term study, followed by a dose optimization phase and a long-term randomised withdrawal study in responders. A total of 584 patients were included in the short-term fixed dose study and 489 patients were included in the randomised withdrawal study.
Efficacy results showed statistically significant effects in the short-term study on both symptoms and functioning and in the long-term study on relapse rates. Altogether, effect sizes were 0.5-0.6 (depending on the dose) on symptoms and 0.3-0.5 on functioning.

However, several issues were raised with respect to the efficacy of Ritalin LA in adults. One issue concerned the mid-study change of primary endpoint of the randomised withdrawal study (the change in definition of treatment failure) that was based on the results of the study. Although this is still considered a potential source of bias, it is reassuring that results that were presented in the second round using the original definition were in the same direction compared to the results with the modified definition. Specifically, the difference in % of patients relapsing between the Ritalin LA and placebo was 22% (95% CI: 10.9%, 31.3%) according to the original definition compared to 28% (95% CI: 21.3%, 50.0) according to the modified definition. The difference according to the original definition is considered sufficiently large, and not dramatically lower compared to the difference according to the modified definition.
Furthermore, it appears that the mid-study change of primary outcome, was done based on blinded data, and this takes away the concern about contamination of the blind. Various sensitivity analyses all showed a positive effect of Ritalin LA compared to placebo which was both statistically significant and clinically relevant. In addition, the size of the short- and long-term effect seems reasonable.

In addition, the MAH was requested to provide the number of patients included in the randomised withdrawal study when the change was made with respect to the primary endpoint (treatment failure).
An additional doubt concerning efficacy was with respect to the lack of an *a priori* definition of responders and the hence the reliability of the responders analysis in the short-term study. While it is true that 30% improvement from baseline severity scores is a common definition of responders in ADHD trials, there are studies that use other definitions. The study of Michelson et al (2002) used 25% improvement as a definition of response and the study by Wender et al (2011) used a 50% improvement. Since there was no certainty that the other response definitions would provide similar results to those presented in this study based on 30% improvement. The company was requested to present results of responders analyses based on 25% and 50% improvement.

The company provided satisfactory responses to the issues regarding the number of patients included in the randomised withdrawal study when the change was made with respect to the primary endpoint (treatment failure). Specifically, approximately 40% of patients entered period 3 after implementation of the protocol amendment and 60% were included before the amendment. Likewise, reassuring results of the additional analysis requested with respect to alternative definitions of responders demonstrated that different responders definitions (>25%, >30%, and >50% improvement form baseline) lead to the same overall difference from placebo (i.e. around 21-22%).

Third party corroboration

The ascertainment of childhood onset of ADHD in the adult study is considered a concern. It was indicated that none of the patients in the adult study had a third party corroboration of childhood onset, while this is explicitly stated to be mandatory for studies in adult ADHD in the EMA-guideline.

Comparisons with the evidence submitted for Strattera and Concerta indicate that of the 10 placebo controlled studies that were submitted for the Strattera ADHD adult indication, only one study (LYDO, a randomised withdrawal study) included third party corroboration of childhood onset (i.e. by family members, school or medical records).

Concerta (which like Ritalin LA contains extended release methylphenidate) is not indicated in adults, except for those who were already treated in adolescence and whose symptoms persist into adulthood and have shown clear benefit from treatment. The adults studies in the Concerta dossier included third party corroboration only "if available" and the study reports do not indicate in what proportion of patients such corroboration was in fact available. In this aspect, the Ritalin LA dossier is similar to the case of Concerta and different from the atomoxetine dossier which partly complied with the ADHD guideline and has been approved for adults. Therefore, as for Concerta, Ritalin LA is not indicated in adults, except for those who were already treated in adolescence and whose symptoms persist into adulthood and have shown clear benefit from treatment.

It is noted that the SmPC of Strattera specifies in the indication section that "In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Third-party corroboration is desirable and Strattera should not be initiated when the verification of childhood ADHD symptoms is uncertain".

The NICE guideline on diagnosis and management of ADHD in children, young people and adults (March 2009) indicates that: "The age criterion is crucial to distinguish ADHD from later onset conditions and, unless care is taken to rule out the existence of the other conditions, there may be a high rate of falsely identified cases". However, neither NICE nor DSM provide any indication how age of onset should be assessed.

A high rate of falsely identified and subsequently treated adults is undesirable, also because symptoms of e.g. mania which are misdiagnosed as ADHD, may worsen if treated with methylphenidate.

Therefore, the lack of third party corroboration of childhood onset of ADHD, coupled with the occurrences of AEs of mania and psychosis in the literature on methylphenidate in adults (i.e. Adler et al), and the high frequency of occurrence of psychiatric TEAEs in the submitted adult study is considered a major drawback of the Ritalin LA submission for the adult indication, starting with a new treatment.

Comparison to other treatments in adults

In the table below a structured comparison is made between various parameters of other known ADHD products approved or partly approved for use in adults in comparison with the efficacy and safety of Ritalin LA.

