Redacted 1

pages of trade

secret and/or

confidential

commercial

information

B. In-Process Controls & Tests

(Vol. 1.3, page 4-79)

The in-process control described in the flow diagram above briefly explained as follows:

Table 4: In-process controls for the IR and DR beads formation

Process step #	Test	Specifications

Evaluation: Inadequate for in-process controls. The in-process controls listed above are inadequate for manufacturing of IR and DR beads. The in-process controls are meant to also include the drug layering parameters and efficiency, encapsulation weights to name a few. The dissolution specifications at the in-process controls for DR beads are also broad and need to be reflective of the recommended dissolution specifications for the final drug product.

COMMENT 2: **The in-process controls for IR and DR beads formation are inadequate. Please provide detailed in-process controls at every step of manufacturing to ensure quality control. The dissolution specifications for the DR (delayed release) beads at the in-process controls should be identical to the proposed specifications for the final drug product.**

C. Reprocessing Operations

(Vol. 1.3, page 4-78)

The sponsor states that: *"The times, temperatures, etc., stated in the summary of production are valid for a given batch size provided in the drug product – Manufacturing Formula and using the stated equipment. In the case of minor variations in batch size or use of other equipment of the same type (while maintaining the same basic production steps), these values may vary for technical reasons to ensure that the final product fulfils the requirements and corresponds to the established specifications."*

Evaluation: Inadequate. The sponsor needs to commit to reporting information about reprocessing operations in a supplement or annual report as per the Guidance on Changes to an Approved NDA or ANDA, November 1999.

COMMENT 3: **Reprocessing operations on page 4-78, Vol. 1.3 state that *"The times, temperatures, etc., stated in the summary of production are valid for a given batch size provided in the drug product – Manufacturing Formula and using the stated equipment. In the case of minor variations in batch size or use of other equipment of the same type (while maintaining the same basic production steps), these values may vary for technical reasons to ensure that the final product fulfills the requirements and corresponds to the***

established specifications." **The statement is unacceptable based on the Guidance for Changes to an Approved NDA or ANDA. Please commit to reporting the changes in conditions and equipment related to reprocessing appropriately in a supplement or annual report as per the Guidance for Changes to an Approved NDA or ANDA, November 1999.**

2.6. Regulatory Specifications and Test Methods for Drug Product

(Vol. 1.1, page 3-37, Vol. 1.3, pages 4-106 – 4-285, Vol. 1.4, pages 4-1 – 4-232)

A. Sampling Procedures

Refer to Section 2.5 A, B, and C for evaluation and comment on inadequate in-process controls and lack of reprocessing commitment.

B. Regulatory Specifications and Methods

Regulatory specifications as reported in Vol. 1.1, page 3-37 are as follows:

Proposed specifications for the commercial drug product

Title of Test	Specification
Appearance	20 mg white capsule, imprinted with "NVR" in tan ink on the cap and "R20" in tan ink on the body, containing white to off-white beads that are roughly spherical in shape. Free from visible impurities, uniform in appearance. 30 mg yellow capsule, imprinted with "NVR" in tan ink on the cap and "R30" in tan ink on the body, containing white to off-white beads that are roughly spherical in shape. Free from visible impurities, uniform in appearance. 40 mg light brown capsule, imprinted with "NVR" in tan ink on the cap and "R40" in tan ink on the body, containing white to off-white beads that are roughly spherical in shape. Free from visible impurities, uniform in appearance.
Identification	The sample and standard chromatogram
Identification	The of the methylphenidate HCl in the sample solution corresponds to the n of the reference standard
Assay -	of label claim
Related substances	Individual unknown impurities: Total unknown impurities: Total impurities:
Content uniformity	Complies with the current USP specifications
Mean mass of contents	
Dissolution	
Residual solvents	
Microbial limits	Meets current USP and Ph.Eur. requirements. Total aerobic microbial count: not more than Total combined molds/yeasts count: not more than Specific species of micro-organisms:

2.6.1 Summary of dissolution data and related impurities for 20, 30 and 40 mg capsules.

The tables below summarize the dissolution data from 12 month stability studies at 25 °C/60%RH. The values represent a mean of 6 data points at each time point.

Table 5: Summary of 12 month dissolution stability data at 25 °C/60%rh for 20, 30 and 40 mg

Strength/Package	Batch #	Time (months)	Dissolution %
20 mg/ — cc/ — count	RD099905	0	
		3	
		9	
	RD099906	0	
		6	
		12	
	RD099907	0	
		3	
		9	
20 mg/ — cc/100 count	RD099905	0	
		6	
		12	
	RD099906	0	
		3	
		9	
	RD099907	0	
		6	
		12	
30 mg/ — cc/ — count	RD099908	0	
		6	
		12	
	RD109901	0	
		3	
		9	
	RD109902	0	
		6	
		12	
30 mg/ — cc/100 count	RD099908	0	
		3	
		9	
	RD109901	0	
		6	
		12	
	RD109902	0	
		3	
		9	

Strength/Package	Batch #	Time (months)	Dissolution %
40 mg/ cc/ count	RD109903	0	
		3	
		9	
	RD109904	0	
		6	
		12	
	RD109905	0	
		3	
		9	
40 mg/ cc/100 count	RD109903	0	
		6	
		12	
	RD109904	0	
		3	
		9	
	RD109905	0	
		6	
		12	
Dissolution Value Range from Data			

The dissolution data at 30 °C/60%RH for 12 months is comparable to the 25 °C/60%RH dissolution data. However, eight of the eighteen batch package combinations failed the proposed upper limit of — at the — time point for 40 °C/75%RH. The batches that exceeded the proposed upper limit of — at the —time point are: RD099905 for 20 mg in RD099907 for 20 mg in — RD099908 for 30 mg in — RD109901 for 30 mg in — RD109902 for 30 mg in — RD109908 for 30 mg in — RD109903 for 40 mg in — and RD109905 for 40 mg in —

Evaluation: The dissolution data does not provide any information on the IR component of the drug product. The sponsor needs to provide dissolution data at — to establish effectiveness of the IR beads. In addition the dissolution specifications need modification to reflect the data. The ranges for dissolution data from 9 batches at 12 months is compared to the proposed specifications by the sponsor:

Time (hours)	
Dissolution range from data in NDA	
Proposed Specifications by the Sponsor	

The dissolution specifications should be more reflective of the data. Please refer to the Biopharm review for details and comments about change in dissolution specifications.

Table 6: Summary of related impurities at 25 °C/60%rh for 20, 30 and 40 mg capsules

Strength/ Package	Batch #	Time (months)	Max. unknown impurity %	Total unknown impurity %	Total impurity %
20 mg/ cc/ - count	RD099905				
	RD099906				
	RD099907				
20 mg/ cc/100 count	RD099905				
	RD099906				
	RD099907				
30 mg/ cc/ ~ count	RD099908				
	RD109901				
	RD109902				
30 mg/ cc/100 count	RD099908				
	RD109901				
	RD109902				
40 mg/ cc/ _ count	RD109903				
	RD109904				
	RD109905				

Strength/ Package	Batch #	Time (months)		Max. unknown impurity %	Total unknown impurity %	Total impurity %
40 mg/ cc/100 count	RD109903	0				
		6				
		12				
	RD109904	0				
		3				
		9				
	RD109905	0				
		6				
		12				

[1] – ND: Not detected, ≤ 0.01%, Limit of Quantitation; LOQ =
[2] – RRT 4.73, page 39, Vol. 2.1
[3] – RRT 1.22, page 44, Vol. 2.1
[4] – RRT 1.22, page 46, Vol. 2.1
[5] – RRT 1.22, page 49, Vol. 2.1
[6] – RRT 1.22, page 51, Vol. 2.1

Evaluation: 12 month stability data shows that the only major impurity present is Even though the detection limit and the limit of quantitation are no other impurity is detected. The drug product specifications for related impurities need to be reflective of the release and stability data for related impurities. The specifications reflective of the data should be: Individual Unknown Impurities: NMT Total unknown Impurities: NMT Total impurities: NMT

In addition, the analytical methods section is extremely poorly organized for review. The sponsor is requested to organize the analytical methods in an orderly manner in COMMENT 5

COMMENT 4: **The specifications for related impurities should be reflective of the release and stability data. It is recommended that the specifications are modified to: Individual Unknown Impurities: Total Unknown Impurities: NMT and Total Impurities: based on sufficient data from 9 batches for 12 months.**

2.6.3 Methods for different specifications

The analytical methods section is extremely poorly organized for review. The sponsor is requested to organize the analytical methods in an orderly manner.

COMMENT 5: **The analytical methods section is poorly organized. Please submit the information in an orderly manner for a complete review of your application. The analytical methods for identification by , determination of assay and related substances, dissolution and residual solvents must include: 1) a final method code, 2) specifications, 3) sampling plan, and 4) detailed analytical method. The sampling plan must include the final parameters used such as mobile phase, sample solvent, column type, sample concentration, flow rate, detector wavelength, injection volume, run time, column temperature, wash and equilibrium conditions for an method.**

2.6.4 Batch analysis data

(Vol. 1.5, pages 4-35 – 4-193)

Batch analysis data for different lots presented in the NDA are summarized below.

Table 7: Summary of batch analysis data

Type of data	Batch #
Full scale lots	RD099905, RD099906, RD099907 for 20 mg, RD099908, RD109901, RD109902 for 30 mg, and RD109903, RD109904, RD109905 for 40 mg with [redacted] cc bottle with CR closure containing [redacted] induction seal
Supporting Stability in Clinical Trials	RD089810, RD089811, RD089812 for 17.5, 20, 25 mg with [redacted] in [redacted] bottle with [redacted] seal for Phase I trials RD089805 for 20 mg with [redacted] bottle with [redacted] seal for Phase I trial RD109907, RD109908, RD109909, RD109906 for [redacted] 20, 30, 40 mg with [redacted] bottles with [redacted] seal for Phase III

2.7 Container/Closure System

(Vol. 1.5, pages 4-1 – 4-34)

The proposed container closure for Ritalin® LA is white square [redacted] bottles with [redacted] mm child resistant closure with [redacted] induction seal. [redacted] bottles are to be used for [redacted] and 100 count of Ritalin® LA.

The supporting document (page 2 of this review) lists the DMF information about the [redacted] for Ritalin® LA. The [redacted] is not acceptable as per the review by P. Peri on Dec-29-2000 and the DMF holder is refusing to provide the information on the [redacted] and appropriate regulations code per repeated efforts by the reviewer.

The bulk container packaging for the drug product uses [redacted] The information about the [redacted] is provided on pages 4-7 to 4-10, Vol. 1.5. The specification sheet for [redacted] and a letter of guarantee for food packaging are included from [redacted] The [redacted] are composed of [redacted] (21 CFR 177.1520(c) 2.1), and [redacted] 21 CFR 177.1520(c) 3.1 (a).

The sponsor is proposing equivalency protocol for new [redacted] bottle and closure supplier (pages 4-33 – 4-34, Vol. 1.5). The equivalency protocol includes testing USP<661>, USP<671> for the new bottle supplier and USP<671> for the closure. In addition both the new bottle and closure will be placed on stability through the expiration period.

Evaluation: DMF number for [redacted] product ([redacted] is not provided. It is, however, acceptable since [redacted] has provided guarantee of [redacted] as food packaging and the resins are also 21 CFR. The sponsor also proposes an equivalency protocol for new [redacted] suppliers. The equivalency protocol includes testing USP<661> and <671> for the new [redacted] supplier and <671> for the [redacted] Unacceptable because the criteria of the [redacted] is not included.

COMMENT 6: DMF [redacted] is inadequate. [redacted] from [redacted] (DMF [redacted]) are therefore, unacceptable as a [redacted] for Ritalin® LA until adequate information is provided for an acceptable DMF [redacted]

COMMENT 7: You have proposed an equivalency protocol to qualify new [redacted] suppliers (Vol. 1.5 pages 4-33 - 4-34), using USP <661> and <671> testing. Please submit acceptance criteria for this protocol that are commensurate with the expected shelf-life of the drug product.

2.8 Microbiology

None

2.9 Drug Product Stability

(Vol. 1.5, pages 4-35 – 4-193))

The tables below summarize the stability protocol and 12 month primary stability studies for drug product manufactured at ELAN and packaged in [redacted] bottles. The 12 month stability data contains 12 months data at 25 °C/60%RH, [redacted] months at 30 °C/60%RH and 6 months at 40 °C/75%RH.

Table 8: Stability protocol for 20, 30 40 mg Ritalin LA capsules

Testing matrix at 25°C/60%RH																				
Set		A						B								C				
Strength		20 mg		30 mg		40 mg		20 mg		30 mg		40 mg		20 mg		30 mg		40 mg		
Batch number		RD099905		RD099906		RD109903		RD099908		RD109901		RD109904		RD099907		RD109902		RD109905		
Container/closure bottle/PP closure/induction seal		90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	90cc	175cc	
Container fill (count)			100		100		100		100		100		100		100		100		100	
Schedule		T1	T2	T2	T1	T1	T2	T2	T1	T1	T2	T2	T1	T1	T2	T2	T1	T1	T2	
Interval (months)	0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	3	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	
	6	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	
	9	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	
	12	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	
	18	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	
	24	-	X	X	-	-	X	X	-	-	X	X	-	-	X	X	-	-	X	
	36	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
	48	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	
	60	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	

\- = No testing, samples available if necessary

X = Planned testing

[X] = Optional testing

Table 9: Summary of batches for 12-month primary stability data

Type of Stability study	Dosage	KN Variant	Batch #	# of capsules	Date of Production	Data at 25 °C /60%rh
Primary Stability Data	20 mg	3753001.0.0.004.A	RD099905		3/22/99	12 months, 6 months at 40°C/75%rh and 12 months at 30 °C/ 60%rh
			RD099906		7/28/99	
			RD099907		7/29/99	
	30 mg	3757747.0.0.002.A	RD099908		3/22/99	
			RD109901		7/28/99	
			RD109902		7/29/99	
	40 mg	3757754.0.0.001.A	RD109903		3/22/99	
			RD109904		7/28/99	
			RD109905		7/29/99	

The primary stability batches are considered full-scale and representative of the intended commercial production batches and packaged in the intended commercial container closure. The only difference between the primary registration stability batches and the commercial batches are in the number of capsules produced. However, the number of capsules produced was —— of the commercial capsule batch size.
Additional stability data presented is provided as shown below.

Table 10: Summary of batches for supportive stability data

Dosage	Formulation/ Package	K/N variant/ Batch #	# of capsules	Date of Manufacture	Data conditions
17.5 mg	—— in 90 cc —— bottle with —— seal (2 capsules/ bottle)	3752995.00.00 1.A/RD089810	——	July 1998 for Phase I batches	24 months at 25 °C/60%rh and 6 months at 40 °C/ 75%rh, one data point at 24 months for 30 °C/60%rh
20 mg		3753001.00.00 1.A/RD089811	——		
25 mg		3753019.00.00 1.A/RD089812	——		
20 mg	—— in 90 cc ——with —— seal (2 capsules/ bottle)	3753001.00.00 2.B/RD089805	——	July 1998 for Phase I trials	12 months at 25 °C/60%rh and 6 months at 40 °C/ 75%rh
——	—— in 90 cc —— with plastic CR closure with —— induction seal (10 capsules/ bottle)	3757739.00.00 2.A/RD109907	——	July 1999 for Phase III trials	9 months at 25 °C/60%rh, 6 months at 40 °C/ 60%rh and 9 months at 30 °C/ 60%rh
20 mg		3753001.00.00 3.A/RD109908	——		
30 mg		3757747.00.00 1.A/RD109909	——		
40 mg		3757754.00.00 1.A/RD109906	——		

The sponsor provides supportive stability data for phase I clinical trials using two capsules in 90 cc —— bottles with ——seal and —— ——. Three

dosage strengths of — ıg, 20 mg and - mg with IR/DR of ——— were used. The formulation for phase I 20 mg capsules ——— is the same as phase III and 20 mg proposed commercial drug product except for the capsule size and color. In addition, the phase I supplies were packaged with a while the commercial supplies are not.

Samples for supportive stability were tested at 0, 3, 6, 12, 18 and 24 months at 25 °C/60%RH and until 6 months at 40 °C/75%RH. A data point is collected at 24 months for 30 °C/60%RH. The assay values range between ——— is NMT ——— is at a maximum of —› at 24 months and the total impurities are NMT — Dissolution data for 20 mg batch is within the proposed specifications. In addition, 24 month stability data is provided for the bulk container (batches RD089810, RD089811 and RD089812 at 25 °C/60%RH. The data meets the proposed regulatory specifications.

In addition to 12 month stability data of 20 mg with ——— formulation in —— bottle with —— seal is provided. 9 month stability data is also included for Phase III trials with 10, 20, 30, 40 mg with ——— in _ with ——— induction seal closure.

2.9.1 Expiry Period

Novartis is requesting a shelf life of 2 years for Ritalin® LA under the storage conditions of 15-30 °C (59-86 °F). The NDA contains acceptable 12 months stability data at 25 °C/60%RH and 30 °C/60%RH. In addition, 6 months stability data at 40 °C/75%RH is also provided. However, eight of the eighteen batch package combinations failed dissolution specifications at the— time point for 40 °C/75%RH at 6 months. Based on the results form stability data, only —— expiry period may be granted for Ritalin® LA which can be extended based on additional real-time data.

COMMENT 8: Please clarify the information regarding container closures on stability protocol by correlating the suppliers of materials with reference to their DMF numbers with the to be marketed packages on stability. Please summarize in a tabular form which supplier's materials for ——— were used in the stability studies.

COMMENT 9: You have provided 12 months acceptable stability data at 25 °C/60%RH for Ritalin LA. The 6 month stability data at 40 °C/75%RH shows that eight of the eighteen batch package combinations failed the dissolution test at the — time point. Expiry period of only —— is acceptable for Ritalin® LA reflective of the stability data. The expiry period may be extended based on additional real-time data through a Prior Approval Supplement.

2.10. Investigational Formulations

(Vol. 1.5, pages 4-194 – 4-205, 4-208 – 4-247)

Batch data is provided for the following batches used in clinical trials:

Table 11: Batch and protocol information on clinical batches

Dose Strength (IR/DR)	Batch #	Use of Batch	Batch Size
17.5 mg (10/7.5)	RD089810	Protocol 02 Pediatric PK/PD Study	[redacted]
20 (10/10)	RD089811	Protocol 02 Pediatric PK/PD Study	[redacted]
25 (10/15)	RD089812	Protocol 02 Pediatric PK/PD Study	[redacted]
40 (20/20)	RD109906	Protocol 04 Food Effect Study	[redacted]

The bead formulation of all the dose strengths is same as the to be marketed formulations. The batch data for all the above are within the proposed specifications. In addition, the following batches were used to manufacture the clinical batches (Vol. 2.1, page 11): RD099906 (20 mg), RD109901 (30 mg) and RD109904 (40 mg). All of these batches are evaluated in the stability protocol.

Evaluation: Acceptable

2.11. Environmental Assessment

(Vol. 1.5, pages 4-206 – 4-207)

The sponsor requests for a categorical exclusion under 21 CFR 25.31(b). Novartis Pharmaceuticals certifies that the concentration of the active moiety methylphenidate hydrochloride will be significantly less than 1 ppb. ***Evaluation:*** Acceptable

2.12. Methods Validation

Vol. 1.7, pages 4-1 – 4-423

Methods validation section reports that the following samples will be provided to FDA laboratories for validation of analytical methods.

Table 12: List of samples to FDA laboratories for methods validation

Material	Batch number	Amount
Ritalin Drug Substance, reference standard	to be determined	[redacted]
α-Phenyl-2-piperidineacetic acid hydrochloride (ritalinic acid)	to be determined	[redacted]
[redacted] of methylphenidate hydrochloride	to be determined	[redacted]
RIT124 Capsules, 20mg	to be determined	[redacted]
RIT124 Capsules, 30mg	to be determined	[redacted]
RIT124 Capsules, 40mg	to be determined	[redacted]

The sponsor is requested to provide analytical methods in an orderly manner for review (see section 2.6.3). After review of the analytical methods, the analytical methods for the FDA labs will be determined.

Evaluation: Acceptable for list of samples for FDA labs but pending for the analytical methods.

2.13. Labeling

(Vol. 1.2, pages 2-1 – 2-25)

A separate label for Ritalin® LA is provided. The following sections of the label are evaluated:

Description – The description section of the label contains the chemical name, structure of Ritalin and chemical and physical characteristics. The inactive ingredients are also listed for 20, 30 and 40 mg capsules. The description section also compares Ritalin IR to Ritalin® LA in terms of its release properties.

How Supplied – Ritalin® LA is to be marketed in 20, 30 and 40 mg dosage strengths. The 20, 30 and 40 mg capsules are white, yellow and light brown respectively. The sponsor proposes to market in two sizes of — bottles containing — 100 capsules. The NDC numbers for each dosage and package are provided.

Storage Condition – The storage statement reads "Store at 25 °C (77 °F), excursions permitted to 15-30 °C(59-86 °F)

Draft Container Labels – The draft container labels are provided for 20, 30 and 40 mg capsules to be marketed as — 100 count each. The container labels include:

- Name of Ritalin® LA with LA and the dosage strength highlighted in red,
- Symbol of R_x only and the controlled Class II substance,
- Storage conditions,
- Name and address of Novartis,
- Expiration and Lot number, and NDC number.

Patient Information – The sponsor has also provided a sample of patient information. The package contains information about Ritalin® LA for patients or their parents or caregivers. The topics include:

- What is Ritalin® LA and its active ingredient
- What is ADHD,
- How does Ritalin work,
- Before Ritalin treatment,
- Who should not take Ritalin products,
- During Ritalin® LA treatment,
- How to take Ritalin® LA,
- How to store Ritalin® LA,
- What side effects are possible with Ritalin® LA, and
- Other important information for safe use of Ritalin.

Evaluation:

Biopharm and medical reviews to address the bioavailability issues for the proposed intake of Ritalin® LA by sprinkling beads on soft foods. The color on the container label for different dosage strengths is currently red. It must be different for clarity purposes.

COMMENT 10: **The container labels include the dosage strength written in red color for 20, 30 and 40 mg of Ritalin® LA. Please change to three distinct colors to depict the dosage strength on container labels to increase clarity.**

2.14. Establishment Inspection

(Vol. 1.3, pages 4-46 for drug substance, 4-68 for drug product)

The sites for drug substance manufacture, drug product manufacture, packaging, and stability testing were submitted to EES. EES recommends an overall withhold due to data and laboratory integrity issues at the ELAN Holdings site. Please refer to details on page 3 of this review under "Other Requests".

Evaluation: **Inadequate. Withhold based on inspections by FDA Compliance.**

COMMENT 11: **Inspection of Elan Holdings by FDA Compliance revealed cGMP problems. Elan Holding is unacceptable as a drug product manufacturer, tester and packager until these problems are resolved with FDA Compliance.**

3. REVIEW SUMMARY

1. DRUG SUBSTANCE	Acceptable as per N10-187
2. DRUG PRODUCT	
2.1/2.2 Components/Composition	INADEQUATE Review #1
2.3 Specifications and Methods for Drug Product Ingredients	Acceptable Review #1
2.4 Manufacturer	Acceptable Review #1
2.5 Methods of Manufacturing and Packaging	INADEQUATE Review #1
2.6 Regulatory Specifications and Methods	INADEQUATE Review #1
2.7 Container Closure System	INADEQUATE Review #1
2.8 Microbiology	NA
2.9 Drug Product Stability	INADEQUATE Review #1
2.10 INVESTIGATIONAL FORMULATIONS	Acceptable Review #1
2.11 ENVIRONMENTAL ASSESSMENT	Acceptable Review #1
2.12 METHODS VALIDATION	Acceptable Review #1
2.13 LABELING	INADEQUATE Review #1
2.14 ESTABLISHMENT INSPECTION	INADEQUATE Review #1

4. DRAFT DEFICIENCY LETTER

1. [redacted] is proposed to be [redacted] in the final Ritalin® LA formulation. For example, the 20 mg capsule contains [redacted] Please explain in detail the derivation of [redacted] value for [redacted] in each dosage strength.
2. The in-process controls for IR and DR beads formation are inadequate. Please provide detailed in-process controls at every step of manufacturing to ensure quality control. The dissolution specifications for the DR (delayed release) beads at the in-process controls should be identical to the proposed specifications for the final drug product.
3. Reprocessing operations on page 4-78, Vol. 1.3 state that "The times, temperatures, etc., stated in the summary of production are valid for a given batch size provided in the drug product – Manufacturing Formula *and using the stated equipment. In the case of minor variations in batch size or use of other equipment of the same type (while maintaining the same basic production steps), these values may vary for technical reasons to ensure that the final product fulfills the requirements and corresponds to the established specifications.*" The statement is unacceptable based on the Guidance for Changes to an Approved NDA or ANDA. Please commit to reporting the changes in conditions and equipment related to reprocessing appropriately in a supplement or annual report as per the Guidance for Changes to an Approved NDA or ANDA, November 1999.
4. The specifications for related impurities should be reflective of the release and stability data. It is recommended that the specifications are modified to: Individual Unknown Impurities: [redacted], Total Unknown Impurities: NMT [redacted], and Total Impurities: [redacted] based on sufficient data from 9 batches for 12 months.
5. The analytical methods section is poorly organized. Please submit the information in an orderly manner for a complete review of your application. The analytical methods for identification by [redacted] determination of assay and related substances, dissolution and residual solvents must include: 1) a final method code, 2) specifications, 3) sampling plan, and 4) detailed analytical method. The sampling plan must include the final parameters used such as mobile phase, sample solvent, column type, sample concentration, flow rate, detector wavelength, injection volume, run time, column temperature, wash and equilibrium conditions for an [redacted] method.
6. DMF [redacted] from [redacted] for [redacted] is inadequate. [redacted] from [redacted] (DMF [redacted] are therefore, unacceptable as a [redacted] for Ritalin® LA until adequate information is provided for an acceptable DMF [redacted]
7. You have proposed an equivalency protocol to qualify new container closure suppliers (Vol. 1.5 pages 4-33 - 4-34), using USP <661> and <671> testing. Please submit acceptance criteria for this protocol that are commensurate with the expected shelf-life of the drug product.
8. Please clarify the information regarding [redacted] on stability protocol by correlating the suppliers of materials with reference to their DMF numbers with the to be marketed packages on stability. Please summarize in a tabular form which supplier's materials for [redacted] were used in the stability studies.
9. You have provided 12 months acceptable stability data at 25 °C/60%RH for Ritalin LA. The 6 month stability data at 40 °C/75%RH shows that eight of the eighteen batch

package combinations failed the dissolution test at the — time point. Expiry period of only — is acceptable for Ritalin® LA reflective of the stability data. The expiry period may be extended based on additional real-time data through a Prior Approval Supplement.

10. **The container labels include the dosage strength written in red color for 20, 30 and 40 mg of Ritalin® LA. Please change to three distinct colors to depict the dosage strength on container labels to increase clarity.**
11. **Inspection of Elan Holdings by FDA Compliance revealed cGMP problems. Elan Holding is unacceptable as a drug product manufacturer, tester and packager until these problems are resolved with FDA Compliance.**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Gurpreet Gill-Sangha
8/17/01 10:25:57 AM
CHEMIST

CMC Review #1

Robert H. Seevers
8/17/01 12:58:54 PM
CHEMIST

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East Hanover, New Jersey

Clinical Development

RIT124D / Ritalin- —

Integrated summary of safety

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Signatures

International Clinical Leader

I hereby certify that this document accurately summarizes the safety data of the Ritalin- clinical studies.

Goeril Karlsson, Ph.D.
International Clinical Leader _____ signature _____ date

International Clinical Statistician

I hereby certify that this document accurately summarizes the statistical interpretation of the data analyses.

Harald Pohlmann, M.Sc.
International Clinical Statistician _____ signature _____ date

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ADHD	Attention-Deficit Hyperactivity Disorder
AUC	area under the curve
b.i.d.	bis in diem/twice a day
CP	Clinical Pharmacology
DISC	Diagnostic Interview Schedule for Children
d-MPH	d-isomer or active enantiomer of methylphenidate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
FDA	Food and Drug Administration
HCl	hydrochloride
IR	immediate-release
ISS	Integrated Summary of Safety
LA	long-acting
l-MPH	l-isomer or enantiomer of methylphenidate
MPH	methylphenidate hydrochloride
NDA	New Drug Application
nec	not elsewhere classified
NOEL	no-observed-effect level
nos	not otherwise specified
NTP	National Toxicology Program
p.o.	per os/orally
PK	pharmacokinetics
ppm	parts per million
QD	qua' que diem/once a day
RBCs	red blood cells
RS:L	designates a formulation of Ritalin —
S	designates a formulation of Ritalin- —
SAE	serious adverse event
SD	standard deviation
SODAS	Spheroidal Oral Drug Absorption System
SOP	Standard Operating Procedures
WBCs	white blood cells
WHO	World Health Organization

1. Introduction and overview

1.1. Introduction

Background and rationale

Attention-Deficit Hyperactivity Disorder (ADHD) is a recognized medical problem characterized by persistent core symptoms of inattention, hyperactivity and impulsivity. The prevalence (in the US) is estimated at 3%-5% in school-age children and up to 2% in adults. The symptoms of ADHD lead to impairments in cognitive and behavioral areas such as learning, social and family interactions as well as self-esteem. Data from follow-up studies suggest that children with ADHD are at risk for developing other psychiatric disorders in childhood, adolescence and adulthood such as antisocial behaviors, alcoholism and substance abuse as well as depressive and anxiety disorders.

Stimulants are considered the treatment of choice and methylphenidate hydrochloride (MPH) is most commonly used. The mechanism of the therapeutic action of methylphenidate in ADHD is not known. Methylphenidate is thought to increase the availability of dopamine and norepinephrine through blocking the reuptake of these monoamines into the presynaptic neuron and increasing their release into the extraneuronal space.

The efficacy and safety of MPH is well established [6, 7]. In addition to improving core symptoms of ADHD, it also improves behaviors associated with ADHD such as impaired academic performance and social function. Nervousness and insomnia are the most common adverse reactions to MPH. Loss of appetite, abdominal pain, weight loss during prolonged therapy, and tachycardia are other known adverse effects associated with MPH use. Usually these adverse reactions are mild and transient.

Ritalin® tablets (MPH) have been marketed for many years (since 1955 in the USA) and are indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for patients with ADHD. Ritalin is a short acting medication with a half-life of approximately two to three hours, thus b.i.d. administration of the drug (morning and mid-day) is required in order to maintain efficacy during school hours.

Ritalin- — (Ritalin LA) is a new, modified-release oral dosage form of Ritalin. The objective of the Ritalin- — program was to develop a once-daily dosage form which mimics the pharmacokinetic profile of Ritalin administered b.i.d. (morning and mid-day). The new dosage form thus delivers, in a single administration, a bimodal release of MPH with an initial release occurring immediately after dosing and a second release approximately four hours after dosing. This was achieved through use of technology known as a Spheroidal Oral Drug Absorption System (SODAS) which was developed and provided by Elan Pharmaceuticals, Ireland.

Availability of Ritalin- — will obviate the need for the mid-day dose and thus fulfill an unmet medical need by eliminating emotional trauma, inconvenience and resourcing related to dispensing the medication at school. This would also reduce the potential for diversion of MPH for non-prescription use in schools.

Ritalin— clinical program

The clinical program of Ritalin- — consisted of six studies; two clinical and four clinical pharmacology studies.

The two clinical studies (Protocols 02 and 07) evaluated the efficacy, safety and pharmacokinetics of Ritalin- in children with ADHD 6-12 years of age. The clinical pharmacology studies (Protocols 01, 04, 06. and 09) evaluated the pharmacokinetics and tolerability of Ritalin- in adult healthy volunteers.

Protocol 02 was a multicenter, double-blind, placebo-control, five-period crossover study in a laboratory classroom setting. It evaluated the pharmacodynamic (efficacy) and pharmacokinetic profile of four formulation/dose variants of Ritalin- —— (Formulation 1) 17.5mg, 20mg, and 25mg; S (Formulation 2) 20mg) in 34 children with ADHD. Subjects were enrolled if they met DSM-IV criteria for ADHD (combined type) and had been treated with MPH for at least four weeks prior to enrollment. After a 1-week Baseline Phase during which the subjects received open-label Ritalin 10mg b.i.d., subjects were randomized into the Treatment Phase and received single doses of the four formulation/dose variants of Ritalin- — and placebo during five one-day Treatment Evaluation Periods. On days between the Treatment Evaluation Periods, subjects received open-label Ritalin at their usual regimen.

Protocol 07 was a multicenter, double-blind, placebo-control, parallel-group study in the usual school and home settings of 161 children with ADHD. It evaluated the efficacy and safety of Ritalin- — at daily doses of up to 40mg. Subjects were enrolled if they met DSM-IV criteria for ADHD (any type). Subjects could be either previously treated with MPH or *de novo*. After a single-blind Titration Period of up to four weeks, during which the "optimal" dose (within the dose-range 10-40mg) for each subjects was identified, subjects entered a one-week single-blind Placebo-Washout Period. Subjects were then randomized to the Double-blind Treatment Phase to receive their individually titrated dose (10, 20, 30 or 40mg) of Ritalin- — or placebo for up to two weeks. Subjects who completed the Double-blind Treatment Phase were allowed to enter a 12-week Extension Phase, during which they received Ritalin- —, in an open-label fashion. With the exception of serious adverse events (SAEs), data from the Extension Phase are not included in this NDA.

All four clinical pharmacology studies used similar open-label, two- to four-period crossover designs and evaluated doses of 20mg (Protocol 01 and 09) and 40mg (Protocol 04 and 06) Ritalin- —. Protocols 01 and 06 evaluated the bioavailability of Ritalin- — relative to Ritalin administered b.i.d.. Protocols 04 and 09 evaluated the effect of food on the pharmacokinetic profile of Ritalin- —.

With over 40 years of use, the safety profile of Ritalin is well known. The safety data from the Ritalin- — clinical studies, which are presented in this ISS, demonstrated that Ritalin- — is safe and well-tolerated in the target population of children with ADHD. No new safety concerns uniquely associated with the new dosage form, Ritalin- —, were identified.

1.2. Regulatory guidelines and discussions with FDA

On April 4, 2000 a Pre-NDA meeting was held between representatives of the Sponsor and the FDA. The sponsor's proposed content for this Integrated Summary of Safety (ISS) was

discussed at that meeting and the FDA agreed that the proposed content, groupings for presenting the safety data and tables were acceptable. The FDA also requested a separate analysis of adverse events that occurred during the Placebo-Washout Period of Protocol 07. The requested analysis was conducted and is provided in this application.

In addition, the FDA suggested modifying the upper limit of the range for clinically notable values of alkaline phosphatase and the notable criteria for vital signs for pediatric patients. These notable ranges and criteria have been modified.

The FDA also requested that narratives be provided for subjects who discontinued for non-serious adverse events in addition to the standard narratives for discontinuations due to serious adverse events (SAEs) and laboratory abnormalities. The requested narratives were completed and are provided in this application.

1.3. Presentation overview

The data in this ISS are organized in three parts. The first part is the ISS text (description and discussion of the data), the second part consists of four post-text supplements (Table of studies, post-text tables and listings, narratives and criteria for clinically notable laboratory values and vital signs) and the third part consists of two appendices (referenced literature and a description of statistical methods).

The Ritalin- — clinical program consisted of six studies; two clinical studies (Protocols 02 and 07) conducted in children with ADHD aged 6-12 years (Table 1-1) and four clinical pharmacology studies (Protocols 01, 04, 06 and 09) conducted in adult healthy volunteers (Table 1-2).

Two Ritalin- formulation variants (RS:L and S) were initially evaluated in Protocols 01, 09 and 02. Of the two variants, RS:L had pharmacokinetic characteristics which most resembled Ritalin administered b.i.d. and was therefore selected for further development (Protocol 04, 06 and 07) as the final formulation. This ISS presents safety data obtained with the RS:L formulation variant only.

A total of 256 subjects, 195 children and 61 adult healthy volunteers, were exposed to Ritalin- — (RS:L) in the six Ritalin- — studies.

The data generated from the Ritalin- — studies were classified into four groupings for the presentation of exposure and safety data in this ISS. Due to the differences in design (crossover versus parallel-group), the data from the two clinical studies were not pooled for any grouping. The data from the four clinical pharmacology studies were pooled. The four groupings are shown in Table 1-3.

The data from the six Ritalin — studies originate from two databases. Protocols 02, 07, 04 and 06 come from the Novartis database and Protocols 01 and 09 come from databases owned by Elan Pharmaceuticals, Ireland.

The clinical and clinical pharmacology studies are summarized in more detail in the Table of studies, which can be found in Post-text supplement 1.

Table 1-1. Clinical studies

Protocol No.	Type of Control	No. of Subjects	Population
02	Placebo	34	Children 6 – 12 yrs with ADHD
07	Placebo	161	Children 6 – 12 yrs with ADHD

Table 1-2. Clinical pharmacology studies

Protocol No.	Purpose & Design	Type of Control	No. of Subjects*	Population
01	PK / tolerability	Ritalin® tablets	9	Adult volunteers
09	Food interaction	None	15	Adult volunteers
04	Food interaction	None	20	Adult volunteers
06	Relative bioavailability	Ritalin® tablets	17	Adult volunteers

*No. of subjects who received Ritalin :L. Protocol 09 included a total of 17 subjects, however, two subjects received only Ritalin- and are not included in this ISS.

Table 1-3. Groupings used to present safety data

Grouping	Source	Purpose	Protocol
1	All treated subjects in Protocol 07 (treated with Ritalin- during Titration Period, with placebo during Placebo-Washout Period and with Ritalin during Double-blind Treatment Phase)	Evaluate exposure to multiple-dose Ritalin-	07
2	All randomized subjects in Protocol 07 (treated with Ritalin- or placebo in the Double-blind Treatment Phase)	Evaluate adverse events associated with multiple-dose Ritalin- relative to placebo	07
3	All treated subjects in Protocol 02	Evaluate adverse events associated with repeated single-dose Ritalin- (RS:L) relative to placebo	02
4	All healthy volunteers in clinical pharmacology studies	Evaluate exposure and tolerability in adult healthy volunteers	01, 04, 06, 09

Throughout the ISS, *Groupings 1-3* are presented under sections "key safety population" and *Grouping 4* under sections "other populations".

1.4. Summary of statistical methods

The safety variables that are analyzed in this ISS include adverse events, laboratory data (hematology and blood chemistry), vital signs and body weight. In addition, demographic and baseline characteristics, extent of exposure to study drug, medical histories/continuing medical conditions and concomitant medications are summarized. All data summaries are descriptive. No inferential statistical analyses were performed. A detailed description of the statistical methods can be found in Appendix 2.

2. Drug exposure

Drug exposure was summarized for *Groupings 1, 2, 3* (key safety population) and *4* (other populations).

For *Groupings 1* and *2* (multiple-dose exposure), duration of exposure to study drug was summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum) and by categories of cumulative exposure (each subject was counted in the category corresponding to his/her total duration of exposure and in all lower categories). For *Grouping 1*, duration of exposure was calculated as the interval between the start of dosing with Ritalin- and the last day on Ritalin-; this means that the imbedded interval without Ritalin- exposure (i.e. Placebo-Washout Period) is included in the duration of exposure. For *Grouping 2*, duration of exposure was calculated as the interval between the first and last dose of double-blind treatment.

For *Groupings 3* and *4* (repeated single-dose exposure), exposure is provided in a non-cumulative manner by presenting the number of subjects who received 1, 2 and 3 single doses of Ritalin-

2.1. Overall exposure in the key safety population

Duration of exposure in *Grouping 1* is summarized in Tables 2-1 and 2-2. Mean duration of exposure to Ritalin- was 35.7 days (range 2 to 64 days); 68.9% of the subjects were exposed for at least 30 days.

Table 2-1. Duration of exposure to study drug, summary statistics / Grouping 1: All treated subjects in Protocol 07

	Ritalin- N=161
Mean (days)	35.71
SD	12.96
Median	35
Minimum	
Maximum	

Source: Post-text table 2.1-3.

Table 2-2. Cumulative duration of exposure to study drug / Grouping 1: All treated subjects in Protocol 07

Duration of Exposure	Ritalin- N=161 n (%)
≥ 1 Day	161 (100)
≥7 Days	157 (97.5)
≥14 Days	152 (94.4)
≥ 30 Days	111 (68.9)

Source: Post-text table 2.1-4.

Duration of exposure in *Grouping 2* is summarized in Post-text tables 2.1-1 and 2.1-2. Mean duration of exposure to both Ritalin — and placebo was 13.9 days (range —— days Ritalin ——— days placebo). Of the 65 subjects randomized to Ritalin- —, most (n=47) were receiving daily doses of 30mg or 40mg.

Exposure in *Grouping 3* was a maximum of three single doses of Ritalin- ——. All 34 subjects received at least two doses, 31 of the subjects received all three doses. Thirty-two of the subjects received placebo. Single doses ranged from 17.5mg-25mg (source: Clinical study report [1]).

2.2. Exposure in other populations

Exposure in *Grouping 4* is summarized in Post-text table 2.3-1. Exposure in this grouping was a maximum of three single doses of Ritalin- —). Thirteen of the 61 subjects (21.3%) received one single dose, 16 (26.2%) received two single doses, and 32 (52.5%) received three single doses. Single doses were either 20mg or 40mg. There was no exposure to placebo in this grouping.

2.3. Summary of exposure

The most extensive multiple-dose exposure to Ritalin — was evaluated in *Grouping 1*. Mean duration of exposure was 35.7 days, and 68.9% of the subjects were treated for at least 30 days. Mean duration of exposure in *Grouping 2* was 13.9 days on both Ritalin- — and placebo. The majority of Ritalin- — subjects in *Grouping 2* received daily doses of 30 or 40 mg.

Repeated single-dose exposure was evaluated in *Groupings 3* and *4*. Exposure to Ritalin- — in these two groupings was a maximum of three single doses ranging from 17.5mg-40mg.

3. Demographics and other features

Baseline demographics were summarized for *Groupings 1, 3* and *4*.

For all three groupings, the following demographics were summarized: sex, race, age and weight. In addition, relevant medical histories/continuing medical conditions and concomitant medications/significant non-drug therapies initiated after start of study drug were summarized for *Groupings 1* and *3*. DSM-IV diagnosis of ADHD subtype was summarized for *Grouping 1*.

3.1. Demographics of the key safety population

Demographics and ADHD subtypes for *Grouping 1* are summarized in Table 3-1. The subjects were primarily Caucasian (85.7%) and male (75.8%) with a mean age of 8.8 years. The majority of the subjects had a diagnosis of ADHD combined type (75.8%) as determined by the Diagnostic Interview Schedule for Children (DISC).

Table 3-1. Demographics and background characteristics / Grouping 1: All treated subjects in Protocol 07

Demographic variable	Ritalin- N=161
Sex (%)	
Male	122 (75.8)
Female	39 (24.2)
Race (%)	
Caucasian	138 (85.7)
Black	6 (3.7)
Oriental	2 (1.2)
Other	15 (9.3)
Age (years)	
N	161
Mean	8.81
SD	1.89
Weight (kg)	
N	160
Mean	34.25
SD	11.76
Height (cm)	
N	161
Mean	136.38
SD	11.84
DISC DSM-IV diagnosis (%)	
Inattentive	30 (18.6)
Hyperactive-impulsive	2 (1.2)
Combined type	122 (75.8)
No DISC diagnosis	7 (4.3)

Source: Post-text table 3.1-1.

Demographics for *Grouping 3* are summarized in Table 3-2. The demographics of subjects in this grouping were similar to those seen in *Grouping 1*. All subjects in *Grouping* 3 had a diagnosis of ADHD combined type, per protocol.

Table 3-2. Baseline demographics / Grouping 3: All treated subjects in Protocol 02

Demographic variable	Ritalin- — N=34
Sex (%)	
Male	26 (76.5)
Female	8 (23.5)
Race (%)	
White	26 (76.5)
Black	2 (5.9)
Asian/Oriental	1 (2.9)
Other	5 (14.7)
Age (years)	
N	34
Mean	9.59
SD	1.46
Weight (kg)	
N	33
Mean	38.50
SD	14.96

Source: Post-text table 3.1-2.

3.2. Concomitant medications of the key safety population

Concomitant medications and significant non-drug therapies taken after start of study drug are summarized for *Grouping 1* in Post-text table 3.3-1 and for *Grouping 3* in Post-text table 3.3-2. Concomitant medications and significant non-drug therapies were generally used by few subjects. The most commonly used were analgesics, anti-asthmatics, cold and allergy treatments, antibiotics and vitamins.

3.3. Other features of the key safety population

Relevant medical histories/continuing medical conditions are summarized for *Grouping 1* in Post-text table 3.2-1 and for *Grouping 3* in Post-text table 3.2-2. Relevant medical histories/continuing medical conditions in *Grouping 1* were reported for approximately 80% of the subjects. Individual conditions were generally reported by few subjects and were common conditions such as asthma, ear infections, headache, allergies, enuresis and abdominal pain. The relevant medical histories/continuing conditions of subjects in *Grouping 3* were similar to those in *Grouping 1*.

3.4. Demographics of other populations

Demographics for *Grouping 4* are summarized in Post-text table 3.5-1. Subjects were predominantly Caucasian (70.5%) and male (75.4%) with a mean age of 29.5 years.

3.5. Summary of demographics

Subjects in *Grouping 1* were primarily Caucasian (85.7%) and male (75.8%) with a mean age of 8.8 years. The majority of the subjects (75.8%) had a DSM-IV diagnosis of ADHD combined type. The demographics of subjects in *Grouping 3* were very similar.

Subjects in *Grouping 4* were also predominantly Caucasian (70.5%) and male (75.4%) with a mean age of 29.5 years.

4. Subject disposition

4.1. Overall disposition in the key safety population

Subject disposition is summarized for *Grouping 1* in Table 4-1 and for *Grouping 2* in Table 4-2.

For *Grouping 1*, a total of 164 subjects were enrolled in Protocol 07; of these, 130 (79.3%) completed all phases/periods of the study (i.e. Titration, Placebo-Washout, Double-blind Treatment). Three of the 164 enrolled subjects had no post-dose safety evaluations and were not included in any analyses for *Grouping 1*.

For *Grouping* 2, a total of 137 subjects were randomized into the Double-blind Treatment Phase of Protocol 07; 66 subjects to Ritalin-, 71 to placebo. Of these, most completed double-blind treatment: 61 (92.4%) in the Ritalin- group and 69 (97.2%) in the placebo group. One of the 66 subjects randomized to Ritalin- did not receive double-blind treatment and was therefore not included in any of any analyses for *Grouping 2.*

A total of 34 subjects (20.7%) prematurely discontinued from the study, but only 7 subjects discontinued during the Double-blind Treatment Phase (5 Ritalin- 2 placebo). Reasons for discontinuation are summarized for all subjects in Table 4-1 and for randomized subjects in Table 4-2.

Table 4-1. Subject disposition / Grouping 1: All enrolled subjects in Protocol 07

Disposition/Reason	All enrolled N=164[1] n (%)
Completed	130 (79.3)
Discontinued	34 (20.7)
Adverse event(s)	7(4.3)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedures result(s)	0 (0.0)
Unsatisfactory therapeutic effect	9 (5.5)
Subject's condition no longer requires study drug	0 (0.0)
Protocol Violation	2 (1.2)
Subject withdrew consent	8 (4.9)
Lost to follow-up	3 (1.8)
Administrative problems	5 (3.0)
Death	0 (0.0)

[1]Includes three subjects who had no post-dose safety evaluations. These subjects were not included in any safety analyses for Grouping 1.

Source: Post-text table 4.1-2.

Table 4-2. Subject disposition by treatment / Grouping 2: All randomized subjects in Protocol 07

Disposition/Reason	Ritalin- — N=66[1] n (%)	Placebo N=71 n (%)
Completed	61 (92.4)	69 (97.2)
Discontinued	5 (7.6)	2 (2.8)
Adverse event(s)	2 (3.0)	1 (1.4)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)
Abnormal test procedures result(s)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	1 (1.5)	1 (1.4)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)
Protocol Violation	0 (0.0)	0 (0.0)
Subject withdrew consent	1 (1.5)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Administrative problems	1 (1.5)	0 (0.0)
Death	0 (0.0)	0 (0.0)

[1]Includes one subject who was randomized but did not receive double-blind treatment. This subject was not included in any safety analyses for Grouping 2.

Source: Post-text table 4.1-1.

Subject disposition for *Grouping 3*: Thirty-four subjects were randomized and received Ritalin-[f] — .) in this grouping. All 34 subjects completed the study. Five subjects missed an evaluation at some time during the study but all remained in the study for the final evaluation (source: Clinical study report [1]).

4.2. Disposition in other populations

Subject disposition in *Grouping 4* is summarized in Post-text table 4.3-1. Of the 61 subjects enrolled, 56 subjects (91.8%) completed their studies. Five subjects discontinued prematurely: three due to adverse events, one due to withdrawal of consent, and one due to administrative problems.

4.3. Summary of disposition

For *Grouping 1*, a total of 164 subjects were enrolled in Protocol 07. Of these, 161 received Ritalin – and had at least one post-dose safety evaluation and were included in the analyses for *Grouping 1*. One-hundred-thirty subjects (79.3%) completed the study. Of the 34 subjects (20.7%) who prematurely discontinued the study, most discontinued due to unsatisfactory therapeutic effect (n=9), withdrawal of consent (n=8) and adverse events (n=7).

For *Grouping 2*, a total of 137 subjects (66 Ritalin- – 71 placebo) were randomized into the Double-blind Treatment Phase of Protocol 07. Of these, 136 (65 Ritalin- – 71 placebo) received double-blind treatment and were included in the analyses for *Grouping 2*. In the Ritalin- – group, 92.4% completed the Double-blind Treatment Phase compared to 97.2% in the placebo group. Seven subjects (5 Ritalin- – 2 placebo) prematurely discontinued the Double-blind Treatment Phase mainly due to adverse events (2 Ritalin- – 1 placebo) and unsatisfactory therapeutic effect (1 Ritalin- – 1 placebo).

All 34 subjects in *Grouping 3* completed the study. In *Grouping 4*, 56 of the 61 subjects (91.8%) completed their studies.

5. Adverse events

Adverse events are defined as those events that are newly occurring or a worsening of pre-existing conditions (i.e. treatment-emergent adverse events).

A serious adverse event (SAE) is defined as an undesirable sign, symptom or medical condition which is fatal or life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is medically significant, defined as placing the subject in jeopardy or requiring medical or surgical intervention to prevent one of the outcomes listed above.

The sections below present the information on treatment-emergent adverse events and SAEs.

Adverse events were summarized for *Groupings 1, 2, 3* and *4*. All adverse events (regardless of study drug relationship) were summarized in descending order of frequency.

For Grouping 2, adverse events with onset in the Double-blind Treatment Phase were counted. This is the only grouping that allows an adequate comparison with placebo.

For Grouping 1, adverse events with onset during the single-blind Titration and Placebo-Washout Periods as well as during Ritalin – treatment in the Double-blind Treatment Phase were counted for Ritalin- –

5.1. Overall adverse events in the key safety population

5.1.1. Most frequently affected system organ classes

The most frequently affected system organ classes for *Grouping 2* are summarized in Table 5-1. The proportion of subjects reporting adverse events was similar for Ritalin and placebo (24.6% and 23.9%, respectively). Nervous system disorders (n=6, 9.2% Ritalin — n=2, 2.8% placebo) and gastrointestinal disorders (n=1, 1.5% Ritalin — n=6, 8.5% placebo) were the most frequently affected system organ classes.

Table 5-1. Frequently affected system organ classes (≥2% for any group) / Grouping 2: All randomized subjects in Protocol 07

Primary System Organ Class	Ritalin N=65 n (%)	Placebo N=71 n (%)
Any primary system organ class	16 (24.6)	17 (23.9)
Nervous system disorders	6 (9.2)	2 (2.8)
Infections and infestations	3 (4.6)	3 (4.2)
General disorders and administration site conditions	2 (3.1)	0 (0.0)
Injury and poisoning	2 (3.1)	1 (1.4)
Metabolism and nutrition disorders	2 (3.1)	0 (0.0)
Psychiatric disorders	2 (3.1)	1 (1.4)
Respiratory, thoracic and mediastinal disorders	2 (3.1)	3 (4.2)
Gastrointestinal disorders	1 (1.5)	6 (8.5)
Skin & subcutaneous tissue disorders	0 (0.0)	2 (2.8)

Source: Post-text table 5.1-1.

The most frequently affected system organ classes for *Grouping 1* are summarized in Post-text table 5.1-2. Nervous system disorders, gastrointestinal disorders and infections and infestations were the most frequently affected system organ classes.

5.1.2. Frequency of adverse events

Common adverse events (reported by at least 2% of subjects in any group) in *Grouping 2* are summarized in Table 5-2. Individual adverse events were reported by few subjects. Anorexia (n=2) and insomnia (n=2) were the most frequently reported adverse events in the Ritalin — group that were not also reported in the placebo group. Both anorexia and insomnia are known adverse events for Ritalin. Headache, vomiting and sore throat were the most frequently reported adverse events in the placebo group.

Table 5-2. Common adverse events (≥2% of any group) / Grouping 2: All randomized subjects in Protocol 07

Preferred term	Ritalin- — N=65 n (%)	Placebo N=71 n (%)
Anorexia	2 (3.1)	0 (0.0)
Insomnia nec	2 (3.1)	0 (0.0)
Sore throat nos	0 (0.0)	3 (4.2)
Headache nos	1 (1.5)	2 (2.8)
Vomiting nos	0 (0.0)	2 (2.8)

Source: Post-text table 5.1-1.

Common adverse events (reported by at least 2% of subjects) in *Grouping 1* are summarized in Table 5-3. The adverse events reported were generally known adverse events for Ritalin or were common childhood disorders.

Table 5-3. Common adverse events (≥2%) / Grouping 1: All treated subjects in Protocol 07

Preferred term	Ritalin- — N=161 n (%)
Headache nos	26 (16.1)
Insomnia nec	17 (10.6)
Abdominal pain upper	12 (7.5)
Anorexia	11 (6.8)
Appetite decreased nos	11 (6.8)
Nasopharyngitis	11 (6.8)
Irritability	8 (5.0)
Lethargy	8 (5.0)
Upper respiratory tract infection nos	7 (4.3)
Vomiting nos	6 (3.7)
Cough	5 (3.1)
Dermatitis nos	5 (3.1)
Ear infection nos	5 (3.1)
Nausea	5 (3.1)
Pyrexia	4 (2.5)
Joint sprain	4 (2.5)

Source: Post-text table 5.1-2.

Common adverse events (reported by at least 1% of subjects) reported during the Placebo-Washout Period of Protocol 07 are summarized in Table 5-4. The proportion of subjects reporting adverse events during this period was 18.1%. The adverse events reported during the Placebo-Washout Period were similar in nature to those reported during treatment with Ritalin- —

Table 5-4. Common adverse events (≥1%) / Grouping 1: Placebo-Washout Period Protocol 07

Preferred term	Placebo-Washout Period N=138 n (%)
Any adverse event	25 (18.1)
Headache nos	8 (5.8)
Diarrhea nos	3 (2.2)
Cough	2 (1.4)
Ear infection nos	2 (1.4)
Increased activity	2 (1.4)
Upper respiratory tract infection nos	2 (1.4)

Source: Post-text table 5.1-1.

The adverse events reported for *Grouping 3* are summarized in Table 5-5. The frequency of adverse events reported for Ritalin — was higher than that reported for placebo. However, because subject exposure to Ritalin- — was two to three times that of placebo, the observation period during which adverse events could be reported for Ritalir — was longer than for placebo.

Table 5-5. All adverse events / Grouping 3: All treated subjects in Protocol 02

Preferred term	Ritalin- N= 34[1] n (%)	Placebo N= 32[2] n (%)
Any adverse event	15 (44.1)	2 (6.3)
Dermatitis nos	3 (8.8)	0 (0.0)
Headache nos	3 (8.8)	1 (3.1)
Abdominal pain upper	2 (5.9)	1 (3.1)
Dizziness (excluding vertigo)	2 (5.9)	0 (0.0)
Fatigue	2 (5.9)	0 (0.0)
Injury nos	2 (5.9)	0 (0.0)
Tic	2 (5.9)	0 (0.0)
Anorexia	1 (2.9)	0 (0.0)
Dysphoria	1 (2.9)	0 (0.0)
Nausea	1 (2.9)	0 (0.0)
Pupils unequal	1 (2.9)	0 (0.0)
Tinea Nos	1 (2.9)	0 (0.0)
Vasovagal attack	0 (0.0)	1 (3.1)

[1]Each subject received up to three single doses of Ritalin —

[2]Each subject received a single dose of placebo.

Source: Post-text table 5.1-3.

5.1.3. Discontinuations due to adverse events

Discontinuations due to adverse events in Protocol 07 are listed in Table 5-6. Seven subjects discontinued due to adverse events. These adverse events occurred while the subjects were

receiving Ritalin- — The disposition data (Table 4-2) indicate that one subject (501/12) discontinued due to an adverse event after having been randomized to placebo, however, the adverse event (lethargy) actually started while he was treated with Ritalin- — during the Titration Period (Source: Clinical study report [2]).

There were no discontinuations related to adverse events in Protocol 02.

Table 5-6. Adverse events that caused premature discontinuation / Protocol 07

Preferred term	Treatment/ Phase[1]	Country/ Center	Subj. No.	Age/ Sex	Last total daily dose	Study day	Rel. to study drug	Severity
Fatigue	Ritalin — Titration	USA/503	8	8/M	10	8	yes	Mild
Lethargy	Ritalin — Titration	USA/501	12	12/M	10	10	no	Moderate
Anger, Hypomania	Ritalin — Titration	USA/503	4	6/M	10	2	Yes	Moderate
Anger	Ritalin- — Titration	USA/506	9	9/M	20	11	no	Moderate
Anxiety nec, Depressed mood	Ritalin- — Titration	USA/513	6	11/M	30	1	Yes	Moderate
Migraine nos	Ritalin- — Titration	USA/501	7	11/M	10	2	yes	Mild
Depression nec	Ritalin- — Double-blind	USA/503	6	8/M	30	35	no	Severe

[1]Treatment/Phase during which adverse event started.

Source: Clinical study report, Post-text listing 10.2-2 [2]

5.2. Deaths and other serious or clinically significant adverse events in the key safety population

5.2.1. Deaths and other serious adverse events

No deaths occurred in any of the Ritalin — studies and only one serious adverse event (SAE) was reported in the studies included in this ISS. Subject 503/6 in Protocol 07 had depression requiring hospitalization while receiving Ritalin- — Within eight days of onset of the event, the subject was discharged from the hospital. The subject's depression was improved but was still ongoing at the time of discharge. The subject was discovered during the study to have a history of depression. In the opinion of the investigator the event was not suspected to be study drug related. The narrative for this subject can be found in Post-text supplement 3.

5.2.2. Discontinuations for SAEs or other significant adverse events

The subject (503/6) who reported the SAE (depression) in Protocol 07 was discontinued for that event. There were no discontinuations for other significant adverse events.

5.3. Adverse events in other populations

Common adverse events (reported by at least 2% of subjects) in *Grouping 4* are summarized in Table 5-7. There were no deaths or SAEs in *Grouping 4*. Three subjects discontinued due to adverse events (Post-text Listing 5.3-1).

Table 5-7. Common adverse events (≥2%) / Grouping 4: All healthy volunteers

Preferred Term	Ritalin- N = 61[1] n (%)
Any adverse event	32 (52.5)
Headache nos	11 (18.0)
Dizziness (excluding vertigo)	8 (13.1)
Nausea	5 (8.2)
Somnolence	4 (6.6)
Dry mouth	3 (4.9)
Hot flushes nos	2 (3.3)
Paraesthesia nec	2 (3.3)
Sore throat nos	2 (3.3)

[1]Each subject received one to three single doses of Ritalin-

Source: Post -text table 5.3-1.

5.4. Deaths and other serious adverse events from ongoing studies

The only study that is not part of this ISS is the 12-week ongoing open-label Extension Phase of Protocol 07. A total of 125 subjects entered the Extension Phase. No deaths occurred and only one SAE (abdominal pain) was reported in the Extension Phase prior to the last subject's last visit of the Double-blind Phase of Protocol 07, the cut-off point for reporting of SAEs from ongoing studies in this ISS. The subject (512/3) did not discontinue study drug for this event. In the opinion of the investigator the event was not suspected to be study drug related. The narrative for this subject can be found in Post-text supplement 3.

5.5. Summary of adverse event findings

The proportion of subjects reporting adverse events in *Grouping 2* was similar for Ritalin- and placebo (24.6% and 23.9%, respectively). Nervous system disorders (n=6, 9.2% Ritalin-, n=2, 2.8% placebo) and gastrointestinal disorders (n=1, 1.5% Ritalin- n=6, 8.5% placebo) were the most frequently affected system organ classes. Individual adverse events were reported by few subjects, the most frequently reported were anorexia (n=2), insomnia (n=2) and headache (n=1) in the Ritalin- group and sore throat (n=3), headache (n=2) and vomiting (n=2) in the placebo group. Anorexia, insomnia and headache are known adverse events for Ritalin.

Adverse events reported in *Groupings 1, 3* and *4* were not unexpected in their frequency or their nature. The adverse events reported in *Groupings 1* and *3* which are not already listed in the Ritalin Product Information were generally well known common diseases of childhood.

No deaths or unexpected adverse events were reported and only two SAEs, depression (Protocol 07) and abdominal pain (Protocol 07 Extension Phase), were reported overall.

The data presented demonstrate that the adverse event profile of Ritalin- was consistent with the known adverse event profile of Ritalin.

6. Laboratory data

Laboratory data (hematology and blood chemistry) were summarized for *Groupings 1, 3* and *4*.

For *Grouping 1*, analyses of laboratory data included shift tables based on laboratory normal ranges, frequencies of treatment-emergent (newly occurring) clinically notable values and summary statistics (N, mean, standard deviation, median, minimum, maximum) across time.

For *Groupings 3* and *4*, frequencies of treatment-emergent clinically notable values and summary statistics across time are presented.

Criteria for clinically notable laboratory values are provided in Post-text supplement 4.

6.1. Blood chemistry in the key safety population

Blood chemistry data for *Grouping 1* are summarized in Post-text tables 6.1-1, 6.1-2 and 6.1-3. A total of four clinically notable blood chemistry values were reported. Two were increases and two were decrease in alkaline phosphatase. Summary statistics across time and shift tables did not indicate any noteworthy trends for any parameter.

Blood chemistry data for *Grouping 3* are summarized in Post-text table 6.1-4. Summary statistics across time did not indicate any noteworthy trends for any parameter. No clinically notable blood chemistry values were observed in this grouping.

6.2. Hematology in the key safety population

Hematology data for *Grouping 1* are summarized in Post-text tables 6.2-1, 6.2-2 and 6.2-3. A total of three clinically notable hematology values were reported. Two were increases in WBC and one was a decrease in lymphocytes. Summary statistics across time and shift tables did not indicate any noteworthy trends for any parameter.

Hematology data for *Grouping 3* are summarized in Post-text tables 6.2-4 and 6.2-5. A total of eight clinically notable hematology values were reported. These included increases in eosinophils, monocytes and WBCs. One subject had a decrease in total neutrophils. Summary statistics across time did not indicate any noteworthy trends for any parameter.

6.3. Laboratory data in other populations

Laboratory data for *Grouping 4* are summarized in Post-text tables 6.6-1 and 6.6-2. A list of subjects with clinically notable laboratory values is found in Post-text listing 6.6-1. Ten subjects had clinically notable laboratory values. Three subjects had increases in triglycerides (two subjects were in the studies evaluating the effect of a high fat meal on the bioavailability of Ritalin- —, one had an increase in glucose and one an increase in eosinophils. Decreased values were reported in one subject each for sodium, inorganic phosphorus, uric acid hematocrit, RBCs and WBCs. Summary statistics across time did not indicate any noteworthy trends for any parameter.

6.4. Summary of findings from laboratory data

Laboratory values were essentially unchanged from baseline to the final evaluation in all groupings. Occasional clinically notable values were reported, but no clinically significant pattern was observed and no indication of an effect of Ritalin- — was evident in these data.

7. Vital signs and body weight

Vital signs and body weight were summarized for *Groupings 1, 3* and *4*.

For *Grouping 1*, analyses of vital signs included frequencies of treatment-emergent (newly occurring) clinically notable vital signs and summary statistics across time. Summary statistics (N, mean, standard deviation, median, minimum, maximum) across time were also calculated for body weight.

For *Grouping 3*, summary statistics of vital signs and body weight were calculated across time.

For *Grouping 4*, analyses included frequencies of treatment-emergent clinically notable vital signs and summary statistics across time for body weight. Only subjects in Protocols 04 and 09 had pre- and post-study weight evaluations and were included in the analysis of body weight.

Criteria for clinically notable vital signs are provided in Post-text supplement 4.

7.1. Vital signs in the key safety population

Vital signs for *Grouping 1* are summarized in Post-text table 7.2-1 and 7.2-2. Clinically notable changes in blood pressure were reported during Ritalin- — treatment, but no clinically significant pattern was evident: there were three increases and three decreases in systolic blood pressure and six increases in diastolic blood pressure.

During Ritalin — treatment there were twenty clinically notable decreases and two clinically notable increases in pulse rate. Clinically notable decreases in pulse rate were also reported five times in subjects receiving placebo.

Summary statistics across time did not indicate any noteworthy trends for any parameter.

Vital signs for *Grouping 3* are summarized in Post-text table 7.2-3. Summary statistics across time did not show any noteworthy trends for any parameter.

7.2. Body weight in the key safety population

Body weight for *Grouping 1* is summarized in Post-text table 7.3-1 and for *Grouping 3* in Post-text table 7.3-2. Summary statistics across time did not indicate any noteworthy trends in either grouping.

7.3. Vital signs and body weight in other populations

Vital signs for *Grouping 4* are summarized in Post-text table 7.5-1. One decrease in systolic blood pressure and one decrease in diastolic blood pressure were reported. Two subjects had clinically notable decreases in pulse rate.

Body weight for *Grouping 4* is summarized in Post-text table 7.5-2. As would be expected with the short duration of the clinical pharmacology studies, weights were practically unchanged from pre-treatment to post-treatment evaluation.

7.4. Summary of findings from vital signs and body weight

Vital signs and body weight data did not reveal any systematic changes indicative of an effect of Ritalin- — treatment. Changes across time were very small, and changes in individual subjects did not form any clinically significant pattern. In *Grouping 1*, the most frequent notable changes in vital signs were decreases in pulse rate.

8. Special topics

8.1. Pregnancies

No pregnancies occurred during the studies with Ritalin- —

9. Other supportive studies

None.

10. Safety data from other sources

None.

11. Animal and other non-clinical data

The risks associated with MPH according to findings in toxicology studies are addressed in the approved labeling for Ritalin®. There are no concerns about additional risks expected to be uniquely associated with the exposure to Ritalin- — Studies to specifically investigate the toxicology of Ritalin- — are therefore not considered necessary. New animal studies

conducted with MPH were limited to reproductive toxicity studies. which were requested by the FDA.

The below sections summarize the results of four reproductive toxicity studies: one in mice, one in rats, and two in rabbits.

11.1. Reproductive toxicity studies

The assessment of effects on fertility and general reproductive performance is based on a study in mice [8] conducted by the . Mice were exposed to MPH in feed for up to 1,000 ppm (corresponding to approximately 160 mg/kg for males and 150 mg/kg for females). The results showed that MPH did not affect fertility or general reproductive performance.

The assessment of effects on embryo-fetal development is based on three studies, one in rats and two in rabbits.

In the study in rats, female animals were exposed to MPH doses of up to 75 mg/kg during organogenesis. MPH did not show any indication of a teratogenic potential [3].

Of the two studies in rabbits, one study was initiated as part of the Ritalin program. An earlier study was conducted prior to the development of Ritalin- when Novartis was investigating the active enantiomer of MPH (d-MPH).

In the study initiated as part of the Ritalin program (2nd study in rabbits, Table 11-1), female rabbits were exposed to MPH at dose levels of 0, 20, 60, or 200 mg/kg/day during organogenesis. At 200 mg/kg/day, two fetuses in two separate litters had spina bifida with malrotated hind limbs. These malformations were not present in the control group. One high dose female was found dead during the study. Clinical signs of exaggerated pharmacological activity observed at 200 mg/kg/day included cage licking or biting, increased respiration and dilated pupils [4].

In the earlier study (1st in rabbits, Table 11-1), female rabbits were exposed to d-MPH at dose levels of 15, 50, and 150 mg/kg/day. No spina bifida was observed in any of these dose groups. This study also included a dose group of 300 mg/kg racemic MPH (dl-MPH) for comparison. This high dose caused mortalities, but no spina bifida was observed in the surviving 12 litters (92 fetuses) [5]. The significance of the absence of spina bifida in this study at an MPH dose higher than 200 mg/kg/day is unknown.

The mean plasma AUC values of MPH that were found in the two embryo-fetal development studies in rabbits are listed in Table 11-1, along with AUC values following a 40 mg oral dose in humans [9].

The no-observed-effect level (NOEL) of MPH for the pregnant rabbits and for embryo-fetal development in rabbits was 60 mg/kg, corresponding to a maternal plasma $AUC_{(0\text{-}24h)}$ of 63.1 ng.h/mL for the d-isomer and 83.3 ng.h/mL for the l-isomer.

Table 11-1. AUC values of d- and l-MPH in rabbit and human

	d-MPH mean ± SD	l-MPH mean ± SD
1st study in rabbits*		
15 mg/kg/day d-MPH	34.4 ± 31.7	
50 mg/kg/day d-MPH	87.3 ± 34.0	
150 mg/kg/day d-MPH	600.0 ± 243.0	
300 mg/kg/day dl-MPH	1107.0 ± 922.0	408 ± 133
2nd study in rabbits*		
20 mg/kg/day dl-MPH	8.4 ± 4.53	47.9 ± 11.6
60 mg/kg/day dl-MPH	63.1 ± 22.6	83.3 ± 11.3
200 mg/kg/day dl-MPH	776.0 ± 124.0	263.0 ± 50.5
AUC $_{(0-inf)}$ ng.h/ml in human #		
40 mg (2 x 20 mg IR tablets)	120.21 ± 30.68	14.79 ± 4.14

* = exposure $AUC_{(0-24h)}$ in ng.h/ml
# = 13 male healthy volunteers 18 to 30 years of age. MPH is usually taken in two doses of 10 or 20 mg. In the absence of relevant exposure data following the maximum recommended human dose of 60 mg, the published $AUC_{(0-inf)}$ levels following a 40 mg oral dose were used for exposure comparison [9].

11.2. Summary of findings from animal data

Spina bifida was observed in one of two reproductive toxicity study in rabbits at a dose level of 200 mg/kg/day. This dose, which resulted in excessive pharmacological activity, is approximately 167 times and 78 times higher than the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. These calculations are based on the maximum recommended human dose of 60 mg, and body weights of 4 kg and 50 kg for rabbit and human, respectively.

Based on these results, it was concluded that MPH was possibly teratogenic in rabbits at doses causing excessive pharmacological activity and at exposure levels for the d- and l- isomers 6.5- and 17.8-fold higher than those found in humans. MPH did not affect fertility or general reproductive performance in mice and was neither embryotoxic nor teratogenic in rats.

12. Dose or drug level effects on safety findings

12.1. Animal studies

Spina bifida was observed in one of two reproductive toxicity studies in rabbits at the dose level of 200 mg/kg/day. This dose is approximately 167 times and 78 times higher than the maximum recommended human dose on a mg/kg and a mg/m^2 basis, respectively. The no-observed-effect level (NOEL) of MPH for the pregnant rabbits and for embryo-fetal development in rabbits was 60 mg/kg, corresponding to a maternal plasma $AUC_{(0-24h)}$ of 63.1 ng.h/mL for the d-isomer and 83.3 ng.h/mL for the l-isomer (Table 11.1). This is approximately 6.5 and 17.8 times the human exposure for the d- or l-isomer, respectively.

MPH did not affect fertility or general reproductive performance in mice up to a dose level of 1,000 ppm in feed (corresponding to approximately 160 mg/kg for males and 150 mg/kg for

females). MPH was neither embryotoxic nor teratogenic in rats up to a dose level of 75 mg/kg/day, corresponding to a maternal plasma $AUC_{(0-24h)}$ of 3104 ng.h/mL for d-MPH and 1139 ng.h/mL for l-MPH. This is approximately 25.8 and 77 times the human exposure for d- and l-MPH, respectively

12.2. Clinical and clinical pharmacology studies

Ritalin® has been marketed for many years and its safety profile is known. Ritalin- —, a new once-daily dosage form of Ritalin, mimics in one single dose the pharmacokinetics of Ritalin administered b.i.d.. The doses of 10-40mg/day evaluated in the Ritalin- studies were selected based on the approved dose-range of Ritalin (10-60mg/day). Overall bioavailability of MPH following Ritalin- —20mg was shown to be comparable to Ritalin 10mg administered b.i.d. [1].

13. Drug-drug, drug-disease, drug-demographic interactions

Ritalin® has been marketed for many years and its safety profile is known. Drug-drug and other potential interactions are addressed in the approved labeling of Ritalin. Ritalin- — a new once-daily dosage form of Ritalin, mimics in one single dose the pharmacokinetics of Ritalin administered b.i.d.. No new risks uniquely associated with Ritalin- — are expected.

14. Pharmacological effects other than the one of interest

None.

15. Long-term adverse effects and withdrawal effects

Long-term adverse effects and withdrawal effects are addressed in the approved labeling of Ritalin® Ritalin- —, a new once-daily dosage form of Ritalin, mimics in one single dose the pharmacokinetics of Ritalin administered b.i.d.. No new risks uniquely associated with Ritalin- — are expected.

Although withdrawal effects were not specifically evaluated, the data from the Placebo-Washout Period of Protocol 07 show that the nature of the adverse events reported during this period were not different from those reported during treatment with Ritalin- —

16. Summary and conclusions

Ritalin® has been marketed for over 40 years and its safety profile is well known. This ISS describes the safety of Ritalin- —, a new once-daily modified-release dosage form of Ritalin.

Ritalin- — mimics in one single dose the pharmacokinetic profile of Ritalin administered b.i.d. (morning and mid-day) and delivers, in a single administration, a bimodal release of MPH with an initial release occurring immediately after dosing and a second release approximately four hours after dosing. Ritalin- — thus obviates the need for the mid-day dose.

The Ritalin- — clinical program consisted of six studies; two clinical studies (Protocols 02 and 07) conducted in children with ADHD aged 6-12 years and four clinical pharmacology studies (Protocols 01, 04, 06 and 09) conducted in adult healthy volunteers. The data from the Ritalin- – clinical program presented in this ISS included a total of 256 subjects: 195 children and 61 adult healthy volunteers.

The data generated from the Ritalin- —program were classified into four groupings for this ISS: *Grouping 1* (All treated subjects in Protocol 07) evaluated exposure to multiple-dose Ritalin- – *Grouping 2* (All randomized subjects in Protocol 07) evaluated adverse events associated with multiple-dose Ritalin- – relative to placebo, *Grouping 3* (All treated subjects in Protocol 02) evaluated adverse events associated with repeated single-dose Ritalin- — relative to placebo, and *Grouping 4* (All treated healthy volunteers in clinical pharmacology studies) evaluated repeated single-dose exposure and tolerability of Ritalin- – in healthy volunteers.

Multiple-dose exposure to Ritalin- – is evaluated most extensively in *Grouping 1*. In this grouping, subjects who were randomized to Ritalin- – after the Titration Period were exposed to Ritalin- — for a total of up to seven weeks (including one week Placebo-Washout). Subjects randomized to placebo were exposed to Ritalin- — (in the Titration Period) for up to four weeks. Mean exposure to Ritalin- — was 36 days, and 69% of the subjects were treated for at least 30 days. Repeated single-dose exposures to Ritalin- – in *Groupings 3* and *4* were for a maximum of 3 days.

Baseline demographics for subjects in *Groupings 1-3* showed that the population was representative of the overall pediatric population treated for ADHD. The subjects were predominantly Caucasian males with a mean age of approximately nine years. Coexistent medical conditions were generally common conditions and the concomitant medications taken by these subjects were those commonly used in the general population.

Premature discontinuations occurred in a total of 20.7% (34/164) of the subjects in *Grouping 1*. Most discontinuations were due to unsatisfactory therapeutic effect, withdrawal of consent or adverse events. The majority of these discontinuations occurred prior to randomization; only seven occurred during the Double-blind Treatment Phase. Discontinuations during the Double-blind Treatment Phase (*Grouping 2*) were mainly due to adverse events (2 Ritalin- – 1 placebo) and unsatisfactory therapeutic effect (1 Ritalin- — 1 placebo). All subjects in *Grouping 3* completed the study, and 92% (56/61) of the subjects in *Grouping 4* completed their study.

Frequency and nature of adverse events relative to placebo are evaluated in *Grouping 2*, the only grouping that allows an adequate comparison of adverse events with placebo. The proportion of adverse events reported in this grouping was similar for Ritalin- — (24.6%) and placebo (23.9%). Individual adverse events were reported by few subjects; the most frequently reported were anorexia, insomnia and headache, each reported by one to two subjects in the Ritalin- — group and sore throat, headache and vomiting, each reported by two to three subjects in the placebo group. Anorexia, insomnia and headache are known adverse events for Ritalin. The adverse events reported by subjects in the other groupings (*Groupings 1, 3* and *4*) were not unexpected in their frequency or their nature. The adverse events reported during the

Ritalin- clinical studies which are not already listed in the Ritalin Product Information were generally well known common diseases of childhood.

No deaths occurred during the Ritalin- studies and only two SAEs, depression (Protocol 07) and abdominal pain (Protocol 07 Extension Phase), were reported overall. In the opinion of the investigator neither SAE was suspected to be study drug related.

Laboratory values were essentially unchanged from baseline to the final evaluation in all the groupings. Occasional abnormalities for individual subjects were seen, but no pattern was observed and no indication of a drug effect was evident in the data.

Vital signs and body weight data collected during the studies did not reveal any changes indicative of an effect of Ritalin- treatment. Mean and median changes across time were very small and changes for individual subjects did not form any pattern. The most frequent notable changes in vital signs were decreases in pulse rate, which were reported 20 times by subjects receiving Ritalin- and five times in subjects receiving placebo.

In the animal data, spina bifida was observed in one of two reproductive toxicity studies with MPH in rabbits. Based on those results, MPH is considered to be possibly teratogenic in rabbits at doses causing excessive pharmacological activity and resulting in exposure levels 6.5 and 17.8 fold higher than levels seen in humans for d- and l-MPH, respectively. No well-controlled data in pregnant women are available, therefore, MPH should only be used during pregnancy if the potential benefits outweigh the potential risk to the fetus. MPH did not affect fertility or general reproductive performance in mice and was neither embryotoxic nor teratogenic in rats.

In conclusion, with over 40 years of use, the safety of Ritalin is well known. The data presented in this ISS demonstrate that Ritalin- a new once-daily dosage form of Ritalin, which mimics the pharmacokinetic profile of Ritalin b.i.d. has a safety profile which is consistent with the known profile of Ritalin. The data also demonstrate that there are no new safety concerns uniquely associated with this new dosage form.

17. Reference list

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