Table 14. Comparison between Ritalin LA, Concerta, and Strattera in parameters of adults studies and SmPC

	Ritalin LA	**Strattera**	**Concerta**
Active substance	Methylphenidate	Atomoxetine	Methylphenidate
Indication	ADHD in adults; 3rd party corroboration of childhood onset if possible	ADHD in adults; need 3rd party corroboration of childhood onset	Adults who were successfully treated in adolescence whose symptoms persist into adulthood.
Submitted studies	1 short-term 1 long-term 1 rand. withdrawal	6 short-term 3 long-term 1 rand. withdrawal.	3 short-term 1 rand. withdrawal
3rd party corroboration of childhood onset	no	Only in 1 of the 10 studies (LYDO; randomised withdrawal study)	"if available" ≈ not required
Baseline severity	Moderate DSM-IV ADHD RS =	Moderate CAARS* = 35	Moderate CAARS = 37

	39		
Effect size	On symptoms: 0.5-0.6 On functioning: 0.3-0.5	On symptoms (acute): 0.4 Long-term: 0.3	On symptoms: 0.3-0.6
Responders[**]	Difference of 21%-22% from placebo	Difference of 10%-13% from placebo	Difference of 16%-32% from placebo
Psychiatric TEAEs first study periods	44.1%	16.7%	39.6%
Discontinuations due to psychiatric TEAEs in first study periods	8.7%	2.3%	2.7%
Mean increase systolic blood pressure extension studies	4.4 mmHg (80 mg)	3.73 mmHg	2.4 mmHg (all dose-levels)

[*]CAARS = Conners' Adult ADHD Rating Scales
[**] Responders were defined as 30% improvement from baseline on the primary severity scale in the Ritalin LA and Concerta studies and as 25% improvement in the Strattera studies

The effect size in the treatment of adults is moderate and comparable to that obtained with Strattera and Concerta, the two other products for the treatment of adults with ADHD. However, the difference form placebo in percent responders is larger in Ritalin LA compared to Strattera. Specifically, effect size of Ritalin LA is 0.5-0.6 (depending on the dose), of Strattera it is 0.4 and of Concerta it ranges between 0.3 and 0.6 (depending on the dose) and the percent responders is 21-22% for Ritalin LA and 10-13% for Strattera.
Regarding safety, psychiatric TEAEs occur in considerably higher frequency in methylphenidate-treated adults as compared to placebo and compared to children and adolescents. This contrasts with atomoxetine which is considered psychiatrically safe in adults. In addition, mean increase in (systolic) blood pressure is slightly higher in Ritalin LA as compared to both atomoxetine and Concerta.

Clinical safety

Children and adolescents
AEs in pediatric patients in the submitted studies were generally in accordance with the known safety-profile of methylphenidate-containing products.

Adults
Overall, with respect to cardiac safety, there remains a serious concern regarding the implication of an increase in systolic BP of 4 mmHg with long-term treatment (i.e. lasting for years). Discontinuation of treatment may induce relapse or recurrence of the disorder.

In addition, psychiatric AEs were common (i.e. total of 43%, including insomnia 11%, anxiety 7%, irritability 7%, and restlessness 7%) and some were serious. Since these events were more common in patients with a psychiatric history and since elaborate psychiatric exclusion criteria were implemented in the study, which prevented inclusion of patients with more serious psychiatric comorbidity, it is concluded that the rate of psychiatric AEs would have been even higher without these exclusions. The feasibility of implementing these exclusion criteria through contra-indications in clinical practice is doubtful.

V. 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 via national procedures and approved by each European Health Authority.
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 groups was considered necessary.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ritalin LA 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, modified-release capsules has a proven chemical-pharmaceutical quality. This concerns a line extension to the registered Ritalin tablets: a modified-release capsule formulation is introduced to mimic b.i.d administration of Ritalin immediate-release tablets.

The application was discussed in the Board meetings of 8 January 2015, 30 July 2015 and 10 March 2016. It was considered that sufficient data were provided regarding the new pharmaceutical form and dosage. Efficacy diminishes later in the day compared to the immediate-release Ritalin formulation, but is similar to other prolonged-release methylphenidate formulations such as Medikinet Retard and Concerta.

Given the efficacy and safety results that were reviewed, the Board considered that the benefit-risk balance is positive for the indication 'Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient'.

In addition to the ADHD indication in children and adolescents approved for Ritalin, the company applied for an indication in adults. To support this the MAH submitted clinical efficacy data from one short-term study in adults with ADHD, coupled with a long-term randomised withdrawal study and followed by a long-term open-label extension study (total exposure up to 66 weeks).
The evidence presented indicated that the effect size is moderate for this product (ranging between 0.5 and 0.6). The MEB concluded that this does not outweigh the risk of psychiatric adverse events and long-term cardiovascular adverse events and therefore decided that the start of treatment with Ritalin LA in adults is not appropriate. Also, there are doubts about the validity of the diagnosis of the adult patients included in the study, as childhood onset of the disorder was not corroborated by a third party as required by the ADHD guideline.
However, the Board acknowledges that it may be appropriate to continue treatment into adulthood in adolescents whose symptoms persist and who have shown clear benefit from treatment. Therefore this has been included in the indication, in accordance with the approved wording for Concerta prolonged-release tablets.

Ritalin LA modified-release capsules were authorised in the Netherlands on 30 August 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached