CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-346

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-346
Brand Name:	Risperdal Consta
Generic Name:	Risperidone
Type of Dosage Form:	Long Acting Injection
Strengths:	25 mg, 37.5 mg, 50 mg
Indications:	Schizophrenia
Type of Submission:	Response to Not Approvable
Sponsor:	Johnson & Johnson
Submission Date:	April 28, 2003
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates the Sponsor's response to the recommendations made by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) in the not approvable Action Letter (issued June 28, 2002) for NDA 21-346.

The Clinical Pharmacology and Biopharmaceutics Recommendations for that submission were not related to the not approvable deficiencies. The action letter noted that these recommendations should be addressed if the Sponsor wished to re-submit the application. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommended the following:

- A Phase IV commitment for proposed final *in vitro* release specifications based on 24-month stability data, and clarification of acceptance criteria for out-of-trend results.
- A revision to the sponsor-proposed interim dissolution specifications.
- Appropriate documentation of population pharmacokinetic analysis in future submissions.

In addition, the OCPB review of the original NDA (see OCPB review of 6/21/02) recommended some specific changes to the proposed labeling that have not yet been communicated to the Sponsor.

The Sponsor has provided responses as follows:

- The Sponsor has agreed to a Phase IV commitment to submit the *in vitro* release data from the on-going stability tests on validation lots of all strengths within 4 months after the 24 month stability data are available, together with a proposal of

the final *in vitro* release specifications based on this data. This will include release specifications for individual samples, in addition to the specifications of the means. The Sponsor states that the 24-month data will be available in [redacted]

- The Sponsor has also clarified the acceptance criteria for the release of batches if an out-of-trend result is obtained.
- The Sponsor has agreed to the OCPB recommendations to include formal limits for individual samples in the dissolution specifications, and agreed to the OCPB recommendations for that specification. For the OCPB-proposed tightening of the interim specification of the means for the T50% time point, the Sponsor agreed with the upper shelf-life limit. However, the Sponsor has proposed maintaining their original proposed lower shelf-life limit based on stability data for the interim dissolution specification. The Sponsor's proposed interim shelf-life specifications are as follows (the Sponsor proposed change is in bold):

Test Method*(medium pH 7.4)	Test Point	Specification (mean)	Specification‡‡ (individual sample)
In vitro release (37 °C water bath)	Day 1 Day 15	[redacted]	
In vitro release (45 °C water bath)	$T_{50\%}$ Day 8		

* Samples tested in triplicate; ‡‡ All individual samples should meet this criteria.
** Proposed by OCPB (NA Letter of 6/28/02)
***Sponsor requests a specification of [redacted] for mean T50% for shelf life and [redacted] for release. **Note:** While we don't think a separate specification is needed for T50% for release and shelf-life, we find the Sponsor's proposal reasonable and accept the mean T50% specification of [redacted] as an interim specification.

- The Sponsor acknowledged the request to provide in future submissions all the population PK data sets in the agreed upon electronic format and to provide the NONMEM control streams used in the analysis, not the examples only.

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has the following recommendations.

1) The OCPB finds the Sponsor's responses acceptable, including the proposed interim dissolution specifications. However, the dissolution specifications will be re-evaluated when the response to the Phase IV commitment for the proposed

final *in vitro* release specifications based on 24-month stability data will be submitted.

2) The OCPB recommends some revisions of the proposed label's text. (Please refer to Section 3.2.3). In addition to the specific recommendations throughout the label, the Sponsor should review the DRUG INTERACTION section regarding "Drugs that Inhibit CYP 2D6 and Other CYP Isozymes" that refers to "MP" as a P450 isozyme. The Sponsor is asked to describe MP in a manner consistent with the currently used nomenclature for CYP isozymes, and to provide a summary of the data used to identify the specific P450 isozyme to which they refer (e.g. the inhibitor of that pathway may indicate which P450 is responsible).

Please forward the comments above and the labeling comments in Section 3.2.3 to the Sponsor.

Sally Usdin Yasuda, MS, PharmD
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana Uppoor, PhD
Team Leader, Neuropharmacological Drug Section, DPE I
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cc: HFD-120 NDA 21-346, E. Hearst
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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

RISPERDAL CONSTA is a depot injection (microspheres) of risperidone for treatment in schizophrenia in adult patients. According to the OCPB review of original NDA 21-346, after IM injection, the drug is slowly released over 4-6 weeks through a combined process of hydrolysis and erosion of the microspheres (2-3 weeks lag phase until drug absorption starts). RISPERDAL CONSTA (NDA 21-346, submitted August 31, 2001) received a not approvable action letter on June 28, 2002, to which the present submission is a complete response.

The Clinical Pharmacology and Biopharmaceutics Recommendations for that submission were not related to the not approvable deficiencies. The action letter noted that these recommendations should be addressed if the Sponsor wished to re-submit the application. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommended the following:

- A Phase IV commitment for proposed final *in vitro* release specifications based on 24-month stability data, and clarification of acceptance criteria for out-of-trend results.
- A revision to the sponsor-proposed interim dissolution specifications.
- Appropriate documentation of population pharmacokinetic analysis in future submissions.

In addition, the OCPB review of the original NDA recommended some specific changes to the proposed labeling.

The response to the Clinical Pharmacology and Biopharmaceutics recommendations will be addressed here.

3.2 Current Submission

3.2.1 Dissolution Specifications

- *Has the Sponsor agreed to a Phase IV Commitment regarding dissolution specifications?*

The OCPB requested as a Phase IV commitment that the Sponsor submit the *in vitro* release data from the on-going stability tests on validation lots of all strengths within 4 months after the 24 month stability data is available, together with a proposal of the final *in vitro* release specifications based on this data. This should include release specifications for individual samples, in addition to the specifications of the means. The

Sponsor has agreed to this commitment. The Sponsor states that the 24-month data will be available in [redacted]

The Sponsor has also clarified the acceptance criteria for the release of batches if an out-of-trend result was obtained (i.e., what actions are taken if re-testing shows consistent out-of-trend results for individual samples). According to the OCPB review of the original NDA, out-of-trend is a situation in which the reported value is within specification, but either the reported value or individual replicates is outside of the recent historical trend. The Sponsor states that if an individual sample is out of specification or out of trend, a laboratory investigation would be conducted. If results are confirmed, a formal Quality Assurance investigation of the product would be initiated, with release of the lot in question contingent on the outcome. A lot that is out of specification with regard to release rate would not be released. Any out of trend result would be evaluated to determine the significance of the finding and potential impact.

- *Did the Sponsor agree to the recommended interim specifications?*

The OCPB recommended that the interim dissolution specifications (shelf-life specifications) be as follows (OCPB revisions in bold):

Test Method*(medium pH 7.4)	Test Point	Specification (mean)	**Specification‡‡ (individual sample)**
In vitro release (37 °C water bath)	Day 1	[redacted]	
	Day 15		
In vitro release (45 °C water bath)	$T_{50\%}$		
	Day 8		

* Samples tested in triplicate; ‡‡ All individual samples should meet this criteria.

The Sponsor has agreed with the recommendation to include formal limits for individual samples in the specifications and agreed that all valid individual sample results should meet the criteria proposed by the OCPB. The Sponsor has also agreed to the change in the specification of the means for the $T_{50\%}$ time point with respect to the upper limit. However, the Sponsor has suggested a lower limit of [redacted] for shelf-life) and [redacted] (for release), based on stability data. The OCPB finds the sponsor's proposed change to the interim specification acceptable (the mean specification for T50% is [redacted]).

Note: The interim Specifications will be re-evaluated when the results of the 24-month stability data are available.

3.2.2 Population Pharmacokinetic Analysis

The Sponsor acknowledged the request to provide in future submissions all the population PK data sets in the agreed upon electronic format and to provide the NONMEM control streams used in the analysis, not the examples only.

3.2.3 Recommended Labeling Changes

The OCPB review of the original NDA recommended several changes to the proposed labeling. In the OCPB review of the present submission, the proposed labeling has been reviewed with respect to the recommendations from the OCPB review of the original NDA and with respect to being consistent with the most recent label for risperidone (NDA 21-444). The following recommendations apply to the current proposed labeling for Risperdal Consta. The Sponsor is asked to move the section for dosage in pediatrics and special populations up closer to the DOSAGE ADMINISTRATION section (just before "Instructions for Use"). Revisions to the text of the proposed labeling are shown below, with any text in italics within brackets explaining proposed changes. Only the changed sections are included here, and only the clinical pharmacology sections were reviewed.

CLINICAL PHARMACOLOGY
Pharmacokinetics
Absorption

Elimination

Special Populations
Elderly

PRECAUTIONS
Drug Interactions

3.3 Recommendations

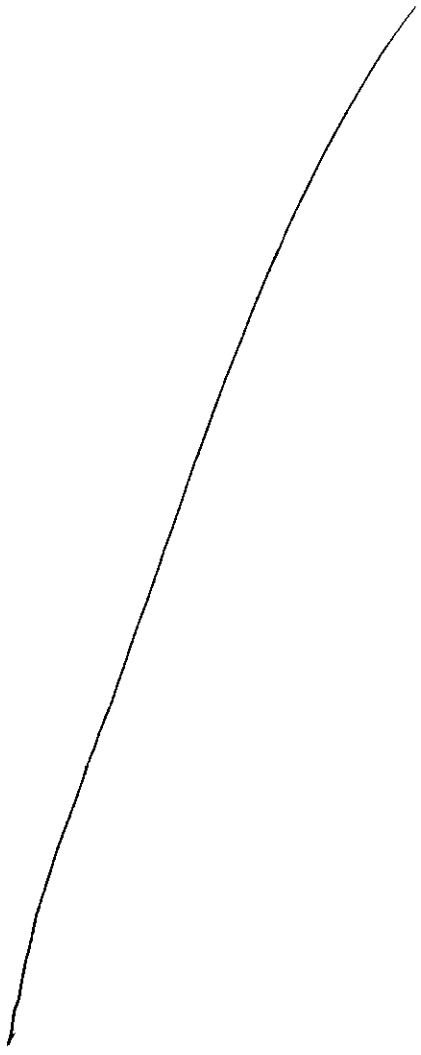
The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the responses to the OCPB recommendations in the not approvable letter to be acceptable.

The OCPB recommends changes in the proposed labeling, identified in section 4.2.3 above. Please forward the labeling comments to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

4 APPENDIX

4.1 Sponsor Proposed Package Insert (Annotated with OCPB Comments and Changes)



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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Sally Yasuda
8/15/03 05:06:29 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/15/03 05:14:31 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-346	Submission Dates: Aug. 31, Oct. 16 & 24, 2001, Mar. 25, Apr. 30, Jun. 14, 2002
Brand Name	Risperdal Consta™
Generic Name	Risperidone
Primary Reviewer	Maria Sunzel, Ph.D.
Pharmacometrics Reviewer	Vanitha Sekar, Ph.D.
Team Leaders	Ramana Uppoor, Ph.D. Pharmacometrics: Jogarao Gobburu, Ph.D.
OCPB Division	HFD-860
ORM Division	HFD-120
Sponsor	Janssen Research Foundation, 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560-0200
Relevant IND(s)	52,982
Submission Type; Code	3S (new formulation)
Formulation; Strength	Depot Injection (microspheres); 25 mg, 37.5 mg & 50 mg risperidone / vial
Indication	Treatment of schizophrenia

1 EXECUTIVE SUMMARY

This review evaluates a new formulation and route of administration of risperidone, namely a depot injection (deep intra-muscular injection), intended for the treatment of schizophrenia in adult patients (>18 years of age). The sponsor intends to market three dosage strengths (25 mg, 37.5 mg, and 50 mg risperidone per vial) of the new microsphere depot injection, and has proposed a dosage regimen of 25 mg as biweekly injections (max. 50 mg every 2 weeks). After the IM injection, following a short burst phase, there is a 3-week lag phase before drug absorption starts, subsequent to this lag phase, the drug is slowly released and absorbed over 4-6 weeks as the microspheres erode.

A total of 13 studies (6 single dose, 7 repeated dose studies) in the target population of schizophrenic patients, as well as a population pharmacokinetic analysis based on 5 of these 13 studies were reviewed. In addition, the regulatory *in vitro* dissolution methods and specifications were evaluated.

Based on the submitted information, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds NDA 21-346 acceptable. The regulatory *in vitro* dissolution methods are also found to be acceptable, but OCPB recommends a Phase IV commitment regarding the dissolution specifications, and recommends interim specifications until all stability data (24 months) from the validation batches is available. The OCPB also proposes revisions to the proposed labeling text.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the Clinical Pharmacology & Biopharmaceutics sections of NDA 21-346 acceptable.

The OCPB finds the proposed *in vitro* dissolution methods (37°C and 45°C) acceptable. However, OCPB recommends that the proposed *in vitro* release specifications are only used in an interim period, until 24-month data is available from the on-going stability tests, and, in addition to the specification of the means, also recommends inclusion of specifications for individual samples. As a Phase IV commitment, the sponsor should submit the *in vitro* release data from the 25 mg, 37.5 mg and 50 mg strengths within 4 months after the 24-month stability data is available (see comments to the sponsor, Section 1.2).

The OCPB recommends revisions to the proposed labeling text, the revisions are described in Section 5 (page 22) of the main review.

1.2 Comments to the sponsor

a) Phase IV commitment: The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the proposed regulatory *in vitro* dissolution methods acceptable. However, OCPB recommends that the proposed *in vitro* release specifications are only used during an interim period, until data is available from the on-going stability tests on the dosage strengths of the to-be-marketed Risperdal Consta products (25°C/60% RH & 5°C conditions). As a Phase IV commitment, the sponsor should submit the *in vitro* release data from the on-going stability tests on validation lots of all strengths within 4 months after the 24-month stability data is available, together with a proposal of the final *in vitro* release specifications based on this data. This proposal should also include release specifications for individual samples, in addition to the specifications of the means. The sponsor is also requested to clarify the acceptance criteria for the release of batches if an 'out-of-trend' result was obtained, i.e. what actions are taken if re-testing show consistent out-of-trend results for individual samples.

b) For the interim specifications, the OCPB proposes one revision (a tightening of the $T_{50\%}$ time-point) to the specification of the means, and also inclusion of formal specifications for individual samples (— of the value). The OCPB recommends the following revisions (marked in bold) regarding the mean ($T_{50\%}$ 45°C water bath) and the inclusion of formal limits for individual samples in the specifications:

Test method* (medium pH 7.4)	Test point	Specification (mean)	**Specification‡‡ (individual sample)**
In vitro release (37°C water bath)	Day 1	[redacted]	[redacted]
	Day 15		
In vitro release (45°C water bath)	$T_{50\%}$		
	Day 8		

* Samples tested in triplicate; **Proposed by the sponsor; ‡‡All individual samples should meet this criteria

c) Population pharmacokinetic analysis: Data sets submitted to the FDA were different from those used by the sponsor in the population pharmacokinetic analysis. The sponsor used one combined file, which consisted of data from all of the 3 Phase III trials. However, the files submitted to the Agency were data for each study. No control streams were submitted. In order for the Agency to evaluate the appropriateness of the sponsor's analysis, exact control streams as well as data sets with identically matching file names should be submitted in all future submissions. In addition, the individual two-stage analysis was not documented at all – only final results were displayed. Lack of submission of appropriate documentation of the analysis to the Agency can lead to duplication of efforts, burdensome reanalysis by the Agency as well as suboptimal use of resources.

Please forward the comments above to the sponsor.

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3 SUMMARY OF CPB FINDINGS

3.1 Background

Risperidone (RIS), a benzisoxazole derivative, is an anti-psychotic with serotonin ($5HT_{2A}$) and dopamine D_2 blocking properties. Risperdal® (risperidone) is approved in the US for the treatment of schizophrenia in adults, and is currently marketed as oral formulations (tablets and solution), in twice daily (BID) or once daily (QD) dosing regimens. The recommended daily oral doses are 2-8 mg/day. The label states that no further clinical efficacy is observed at doses above 6 mg/day.

Risperdal was first approved by the Agency in 1993 (NDA 20-272: 1, 2, 3 & 4 mg IR tablets), with subsequent approvals in 1996 (NDA 20-588: oral solution 1 mg/mL) and 1999 (NDA 20-272: 0.25 & 0.5 mg IR tablets).

The metabolism of risperidone (RIS) to the equipotent metabolite, 9-hydroxy-risperidone (9-OH-RIS), after oral doses of Risperdal is characterized by metabolic polymorphism (CYP2D6). The majority of patients are extensive metabolizers (EM) of RIS, with only a part of the population being poor metabolizers (PMs) of RIS, who do not form or only form lower amounts of 9-OH-RIS. The percentage of PMs in a normal population is estimated to about 5-10% in Caucasians, and a lower estimate for Asians and Africans (about 5% PMs, but this number is less certain). Both RIS and its active metabolite are considered equipotent, the 'active moiety' (RIS+9-OH-RIS plasma concentrations) has been accepted by the Agency as a measure (for descriptive characterization, for bioequivalence individual moieties need to be evaluated), yielding comparable drug plasma concentrations (Cps) between EMs and PMs. Therefore, the same dosage regimen (a titration regimen) is recommended for both groups.

Pharmacokinetic characteristics of RIS & 9-OH-RIS after oral doses of Risperdal:

- Rapid and complete drug absorption (t_{max} 1-2 h after dose intake)
- Absolute bioavailability of RIS: EM = 66%; PM = 84%
- Plasma protein binding: RIS = 90%; 9-OH-RIS = 77% (RIS blood/plasma ratio 0.67)
- Mainly metabolized via CYP2D6, with minor involvement of CYP3A4 (*in vitro* estimates: 85-89% via CYP2D6 & 10-15% via CYP3A4, corresponding to 2-6 mg doses)
- Total radioactivity (RIS + metabolites) excreted via urine (70%) and feces (15%)
- Terminal t½: EM: RIS: 3 h & 9-OH-RIS: 21 h; PM: RIS: 20 h (& 9-OH-RIS: 20 h)
- Linear PK over the dose range of 0.25 mg – 16 mg/day
- Renal impairment: CL is decreased by 60% (dose reduction); Hepatic impairment: unbound drug increased by 35% (dose reduction); Elderly: renal CL is decreased (RIS, 9-OH-RIS) , C_{max} increased by 30-40%, t½ 18% prolonged (dose reduction); race and gender do not influence the PK after oral doses of RIS
- Clinically significant drug-drug interactions (PDR 2002): Fluoxetine & clozapine increase RIS(/9-OH-RIS) Cps; carbamazepine decreases RIS/9-OH-RIS Cps. RIS may enhance hypotensive effects of other drugs, and RIS may antagonize the effects of levodopa and dopamine agonists.

3.2 Current Submission

The sponsor has developed a depot injection intended for the treatment of schizophrenia in adult patients (>18 years of age). In the new formulation, risperidone is encapsulated in microspheres (0.381 g/g microspheres). The product package consists of a vial with microspheres, a pre-filled syringe containing the diluent (2 mL) and needles. The vial content will be mixed with the diluent immediately before administration. The sponsor intends to market three dosage strengths (25 mg, 37.5 mg, and 50 mg risperidone per vial). After the IM injection, the drug is slowly released over 4-6 weeks through a combined process of hydrolysis and erosion of the microspheres (2-3 weeks lag phase until drug absorption starts).

The sponsor has performed 13 studies in total (6 single dose, 7 repeated dose studies, see Appendix, Section 7.1). All studies were performed in the target population, 2101 patients with schizophrenic or schizoaffective disorders were included in the studies. In total, 1673 patients received depot injections (single dose: n=174; repeated doses: n=1499). Plasma samples for drug analysis were collected in all clinical trials, and traditional (all Phase I/II studies) and population pharmacokinetic (PK) analyses (2 Phase I/II trials & 3 Phase III trials) were performed. Risperidone was studied in the dose range 25-100 mg (25-mg increments), but the sponsor concludes that maximal effect is achieved after a 50-mg dose. Therefore, an intermediate dosage strength of 37.5 mg was developed late in the program, and was only evaluated in one single dose trial. The sponsor also attempted to evaluate the exposure – response relationship with regard to safety and efficacy in one Phase III trial.

The following PK information from the submitted trials was reviewed:

- Pharmacokinetics after single doses & repeated doses of risperidone (IM injection)
- Relative bioavailability (clinical trial vs. to-be-marketed formulations & tablets given PO)
- Dose proportionality (25-50-75 mg & 37.5-50-62.5 mg, repeated & single doses)
- Population PK analysis (Phase III trials)
- Two drug interaction studies with oral risperidone and lithium and valproate, respectively

In addition, *in vitro* dissolution methods and specifications, and pharmaceutical information relevant to the *in vivo* performance of the depot formulation, was included in this review.

The following conclusions regarding the, exposure-response relationships, pharmacokinetics, and biopharmaceutics have been made regarding the risperidone depot formulation (biweekly IM injections):

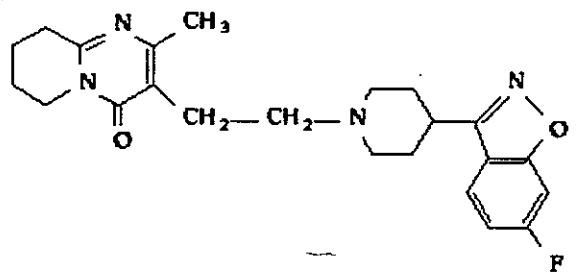
- Plasma levels of active moiety correlated well with dopamine D_2 receptor occupancy, but not with safety assessments, or global assessments (PANSS) of clinical improvement of disease
- The *in vivo* absorption profile was characterized by an initial burst (<1% of the dose) of drug release within 24 h post-injection, a lag phase (of about 3 weeks), followed by a gradual drug release over a period of nearly 3 weeks including a 2-week plateau period
- At steady state, C_{max} and AUC of risperidone, 9-OH-risperidone, and active moiety increased in a dose-proportional manner up to 50 mg
- The proposed oral 3-week substitution therapy at initiation of therapy of IM depot injections before steady state is reached, is acceptable
- Elderly have about 10% lower clearance (active moiety) compared to younger patients (smaller difference compared to oral risperidone data where a 40% difference was observed)
- Shorter periods (≤4 days) of fever are not likely to alter the release rates of drug from the microspheres, based on *in vitro* experiments
- Known drug-drug interactions (e.g. carbamazepine, fluoxetine) were observed in the Phase III trials (PPK analysis), & similar pharmacokinetics of lithium (C_{max}, AUC) or valproate (AUC) were observed with or without risperidone combination therapy
- At steady state, exposure (AUC) after risperidone administration of 25 mg, 50 mg & 75 mg correspond to daily oral doses of 2, 4, & 6 mg, respectively
- The Phase I/II and the to-be-marketed (TBM) formulations (50 mg single doses) are similar with regard to AUC but not C_{max} (45-50% higher for TBM formulation) Note: Pivotal clinical trials (Phase III) were conducted with the TBM depot formulation
- The release properties of the risperidone microspheres have been well characterized *in vitro*
- The analytical methods (RIA & LC-MS/MS) used for the plasma analyses are adequately validated and found acceptable

The proposed *in vitro* dissolution methods are also found to be acceptable, but the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) requests a Phase IV commitment regarding the *in vitro* release specifications, and recommends interim specifications until all stability data from the validation batches is available. The interim specifications contain revisions of the specifications proposed by the sponsor. The OCPB recommends revisions to the proposed labeling. Overall, OCPB finds the Clinical Pharmacology & Biopharmaceutics sections of NDA 21-346 acceptable.

4 QUESTION BASED REVIEW

4.1 General Attributes

What are the molecular formula and chemical properties of risperidone?



Risperidone (R064766), a benzisoxazole derivative, has a molecular weight of 410.49, with a chemical formula of $C_{23}H_{27}FN_4O_2$. It is a [redacted] powder. Risperidone is a weak base (pKa_1= 8.24; pKa_2 = 3.11), and is very lipophilic with a log P of 3.04 between n-octanol and an aqueous buffer (pH 9.9). Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

What are the pharmacological properties of risperidone?

Risperidone is a benzisoxazole derivative that is classified as an atypical antipsychotic. The exact mechanism of antipsychotic action is unknown. Risperidone is a selective monoaminergic antagonist with high affinity (Ki = 0.12 - 7.3 nM) for the serotonin Type 2 ($5HT_2$) and dopamine Type 2 (D_2) receptors. Risperdal is also an antagonist with high affinity to α_1 and α_2 adrenergic, and H_1 histaminergic receptors, and has low to moderate affinity to the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors (Ki = 47 – 253 nM), and weak affinity for the dopamine D_1 and haloperidol-sensitive sigma site (Ki = 620 - 800 nM). Risperidone did not show *in vitro* affinity to cholinergic, muscarinic, or β_1 and β_2 adrenergic receptors (concentrations $>10^{-5}$ M).

4.1.1 Currently approved formulations

Which Risperdal formulations are approved?

Risperdal is currently marketed as immediate release (IR) tablets (0.25, 0.5, 1, 2, 3 and 4 mg) and a solution (1 mg/mL) for oral use.

What oral dosing regimens of Risperdal are recommended for the treatment of schizophrenia?

The recommended oral daily doses are 2-8 mg/day, given as twice daily (BID) or once daily (QD) dosage regimens. Doses up to 16 mg/day have been evaluated, however, maximal antipsychotic effect was observed between 4-8 mg/day. Therapy is initiated at 1 mg BID, with individual dose titration to maximal effect.

In elderly patients, patients with severe renal or hepatic impairment, and patients predisposed to hypotension a starting dose of 0.5 mg BID is recommended, and slower titration regimen than the one employed in the average patient population is recommended.

4.1.2 Depot formulation

Why has the sponsor developed a new depot intramuscular injection?

The sponsor has developed the long-acting depot formulation for intramuscular (IM) injection into the gluteal muscle of risperidone encapsulated in biodegradable microspheres, intended to increase compliance in schizophrenic patients.

How is the new depot injection formulated and packaged?

Risperidone (381 mg/g microspheres) is micro-encapsulated in polylactide-co-glycolide (PLG). The biodegradable PLG polymer is also used in other depot injections that have been approved by the Agency (e.g. Nutropin Depot, Zoladex, Lupron Depot, Trelstar, and Sandostatin LAR Depot), as well as surgical material (e.g. sutures).

The Risperdal Consta long acting injection is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing 2 mL of an aqueous diluent ([redacted]), and needles. The vials contain the same formulation for all dosage strengths, but the vials contain different weight of microspheres for each strength (25, 37.5, or 50 mg risperidone). Prior to the intramuscular (IM) injection, the microspheres are suspended in the diluent.

How does the new depot injection function in vivo?
After injection (IM into the gluteal muscle), the drug is slowly released when the polymeric matrix is hydrolyzed to lactic and glycolic acid, which are further metabolized and/or excreted as carbon dioxide and water. The underlying mechanism for drug release is a combination of both erosion and drug diffusion of the microspheres. The interaction of the drug and the polymer results in a release profile with a distinct lag phase (of about 3 weeks), followed by a gradual, relatively fast release over a period of nearly 3 weeks, including a 2-week period of about zero-order release. An initial burst (<1% of the dose) of drug release is observed *in vivo* within 24 h.

What is the proposed dosing regimen of the long-acting depot formulation?
The recommended dose for adult schizophrenic (>18 years old) and elderly schizophrenic patients is 25 mg IM every 2 weeks. Some patients may benefit from an IM dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg IM every 2 weeks. Oral risperidone or another antipsychotic medication should be given with the first IM injection of the depot formulation and continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site. Upward dosage adjustment (37.5 mg or 50 mg) should not be made more frequently than every 4 weeks. In patients with renal or hepatic impairment, the IM injections (25 mg) are recommended only if oral risperidone doses of 2 mg/day or higher are tolerated.

Was the same risperidone depot formulation used in <u>all</u> in vivo human studies?
No, the sponsor used two different formulations in the human clinical trials (although a 3rd formulation was used in an early Phase I trial). The depot injections used in the Phase I/II studies were produced from the process. The to-be-marketed (TBM) formulation that was used in the Phase III pivotal studies was manufactured at the intended commercial batch size of (more details are given in Section 4.5.1). The different formulations and diluents that were used in the clinical trials are shown in Table 1.

TABLE 1. Information on the formulations of microspheres and the reconstitution diluent used in the human clinical trials.

Trial	Diluent F-n°	Microspheres Manufacturing scale/ F-n° (batch info)	Clinical Phase	In vivo Initial release, (24h)	In vivo Lag time, weeks
RIS-BEL-34[PK 5]			Phase-I		2
RIS-INT-25[PK 6], RIS-INT-38[PK 7] RIS-NED-13[PK 8], RIS-USA-111[PK 9], RIS-INT-31[PK 10], RIS-SWE-17[PK 11], RIS-INT-32[PK 12]			Phase-I/II		2-3
RIS-INT-54[PK 13], RIS-INT-72[PK 14] RIS-INT-61[PK 15], RIS-USA-121[PK 16], RIS-INT-57[PK 17]			Phase-III		3

4.2 General Clinical Pharmacology

Which types of clinical studies were performed to assess the new risperidone depot formulation?
A total of 13 studies (6 single dose, 7 repeated dose studies, see Appendix, Section 7.1) evaluated the risperidone depot formulations, where 1673 patients received risperidone IM injections (single dose: n=174; repeated doses: n=1499). All studies were performed in the target population (patients with schizophrenic or schizoaffective disorders), and concomitant medications (also neuroleptics) were allowed in all Phase I/II trials. Plasma samples for drug analysis were collected in all clinical trials. Traditional (10 Phase I/II studies, n=297) and

population pharmacokinetic analyses (2 of the Phase I/II studies & 3 Phase III studies; n=1370) were performed. Dopamine D_2 receptor occupancy (biomarker) was evaluated in 8 patients. The sponsor also attempted to evaluate the exposure-response relationship with regard to safety and efficacy in one placebo-controlled Phase III trial.

4.2.1 Exposure – response relationships

How was dopamine D_2 receptor occupancy in relation to plasma drug levels evaluated, and was there a relationship?

Dopamine D_2 receptor occupancy was determined by ^{11}C-raclopride (RAC) PET examinations of the putamen 14 days after the 5th biweekly IM injection (at steady state). A blood sample for drug analysis was drawn immediately prior to the RAC injection. A total of 8 patients who received 25 mg, 50 mg, or 75 mg risperidone were evaluated (25 mg n=3; 50 mg n=3; 75 mg n=2). Details are given in Appendix, Section 7.5.1 (Study RIS-SWE-17).

There was a good correlation between D_2 receptor occupancy in the putamen and plasma levels of active moiety, as shown in Figure 1.

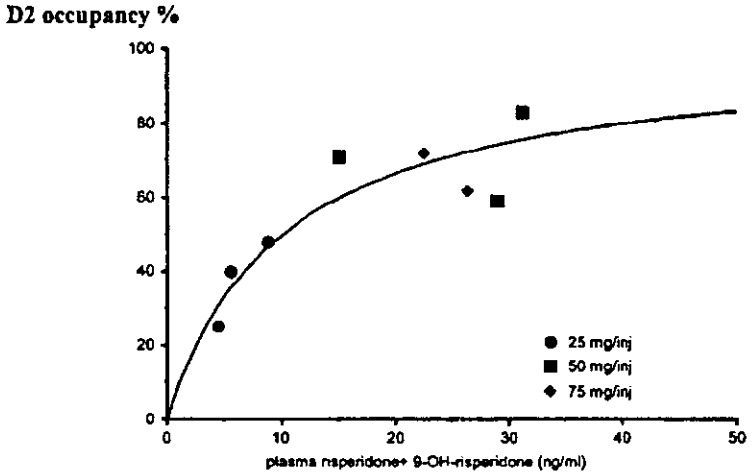


FIGURE 1. % Dopamine (D_2) occupancy (putamen) *vs.* plasma concentrations of active moiety (ng/mL) at steady state in 8 schizophrenic patients. [RIS-SWE-17]

The clinical relevance of the % dopamine D_2 receptor occupancy has not been fully elucidated, but most conventional neuroleptics have a high central dopamine D_2 receptor occupancy (70-90%). The results in this study are in accordance with results reported after oral risperidone (6 mg QD, 4 weeks, 75-80% occupancy in striatum). The receptor occupancy of 5-HT_2 (high affinity *in vitro*) was not evaluated in this study.

How were the exposure-response relationships of efficacy and safety evaluated, and was there a correlation?

The sponsor performed a descriptive analysis (scatter plots) of the plasma concentrations of the active moiety and efficacy and safety variables from one placebo-controlled efficacy study (Phase III, RIS-USA-121, see the pharmacometrics report for a short summary). This was a 12-week study (25, 50 & 75 mg risperidone, biweekly IM injections). About 180 patients completed the trial (about 50 patients/dose group, 30 patients/placebo). The efficacy (positive and negative symptom scale, PANSS) was measured as a change from baseline in total PANSS at endpoint (12 weeks). Safety parameters (vital signs, ECG parameters, & extrapyramidal symptoms rating scale - ESRS) were measured at 4 time points throughout the trial.

There were no apparent trends or correlations between plasma concentrations of active moiety and the efficacy and safety variables. The scatter plots of PANSS and ESRS scores vs. active moiety levels are depicted in Figure 2.

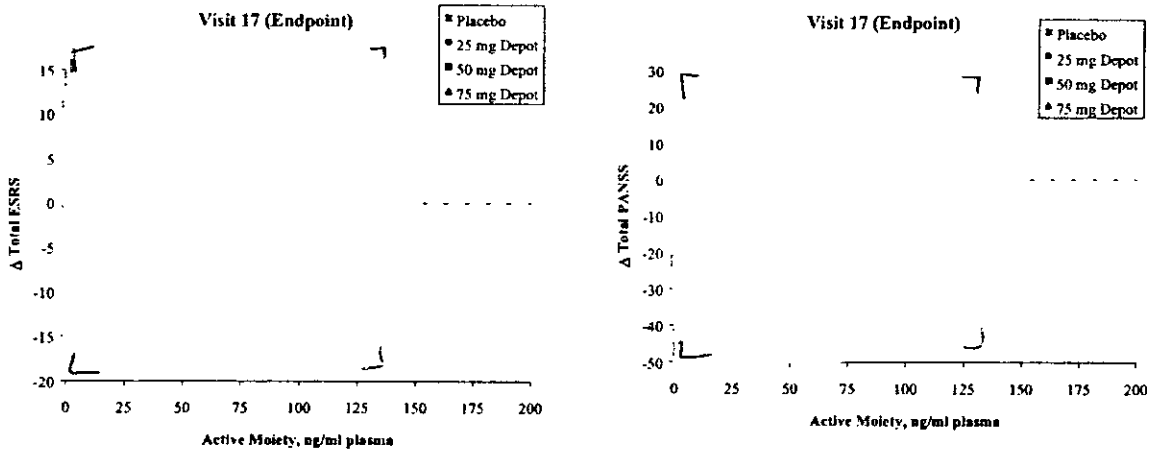


FIGURE 2. Total ESRS (left panel) and total PANSS (change from baseline) *vs.* active moiety plasma concentrations at endpoint (Day 85, RIS-USA-121). Negative PANSS scores indicate clinical improvement.

Since no trends or correlations were observed in the exposure-response evaluations, no further analyses were conducted. The Phase III efficacy trials, did however, show that the risperidone depot formulation was effective at 25 - 75 mg doses in the 12-week trials, and that efficacy was maintained in the open 1-year study extension. No added benefit was observed at doses above 50 mg. Therefore, the sponsor proposes a maximal recommended risperidone dose of 50 mg, administered as biweekly IM depot injections.

4.2.2 General pharmacokinetics

What is the typical shape of a drug plasma concentration-time profile after an IM injection of the risperidone depot formulation?

After the IM injection, following a short burst phase, there is a 3-week lag phase before drug absorption starts, subsequent to this lag phase, the drug is slowly released and absorbed over 4-6 weeks as the microspheres erode. Typical profiles after IM injections of 50 mg are given in Figure 3 below.

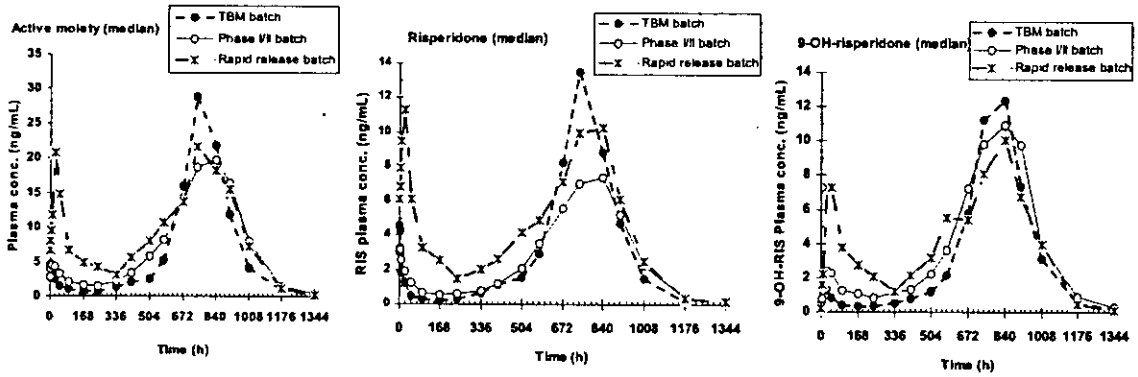


FIGURE 3. Median Cp (ng/mL), *vs.* time (h) of active moiety (left panel), RIS (middle panel), & 9-OH-RIS (right panel) after a single IM injection of 50 mg risperidone as 3 different depot microsphere formulations (graphs depict n=24-27 per time point). Solid circles

/ dashed line: TBM formulation. Unfilled circles / solid line: Phase I/II formulation. Crosses / dashed line: faster releasing formulation. [RIS-INT-54]

Are the pharmacokinetics adequately studied after different doses of the risperidone depot formulation?

Yes, the sponsor has investigated the pharmacokinetics of risperidone, the active metabolite, 9-OH-risperidone, and the active moiety (sum of risperidone and 9-OH-risperidone) after single doses (25-100 mg) and repeated, biweekly, doses (25-75 mg) of IM administered injections of the risperidone microsphere depot formulations in the gluteal muscle. The terminal t½ after injection of the depot formulations reflect the slow absorption of the active moiety after erosion of the microspheres, and is about 6 days after a single 50 mg dose (Appendix, section 7.2.6, RIS-INT-54). This is consistent with the observed lag-phase of approximately 3 weeks. Steady state levels are maintained for 2-3 weeks, and decline rapidly thereafter. This recommended dosing of IM injections every 2 weeks, is therefore appropriate to maintain steady state plasma levels of the active moiety (risperidone + 9-OH-risperidone). Steady state was achieved after the 3rd to 4th biweekly injection.

4.2.3 Dose-proportionality

Has dose proportionality been established for the depot formulations of risperidone?

Yes, dose proportionality has been established after risperidone doses up to 50 mg after IM depot injections (and in some, but not all, studies up to 75 mg). After repeated doses (5 biweekly injections, Phase I/II formulation) dose proportional increases were observed in C_{max}, AUC, C_{min} and C_{av} (average concentrations over the dosing interval) of risperidone, 9-OH-risperidone and active moiety (Appendix, Section 7.3.2, RIS-INT-32). Figure 4 depicts AUC over one dosing interval at steady state *vs.* 25, 50, and 75 mg doses of risperidone, 9-OH-risperidone and active moiety.

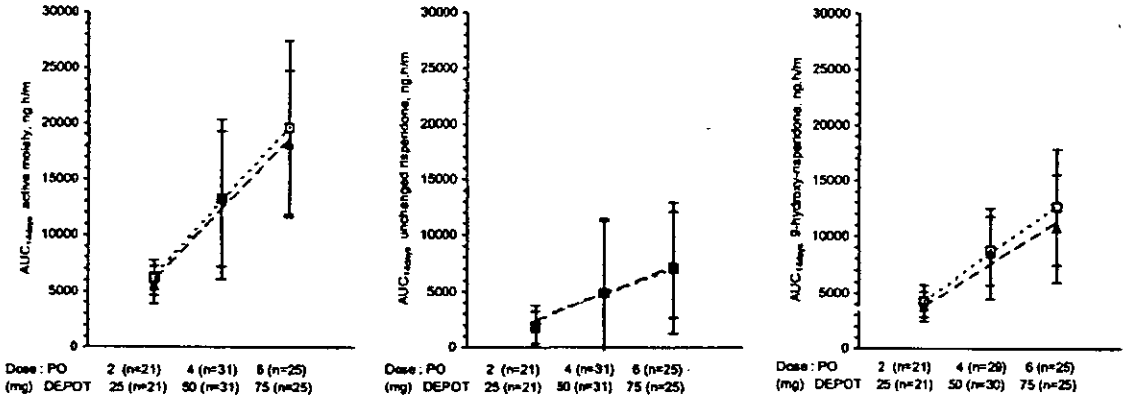


FIGURE 4. Mean (± SD) $AUC_{14\ days}$ *vs.* dose at steady state of the active moiety (left panel), risperidone (middle panel) and 9-OH-risperidone (right panel). Solid symbols & lines: IM depot injections of 25, 50, and 75 mg; open symbols & dashed lines: oral, daily doses of 2, 4, and 6 mg ($AUC_{24\ h}$ x 14) [Study RIS-INT-32]

A relative bioavailability study showed that AUC was comparable between the Phase I/II and TBM formulations (also see Section 4.5.3). In addition, the TBM formulations were used in the Phase III trials, and the population pharmacokinetic analysis of the Phase III data indicate that there is a good correlation between observed and predicted plasma levels of the different analytes. This indicates that linear pharmacokinetics are observed in doses up to 50 mg IM depot of the TBM formulations (also see Appendix, Section 7.7).

4.2.4 Recommended oral therapy at initiation of IM injection therapy

Are the dosing recommendations regarding oral substitution therapy at the initiation of the IM injection therapy adequate?

Yes, the proposed 3-week continuous oral risperidone regimen after initiation of the biweekly IM depot injections of risperidone is adequate. Initially the sponsor investigated a 4-week oral substitution therapy (2 weeks on prescribed oral dose, 2 weeks on ½ prescribed dose), see Appendix, Section 7.3.2 (RIS-INT-32). The chosen, simpler 3-week oral substitution therapy covers the lag-period after the 1st injection, and has been used in the Phase III trials, as shown in Figure 5. Although there is a drop in plasma levels at the stop of oral substitution therapy, the plasma levels are still within the range achieved by oral therapeutic doses, and therefore the recommended dosing recommendations of switching from oral to IM depot risperidone therapy are considered adequate.

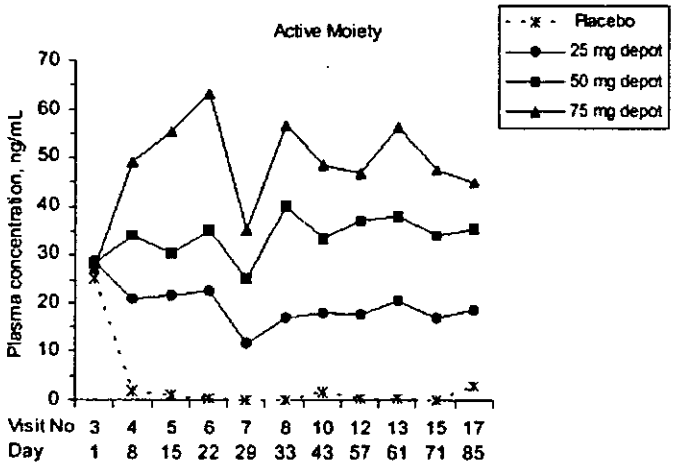


FIGURE 5. Mean plasma levels of active moiety (mostly at pre-injection) during a 12-week Phase III trial (RIS-USA-121). The drop in plasma levels on Day 22 coincides with the stop of oral therapy.

4.3 Intrinsic factors

Did the sponsor investigate what covariates (e.g. demographics or disease states) may influence the disposition of risperidone after IM depot injections?

Yes, the sponsor performed a population pharmacokinetic (PPK) analysis on data from the 3 Phase III trials. Sparse plasma sampling to determine plasma levels of risperidone (RIS), 9-OH-risperidone (9-OH-RIS) and active moiety was undertaken, and a PPK analysis was performed on data from 1370 patients with schizophrenia or schizoaffective disorder who received IM depot injections of RIS (25, 50 or 75 mg biweekly doses). A subset of 57 elderly patients were recruited into one study (RIS-INT-57), otherwise all patients were in the range of 18-65 years of age. Further details regarding the PPK analysis are given in the Appendix, Section 7.7 (Pharmacometrics Review). The following covariates were evaluated: gender, race, phenotype, age, body weight, height, body mass index, lean body mass, creatinine clearance (CrCL), serum creatinine, total protein, AST, ALT, total bilirubin, lactate dehydrogenase, and alkaline phosphatase.

The PPK analysis identified that lean body mass, age, phenotype and lactate dehydrogenase influenced the disposition of the active moiety. The corresponding covariates for risperidone were phenotype, lean body mass and age. Among body size variables (body weight, lean body mass and body mass index), the sponsor concludes that lean body mass was the covariate

affecting active moiety and risperidone clearances. However, the overall magnitude of the effect of lean body mass was small and probably not clinically relevant due to the high residual inter-individual scatter of clearance values. Interestingly, the sponsor's PPK analysis identified three populations, based on phenotype, namely extensive, intermediate and poor metabolizers of risperidone, as shown in Figure 6a. This is consistent with literature data on CYP2D6 polymorphism, and could in part explain the rather high variability observed in the pharmacokinetics of risperidone, 9-OH-risperidone, and active moiety.

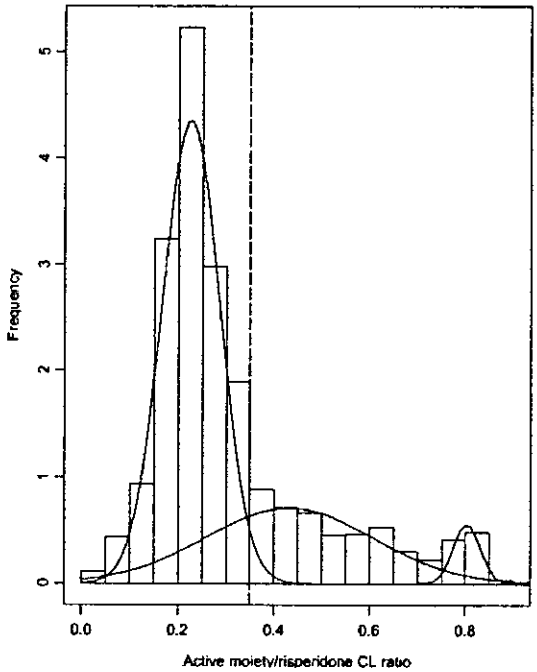


FIGURE 6a. A histogram of active moiety-to-risperidone clearance ratios and the fitted mixture of normal densities. The vertical dashed line shows the selected borderline ratio (0.35) separating extensive and intermediate metabolizers (data from the 3 Phase III trials).

Since special, lower, dosing recommendations are given for orally administered RIS in elderly patients, and patients with renal or hepatic impairment, age, CrCL and variables that influence renal or hepatic function were of special interest, and are described in the following Subsections.

4.3.1 Elderly

Did old age influence the pharmacokinetics of risperidone after the depot injections?

No, the data analyzed from the Phase III trials suggest that the clearance (CL) of RIS and active moiety after the biweekly RIS IM depot injections are only to a minor degree influenced by age. Elderly patients (>65 years of age) had approximately 10% mean lower CL of active moiety when compared to younger patients. When corrected for lean body mass, this age effect was reduced by 5%, suggesting that body size explains some of the variability seen in active moiety clearance with increasing age. Plasma levels in the elderly patients (≥65 yrs) were in the range of values observed in adults (<65yrs). The absence of a marked age effect on plasma exposure and clearance of risperidone and active moiety suggests that the lowest available dose of 25 mg can be recommended in the elderly patient population (same dose as in younger adult patients).

4.3.2 Disease states

4.3.2.1 Renal and hepatic function

Did covariates that are indicative of renal or hepatic function influence the pharmacokinetics of risperidone or the active moiety after the depot injections?

No. All patients that participated in the trials had normal kidney function (based on serum creatinine and CrCL), and normal hepatic function (based on ALT, AST, bilirubin, alkaline phosphatase, & total protein). The PPK analysis indicated that the lactate dehydrogenase influences clearance of the active moiety, but the other laboratory variables that are indicative of liver function did not support this finding. The sponsor concludes that the observed relationship is accidental, and will have no clinical implications.

In summary, no conclusions can be made regarding the influence of renal or hepatic impairment on the pharmacokinetics of RIS or active moiety based on the available data. The sponsor has made adequate dosing recommendations in these disease states, and does not recommend IM injections of RIS unless the renally or hepatically impaired patients can tolerate a minimum oral RIS dose of 2 mg/day.

4.3.2.2 Fever

Has the sponsor evaluated the potential influence of fever on the risperidone microsphere depot formulation?

Yes, as requested by the Agency, the sponsor investigated the potential effects of elevated body temperature on the drug release rates of the microspheres *in vitro*, and also *in vivo* (retrospective analysis of the patient safety database). Fever is defined as an a.m. temperature of >37.2°C (98.9°F) or a p.m. temperature of >37.7°C (99.9°F; Harrison's Principles of Internal Medicine).

The *in vitro* studies were designed to mimic conditions associated with fever during the different phases of drug release. The sponsor evaluated the *in vitro* release (n=3/test) representing the initial release phase (Day 1; 24-h period), the lag phase (Day 15, [redacted] d), and the late release phase (T50%, 4-h & 4-day period). Moderately elevated (38.5°C, 40°C, & 41°C) and highly elevated temperatures (41.5°C & 45°C) were tested. It was shown that release at elevated temperatures was comparable to the 37°C *in vitro* release condition during the different phases and temperatures (Day 1: [redacted] release [redacted] Day 15: [redacted] release at 41°C; T50%: [redacted] days at 41°C, [redacted] at 41.5°C, & [redacted] at 45°C). The results indicate that temperature-associated drug release or aberrant release effects at temperatures associated with fever are unlikely during all phases of drug release.

The entire patient safety database (n=2025) of the clinical studies contained reports of fever in 24 patients (exact temperature not recorded). A total of 21 patients had plasma levels of RIS and active moiety measured that corresponded to the febrile state. Evaluation of these cases showed that all but one patient had no elevated plasma levels, which would indicate early or more rapid release due to short periods of fever. Further, there were no spontaneously reported adverse effects noted for these patients.

In conclusion, the results indicate that the risperidone microsphere depot formulation does not exhibit altered release properties during shorter periods (≤4days) of elevated temperatures.

4.4 Extrinsic factors

4.4.1 Drug-drug interactions

Did the sponsor perform any additional drug-drug interaction studies?

Yes, the sponsor has submitted two traditional pharmacokinetic studies that assess the potential interaction between risperidone and lithium and valproate, respectively (see Appendix, Sections 7.3.3 & 7.3.4).

The potential influence of oral risperidone on the pharmacokinetics of lithium in combination with other antipsychotic drugs or in combination with risperidone (3 mg BID) was assessed at steady state in 13 patients. The 90% confidence intervals for C_{max} and AUC of lithium with and without concomitant risperidone were within the acceptance criteria of 80-125%. Therefore the combination of lithium and risperidone does not seem to warrant special precautions.

The potential influence of oral risperidone on the pharmacokinetics of valproate (1000 mg/day, TID dosing) as monotherapy or after add-on therapy of risperidone (4 mg QD) was assessed at steady state in 22 patients. The 90% confidence intervals for valproate $C_{pre\text{-}dose}$, C_{av}, and AUC_{24h} were within the acceptance criteria of 80-125%, but valproate C_{max} was increased by approximately 20% during RIS combination therapy. This observation will be described in the label (see Section 5), since the valproate and risperidone doses used in the study are below the maximum recommended doses of both drugs.

In addition, the sponsor explored the potential influence of concomitant medications on the PK of the different analytes after risperidone IM depot administration (Phase III trials) in the PPK analysis (Appendix, Section 7.7). All patients included in the trials used for the PPK analysis were taking concomitant medications. Already known drug-drug interactions were observed (already described in the package insert). Carbamazepine (3A4 inducer) reduced the levels of active moiety and risperidone by approximately 50%. Fluoxetine (2D6 inhibitor) increased the levels of active moiety (+30%) and risperidone (>100%). Interestingly, amitriptyline showed similar inhibitory effects on plasma levels of active moiety and risperidone as fluoxetine. However, a traditional repeated dose drug-drug interaction study with intensive blood sampling was performed in schizophrenic patients (n=12). No interaction was observed between amitriptyline (100 mg/day) and risperidone (6 mg/day). Amitriptyline is a CYP2D6 substrate, however, this reviewer did not find any literature reports that indicate that the drug also acts as a CYP2D6 inhibitor. However, the PPK analysis also showed that in all of the cases of suspected drug interactions, except after co-administration with carbamazepine, there is a significant overlap of active moiety/risperidone concentrations with and without concomitant medication. Therefore, the relevance of this observed finding of a potential interaction between amitriptyline and risperidone based on the PPK analysis is unclear, this reviewer does not recommend the inclusion of this observation into the label.

4.5 General Biopharmaceutics

4.5.1 Formulations used in the clinical trials

Which depot formulations were used in the clinical trials?

The sponsor used two different formulations in the human clinical trials (although a 3rd depot formulation was used in an early Phase I trial, also see Table 1, Section 4.1.2). The depot injections used in the Phase I/II studies were produced from the ——— process. The to-be-marketed (TBM) formulation used in the Phase III studies and some of the Phase I studies (RIS-INT-54 & -72) was manufactured at the intended commercial batch size of —— The

quantitative compositions of the microspheres and diluent of TBM formulation are shown in Appendix, Section 7.4.1 and information regarding development history and quantitative compositions used in the clinical trials and are shown in Appendix, Section 7.4.2.

The sponsor has adequately investigated the release controlling factors of the risperidone ER microspheres and optimized the diluent used for suspension of the microspheres prior to injection.

4.5.2 In vivo comparison of the oral and Phase I/II formulations

Has the sponsor compared oral regimens of risperidone to the IM biweekly risperidone regimens of the depot formulations?

Yes, multiple dose study with a parallel group design was performed to compare the oral dosing regimens to the IM depot injection of risperidone. (Study RIS-INT-32, for further details, see Appendix, Section 7.3.2).

The study compared the steady-state bioavailability of risperidone (RIS) and the active moiety (RIS + 9-hydroxy-RIS) after oral treatment (2, 4, & 6 mg QD) to intramuscular (IM) depot injections (5 biweekly inj; 25, 50, & 75 mg RIS; Phase I/II formulation) in 76 schizophrenic patients.

Based on the statistical tests performed on the active moiety, AUC and C_{av} were comparable (i.e. confidence intervals were within 80-125%) between the biweekly depot injections (25, 50 and 75 mg) and the corresponding QD oral regimens (2, 4 and 6 mg), as shown in Table 2 below.

TABLE 2. Summary statistics of the bioavailability parameters of the active moiety comparing the oral *vs.* the risperidone IM depot treatment (calculations on log-transformed data; LS mean = least squares mean). [RIS-INT-32]

Parameter / treatment	risperidone p.o. LS mean**	risperidone depot LS mean	Ratio depot/p.o.	90% confidence interval
2 mg p.o. - 25 mg depot (n=21)				
C_{av}, ng/ml	17.8	15.8	89	81-97
AUC, ng.h/ml	5996	5303	88	81-97
C_{min}, ng/ml	10.9	10.4	95	83-111
C_{max}, ng/ml	31.7	21.4	68	60-76
4 mg p.o. - 50 mg depot (n=31)				
C_{av}, ng/ml	35.8	34.4	96	89-104
AUC, ng.h/ml	12027	11571	96	89-104
C_{min}, ng/ml	19.8	20.2	102	90-115
C_{max}, ng/ml	68.2	49.0	72	65-80
6 mg p.o. - 75 mg depot (n=25)				
C_{av}, ng/ml	53.7	50.3	94	85-102
AUC, ng.h/ml	18056	16886	94	85-102
C_{min}, ng/ml	29.1	27.6	95	78-115
C_{max}, ng/ml	97.3	72.6	75	63-88

The sponsor also performed the same statistical tests on RIS and 9-OH-RIS. The mean % ratio of AUC and C_{av} (depot *vs.* oral treatment, log-transformed data) ranged between 107% and 121 % for RIS and 84% and 94 % for 9-OH-RIS. As shown in Table 2, C_{max} of the active moiety at steady state was about 25-30% lower after the IM depot injections compared to the oral treatment.

In conclusion, the bioavailability (AUC, C_{av}) at steady state after oral doses of 2, 4, and 6 mg correspond to that after 25, 50 and 75 mg risperidone IM injections. The sponsor has determined that based on clinical efficacy in schizophrenic patients, the maximal recommended dose of the depot formulation is 50 mg as biweekly IM injections, whereas the maximal efficacious oral risperidone dose is 6 mg QD. This indicates that the approximately 50% lower, sustained exposure to risperidone achieved after the 50 mg IM injection compared to oral treatment, is equally effective as oral risperidone administration of 6 mg QD.

4.5.3 In vivo comparison of the Phase I/II and TBM formulations

Are the in vivo plasma concentration-time profiles consistent with the in vitro release profiles?

Yes, but during the single- and repeated-dose Phase I/II trials, 9 out of 145 patients (about 6%) had plasma concentrations of active moiety with a marked, high early release (C_{max} 2-5 days post-injection) and an early decline of plasma levels to a minimum after 7-14 days. This phenomenon with high fluctuations of drug levels seemed to be subject specific. The sponsor investigated the potential causes for the early release, and explains the observations to be related to a mild inflammation, which can lower the pH in the local tissue at the injection site. The erosion of the microspheres is not influenced by an acidic pH, but the solubility of risperidone increases 100-fold from pH The diluent used in the Phase I/II trials, was reformulated [redacted], and the new diluent was used in all trials where the to-be-marketed (TBM) microsphere formulation was used.

The phenomenon of early release was low after IM injections of the TBM depot formulations (only 2 out of 130 patients in Phase I/II trials, about 1.5%, see Study RIS-INT-54 in Appendix). None of the patients with early release observed in Phase I/II trials, had safety problems, and the maximal individual plasma concentrations did not exceed those seen with oral daily doses up to 8 mg. Plasma levels were monitored in one Phase-III trial (RIS-INT-61, additional single samples 3 & 7 days post-injection at steady state), and there were no clear indications of early release from the TBM depot formulations compared with the oral risperidone dosing regimens. The comparison between the 4 mg oral vs. the 50 mg IM dose is shown in Figure 6b (similar graphs for 25 mg and 75 mg are not shown in this review).

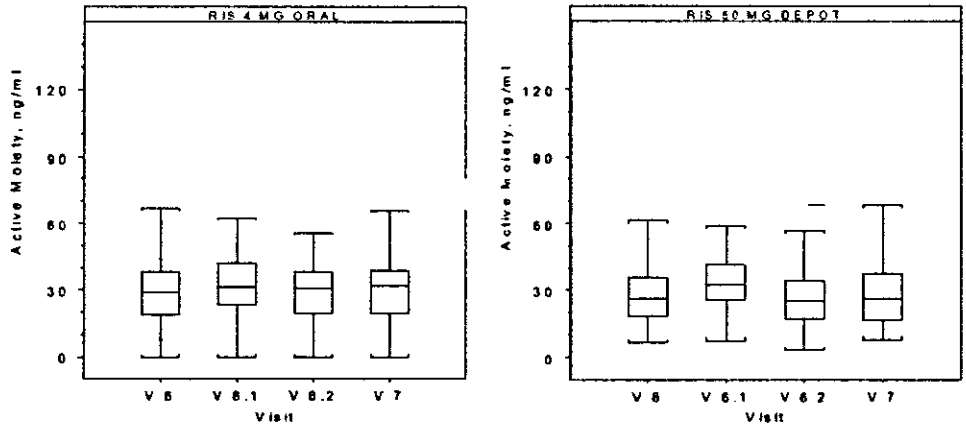


FIGURE 6b. Box and whisker plots of the active moiety plasma concentrations for oral (left panel; 4 mg QD, n=56-70) and IM (right panel 50 mg biweekly; n=73-100) treatment at Visits 6, 6.1, 6.2 and 7 (pre-injection, 4, 7 & 14 days post-injection). Boxes embrace inter-quartile range and horizontal bar represents median; whiskers correspond to 1.5xinter-quartile range; individual values outside whiskers are plotted as horizontal bars.

Has the sponsor compared the pharmacokinetic profiles after injections of the Phase I/II and to-be-marketed depot formulations?

Yes, an *in vivo* bridging study with a cross-over design was performed to compare the Phase I/II and the TBM formulations. (Study RIS-INT-54, for further details, see Appendix, Section 7.2.6).

Single doses of 50 mg risperidone (RIS) depot microspheres of the Phase I/II [redacted], and the TBM formulations [redacted], suspended in the TBM diluent, were given to 28 schizophrenic patients as an IM injection. Plasma levels (RIS, 9-OH-RIS and active moiety) were followed 12 weeks post-injection. There was a 3-week wash-out period between the 2 injections.

Were C_{max} and AUC comparable between the 50-mg doses of the two depot formulations?

The AUC values were comparable, but not C_{max}, for the active moiety after the single IM injections of the Phase I/II and TBM formulations. The ratios and 90% confidence intervals (CI) of C_{max} and AUC for the TBM (test) *vs.* the Phase I/II formulation (reference) are shown in Table 3.

TABLE 3. Ratios (TBM_{test}/ Phase $I/II_{reference}$) and 90% CI's of C_{max} and AUC of RIS, 9-OH-RIS and active moiety for the TBM (Tr. D) and the Phase I/II formulations (Tr. B) after single IM injections 50 mg RIS depot microspheres. Ratios and 90% CI's based on both ln-transformed and untransformed parameter values are shown. [RIS-INT-54]

PARAMETER		Tr. B *vs.* Tr. D							
		Ln-transformed				Untransformed			
		RATIO	90% CI			RATIO	90% CI		
ACTIVE MOIETY									
C_{max}	ng/mL	145.0	122.0	-	172.4	135.8	114.7	-	156.9
AUC_{last}	ng.h/mL	102.5	88.9	-	118.1	99.6	88.1	-	111.2
AUC_{∞}	ng.h/mL	103.6	89.9	-	119.4	100.4	89.2	-	111.7
RISPERIDONE									
C_{max}	ng/mL	153.2	126.6	-	185.4	134.4	110.9	-	158.0
AUC_{last}	ng.h/mL	109.1	93.5	-	127.2	102.5	86.9	-	118.1
AUC_{∞}	ng.h/mL	110.2	93.9	-	129.4	102.9	86.5	-	119.2
9-OH-RISPERIDONE									
C_{max}	ng/mL	142.4	120.5	-	168.2	135.8	114.2	-	157.4
AUC_{last}	ng.h/mL	105.2	88.4	-	125.3	96.7	82.6	-	110.9
AUC_{∞}	ng.h/mL	99.1	87.3	-	112.6	97.1	85.3	-	108.9

Treatment B: Single IM injection of 50 mg risperidone from a [redacted] production process.
Treatment D: Single IM injection of 50 mg risperidone from a phase-II [redacted], production process (no. 136-0767A).

The 50 mg doses of the TBM and the Phase I/II formulations were not comparable with regard to C_{max} (ln-transformed values, see Table 3). Doses of the TBM formulation gave 45-50% higher plasma concentrations (all analytes) during the main drug release phase (t_{max} occurred about 30 days post-injection). The CI's of AUC_{∞} and AUC_{last} were within acceptance criteria (80-125%) for the active moiety, but somewhat outside the limits (high end) for RIS, and partly for 9-OH-RIS (AUC_{last}). It should be noted that the TBM depot formulation was used in all pivotal Phase III trials.

There were few local injection-site reactions, and no major differences were observed in the local tolerability between the TBM and Phase I/II depot formulations. This is expected, since the re-formulated TBM diluent was used in this trial. [redacted]

Is the 37.5-mg dose adequately characterized in vivo?

The sponsor has included an intermediate strength (37.5 mg) as a treatment alternative to the 25 and 50 mg dosage strengths. This 37.5 mg TBM formulation was not investigated in the Phase III trials, but included in a Phase I/II trial (Appendix, Section 7.2.7, RIS-INT-72). Single doses of 37.5 mg, 50 mg and 62.5 mg were administered to patients (n=24-26/dose level). There was a dose proportional increase in C_{max} and AUC for the 37.5 mg and 50 mg doses, which indicates that the 37.5 mg depot formulation is acceptable. Dose proportionality at steady state has also been demonstrated up to doses of 50 mg of the TBM depot formulations (see Section 4.2.3).

What overall conclusions can be made?

The TBM diluent appears to lower the incidence of early partial release of drug from the microspheres, thus ensuring adequate plasma levels of active moiety over the entire 2-week dosing interval. The AUC (active moiety) was similar between the highest TBM strength (50 mg) of the risperidone depot formulations used in the Phase I/II trials, and the TBM formulations. Although the C_{max} of the active moiety was 45% higher after injection of TBM formulation, this does not raise concern, since the TBM formulation has been used in the Phase III trials, and a population pharmacokinetic analysis was performed on the data from the Phase III trials. Further, the relative bioavailability evaluations between oral risperidone regimens and biweekly IM injection regimens with the Phase I/II formulations (previous section), and the results from this study, indicate that the TBM depot formulation will give C_{max} values that are similar to an oral dosing regimen of risperidone. The 37.5 mg risperidone TBM depot formulation has also been investigated *in vivo*, and is found acceptable since C_{max} and AUC were dose proportional compared to the TBM 50 mg depot formulation.

4.5.4 In vitro release methods and specifications

What methods are used to determine the in vitro release and what are the proposed specifications?

Two methods are used in conjunction to determine *in vitro* release of risperidone into a pH 7.4 medium at 37°C and 45°C from the risperidone extended release microspheres for injection. The combination of the two methods enables testing within a reasonable time period while the full release profile is still characterized and evaluated. The rationale, discriminatory power, and justification of the proposed methods are described in further detail in the Appendix, Section 7.5. In brief, the two methods serve as a quality control of the following processes:

1. The 37°C water bath test evaluates the initial portion of the release profile (which reflects the amount of drug released during the first 24 hours), and determines the percent risperidone released on Day 15 (represents the lag phase).
2. The 45°C water bath test evaluates the release phase of risperidone from the drug product by determining $T_{50\%}$ (represents the erosion phase) and release at day 8 (endpoint phase).

The 45°C method proceeds at a rate approximately [redacted] faster than the 37°C procedure. The combination of both methods enables analysis of the four *in vitro* release criteria within 15 days and permits focus on individual segments of the release profile to achieve a greater degree of precision and reproducibility much faster than a single test (37°C) method, as shown in Figure 7. This method has also been shown to be discriminatory (see section 4.5.5 & Appendix, 7.5).

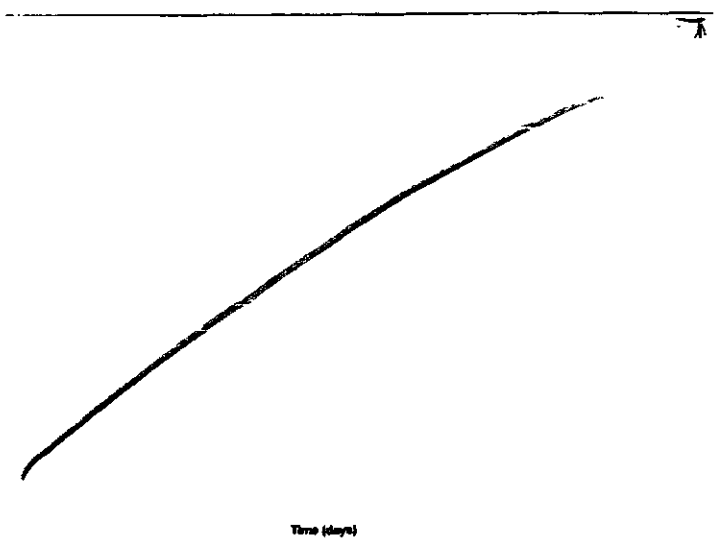


FIGURE 7. *In vitro* dissolution test methods (37°C and 45°C combined); % drug release *vs.* time (days). The results for ———— bulk lots are depicted.

The *in vitro* release procedure evaluates release of risperidone from the polymeric microspheres into a pH 7.4 medium at 37°C and 45°C. Triplicate samples (4 mL) sample are collected (and equal volumes replaced at the time of sampling) from the vessel that contains 200 mL medium.

The sponsor have procedures in place to evaluate 'out-of-trend' and 'out-of-specification' for means (acceptance criteria) for the release of the drug product batches (Appendix, section 7.5).

The batch analysis data for the biobatches and validation batches for stability tests of the TBM depot microspheres for individual, as well as mean data are shown in Tables 3, 4, and 5 in the Appendix, section 7.5.

Based on the presented data the sponsor is requested to tighten the specifications for the $T_{50\%}$ (mean), as well as add formal specifications for the individual samples. The recommended revisions of the *in vitro* release specifications (medium pH 7.4) are as follows:

Test method* (medium pH 7.4)	Test point	Specification (mean)	**Specification (individual sample)**
In vitro release (37°C water bath)	Day 1 Day 15		
In vitro release (45°C water bath)	$T_{50\%}$ Day 8		

* Samples tested in triplicate; **proposed by the sponsor

The use of the revised *in vitro* release specifications are only recommended during an interim period, until data is available from the on-going stability tests on the dosage strengths of the to-be-marketed Risperdal Consta products (25°C/60% RH & 5°C conditions). As a Phase IV commitment, the sponsor is requested to submit the *in vitro* release data from the on-going stability tests (TBM formulations) within 4 months after the 24-month stability data is available, together with a (potentially) revised proposal of the *in vitro* release specifications. This proposal should also include release specifications for individual samples, in addition to the specifications of the means.

In conclusion, the proposed combination of two *in vitro* dissolution methods (37°C & 45°C water baths) is deemed acceptable. The recommended revisions of the specifications should be used during an interim period, until data is available from the ongoing stability studies. As a Phase IV commitment, the sponsor is requested to submit the stability results for review, and final specifications will be set after review of the data and a new proposal of specifications (to be submitted within 4 months after the 24-month data at 5°C is available). In addition, the sponsor is also requested to clarify the acceptance criteria for the release of batches if an 'out-of-trend' result was obtained, i.e. what actions are taken if re-testing show consistent out-of-trend results.

4.5.5 In vitro and in vivo drug release comparisons

Has the sponsor evaluated the relation between in vitro release and the in vivo performance of Risperdal Consta depot injection?

The *in vivo* performance of the depot formulation is characterized by an initial lag-time of 2-3 weeks followed by a gradual release of the main fraction (hydrolysis of polymeric matrix) after which it peaks at 4-5 weeks, and lasts up to 6-7 weeks after a single injection. The *in vitro* release pattern mimics that observed *in vivo* of the to-be-marketed (TBM) formulation, as shown in Figure 8. It should be noted that the final combined *in vitro* release methods (37°C and 45°C water baths) are not used in the comparison in Figure 8, but the sponsor has shown that there is a correlation between the two *in vitro* release methods (see Appendix, section 7.5).

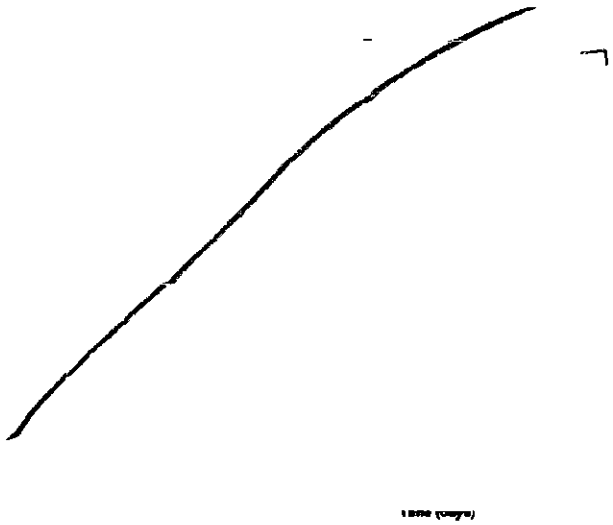


FIGURE 8. Percent released *in vitro* (37°C water-bath technique): left y-axis (0-100%) and % cumulative AUC *in vivo*: right y-axis (0-100%) of the active moiety (RIS + 9-OH-RIS) from a TBM formulation of 50 mg risperidone (RIS-INT-54, treatment B) *vs.* time (days, x-axis as 5-day increments).

In addition, a faster releasing batch of the risperidone formulation (——batch, Batch no. 147-1197) which was intentionally manufactured with specifications out of acceptance range (—— to produce a larger initial burst of drug release, was tested *in vitro* and *in vivo*. This batch would fail the Day 1 *in vitro* specifications of the 37°C water bath test of the initial 2-week lag-phase (pass criterion—— batch no. 147-1197: —. This batch was evaluated *in vivo* in Study RIS-INT-54 (50 mg Formulation E, Appendix Section 7.2.6), and compared to the 50 mg TBM formulation—— *in vitro* drug release on Day 1). The median plasma levels (active moiety) taken at 24 and 48 h post-injection of the faster releasing

formulation were —and —ng/mL, respectively. The corresponding plasma levels at 24 and 48 h post-injection of the TBM formulation were — and — ng/mL, respectively.

This indicates that the *in vitro* drug release specifications will identify factors that are important to the *in vivo* performance of this depot formulation, and serve as an adequate product control.

4.6 Analytical Section

Which analytical methods were used in the plasma analyses? Are the methods acceptable?

The sponsor used two different methods, RIA (radioimmunoassay) and LC-MS/MS (liquid chromatography-mass spectrometry/ mass spectrometry), to determine risperidone (RIS), the active metabolite 9-hydroxy-risperidone (9-OH-RIS) and active moiety. The RIA method has been used in the previous RIS NDAs, but the LC-MS/MS method is new. Details regarding both methods are found in Appendix, Section 7.6.

The RIA methods were used in all Phase I/II trials, except one. The sponsor performed all RIA analyses. One RIA method measured specifically RIS, and the other RIA method measured the active moiety (RIA + 9-OH-RIS). The plasma concentrations of 9-OH-RIS were calculated as the difference between the values of the active moiety and RIS. In most studies the lower limits of quantitation (LLOQ) were —ng/mL for RIS, and —ng/mL for 9-OH-RIS, respectively.

The LC-MS/MS method was used in all Phase III trials, and in one Phase I/II trial. The sponsor analyzed one study, and a contract laboratory performed the analyses for the other three studies. The LC-MS/MS method was validated in regard to accuracy, precision, selectivity, upper & lower LOQ, linearity, extraction recovery, robustness, and stability. The LC-MS/MS method has an LLOQ of — ng/mL for both RIS and 9-OH-RIS (linear range —— ng/mL). The reliability of the LC-MS/MS analysis between laboratories was evaluated, and found to be satisfactory.

A cross-validation between the RIA and the LC-MS/MS methods was conducted with subject samples. This cross-validation showed that the results for the active moiety were comparable between the LC-MS/MS and the RIA methods. It was shown that RIS concentrations measured by the RIA method were slightly overestimated in the lower concentration range (samples contained a portion equal to — of the 9-OH-RIS concentrations).

In conclusion, the bioanalytical methods used for the clinical studies in this NDA are considered adequately documented and validated.

5 LABELING

What changes have been made to the approved label? Are these changes acceptable?

The sponsor proposes a separate label for the Risperdal Consta long-acting injection, but has made revisions on the basis of the approved label for the oral formulations of Risperdal. The sponsor's proposed entire label is included in the Appendix, Section 7.8).

The proposed dosage recommendations for all populations are found acceptable from a pharmacokinetic perspective (DOSAGE AND ADMINISTRATION).

The sponsor is asked to:

- Insert headers in the Pharmacokinetics section (Absorption, Distribution, Metabolism, and Elimination) in the label and organize the pharmacokinetics section in this order, then followed by special populations.
- Section for dosage in pediatrics and special populations should be moved up closer to the DOSAGE AND ADMINISTRATION section (just before 'Instructions for use').

In addition, the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) proposes the following revisions to the sponsor's proposal (unless noted the proposed text is acceptable to OCPB. Strike-through text marks deletions, OCPB's changes and new proposed text are marked in bold, text in italics within brackets explains the proposed changes):

CLINICAL PHARMACOLOGY, ***Pharmacokinetics*** *(unchanged paragraphs in a smaller font size)*:

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme~~,~~ **CYP2D6** ~~———————~~ A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. *[Removed comma, switched order of current & old nomenclature of P450 isozymes]*

CYP2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percent of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP2D6 metabolizers convert it much more slowly. ~~———————~~

The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL CONSTA™.

Special populations

Renal Impairment

Hepatic Impairment

Elderly:
In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥65 years old) treated with RISPERDAL CONSTA™ for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. ——

——, **Dosing** recommendations are the same for otherwise healthy elderly patients and nonelderly patients (See DOSAGE AND ADMINISTRATION). *[The medical officer reviews the adverse events across all populations. Although the statement seems correct, it should not be included in this section, since this is described in PRECAUTIONS, Geriatric use.]*

6 SIGNATURES

Maria Sunzel, Ph.D. _____

RD/FT initialed by Ramana Uppoor, Ph.D. _____

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: June 7, 2002; Attendees: Drs. W Chou, T Laughren, J Lazor, H Malinowski, M Mehta, V Sekar, M Sunzel, & R Uppoor

c.c.: NDA 21-346, HFD-120 (Hardeman, Hearst, Laughren, Oliver, Gill-Sangha), HFD-860 (Mehta, Marroum, Sekar, Uppoor, Gobburu, Sunzel)

7 APPENDIX

7.1 TABLE OF ALL CLINICAL TRIALS

1. INTRODUCTION

This NDA is submitted by Janssen Research Foundation (JRF) for marketing approval of risperidone depot microspheres, a new formulation of risperidone that is encapsulated in extended release microspheres which are suspended in diluent for intramuscular injection.

The clinical development program for risperidone depot microspheres in the treatment of schizophrenia was conducted globally and included ten Phase 1-2 trials and three Phase 3 trials (Table 1). As of the data cutoff date of April 30, 2001, efficacy data supporting this NDA were derived from 1655 patients with schizophrenia; safety data were derived from a total of 2101 patients (1932 patients with schizophrenia, 163 patients with schizoaffective disorder, and 6 patients with schizophreniform disorder). Of these patients, 1499 patients received risperidone depot microspheres in repeated-dose trials, corresponding to approximately 543 patient-years of exposure.

Table 1: Overview of the clinical trials for risperidone depot microspheres

Trial	Study Phase	Primary objective(s)	Risperidone depot microspheres dose (Risperidone tablet)	Treatment duration	Number of patients (Schizophrenic/ schizoaffective/other)
Single-dose trials					
RIS-BEL-34	1	Pharmacokinetic	50 mg	1 injection	8 (8/0/0)
RIS-INT-25	1	Pharmacokinetic	50 mg	1 injection	9 (9/0/0)
RIS-INT-38	1	Pharmacokinetic	100 mg	1 injection	9 (9/0/0)
RIS-NED-13	1	Pharmacokinetic	25 mg	1 injection	8 (8/0/0)
RIS-USA-111	1	Pharmacokinetic	25 mg	1 injection	8 (6/2/0)
RIS-INT-54	1	Pharmacokinetic	25, 50, 75 mg	1 injection	56 (52/4/0)
Subtotal					*98 (92/6/0)*
Single-, intermediate-dose trial					
RIS-INT-72	1	Pharmacokinetic	37.5, 50, 62.5 mg	1 injection	*76 (76/0/0)*
Repeated-dose trials					
RIS-INT-31	1	Pharmacokinetic	25, 50, 75 mg	16 weeks	28 (28/0/0)
RIS-SWE-17	1	Pharmacokinetic	25, 50, 75 mg	16 weeks	13 (13/0/0)
RIS-INT-32	2	Pharmacokinetic	25, 50, 75 mg	15 weeks	82 (68/8/6)
RIS-USA-121	3	Efficacy, safety, pharmacokinetic, (placebo-controlled)	25, 50, 75 mg	12 weeks	439 (400/39/0)
RIS-INT-61	3	Efficacy, safety, pharmacokinetic (noninferiority with risperidone tablet)	25, 50, 75 mg (2, 4, 6 mg)	12 weeks	640 (640/0/0)
RIS-INT-57	3	Long-term safety, efficacy, pharmacokinetic	25, 50, 75 mg	50 weeks	725 (615/110/0)
Subtotal					*1927 (1764/157/6)*
Total					**2101 (1932/163/6)**

7.2 SINGLE DOSE STUDIES IN SCHIZOPHRENIC PATIENTS

7.2.1 RIS-NED-13: A single IM administration of a risperidone depot preparation to schizophrenic patients. A pilot trial for pharmacokinetic and safety evaluation in patients receiving a therapeutic neuroleptic maintenance therapy.

Study Objectives:

- To determine the pharmacokinetics, safety and tolerability and cardiovascular and laboratory safety of a single 25 mg intramuscular (IM) injection of a risperidone depot formulation in chronic schizophrenic patients on neuroleptic maintenance therapy (Phase I/II formulation).

Study Design and Methods: Eight schizophrenic patients (5M/3F, 36-58 years of age) received a single 25 mg IM (gluteal) injection of a risperidone depot formulation in this open, multi-center pilot study. After the injection, the patients remained at the clinic approximately 8 h, and returned for visits up to 8 weeks (56 days) post-injection. Other chronic neuroleptic medications were continued during the trial, except risperidone and carbamazepine. In addition to the safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the tolerability was measured as Extrapyramidal Symptom Rating Score (ESRS) on a weekly basis.

Blood samples for drug analyses were collected during 24 h (Day 0: 0, 1, 2, 4, & 8 h), and on Days 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, and 56. Risperidone (RIS) and active moiety (RIS +9-OH-risperidone) were determined by RIA, the limits of quantitation were [redacted] ng/mL and [redacted] ng/mL, for RIS and active moiety, respectively. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$) for RIS and active moiety were calculated by non-compartmental methods.

Results: All patients completed the study. All patients were on neuroleptic depot medication, and 1 patient also received promethazine orally. One patient (no. 9) received carbamazepine throughout the trial (protocol violation). There was an initial burst release of drug (about 2% of total dose) during the first 24 h (median: RIS C_{max} 1.8 ng/mL; t_{max} 2 h). The main fraction of drug release started at about 3 weeks (median: RIS C_{max} 3.5 ng/mL; t_{max} 35 days), and lasted until 7 weeks after the IM injection, see Figure 1. One patient (no. 6; 36-year old male) had higher plasma concentrations of all measured moieties than the remainder of the patients. Patient no. 6 received the following concomitant drug therapy during the trial: flupentixol depot (IM of 100 mg biweekly), promethazine (25 mg x 4), biperiden (2 mg x 3), and lithium carbonate (1000 mg/day).

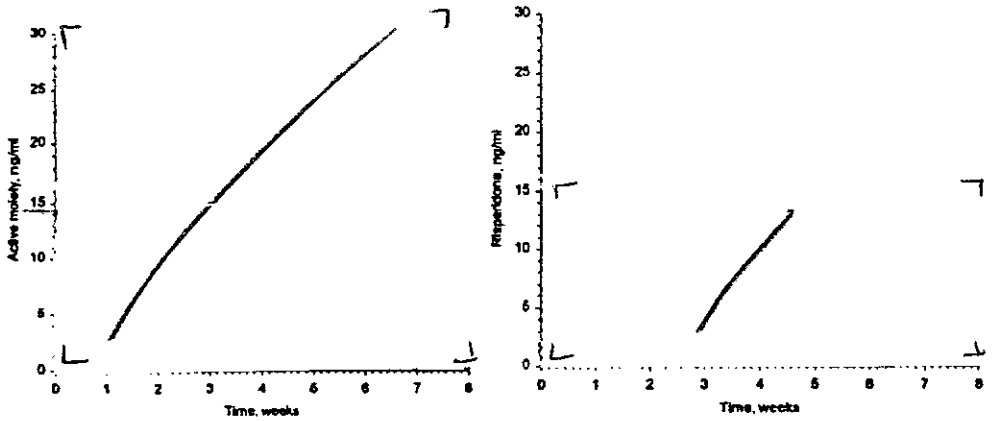


FIGURE 1. Individual plasma concentrations (ng/mL), thick line denotes median, *vs.* time (weeks) of active moiety (left panel) and risperidone (right panel) after a single IM injection of 25 mg risperidone depot microsphere formulation (n=8).

Five of the 8 patients reported AEs (back pain, dizziness, dyspepsia, palpitation, coughing and pharyngitis) after the 25 mg risperidone IM injection. Patient — had abnormal WBC readings (base line 11.2 giga/L, which increased to a maximum of 15.0 giga/L at week 4). SAEs (hospitalization) were reported for 2 patients (— Day 64 due to social reasons:—— due to aggravated condition). There was some improvement in the dyskinesia sub-scale of the ESRS scores, but the total ESRS scores did not show trends (unchanged: n=1; increased n=4; decreased n=3). BP and HR fluctuated during the study period. No local reactions were observed at the injection site.

Comments: This was a pilot study, and the depot formulation performed relatively well. There was not an obvious relation between the reported AEs and the drug plasma concentrations. According to the sponsor, the plasma drug levels during the main release were similar to a daily oral risperidone intake of 0.5-1 mg BID.

7.2.2 RIS-USA-111: Pharmacokinetic evaluation of a single IM administration of 25 mg risperidone of a depot formulation in chronic schizophrenic and schizoaffective patients.

Study Objectives:

- To determine the pharmacokinetics, safety and tolerability and cardiovascular and laboratory safety of a single 25 mg intramuscular (IM) injection of a risperidone depot formulation in chronic schizophrenic and schizoaffective patients on neuroleptic maintenance therapy (Phase I/II formulation).

Study Design and Methods: Eight schizophrenic and schizoaffective patients (7M/1F, 19-48 years of age, 6 Caucasians/ 2 Hispanics) received a single 25 mg IM (gluteal muscle) injection of a risperidone depot formulation in this open, single-center study, performed in the U.S. After the injection, the patients remained at the clinic up to 17 days, and returned for weekly visits up to 8 weeks (56 days) post-injection. Other chronic neuroleptic medications were continued during the trial (max. haloperidol dose of 10 mg/day). In addition to the safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the tolerability was measured as Extrapyramidal Symptom Rating Score (ESRS) on a weekly basis. Efficacy ratings (PANSS and CGI) were made on Days 7, 14, 28, 42, and 56.

Blood samples for drug analyses were collected during 24 h (Day 0: 0, 1, 2, 4, & 8 h), and on Days 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, and 56. Risperidone (RIS) and active moiety (RIS +9-OH-risperidone) were determined by RIA, the limits of quantitation were —ng/mL and —— ng/mL, for RIS and active moiety, respectively. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$) for RIS and active moiety were calculated by non-compartmental methods.

Results: Seven patients completed the study, the last patient (no. 2) dropped out due to a jail sentence. Five patients received additional antipsychotic drugs (haloperidol & thiothixene). There was an initial burst release of drug during the first 24 h (median: RIS C_{max} 1.5 ng/mL; t_{max} 2 h). The main fraction of drug release started at about 3 weeks (median: RIS C_{max} 2.0 ng/mL; t_{max} 34 days), and lasted until 7 weeks after the IM injection, see Figure 1. One patient (no. 3; 40-year old male) had higher plasma concentrations of all measured moieties than the remainder of the patients. Patient no. 3 received the following concomitant drug therapy during the most parts or the entire trial: oral haloperidol (5 mg BID) and fluoxetine (40 mg QD).

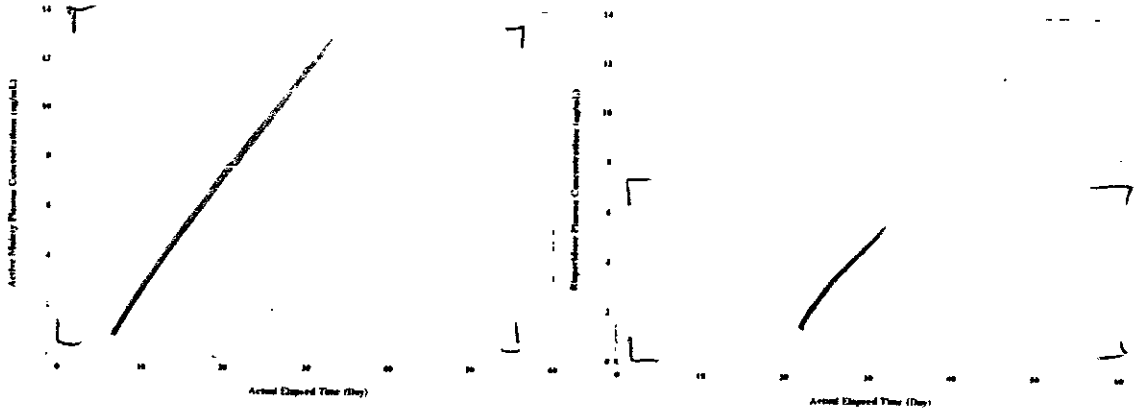


FIGURE 1. Individual plasma concentrations (y-axis 0-14 ng/mL) *vs.* time (x-axis 0-60 days, 10-day increments) of active moiety (left panel) and risperidone (right panel) after a single IM injection of 25 mg risperidone depot microsphere formulation (n=7).

The summary pharmacokinetic parameters are shown in Table 1.

TABLE 1. Pharmacokinetics of risperidone and the active moiety after a single IM injection of the 25 mg risperidone depot formulation (n=7).

Risperidone:

Day 1 to Day 56	Mean (SD)	CV (%)	Median (Min - Max)
AUC_{0-t} (ng•hr/mL)	1108 (1091)	98.4	840
AUC_{0-inf} (ng•hr/mL)	1354 (1184)	87.5	927
λ_z (hr^{-1})	0.005 (0.002)	41.7	0.004
$T_{1/2}$ (hours)	163 (53.7)	33.0	175
Day 1 to Day 7	**Mean (SD)**	**CV (%)**	**Median (Min - Max)**
T_{max1} (hours)	2.38 (2.33)	97.9	2.00
C_{max1} (ng/mL)	1.77 (0.77)	43.2	1.47
Day 7 to Day 56	**Mean (SD)**	**CV (%)**	**Median (Min - Max)**
T_{max2} (hours)	795 (166)	20.9	816
C_{max2} (ng/mL)	2.54 (1.83)	72.4	1.99

Active moiety (RIS + 9-OH RIS):

Day 1 to Day 56	Mean (SD)	CV (%)	Median (Min - Max)
AUC_{0-t} (ng•hr/mL)	3498 (1398)	40.0	3804
AUC_{0-inf} (ng•hr/mL)	4110 (915)	22.3	4151
λ_z (hr^{-1})	0.005 (0.002)	33.4	0.005
$T_{1/2}$ (hours)	148 (50.9)	34.3	145
Day 1 to Day 7	**Mean (SD)**	**CV (%)**	**Median (Min - Max)**
T_{max1} (hours)	14.3 (15.0)	105	8.00
C_{max1} (ng/mL)	2.65 (1.08)	40.6	2.25
Day 7 to Day 56	**Mean (SD)**	**CV (%)**	**Median (Min - Max)**
T_{max2} (hours)	795 (166)	20.9	816
C_{max2} (ng/mL)	8.13 (3.55)	43.7	8.95

All patients (n=7) reported at least 1AE after the 25 mg risperidone IM injection. The AEs that were reported in ≥2 patients were headache, fatigue, dizziness, constipation, coughing and pharyngitis. Five patients had pathologically high glucose levels at some point in the study. The

total ESRS score peaked on Day 28, concurring with the maximal decrease in PANSS. The total ESRS scores did not show any significant trends between the start and end of the trial. BP and HR fluctuated during the study period. Apart from initial redness, no local reactions were observed at the injection site except a mild swelling and induration reported up to24 h post-injection in one patient (no.5).

Comments: The depot formulation performed relatively well. The large variability observed in the pharmacokinetic parameters of risperidone is most likely due to a poor metabolizer of risperidone. Patient no. 3 had a high risperidone AUC (3800 ng.h/mL), but a low 9-OH-risperidone AUC (73 ng.h/mL), compared to the other patients (mean (n=7): $AUC_{9\text{-}OH\text{-}RIS}$= 3208 ng.h/mL).

7.2.3 RIS-BEL-34: A single IM administration of a risperidone depot preparation to schizophrenic patients. A pilot trial for pharmacokinetic and safety evaluation.

Study Objectives:

- To determine the pharmacokinetics, safety and tolerability and cardiovascular and laboratory safety of a single 50 mg intramuscular (IM) injection of a risperidone depot formulation in chronic schizophrenic patients (early Phase I formulation only used in this study, initial release 4.3%).

Study Design and Methods: Eight chronic schizophrenic patients (6M/2F, 20-56 years of age) received 1 single 50 mg IM (gluteal muscle) injection of a risperidone depot formulation in this open, multi-center pilot study. After the injection, the patients remained at the clinic about 8 h, and returned for visits up to 8 weeks (56 days) post-injection. Other chronic neuroleptic medications were allowed during the trial, except risperidone and carbamazepine. In addition to the safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the tolerability was measured as Extrapyramidal Symptom Rating Score (ESRS) on a weekly basis.

Blood samples for drug analyses were collected during 24 h (Day 0: 0, 1, 2, 4, & 8 h), and on Days 1, 2, 3, 4, 7, 10, 14, 21, 28, 35, 42, 49, and 56. Risperidone (RIS) and active moiety (RIS +9-OH-risperidone) were determined by RIA, the limits of quantitation were —— ng/mL and —— ng/mL, for RIS and active moiety, respectively. The pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$) for RIS and active moiety were calculated by non-compartmental methods.

Results: All patients completed the study (Patients 3 & 5 seemed to be poor metabolizers). There was an initial burst release of drug (about 4.3% of total dose) during the first 24 h (median: RIS C_{max} 4.72 ng/mL; t_{max} 8 h). The main fraction of drug release started after 2 weeks (median: RIS C_{max} 4.28 ng/mL; t_{max} 28 days), and lasted until 6 weeks after the IM injection, see Figure 1. Two patients (nos. 5 & 6) had early drug release (C_{max} occurred between weeks 1-2, and 4-5, respectively).

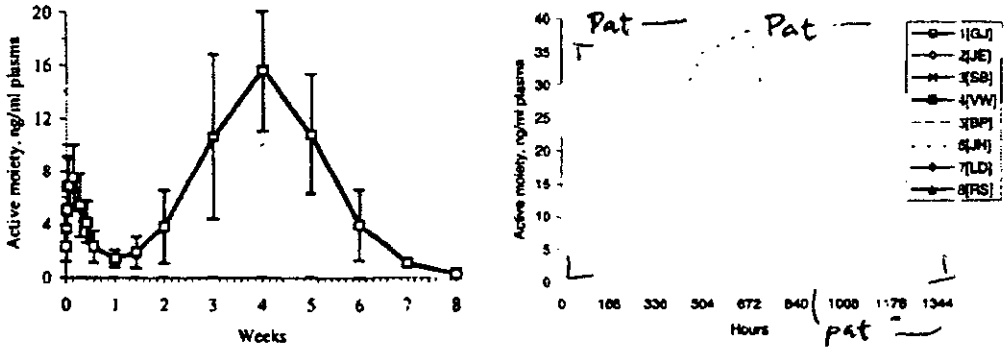


Figure 1. Plasma concentrations of active moiety *vs.* time. Left panel: mean ± SD (ng/mL, Pat 3, 5, & 6 excluded from calculations). Right panel: Individual profiles

One patient reported agitation, insomnia, diarrhea, vomiting, the other 7 had few AEs (agitation: n=3, insomnia: n=2) after the 50 mg risperidone IM injection. Patient 6 had an abnormal lab value (granulocytosis). There were no significant changes in the ESRS scores. BP and HR fluctuated during the study period. No local reactions were observed at the injection site.

Comments: This was a pilot study, and the depot formulation performed relatively well. However, the initial burst of drug release during 0-24 h post-injection, coupled with the three atypical plasma-time profiles in patients 3, 5, & 6 (37% of patients), indicates that the pilot formulation may not be optimal. There was not an obvious relation between the reported AEs and the drug plasma concentrations. According to the sponsor, the plasma drug levels during the main release were similar to a daily oral risperidone intake of 1-2 mg BID.

7.2.4 RIS-BEL-25: Pharmacokinetic evaluation of a single IM administration of 50 mg of a risperidone depot preparation. (Separate safety report with a different title)

Study Objectives:

- To determine the pharmacokinetics, safety and tolerability and cardiovascular and laboratory safety of a single 50 mg intramuscular (IM) injection of a risperidone depot formulation in chronic schizophrenic patients (Phase I/II formulation).

Study Design and Methods: Nine chronic schizophrenic patients (6M/3F, 24-57 years of age, all Caucasians) received 1 single 50 mg IM (gluteal muscle) injection of a risperidone depot formulation in this open, multi-center study. After the injection, the patients remained at the clinic approximately 8 h, and returned for visits up to 10 weeks (70 days) post-injection. Other chronic neuroleptic medications were allowed during the trial, except oral risperidone. In addition to the safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the tolerability was measured weekly by the Extrapyramidal Symptom Rating Score (ESRS).

Blood samples for drug analyses were collected during 24 h (Day 0: 0, 1, 2, 4, & 8 h), and on Days 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, and 70. Risperidone (RIS) and active moiety (RIS +9-OH-risperidone) were determined by RIA, the limits of quantitation were — ng/mL and — ng/mL, for RIS and active moiety, respectively. Concentrations of the active metabolite, 9-OH-risperidone (9-OH-RIS) were calculated from RIS and active moiety concentrations. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$) of RIS, 9-OH-RIS and active moiety were calculated by non-compartmental methods.

Results: All patients completed the study (Patients 1, 6, 8 & 9 seemed to be intermediate to poor metabolizers). There was an initial burst release of drug (about 2% of total dose) during the first

24 h (median: RIS C_{max} 5.6 ng/mL; t_{max} 2 h). The main fraction of drug release started after 3 weeks, with a peak at 5 weeks (median: RIS C_{max} 15.9 ng/mL; t_{max} 35 days), and lasted until 7 weeks after the IM injection, see Figure 1. One patient (no. 9; 24-year old male, 180 cm, 65 kg) had substantially higher RIS concentrations compared to the other eight patients (see Figure 1). Patient no. 9 received haloperidol (1 mg BID), pimozide (4 mg QD) and trihexyphenidyl (2 mg BID) concomitantly. He was the only patient in the study that received pimozide (Orap) in the study.

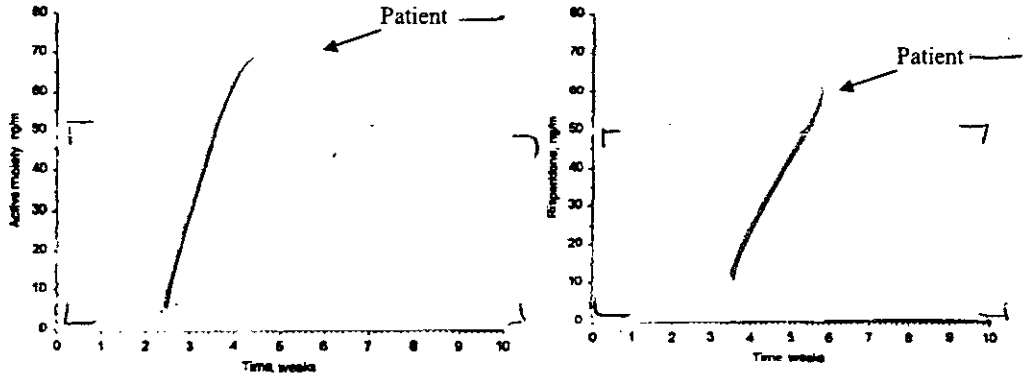


Figure 1. Individual plasma concentrations (ng/mL), thick line denotes median, *vs.* time (weeks) of active moiety (left panel) and risperidone (right panel) after a single IM injection of 50 mg risperidone depot microsphere formulation (n=9).

The summary pharmacokinetic parameters are shown in Table 1.

TABLE 1. Pharmacokinetics of risperidone and the active moiety after a single IM injection of the 50 mg risperidone depot formulation.

Pharmacokinetics :		
Risperidone	Median (n=9)	Mean ± SD (n=5)[a]
Initial burst		
t_{max}, h	2.02	2.60 ± 1.32
C_{max}, ng/ml	5.60	4.87 ± 1.06
Main fraction		
t_{max}, day	35	26.8 ± 11.1
C_{max}, ng/ml	15.9	9.80 ± 6.29
λ_z, 1/h	0.00645	0.00648 ± 0.00236
AUC_{last}, ng.h/ml	8092	4886 ± 2476
AUC_{∞}, ng.h/ml	8109	4905 ± 2479
Active moiety (risperidone plus 9-hydroxy-risperidone)	Median (n=9)	Mean ± SD (n=8)[b]
Initial burst		
t_{max}, h	8.0	20.8 ± 31.7
C_{max}, ng/ml	5.60	7.01± 3.28
Main fraction		
t_{max}, day	35	34.3 ± 12.4
C_{max}, ng/ml	22.8	24.4 ± 8.7
λ_z, 1/h	0.00732	0.00740 ± 0.00438
AUC_{last}, ng.h/ml	14246	13677 ± 3087
AUC_{∞}, ng.h/ml	14319	13872 ± 3122

[a] Excluding subjects ——— , (see text).
[b] Excluding subject ——— (see text).

Five of the nine patients reported AEs after the 50 mg risperidone IM injection. The reported AEs were orthostatic hypotension, insomnia, aggravated psychotic condition (Day 59), hospitalization after injury (physically abusive boyfriend), pain, headache, vertigo, hyponatraemia, bronchitis and pharyngitis. Patient 9 (high risperidone plasma concentrations) did not report any AEs, had normal lab values, but experienced hypotension. Standing SBP decreased from 102 (base line) to 82 mm Hg on Day 70; supine SBP decreased from 112 (base line) to 84 & 89 mm Hg on Days 42 & 70; and supine DBP decreased from 67 (base line) to 45 mm Hg on Day 49 in Patient 9. There were no significant changes in the ESRS scores. No local reactions were observed at the injection site.

Comments: The depot formulation performed relatively well.

However, the very high risperidone plasma concentrations in Patient 9, raises concern. A possible explanation to the high plasma levels in this subject may be the concomitant administration of pimozide (Orap). One literature report, indicates that pimozide inhibits CYP2D6 (the enzyme responsible for RIS metabolism to 9-OH-RIS) *in vitro* (Desta *et al*, JPET 285: 428-437, 1998). Since the patients' CYP2D6 genotypes were not determined in the study, it is not feasible to determine if Patient 9 is a poor metabolizer due to a gene mutation, or if the observed high plasma drug levels are due to a drug-drug interaction. There was not an obvious relation between the reported AEs and the drug plasma concentrations, however, the hypotension that Patient no. 9 experienced might be related to the observed, high plasma concentrations of risperidone. According to the sponsor, the plasma drug levels during the main release were similar to a daily oral risperidone intake of 1-2 mg BID.

7.2.5 RIS-INT-38: Pharmacokinetic evaluation of a single IM administration of 100 mg of a risperidone depot. (Pharmacokinetics / safety evaluations; report parts I/II)

Study Objectives:

- To determine the pharmacokinetics, safety and tolerability and cardiovascular and laboratory safety of a single 100 mg intramuscular (IM) injection of a risperidone depot formulation in chronic schizophrenic patients (Phase I/II formulation).

Study Design and Methods: Nine chronic schizophrenic patients (6M/3F, 24-57 years of age, 8 Caucasians/ 1 Black) received 1 single 100 mg IM (gluteal) injection of a risperidone depot formulation in this open, single-center study, performed in South Africa. After the injection, the patients remained at the clinic approximately 8 h, and returned for visits up to 10 weeks (70 days) post-injection. All patients stopped their chronic neuroleptic medications at the start of the trial, but oral neuroleptic treatment was reinstated if the patient's clinical status deteriorated during the trial (oral risperidone was not allowed). In addition to the regular weekly safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the tolerability was measured weekly by the Extrapyramidal Symptom Rating Score (ESRS), and efficacy (PANSS and CGI) was measured on a biweekly basis.

Blood samples for drug analyses were collected during 24 h (Day 0: 0, 1, 2, 4, & 8 h), and on Days 1, 2, 4, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, and 70. Risperidone (RIS) and active moiety (RIS +9-OH-risperidone) were determined by RIA, the limits of quantitation were —— ng/mL and —— ng/mL, for RIS and active moiety, respectively. Concentrations of the active metabolite, 9-OH-risperidone (9-OH-RIS) were calculated from RIS and active moiety concentrations. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$) of RIS, 9-OH-RIS and active moiety were calculated by non-compartmental methods.

Results: Eight patients completed the study, patient no. 9 (male, 49 years of age) dropped out of the study on Day 29, since he was uncooperative. All patients (n=8) needed additional antipsychotic drugs during the trial (additional drugs reintroduced after Day 14-62 post injection).

Patients 3 and 6 seemed to be intermediate to poor metabolizers. There was an initial burst release of drug (about 2% of the dose) during the first 48 h (median: RIS C_{max} 7.2 ng/mL; t_{max} 4 h). The main fraction of drug release started after 3 weeks, with a peak at 5 weeks (median: RIS C_{max} 23.1 ng/mL; t_{max} 28 days), and lasted until 7 weeks after the IM injection, see Figure 1. One patient (no. 4; 60-year old white male, 173 cm, 58 kg) had substantially higher RIS plasma levels compared to the other 7 patients. Patient no. 4 received a depot IM injection of 25 mg fluphenazine decanoate on Day 62 (protocol violation, only oral medications per protocol), and was also taking ibuprofen (250 mg prn) for osteoarthritis, and propranolol (10 mg prn) for headaches, during the trial

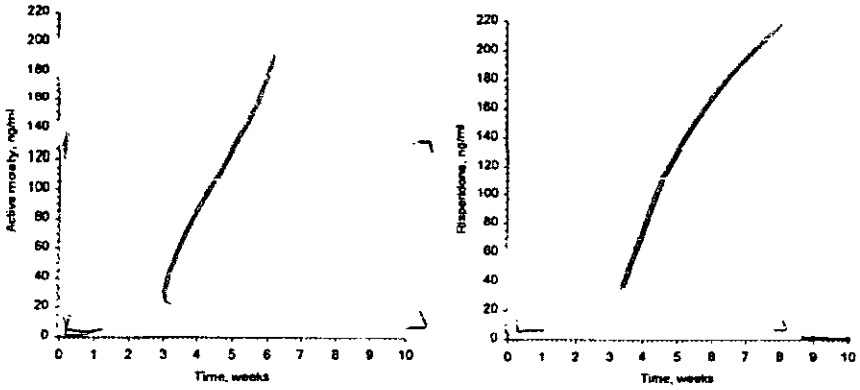


FIGURE 1. Individual plasma concentrations (ng/mL), thick line denotes median, *vs.* time (weeks) of active moiety (left panel) and risperidone (right panel) after a single IM injection of 100 mg risperidone depot microsphere formulation (n=8). [RIS-INT-38]

The summary pharmacokinetic parameters are shown in Table 1.

TABLE 1. Pharmacokinetics of risperidone and the active moiety after a single IM injection of the 100 mg risperidone depot formulation. [RIS-INT-38]

Pharmacokinetics		
Risperidone	Median (n=9)	Mean[a] ± SD[a] (n=6)
Initial burst		
t_{max}, h	4.0	7.7 ± 8.2
C_{max}, ng/ml	7.15	8.80 ± 4.09
Main fraction	(n=8)[b]	(n=5)[a,b]
t_{max}, day	28	33.6 ± 5.9
C_{max}, ng/ml	23.1	16.1 ± 10.1
λ_z, 1/h	0.00513	0.00735 ± 0.00377
AUC_{last}, ng.h/ml	9411	6799 ± 2696
AUC_{∞}, ng.h/ml	9446	6884 ± 2646
Active moiety (risperidone plus 9-hydroxy-risperidone)	Median (n=9)	Mean[a] ± SD[a] (n=8)
Initial burst		
t_{max}, h	24.0	21.3 ± 15.0
C_{max}, ng/ml	10.3	12.3 ± 7.2
Main fraction	(n=8)[b]	(n=7)[b,c]
t_{max}, day	35	31.4 ± 10.3
C_{max}, ng/ml	52.9	50.6 ± 13.1
λ_z, 1/h	0.00703	0.00674 ± 0.00270
AUC_{last}, ng.h/ml[b]	24597	22907 ± 4747
AUC_{∞}, ng h/ml	24630	23172 ± 4925

[a] excluding subjects 3, 4, 6 (see text)
[b] excluding subject 9 for parameters of the main fraction (see text).
[c] excluding subject 4 (see text).

All patients reported AEs after the 100 mg risperidone IM injection. The most frequently reported AEs were headache and viral infection (n=4), extrapyramidal disorder (n=3), and aggravated psychotic condition (moderate in 6 patients). Patient 4 (high plasma concentrations) reported dizziness on Day 1, intermittent headaches during the entire trial, a viral infection on Days 49-53, and had pronounced changes in vital signs during the first 24 h after injection (max changes: SBP + 28 mm Hg, DBP –6 mm Hg, HR –24 bpm).. Two patients reported mild to moderate pain from the injection site during Day 1-2 (no local reactions were observed at the injection site). There were no significant changes in the ESRS scores in 3 patients, an increase was reported in 6 patients (highest changes were observed after the reintroduction of a 2nd antipsychotic drug about 5 weeks after injection). Six of the 9 patients showed a clinical improvement (≥20% reduction from base line) on the PANSS score, but this was an open trial where all patients required additional antipsychotic drug treatment. Therefore, the efficacy evaluation is somewhat difficult to interpret.

Comments: The depot formulation performed relatively well, with no local injection site reactions (pain reported in 2 patients). There was not an obvious relation between the reported AEs and the drug plasma concentrations. According to the sponsor, the plasma drug levels during the main release were similar to a daily oral risperidone intake of 2-4 mg BID.

7.2.6 RIS-INT-54: Single-dose bioavailability and safety of risperidone in chronic schizophrenic subjects following IM injection of risperidone depot microspheres from two production scale sizes and administered in a reformulated diluent.

Study Objectives:

1. To determine the pharmacokinetics and safety of risperidone (RIS) and the active moiety after single doses of 25, 50, and 75 mg (IM injection) of the to-be-marketed (TBM) RIS depot microspheres formulation (—, batch size, used in the Phase III trials)
2. To compare the pharmacokinetics of RIS and the active moiety after a single IM injection of 50 mg of the TBM and the Phase I/II (' — batch size) RIS depot microspheres formulations
3. To determine the pharmacokinetics of RIS and the active moiety after a single IM injection of 50 mg of an investigational RIS depot microspheres formulation (←—, batch size) which had a higher initial release and shortened lag-time *in vitro* compared to the Phase I/II formulation

Study Rationale: This study is considered pivotal by the sponsor, and gives information on the dose proportionality of three different doses of the TBM (Phase III) formulation. In addition, the relative bioavailability of the clinical trial formulation used in Phase I/II was compared to the TBM formulation, used in the Phase III trials (50 mg). A 3rd depot formulation with different release characteristics *in vitro* was administered to humans, which gives added information on how well the *in vitro* dissolution method predicts the *in vivo* performance of the formulation.

Study Design and Methods: Fifty-six chronic schizophrenic patients (38M/18F, 23-65 years of age, 54 Caucasians/ 2 Black) received single IM (gluteal) injections of RIS depot formulations in this open, randomized cross-over, multi-center study, performed in Croatia (n=32) and South Africa (n=24). The study consisted of two parts, with a 3-week washout period separating Part I and II. The patients were divided into four different treatment groups in Part I, and crossed over to a different treatment in part II of the study, according to the study design depicted in Table 1 (see next page).

Each treatment (A/B/C/D/E) consisted of a 12-week period where a single IM injection of a RIS depot microsphere formulation was administered on Day 1. Each patient received two IM treatments (3-week wash-out period in-between). The diluent used to suspend the microspheres immediately prior to the IM injection, was the diluent used in the Phase III trials (TBM diluent),

and had not been used in previous trials. For further details regarding the diluent, see Sections 7.4.1 and 7.4.2 of this Appendix.

TABLE 1. Study design (RIS-INT-54)

Part I (total no. patients = 56):			
Treatment A (n=14) **25 mg TBM*** formulation [redacted]	**Treatment C (n=14)** **75 mg TBM*** formulation [redacted]	**Treatment B (n=14)** **50 mg TBM*** formulation [redacted]	**Treatment D (n=14)** **50 mg Phase I/II**** formulation [redacted]
Part II: All patients receiving Treatment A or C continue with Treatment E:		All patients receiving Treatment B or D cross over to opposite treatment (B or D):	
Treatment E (n=28) **50 mg test batch†** formulation [redacted] (faster release/shorter lag time *in vitro*)		**Treatment B (n=14)** **50 mg TBM*** formulation [redacted]	**Treatment D (n=14)** **50 mg Phase I/II**** formulation [redacted]

*To-be-marketed (TBM) depot formulation (25, 50 & 75 mg RIS) used in the Phase III trials
**Clinical trial depot formulation (50 mg RIS) used in the Phase I/II trials
† Test depot formulation (50 mg RIS) with faster release properties *in vitro* (not used in any other human trial)

The patients were allowed to continue their chronic anticholinergic and neuroleptic drug regimens, but concomitant drug intake of RIS, clozapine, olanzapine, sertindole, seroquel or other newly registered antipsychotic drugs were not allowed. In addition to the regular weekly safety monitoring [blood pressure (BP), heart rate (HR), clinical laboratory, AEs], the Extrapyramidal Symptom Rating Score (ESRS) was assessed before and at the end (Day 85) of each treatment, or if symptoms developed or worsened, an extra ESRS was made at that time.

Blood samples for drug analyses were collected on Day 1 (0, 1, 2, 4, & 8 h), 2 (24 h), 3 (48 h), 5 (96 h), 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 50, 57, 64, 71, 78, and 85 after each treatment. RIS and active moiety (RIS +9-hydroxy-risperidone) were determined by RIA, the limits of quantitation were [redacted] ng/mL and [redacted] ng/mL, for RIS and active moiety, respectively. Concentrations of the active metabolite, 9-hydroxy-risperidone (9-OH-RIS) were calculated from RIS and active moiety concentrations. The pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-last}}$, $AUC_{0-\infty}$) of RIS, 9-OH-RIS and active moiety were calculated by non-compartmental methods. Relative bioavailability was only calculated for the treatment ratio B/D and 90% confidence intervals were constructed for C_{max} & AUC (treatment ratio B/D).

Results:
Patient information: A total of 49 patients completed the study, whereas 7 patients did not complete the study. One patient (#. 30014) was lost to follow-up in part II, the other 6 discontinued the study during Part I (withdrew consent: n=3; AE: n=1; death from myocardial infarct: n=2). The number of patients that were randomized to the different treatments described in Table 1 were as follows:
Treatment A/E (25 mg TBM/50 mg test*): n=14 (3F/11M)
Treatment B/D (50 mg Phase I/II /50 mg TBM): n=14 (6F/8M)
Treatment C/E (75 mg TBM/50 mg test*): n=14 (5F/9M)
Treatment D/B (50 mg TBM/50 mg Phase I/II): n=14 (4F/10M)
*50 mg test formulation; faster *in vitro* release

All patients received other antipsychotic drugs, as well as other medications, during the trial.

Pharmacokinetics (PK):

PK comparisons between formulations: The plasma concentration-time (Cp) profiles after a 50 mg dose of the TBM, the Phase I/II and faster releasing formulations given as a single IM injection are depicted in Figure 1. One group of patients received the 50 mg doses of the TBM (Trtmt. B, n=26) and the Phase I/II (Trtmt. D, n=25) in a randomized cross over design. A 2nd group of the patients (Trtmt E, n=25) received the faster releasing formulation (50 mg dose), i.e. the same individuals who received Trtmt B/D did not receive Trtmt E (see Table 1, study design).

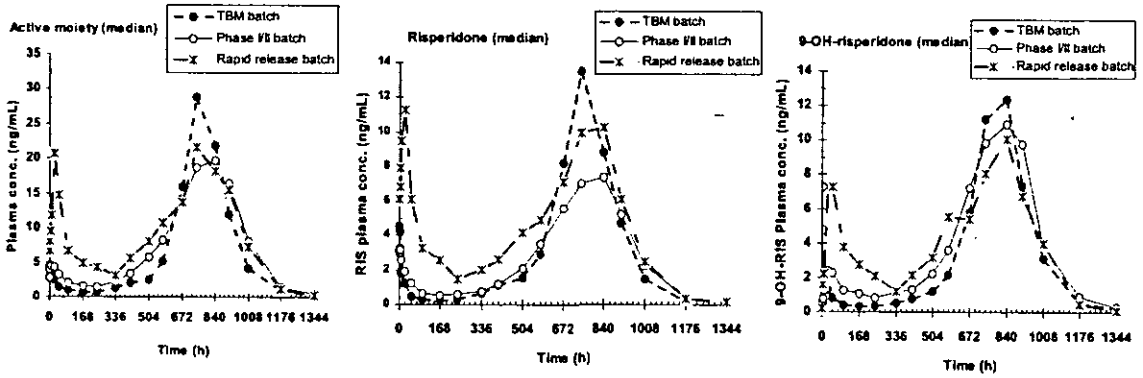


FIGURE 1. Median Cp (ng/mL), *vs.* time (h) of active moiety (left panel), RIS (middle panel), & 9-OH-RIS (right panel) after a single IM injection of 50 mg risperidone as 3 different depot microsphere formulations (graphs depict n=24-27 per time point). Solid circles / dashed line: TBM formulation. Unfilled circles / solid line: Phase I/II formulation. Crosses / dashed line: faster releasing formulation. [RIS-INT-54]

After IM injections of both the TBM or Phase I/II formulations, there was a small, initial burst of drug release during the first 48-72 h, due to the variability in data, there was no major differences between formulations. The main fraction of drug release started after 3 weeks, with a peak about 30 days post-injection of both formulations, and lasted until 7 weeks after the IM injection, as shown in Figure 1.

After injections of the TBM formulations, two patients showed higher initial plasma levels of the active moiety during the initial days post-injection than during the main release (25 mg: n=0; 50 mg: n=1, pat # 30024 - ng/mL at 96 h — ng/mL at 32 days post-inj; 75 mg: n=1, pat # 30032- ng/mL at 48 h, ~ ng/mL at 29 days post-inj). One patient (# 30024) had a normal profile after the Phase I/II injection, whereas patient # 30032 had a similar initially higher plasma drug profile after the injection of the faster releasing formulation.

After injections of the faster releasing formulation, eight patients had higher initial plasma concentrations 0-48 h post-dose than during the main release. All 8 of these patients had a normal plasma drug profile after the injection of the TBM formulations (25 or 75 mg).

After injections of the Phase I/II formulation, three patients showed higher initial plasma concentrations 0-48 h post-dose than during the main release. All 3 patients had a normal plasma drug profile after the injection of the 50 mg TBM formulation.

The initial *in vitro* release for the faster releasing, the Phase I/II, and TBM formulations were and (% of dose), respectively. The *in vivo vs. in vitro* performance of the formulations, is also discussed in Section 4.5.5 of the main review.

The summary pharmacokinetic parameters for RIS, 9-OH-RIS and the active moiety for all treatments (A/B/C/D/E) are shown in Table 2.

TABLE 2. Pharmacokinetics of RIS, 9-OH-RIS, and the active moiety after single IM injections of the different risperidone depot formulations. [RIS-INT-54]

PARAMETER		Mean ± SD (and median) on original data					
		ACTIVE MOIETY		RISPERIDONE		9-OH-RISPERIDONE	
Treatment A (N=14)							
C_{max}	ng/mL	16.1 ± 7.12	(15.4)	7.34 ± 5.71	(5.51)	9.04 ± 3.94	(8.03)
AUC_{last}	ng.h/mL	5644 ± 2513	(5086)	2626 ± 2479	(1380)	3022 ± 1059	(2791)
AUC_{∞}	ng.h/mL	5766 ± 2485	(5238)	2778 ± 2537	(1425)	3144 ± 1057	(3108)
t_{max}	h	832.72 ± 96.52	(839.28)	767.72 ± 234.24	(839.28)	839.67 ± 93.11	(840.13)
t_{max}	days	34.7 ± 4.0	(35.0)	32.0 ± 9.8	(35.0)	35.0 ± 3.9	(35.0)
$t_{\frac{1}{2}term}$	h	130.81 ± 118.57	(75.61)	84.18 ± 50.65	(65.34)	146.20 ± 138.34	(89.37)
Treatment B (N=26)							
C_{max}	ng/mL	39.8 ± 15.7	(36.5)	21.6 ± 15.0	(20.1)	19.9 ± 12.0	(17.5)
AUC_{last}	ng.h/mL	11978 ± 4469	(10971)	5873 ± 3604	(5603)	6094 ± 4050	(5256)
AUC_{∞}	ng.h/mL	11654 ± 4129	(10397)	6054 ± 3600	(5637)	5772 ± 3611	(5156)
t_{max}	h	786.44 ± 170.16	(744.03)	776.29 ± 176.11	(744.03)	797.53 ± 176.66	(744.30)
t_{max}	days	32.8 ± 7.1	(31.0)	32.3 ± 7.3	(31.0)	33.2 ± 7.4	(31.0)
$t_{\frac{1}{2}term}$	h	95.12 ± 75.74	(71.98)	72.19 ± 30.82	(65.87)	106.86 ± 84.97	(80.45)
Treatment C (N=14)							
C_{max}	ng/mL	66.3 ± 37.9	(50.5)	43.5 ± 41.1	(23.7)	26.4 ± 10.2	(23.9)
AUC_{last}	ng.h/mL	21687 ± 8311	(19450)	13117 ± 9635	(9349)	8619 ± 4048	(8971)
AUC_{∞}	ng.h/mL	21727 ± 8313	(19494)	13153 ± 9626	(9424)	9588 ± 3452	(9099)
t_{max}	h	812.22 ± 241.38	(875.74)	793.49 ± 239.05	(874.69)	827.66 ± 242.69	(840.15)
t_{max}	days	33.8 ± 10.1	(36.5)	33.1 ± 10.0	(36.4)	34.5 ± 10.1	(35.0)
$t_{\frac{1}{2}term}$	h	76.71 ± 20.63	(73.31)	67.60 ± 26.07	(63.60)	86.71 ± 29.57	(76.59)
Treatment D (N=25)*							
C_{max}	ng/mL	28.4 ± 14.7	(27.6)	14.1 ± 12.2	(9.21)	14.9 ± 8.50	(14.8)
AUC_{last}	ng.h/mL	11748 ± 4598	(11039)	5282 ± 3672	(3658)	6260 ± 4082	(6041)
AUC_{∞}	ng.h/mL	11393 ± 4571	(10749)	5393 ± 3731	(3691)	6152 ± 3460	(6083)
t_{max}	h	747.85 ± 259.00	(840.02)	695.06 ± 302.91	(839.62)	733.85 ± 296.94	(840.12)
t_{max}	days	31.2 ± 10.8	(35.0)	29.0 ± 12.6	(35.0)	30.6 ± 12.4	(35.0)
$t_{\frac{1}{2}term}$	h	107.50 ± 82.42	(87.04)	95.76 ± 43.35	(80.27)	116.95 ± 83.21	(92.07)
Treatment E (N=25)							
C_{max}	ng/mL	43.6 ± 32.1	(33.9)	25.7 ± 22.5	(17.8)	19.7 ± 14.0	(14.5)
AUC_{last}	ng.h/mL	14763 ± 5783	(14849)	7880 ± 5298	(6706)	6962 ± 4129	(5976)
AUC_{∞}	ng.h/mL	14831 ± 5952	(14069)	7985 ± 5445	(6734)	7504 ± 3954	(6307)
t_{max}	h	544.31 ± 391.21	(743.95)	433.04 ± 400.18	(743.55)	531.86 ± 373.07	(743.92)
t_{max}	days	22.7 ± 16.3	(31.0)	18.0 ± 16.7	(31.0)	22.2 ± 15.5	(31.0)
$t_{\frac{1}{2}term}$	h	110.59 ± 75.62	(84.70)	87.62 ± 34.41	(82.28)	120.17 ± 80.54	(94.00)

* Without subjects 30055 and 30061 (dropped out during treatment).
Treatment A: Single IM injection of 25 mg risperidone from a [redacted] production process.
Treatment B: Single IM injection of 50 mg risperidone from a [redacted] production process.
Treatment C: Single IM injection of 75 mg risperidone from a [redacted] production process.
Treatment D: Single IM injection of 50 mg risperidone from a pnase-II [redacted] production process (no [redacted]).
Treatment E: Single IM injection of 50 mg risperidone from a [redacted] production process (no [redacted]).

Relative Bioavailability: Based on ln-transformed values (confidence intervals), C_{max} was not comparable between the TBM and the Phase I/II formulations. The TBM formulation gave approximately 50% higher plasma concentrations during the main drug release phase (at 30 days post-injection). The AUC_{∞} and AUC_{last} was within acceptance criteria (80-125%) for the active moiety, but somewhat outside the limits (high end) for RIS (93.5-127.2% & 93.9-129.4%), and in part for 9-OH-RIS (AUC_{last} 88.4-125.3%). The ratios and 90% confidence intervals (CI) of C_{max} and AUC for the TBM (test; Treatment B) *vs.* the Phase I/II formulation (reference; Treatment D) are shown in Table 3, Section 4.5.3, of the main review.

Dose proportionality (TBM formulation): Three different single IM injections (25, 50 and 75 mg doses) of RIS as the TBM formulation were given in the study. One group of patients (n=14) received either the 25 mg (Treatment A) or 75 mg (Treatment C) doses in a randomized manner, and the second group of the patients (n=26) received the 50 mg dose (i.e. the same individuals did not receive all three doses). The pharmacokinetic parameters of active moiety, RIS and 9-OH-RIS are depicted in Table 2 (see previous page).

In principle, there was a proportional increase in both C_{max} and AUC of all measured drug moieties (RIS, 9-OH-RIS and active moiety), after dose normalization to a 50 mg dose, as depicted in Figures 2 and 3.

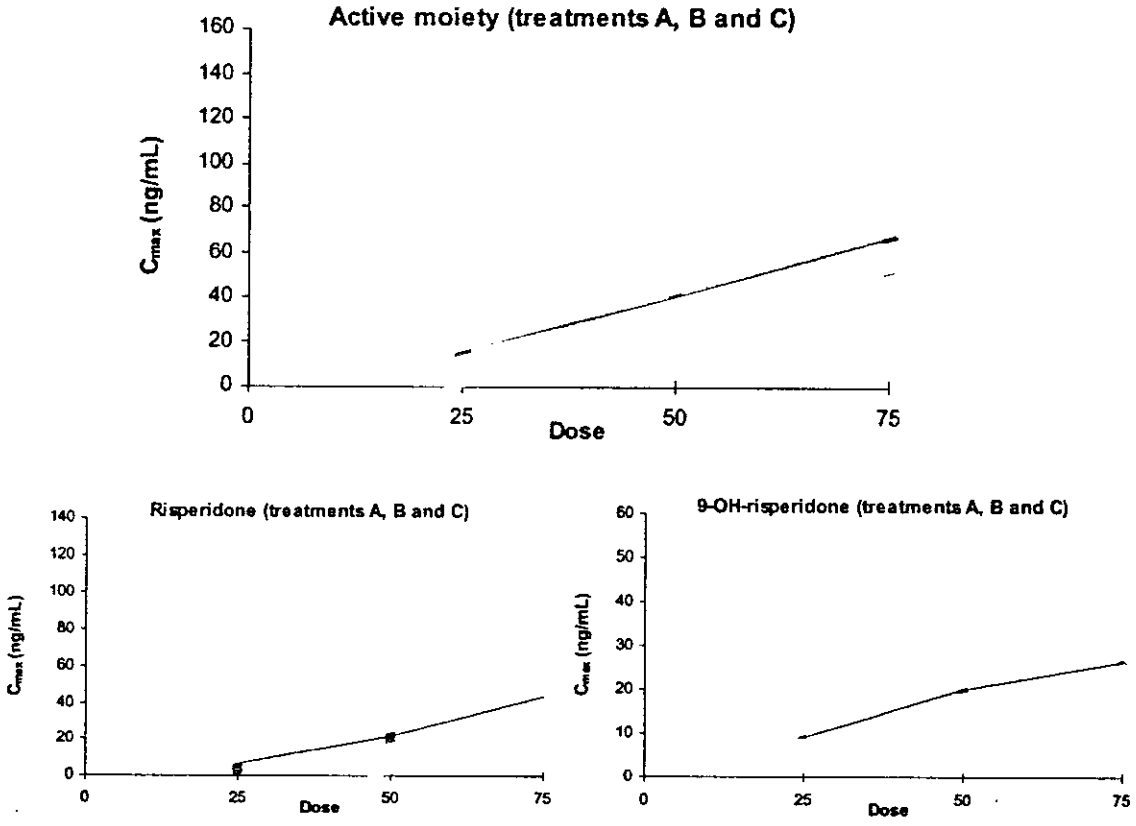


FIGURE 2. Individual (circles) C_{max} (ng/mL) *vs.* risperidone IM dose (mg) of the active moiety (upper panel), RIS (lower left panel), and 9-OH-RIS (lower right panel) after a single IM injection of 25 (n=14), 50 (n=25) or 75 (n=14) mg RIS.

The solid line in the three panels in Figures 2 and 3 depicts the interpolation between mean values of each dose.

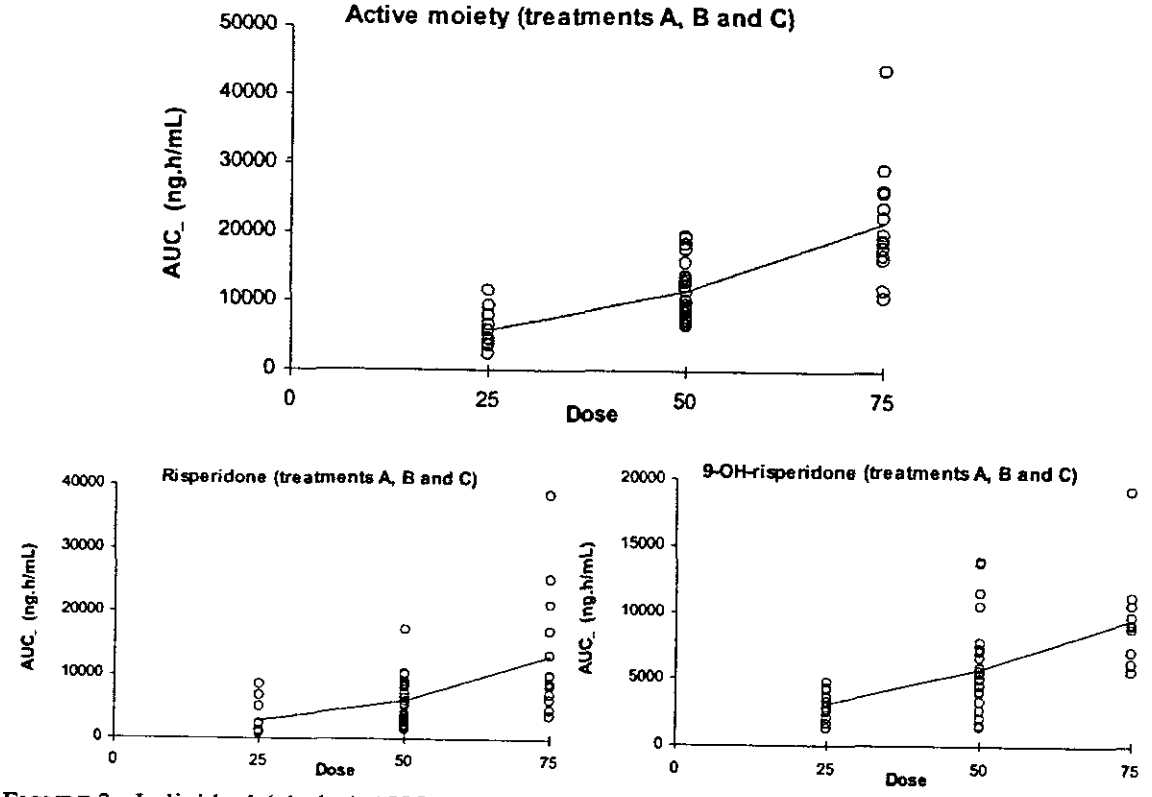


FIGURE 3. Individual (circles) $AUC_{infinity}$ (ng.h/mL) *vs.* risperidone IM dose (mg) of the active moiety (upper panel), RIS (lower left panel), and 9-OH-RIS (lower right panel) after a single IM injection of 25 (n=14), 50 (n=25) or 75 (n=14) mg RIS.

Safety: The most frequently reported AEs (>20% of patients) were anxiety, headache, influenza-like symptoms, insomnia, psychosis (n=4, all hospitalized), and weight gain. Almost all patients (51 of 56) reported AEs. Two patients died of myocardial infarction during the trial, on Day 78 and Day 32 after injection (50 mg TBM and Phase I/II formulations). Clinical laboratory values outside the normal reference ranges, but considered clinically insignificant, were reported in 21 patients. Overall, there was a slight increase in HR, and fluctuations in SBP and DBP after the different treatments. According to the sponsor, there were no relevant changes in ECG parameters (measured pre-dose and 12 weeks post-dose when all drug levels were non-quantifiable). The local tolerability at the injection site was fairly good (mild induration: n=5 where n=3 after TBM inj; mild to moderate pain reported by most patients; moderate redness: n=3).

Comments: After the single risperidone depot injections of the TBM and Phase I/II formulations, the time of initial release, lag time, and main release were comparable between the formulations. The initial *in vitro* release profiles for the Phase I/II and TBM formulations were 2.8%, and 1.6% (% of dose), respectively. This small difference (1.2%) in initial release was not observed *in vivo*, where both formulations were comparable. Based on active moiety, the exposure (AUC) was comparable between the TBM and Phase I/II batches, but not with respect to C_{max} (active moiety 45% higher after injection of TBM formulation). The TBM formulation has been used in the Phase III trials. The PK parameters after injections of the 25, 50 and 75 mg TBM depot formulations increased proportionally with dose. Injection with a depot formulation with an intentionally faster *in vitro* release profile (outside range of specifications) resulted in *in vivo*

plasma concentration-time profiles with an earlier, higher initial C_{max} as well as earlier release of the main fraction of the depot formulation. This indicates that the performance of a formulation *in vitro* can be indicative of the *in vivo* performance, which is an important aspect of product control.

There were few local injection-site reactions, and no major differences were observed in the local tolerability between the TBM and Phase I/II depot formulations. The re-formulated vehicle (used in the Phase III trials) was used for all formulations in this trial [redacted] Therefore, it is expected that both the TBM and Phase I/II depot formulations have a comparable tolerability at the site of injection in this study.

7.2.7 RIS-INT-72: Open-label, parallel group trial in subjects with schizophrenia to document the pharmacokinetic inter-subject variability of risperidone and active moiety after a single IM injection of the risperidone depot microspheres formulation.

Study Objectives:

- To document the pharmacokinetic (PK) inter-subject variability of risperidone (RIS) and active moiety after single RIS doses of 37.5, 50 and 62.5 mg (IM injection, to-be-marketed, TBM formulation, [redacted] batch size)
- To demonstrate that the PK parameters of these doses were contained within the range of the 25- to 75-mg doses. The 50-mg dose served as the internal reference.

Study Design and Methods: A total of 76 schizophrenic patients received a risperidone IM injection in this open, single-dose, parallel group, multi-center study (10 centers in Belgium, France, South Africa & Sweden). According to the inclusion criteria, patients between 18-55 years of age, with a body mass index of 15-35 were eligible to enter the study. The patients were randomized to 3 different treatments and received a single IM (gluteal) injection of the risperidone TBM depot formulation:

A. A single IM injection of 37.5 mg RIS (Treatment A, group I): n=24 (14 M/10 F, age range: 28 - 52 years; 3 Black, 13 Caucasian, 8 other)
B. A single IM injection of 50 mg RIS (Treatment B, group II): n=26 (19 M/7 F, age range: 23 - 54 years; 5 Black, 14 Caucasian, 7 other); reference treatment
C. A single IM injection of 62.5 mg RIS (Treatment C, group III): n=26 (20 M/6 F, age range: 22 - 55 years; 5 Black, 14 Caucasian, 1 Asian, 6 other)

Other chronic medications (e.g. neuroleptics not classified as atypical) were continued during the trial. Safety monitoring [blood pressure (BP), heart rate (HR), ECG, clinical laboratory, AEs, injection site reactions] was also performed during the trial to determine tolerability and safety.

Blood samples for drug analyses were collected during 24 h (Day 1: 0, 1, 2, 4, & 8 h), and on Days 2, 3, 5, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 50, 57, 64, 71, 78, and 85 post-injection. Risperidone (RIS) and 9-OH-risperidone (9-OH-RIS) were determined by LC/MS-MS with a limit of quantitation of [redacted] ng/mL ([redacted] ng/mL for [redacted] batch of samples, due to small volume of plasma). The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{last}, $AUC_{0-\infty}$, & $t_{½}$) for RIS, 9-OH-RIS and active moiety (RIS + 9-OH-RIS) were calculated by non-compartmental methods. The patients' CYP2D6 genotype was also determined (separate consent form for this test).

Results: A total of 71 patients completed the study (76 patients received the risperidone depot injection). Five patients did not complete the trial (1 pat committed suicide, 2 pats withdrew consent, 2 pats were lost to follow-up), and any available data from these 5 patients were not included in the PK calculations (last plasma sample taken between 2 &39 days post-injection). Of the 5 patients who did not complete the trial, one patient received a 50 mg injection (patient committed suicide), the other 4 patients received a 62.5 mg RIS dose.

The most commonly used concomitant medications were psycholeptics (including neuroleptics; 96% of the patients), anti-Parkinson medications (63% of the patients), and muscle relaxants (40% of the patients).

Overall, approximately 14% of the patients who gave consent to genotyping were found to be poor metabolizers according to the CYP2D6 genotype tests, as shown in Table 1. The following alleles were assessed: CYP2D6 *1/*1, *1/*3, *1/*4, *1/*5, *1/*6, *3/*4, *4/*4,and *4/*6.

TABLE 1. Distribution of patients in each treatment group according to CYP2D6 genotype

	37.5 mg RIS	**50 mg RIS**	**62.5 mg RIS**
Total number patients in PK analysis	24	26	26
CYP2D6 Genotype			
No. patients assessed	20	22	23
Heterozygous extensive metabolizer	7 (35%)	6 (27.3%)	6 (26.1%)
Homozygous extensive metabolizer	12 (60%)	11 (50.0%)	14 (60.9%)
Poor metabolizer	1 (5%)	5 (22.7%)	3 (13.0%)

No early plasma peaks of risperidone was observed during the 1st 24 h post-injection (as previously seen with pilot formulations). However, five patients (2 after 50 mg IM, & 3 after 62.5 mg IM) had an earlier peak Cp (as high or about 50% lower as the main peak Cp) after 5 (n=1), 8 (n=1), 15 (n=2) or 18 (n=1) days post-injection. In addition 1 patient had a high late peak on Day 71 (active moiety 40.8 ng/mL on Day 71, & 22.3 mg/mL on Day 32).

The main fraction of drug release started at about 3 weeks, and lasted until 7 weeks after the IM RIS injections of 37.5 mg, 50 mg and 62.5 mg, as shown in Figure 1. It should be noted that the 50 mg dose resulted in a higher median RIS plasma concentration – time profile (but not of the 9-OH-RIS & active moiety) than the 62.5 mg RIS dose. The higher number of poor metabolizers (PM 22.7%) receiving 50 mg RIS than the other treatment groups (37.5 mg: PM 5%; 62.5 mg: PM 13%) could be part of the reason why this discrepancy was observed.

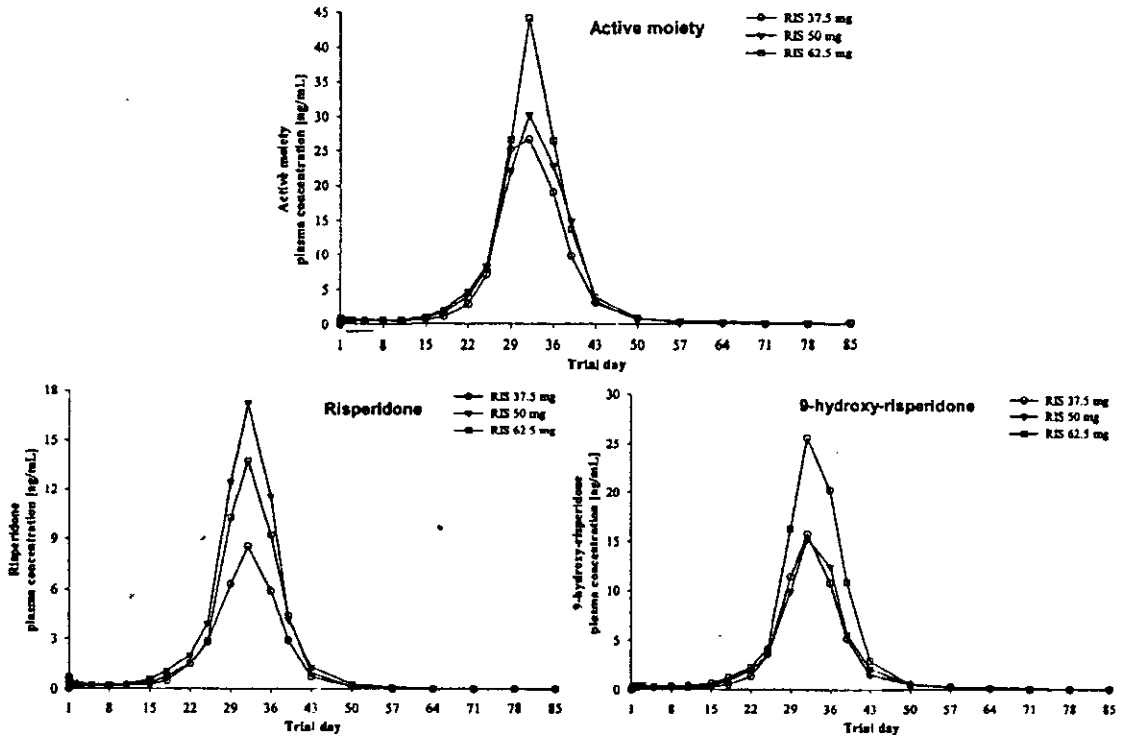


FIGURE 1. Median plasma concentrations (ng/mL), *vs.* time (h) of active moiety (top panel), RIS (lower left panel), and 9-OH-RIS (lower right panel) after a single IM injection of 37.5 mg (circles), 50 mg (triangles), and 62.5 mg (squares) risperidone (graphs depict n=24-26/dose). [Study RIS-INT-072]

Table 2 contains a descriptive statistics of the pharmacokinetic parameters after the three different RIS doses given as IM injections.

TABLE 2. PK parameters [mean ± SD*, (median)] of active moiety, RIS and 9-OH-RIS after IM injections of 37.5 mg, 50 mg, and 62.5 mg RIS. Discrepancy in number of patients/ dose in the text & Table 2 is due to that t½ could not be calculated for all patients, so the sponsor has excluded the data from the summary statistics. [Study RIS-INT-072].

Parameter	Mean ± SD (median)		
	RIS 37.5 mg (N=24)	RIS 50 mg (N=25)	RIS 62.5 mg (N=22)
Active moiety			
C_{max} [ng/mL]	32.13 ± 9.72 (30.15)	43.45 ± 21.01 (40.30)	43.49 ± 17.00 (45.45)
t_{max} [h]	761.19 ± 68.61 (744.10)	776.19 ± 233.77 (744.00)	760.41 ± 70.48 (744.00)
t_{max} [day]	31.72 ± 2.86 (31.00)	32.34 ± 9.74 (31.00)	31.68 ± 2.94 (31.00)
AUC_{last} [ng.h/mL]	9174 ± 2586 (8867)	13999 ± 6282 (11193)	13459 ± 4370 (13721)
AUC_{∞} [ng.h/mL]	8904 ± 2165 (8634)	12788 ± 5098 (10951)	13513 ± 4384 (13754)
$T_{½term}$ [h]	133 ± 103 (92.2)	163 ± 118 (85.1)	152 ± 109 (122)
Risperidone			
C_{max} [ng/mL]	15.1 ± 10.7 (12.0)	23.3 ± 18.6 (18.7)	16.9 ± 9.11 (15.0)
t_{max} [h]	738.16 ± 70.38 (743.96)	750.42 ± 78.96 (744.00)	743.01 ± 58.97 (743.99)
t_{max} [day]	30.76 ± 2.93 (31.00)	31.27 ± 3.29 (31.00)	30.96 ± 2.46 (31.00)
AUC_{last} [ng.h/mL]	4066 ± 2788 (3617)	6841 ± 4827 (5530)	4934 ± 2382 (4476)
AUC_{∞} [ng.h/mL]	3968 ± 2510 (3832)	6629 ± 4496 (5580)	5028 ± 2418 (4565)
$T_{½term}$ [h]	65.1 ± 22.2 (61.4)	102 ± 87.4 (70.7)	93.2 ± 76.7 (60.5)
9-OH-risperidone			
C_{max} [ng/mL]	17.4 ± 5.41 (17.7)	20.9 ± 12.0 (18.7)	27.0 ± 15.1 (27.8)
t_{max} [h]	770.16 ± 82.16 (744.10)	800.02 ± 233.05 (745.10)	770.20 ± 73.15 (744.00)
t_{max} [day]	32.09 ± 3.42 (31.00)	33.33 ± 9.71 (31.05)	32.09 ± 3.05 (31.00)
AUC_{last} [ng.h/mL]	5095 ± 1916 (5209)	7146 ± 4896 (6602)	8507 ± 4370 (8616)
AUC_{∞} [ng.h/mL]	5108 ± 1962 (5197)	6118 ± 3318 (5930)	8555 ± 4397 (8656)
$t_{½term}$ [h]	144 ± 105 (97.4)	169 ± 117 (92.6)	153 ± 107 (110)

*The apparent discrepancy between higher AUC_{last} *vs.* lower AUC_{∞} in the table is due to a lower no. patients (n < heading) included in the mean calc. of AUC_{∞}, since t½ could not be determined for all patients

The correlation between C_{max} and AUC *vs.* dose, after dose normalization to the 50-mg dose, is depicted in Figure 2. There was a fairly dose proportional increase in C_{max} and AUC for the 37.5 mg and 50 mg doses, however, the 62.5 mg and 50 mg doses gave similar estimates for C_{max} and AUC (also see Table 2). There was a high variability between subjects (see Table 2 & Figure 2) with a CV across the dose range for the active moiety of 30-48% in C_{max} and 28-45% in AUC_{last}, respectively.

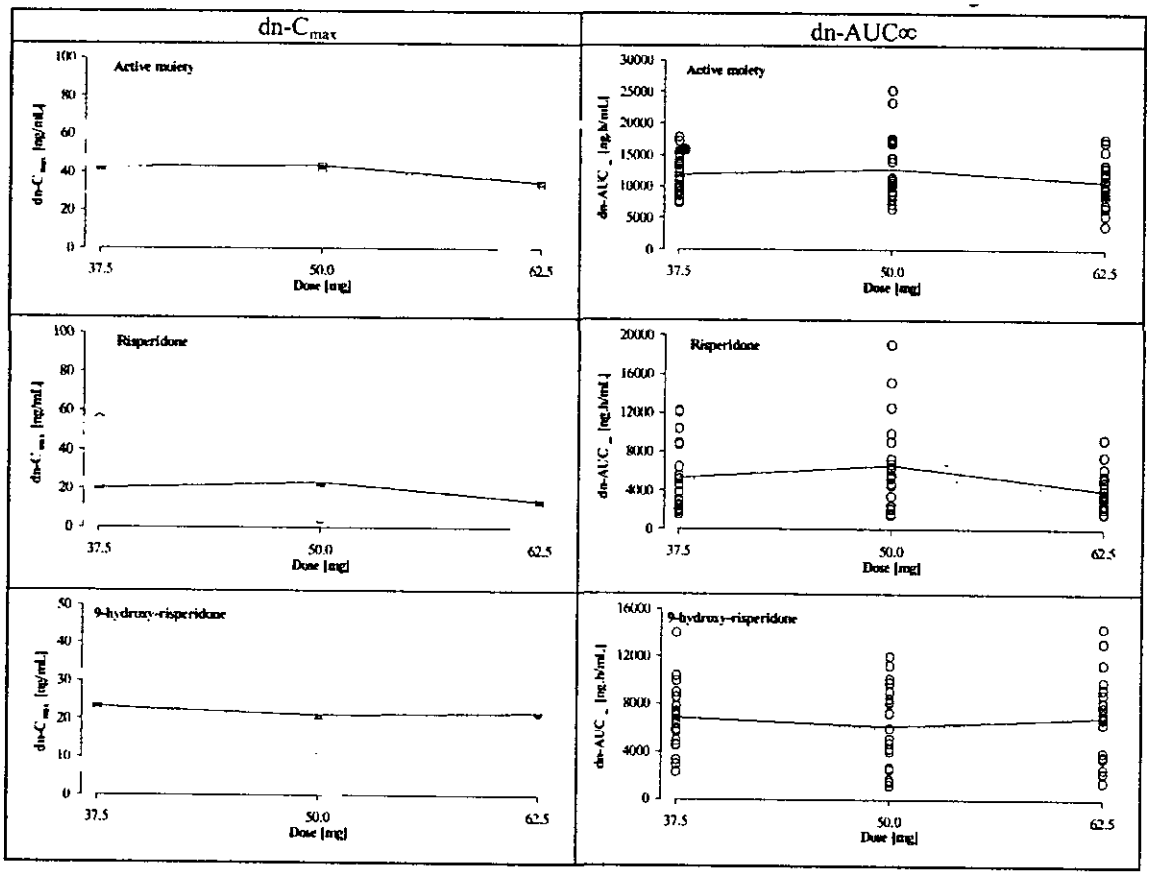


FIGURE 2. Dose proportionality of C_{max} (left panels) and AUC (right panels) vs. dose level, after normalization to a 50-mg dose. Active moiety (top panels), RIS (middle panels), and 9-OH-RIS (lower panels) after a single IM injection of 37.5, 50, and 62.5 mg risperidone (circles = individual values, dashed line = interpolation median values; solid line = interpolation average values). [Study RIS-INT-072]

The sponsor also evaluated the potential influence of body weight (BW) and body mass index (BMI), but no correlations could be determined between BW or BMI and AUC or C_{max}. In fact, similar exposures were observed between patients with low or high BW (range studied: 47 kg - 129 kg) and BMI (range studied: 18-35).

Safety: Overall, 43 (56.6%) subjects reported at least one adverse event (a total of 99 AEs). Adverse events reported in ≥ 3 subjects were headache, insomnia, rhinitis, anxiety, influenza-like symptoms, and psychosis. The overall incidence (i.e., 58.3%, 61.5% and 50.0% with the 37.5, 50, and 62.5 mg dose, respectively) was independent of the dose level. One death (suicide 37 days

post-inj. 50 mg) and 3 serious AEs were reported [1 pat. neoplasm 5 days post-inj. 37.5 mg (benign neck tumor), 1 pat. hospitalized for pneumonia 53 days post-inj. of 50 mg, 1 pat. hospitalized 2 days for anxiety 30 days post-inj. 62.5 mg]. Clinical laboratory values outside the normal reference ranges, but considered clinically insignificant, were reported in 10 patients. There was an increase in HR (max. +16 bpm), and fluctuations in SBP (max –9.2 mmHg) and DBP (max –6 mmHg) after the different treatments. The changes in vital signs were observed on Day 1 (4 h post inj) and on Day 32, the latter coinciding with C_{max}. The sponsor reports that there was a trend of prolonged QTc that was persistent over time in about 10 pat in each dose group (change *vs.* screening between 30-60 ms; central ECG readings at screening & Days 32, 39 and 85). The local tolerability at the injection site was fairly good, 14 patients of the 76 patients reported local reactions (mild induration: n=2; pain: n=7; redness: n=5).

Comments: The C_{max} and AUC increased in a reasonably dose-proportional manner between the 37.5 mg and the 50 mg doses. However, the 62.5 mg and 50 mg doses gave similar estimates for C_{max} and AUC. This trend towards less than dose-proportional increases in the PK was not observed in Study RIS-INT-054, where 25 mg, 50 mg, and 75 mg doses were administered also in a parallel group design. The small dose increments (25%) were lower than the observed coefficient of variation in C_{max} and AUC, which ranged between 30-45% for the different doses. This large inter-individual variability in the data makes it difficult to analyze the dose-proportionality of the studied dose range. However, the parameter estimates for all doses were within the range observed for single injections of the TBM formulation of 25 - 75 mg risperidone. Body weight and BMI had no obvious influence on the pharmacokinetics after the single injections of risperidone.

The TBM depot formulation performed well, with few local injection-site reactions. There was a slight increase in heart rate at peak plasma levels, and a trend towards QTc prolongation in 50% of the patients..

7.3 REPEATED DOSE STUDIES IN SCHIZOPHRENIC PATIENTS

7.3.1 RIS-INT-31 & RIS-SWE-17: A pilot pharmacokinetic dose-proportionality, safety & tolerability study in chronic schizophrenic patients following 5 biweekly IM injections of the depot risperidone preparations containing 25, 50, and 75 mg risperidone in microspheres.

Study RIS-INT-31, which was conducted in Belgium and South Africa, was amended to include additional patients (in Sweden). The sponsor chose to analyze and report the data from the amendment separately in Report RIS-SWE-17. This reviewer chose to combine the two reports, since the same study design was used, although the patients in RIS-SWE-17 received a slightly different formulation, where a smaller particle size of the microspheres than used in the main study. Also, D_2 receptor occupancy (PET) was only determined in RIS-SWE-17 (amendment).

Study Objectives:

- to assess the pharmacokinetic dose-proportionality of 25, 50, and 75 mg risperidone (RIS) depot following repeated intramuscular (IM) injections (Phase I/II formulation)
- to determine D2 receptor occupancy in relation to steady state plasma levels (Amendment: RIS-SWE-17)

The secondary objective was to assess the safety and tolerability of the 25, 50, and 75 mg risperidone doses following multiple IM injections.

Study Design and Methods: This was an open, pilot, multi-center, randomized, parallel-group trial in chronic schizophrenic patients. In the main study (RIS-INT-31), at least 24 patients were to be enrolled (8 patients/dose level, M/F, 18-65 years of age). Five centers in Belgium & South Africa conducted the trial (each center randomized one or more trial blocks of 3 pat./trial block). The protocol was amended (RIS-SWE-17) to include at least 12 additional patients into the trial. Four centers in Sweden conducted the amended portion of the trial (4 pat./trial block). The patients were randomized to receive 5 biweekly IM injections of 25, 50, or 75 mg RIS depot microspheres. The particle size of the RIS microspheres in RIS-SWE-17 was smaller [redacted] than the one used in RIS-INT-31 [redacted]. The Phase I/II depot formulations were used in the trials. The IM injections were given alternately in the right and left gluteal muscles (buttocks).

Other chronic medications (e.g. neuroleptics except oral RIS) were continued during the trial. However, treatment of known hepatic inducers or inhibitors was not allowed (exclusion criterion). The psychopathology of the patients was assessed by the Positive and Negative Syndrome Scale for schizophrenia (PANSS, 30-item rating scale) at study start, after 6 and 17 weeks (or at end-point). Safety monitoring was performed to determine tolerability and safety [blood pressure (BP), heart rate (HR), AEs, injection site reactions measured before and at regular intervals after each injection; weekly from week 10-17]. ECG, physical & neurological examination, and clinical laboratory were measured at screening & at the end of the study.

Blood samples for drug analyses were collected according to the following schedule:
1st IM (Day 1): pre-dose (0), 4, 8, 24, 96 h, and on Day 8 post-dose
2nd IM (Day 15): pre-dose (0), 8, 24 h, and on Day 22 post-dose
3rd IM (Day 29): pre-dose (0), 8, 24 h, and on Day 36 post-dose
4th IM (Day 43): pre-dose (0), 8, 24 h, and on Day 50 post-dose
5th IM (Day 57): pre-dose (0), 4, 8, 24, 72 h, and on Days 62, 64, 67, 69, 71, 78, 85, 92, 99, 106, and 113 post-dose

RIS and active moiety (RIS +9-hydroxy-RIS) were determined by RIA, and the limit of quantitation for both analytes was [redacted] ng/mL. Concentrations of the active metabolite, 9-hydroxy-RIS (9-OH-RIS) were calculated from RIS and active moiety concentrations (Study report RIS-INT-31 was amended to also include 9-OH-RIS). The pharmacokinetic parameters ($C_{pre\text{-}dose}$, C_{min}, C_{max}, t_{max}, AUC_{336h}, $C_{ss,\,average}$, λ_z & %fluctuation) for RIS, 9-OH-RIS, and active moiety were calculated by non-compartmental methods.

In the amended study (SWE-17) D2 receptor occupancy was determined by ^{11}C-raclopride (RAC) PET examinations 14 days after the 5th injection (Day 71), with a pharmacokinetic blood sample drawn immediately prior to the RAC injection.

Results:

Patient disposition and demographics:

RIS-INT-31: A total of 24 patients completed the main study, and 28 patients (20M/8F) received at least one RIS depot injection. Five patients did not complete the trial (1F dropped out due to AEs on Day 5 after 25 mg; 3 pats withdrew consent (1M on Day 1 & 1F on Day 24 after 25 mg; 1M on Day 8 after 50 mg). Ten patients (6M/4F; 31-61 yrs) received 25 mg RIS, 10 patients (9M/1F; 24-64 yrs) received 50 mg RIS, and 8 patients (5M/3F; 30-47 yrs) received 75 mg RIS depot IM injections. In total, 5 poor metabolizers (PMs; 3 in 50 mg dose group; 2 in the 75 mg dose group) were identified by RIS/active moiety AUC ratios of > 0.7. This is an empirical cut-off value (sponsor based the value on previous PK data of RIS) to discriminate between PMs and extensive metabolizers (EMs). All other patients were EMs of RIS.

RIS-SWE-17: A total of 11 patients completed the amended study, and 13 patients (12M/1F) received at least one RIS depot injection. Two patients did not complete the trial (1 pat dropped out due to AEs after the 3rd injection of 25 mg; 1 pat was withdrawn due to non-cooperation (assigned to 75 mg, no information on actual IM injection). Five patients (5M; 25-48 yrs) received 25 mg RIS, 4 patients (3M/1F; 23-44 yrs) received 50 mg RIS, and 4 patients (4M; 34-54 yrs) received 75 mg RIS depot IM injections. All 11 patients were EMs of RIS (based on RIS/active moiety AUC ratios of < 0.7).

The most commonly used concomitant medications in both trials were antipsychotics, anticholinergics, and benzodiazepines (analgesics also commonly used medications in INT-31).

Pharmacokinetics:

RIS-INT-31: After the 1st IM injection of the 25, 50 and 75 mg RIS depot doses, there was an initial burst of drug release similar to that observed after single dose studies of the Phase I/II injections. The initial RIS C_{max} was observed within 8 h post-dose in most patients (median RIS C_{max} 2.36, 5.52 and 4.30 ng/ml after 25, 50 and 75 mg, respectively). The initial RIS C_{max} was lower than the mean RIS C_{max} after 1 mg RIS oral intake (6.5 ng/mL in EMs). The 9-OH-RIS C_{max} was reached within 24 h after the 25 and 75 mg doses (96 h after 50 mg). After the initial drug release (within 24 h after the 1st injection) the plasma levels of RIS and 9-OH-RIS in all three treatment groups were maintained at a minimum level during the following 2 weeks (median: RIS < 4 ng/ml; 9-OH-RIS < 2 ng/ml). After the 2nd and 3rd injections, the plasma levels of active moiety, RIS and 9-OH-RIS started to increase, and essentially reached a steady state from the 4th injection and onwards. After the last injection (5th), steady state was maintained for 4-5 weeks post-dose. The median plasma concentrations of the 50 mg RIS depot injection are depicted in Figure 1.

RIS-SWE-17: The plasma concentration-time curves of RIS, 9-OH-RIS, and active moiety were similar in time course of release patterns to those observed in RIS-INT-31, although somewhat lower for all doses, and are therefore not depicted here.

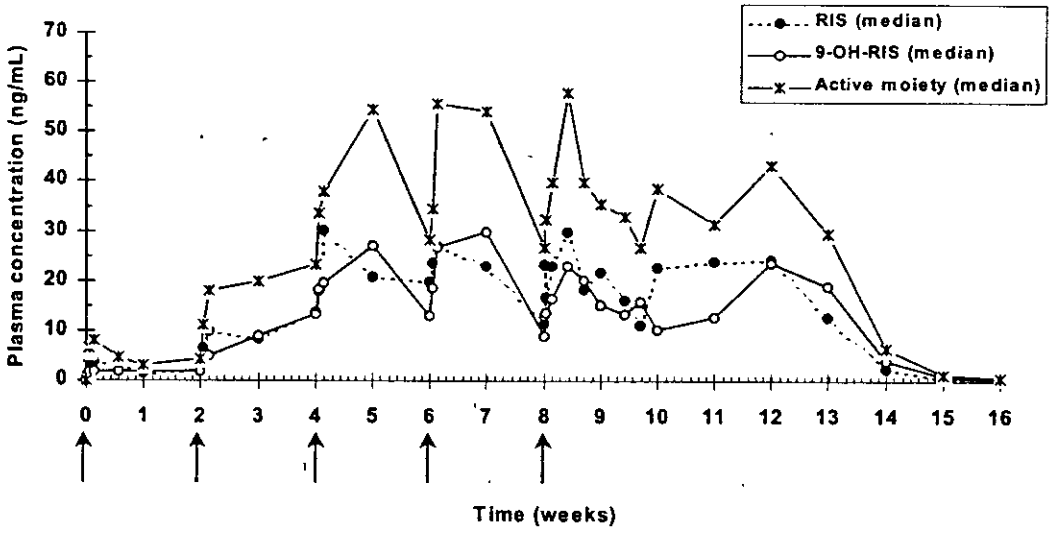


FIGURE 1. Median plasma concentrations (ng/mL) of RIS, 9-OH-RIS and active moiety *vs.* time (weeks) after 5 biweekly IM depot injection of 50 mg RIS (n=9: 3 PM+6 EM). The arrows indicate time of injection. [RIS-INT-31]

The median C_{max}, $C_{pre\text{-}dose}$, and C_{min} (lowest observed concentration over each 2-week dosing interval) of active moiety after each of the 5 biweekly IM injections of 25, 50, and 75 mg RIS are shown in Figure 2.

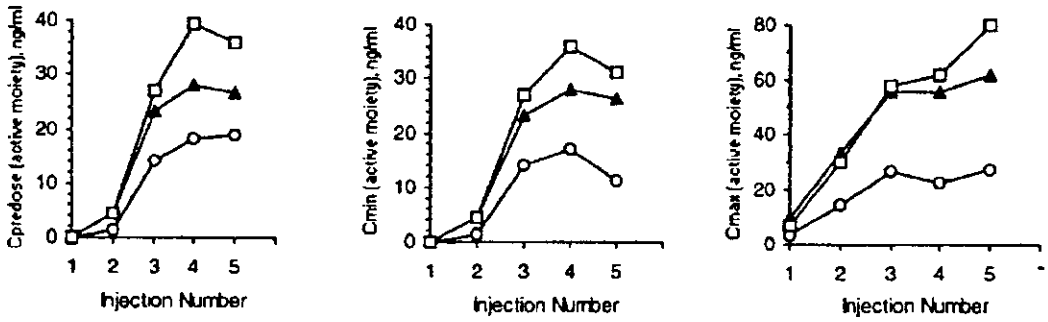


FIGURE 2. Median $C_{pre\text{-}dose}$ (left) C_{min} (lowest observed concentration over each 2-week dosing interval, middle) & C_{max} (right) of the active moiety *vs.* number of biweekly IM depot injections of 25 mg (open circles) 50 mg (solid triangles) and 75 mg (open squares) of RIS. [RIS-INT-31: n=7, 9, & 8/25, 50, 75 mg]

The pharmacokinetic parameter estimates at steady state, during one 2-week dosing interval, after the last (the 5th) biweekly IM injection of 25, 50, and 75 mg RIS are shown in Table 1 (Study RIS-INT-31).

TABLE 1. Summary of steady state PK parameters after the 5th biweekly IM depot injection of 25, 50, or 75 mg RIS [RIS-INT-31].

Pharmacokinetics			
Summary of steady-state pharmacokinetic parameters after the 5th consecutive bi-weekly injection of the risperidone microsheres depot containing 25, 50 or 75 mg risperidone.			
Parameters	Median (Mean ± S.D.)*		
	25 mg bi-weekly (n=7)*	50 mg bi-weekly (n=9)*	75 mg bi-weekly (n=8)*
	Risperidone		
$C_{predose}$, ng/ml	7.36 (7.86 ± 2.88)	11.4 (20.6 ± 19.3)	11.9 (12.7 ± 4.8)
t_{min}, h	287 (278 ± 33)	72.8 (149 ± 162)	252 (188 ± 121)
t_{min}, days	12.0 (11.6 ± 1.4)	3.0 (6.2 ± 6.8)	10.5 (7.8 ± 5.0)
C_{min}, ng/ml	4.04 (4.71 ± 1.98)	11.4 (16.4 ± 13.4)	7.97 (9.47 ± 3.78)
$C_{14\ days}$, ng/ml	6.47 (6.43 ± 2.21)	21.5 (26.5 ± 23.0)	13.2 (13.7 ± 4.5)
t_{max} h	71.9 (89.8 ± 113.5)	***120 (139 ± 111)***	95.9 129 ± 155)
t_{max} days	3.0 (3.7 ± 4.7)	***5.0 (5.8 ± 4.6)***	4.0 (5.4 ± 6.4)
C_{max} ng/ml	14.4 (13.4 ± 4.1)	***33.0 (38.9 ± 24.8)***	19.5 (18.2 ± 6.3)
ratio C_{max}/C_{min}	2.4 (3.1 ± 1.5)	***1.8 (2.8 ± 1.5)***	2.0 (2.0 ± 0.5)
% fluctuation	85.1 (112 ± 55)	***56.2 (88.9 ± 55.4)***	66.9 (65.2 ± 23.4)
AUC_{336h}, ng.h/ml	2732 (2679 ± 670)	7104 (8981 ± 6460)	4650 (4434 ± 1281)
$C_{ss\ average}$, ng/ml	8.14 (7.98 ± 2.00)	21.1 (26.9 ± 19.2)	14.4 (13.4 ± 3.9)
$t_{1/2\ term}$, h	68.0 (80.6 ± 20.5)	111 (105 ± 37)	106 (105 ± 24)
$t_{1/2\ term}$, days	2.8 (3.4 ± 0.9)	4.6 (4.4 ± 1.6)	4.4 (4.4 ± 1.0)
	9-hydroxy-risperidone		
$C_{predose}$ ng/ml	***12.1 (9.66 ± 5.00)***	***9.00 (11.0 ± 6.4)***	***22.6 (27.3 ± 11.2)***
t_{min}, h	***263 (182 ± 171)***	***7.9 (84.7 ± 114.5)***	***168 (181 ± 113)***
t_{min}, days	***11.0 (7.6 ± 7.1)***	***0.3 (3.5 ± 4.8)***	***7.0 (7.5 ± 4.7)***
C_{min} ng/ml	***6.74 (5.70 ± 2.15)***	***7.60 (9.52 ± 6.43)***	***22.0 (23.3 ± 10.8)***
$C_{14\ days}$ ng/ml	***6.74 (7.63 ± 4.06)***	***11.6 (20.8 ± 16.0)***	***35.7 (35.9 ± 10.9)***
t_{max} h	***72.2 (77.7 ± 57.9)***	***216 (195 ± 98)***	***144 (188 ± 147)***
t_{max} days	***3.0 (3.2 ± 2.4)***	***9.0 (8.1 ± 4.1)***	***6.0 (7.8 ± 6.1)***
C_{max} ng/ml	***18.6 (18.3 ± 6.8)***	***29.5 (34.7 ± 22.3)***	***35.7 (46.0 ± 13.7)***
ratio C_{max}/C_{min}	***3.64 (3.32 ± 0.59)***	***3.02 (3.59 ± 1.98)***	***1.97 (2.19 ± 0.75)***
% fluctuation	***114 (110 ± 21)***	***103 (119 ± 53)***	***74.8 (68.6 ± 15.7)***
AUC_{336h} ng.h/ml	***4287 (3955 ± 1470)***	***5450 (6835 ± 3268)***	***9687 (11208 ± 2768)***
$C_{ss\ average}$ ng/ml	***12.8 (11.8 ± 4.4)***	***16.2 (20.6 ± 10.0)***	***28.8 (33.9 ± 8.9)***
$t_{1/2\ term}$ h	***98.5 (103 ± 16)***	***91.8 (111 ± 44)***	***100 (134 ± 116)***
$t_{1/2\ term}$ days	***4.1 (4.3 ± 0.7)***	***3.8 (4.6 ± 1.8)***	***4.2 (5.6 ± 4.8)***
	Active moiety (risperidone + 9-hydroxy-risperidone)		
$C_{predose}$, ng/ml	18.7 (17.5 ± 6.1)	26.7 (31.6 ± 16.2)	35.9 (40.0 ± 11.3)
t_{min}, h	288 (254 ± 114)	0.0 (136 ± 162)	180 (160 ± 142)
t_{min}, days	12.0 (10.6 ± 4.8)	0.0 (5.7 ± 6.7)	7.5 (6.7 ± 5.9)
C_{min}, ng/ml	11.2 (11.1 ± 1.3)	26.4 (28.2 ± 12.9)	31.1 (35.0 ± 9.9)
$C_{14\ days}$, ng/ml	13.0 (14.1 ± 5.0)	43.9 (47.3 ± 30.8)	51.2 (49.6 ± 14.6)
t_{max} h	72.0 (70.9 ± 61.4)	***120 (164 ± 120)***	***84.5 (144 ± 132)***
t_{max} days	3.0 (2.9 ± 2.6)	***5.0 (6.8 ± 5.0)***	***3.5 (6.0 ± 5.5)***
C_{max} ng/ml	27.2 (29.8 ± 6.6)	***57.9 (68.3 ± 29.3)***	***69.6 (62.1 ± 15.9)***
ratio C_{max}/C_{min}	2.5 (2.7 ± 0.6)	***2.2 (2.7 ± 1.4)***	***1.9 (1.8 ± 0.2)***
% fluctuation	86.9 (93.7 ± 20.2)	***74.1 (86.0 ± 47.4)***	***65.9 (57.4 ± 10.3)***
AUC_{336h}, ng.h/ml	6282 (6604 ± 1143)	12823 (15595 ± 5938)	17435 (15642 ± 3243)
ratio AUC_{336h}	0.36 (0.42 ± 0.15)	0.52 (0.54 ± 0.22)	0.28 (0.29 ± 0.07)
$C_{ss\ average}$, ng/ml	18.7 (19.7 ± 3.4)	38.2 (46.8 ± 17.6)	53.2 (47.3 ± 10.5)
$t_{1/2\ term}$, h	86.3 (90.3 ± 18.3)	89.3 (101 ± 38)	102 (121 ± 82)
$t_{1/2\ term}$, days	3.6 (3.8 ± 0.8)	3.7 (4.2 ± 1.6)	4.3 (5.1 ± 3.4)

* Three patients from the 25 mg group and 1 patient from the 50 mg group were drop-outs and were excluded from the mean and median statistics. Two patients from the 75 mg group were excluded as outliers for the mean calculations (they were included in the median statistics).

dumping). No drug related severe adverse events in conjunction with C_{max} were reported for these 2 patients. Both patients were males, one was Belgian (Caucasian, 38 years old), and one was South African (Black, 34 years old). In RIS-SWE-17, this early drug release was not observed in any patient, although 2 subjects who received 75 mg RIS had recurrent higher fluctuations between C_{min} and C_{max} of RIS (RIS C_{max}/C_{min} ratio 14 & 6.5) compared to the other two patients (RIS C_{max}/C_{min} ratio 2.3 & 3.1).

As shown in Figure 3 and Table 1, there was a dose proportional increase in C_{max} and AUC_{336h} between the 25 and 50 mg RIS doses, whereas the corresponding values after the 75 mg dose were only slightly higher than those of the 50 mg dose (RIS-INT-31). The same pattern was observed in study RIS-SWE-17, although only 4 patients / dose level were studied.

Dopamine receptor occupancy (RIS-SWE-17):
Dopamine (D2) receptor occupancy was determined in the putamen by ^{11}C-raclopride (RAC) PET examinations 14 days after the 5th injection (Day 71), with a pharmacokinetic blood sample drawn immediately prior to the RAC injection. The examinations were performed at 2 of the 4 centers, and a total of 8 patients were examined. 7 patients (25 mg n=2; 50 mg n=3; 75 mg n=2) were tested on Day 71, and 1 patient (25 mg RIS) was examined at pseudo-steady state (Day 43, 2 weeks after the 3rd depot inj.). D2 occupancy was calculated using a standard ratio-equilibrium analysis. There was a good correlation between D2 receptor occupancy and plasma levels of active moiety (see main review Section 4.2.1). The individual values are listed in Table 3.

TABLE 3. D2 occupancy (%) and plasma concentrations of active moiety (RIS+9-OH-RIS) in schizophrenic patients (n=7 on Day 71; n=1 on Day 43). Note that a comma, not a period, denotes the decimal of the plasma concentration in the table (e.g. 28,9 = 28.9 ng/mL). [RIS-SWE-17]

Sub. no	CRF ID	Dose depot	Day	D2 occ %	Plasma concentration
				Putamen	Active moiety, ng/ml
1	A3061	50 mg	71	59	
2	A3063	75 mg	71	62	
3	A3062	25 mg	71	25	
7	A3064	75 mg	71	72	
8	A3075	50 mg	71	71	
9	A3066	25 mg	44	48	
11	A3073	25 mg	72	40	
12	A3065	50 mg	71	83	

One patient who received a 50 mg dose had two PET scans, one on Day 71 (2 weeks after the last biweekly depot injection) and one on Day 86 (3 weeks after the last depot injection).
D2 occupancy was 83% and 69 %, respectively. The corresponding plasma concentrations of active moiety in this patient were —— ng/ml (Day 71) and —— ng/ml (Day 86), respectively.

Efficacy:
As a measure of efficacy, PANSS was assessed at selection, week 6, and week 17 (or at the end of the trial). The PANSS (total & subscale) scores remained more or less stable over the investigational period, and some improvement (>20%) was observed in certain individuals. However, no placebo control groups were included in the trials, and patients were allowed to take other oral antipsychotics, therefore, no conclusions can be made regarding the efficacy of the RIS depot in the small number of patients studied.

Safety:
The local tolerability was good, with few, occasional, reports of redness (n=6), swelling (n=3), and indurations (n=2) reported from both trials (in total n=35). However, the investigators reported a higher number of occurrences of mild to moderate pain after the injection (n=16 of a total of 35 patients in both trials).

No consistent changes were observed in the vital signs (both increases and decreases reported in HR, SBP & DBP), ECG or laboratory parameters.

Approximately 60% of the patients in both trials (-31 & -17) reported adverse events (AEs) that were mainly CNS related. In total, 5 serious AEs were reported (RIS-INT-31 n=3; RIS-SWE-17 n=2). The serious AEs were hospitalizations [anxiety: n=3 (25, 50, 75 mg); deliberate overdose: n=1 (75 mg); hemorrhoidectomy: n=1 (25 mg)]. Two patients dropped out from the trials. One patient (RIS-INT-31) dropped out 5 days after the 1st 25-mg injection due to severe agitation, anxiety and restlessness, and the other one (RIS-SWE-17) dropped out after 86 days (6 weeks after the 5th 25-mg injection) due to depression and impotence. All subjects were using concomitant medications throughout the 16-week trials.

Conclusions:
Steady state was reached after approximately 4-6 weeks (3-4 biweekly IM injections) of the depot formulations. The two trials showed dose proportionality between the 25 mg and 50 mg IM depot injections of RIS, however the 75 mg doses yielded only slightly higher median and average PK parameters compared with the IM depot injection of 50 mg.

The calculated PK parameters were lower after the 25, 50 and 75 mg RIS doses in Study RIS-SWE-17 compared to the main study (Table 1). This discrepancy can be due to the large variability in the data in conjunction with the small number of patients in each dose group (n=4) in Study RIS-SWE-17.

An early drug release from the IM depot injection, which may indicate dose dumping, was observed in 2 patients who received the 75 mg dose (RIS-INT-31). This early release pattern was occurring in both patients throughout the trial, after each depot injection, but was not associated with any AEs. Since rather high RIS peak plasma levels were observed (both patients were PMs), AEs at the time of C_{max} would be possible. Also important, lack of efficacy due to subtherapeutic plasma levels could be associated with the low plasma drug levels during most of the dosing interval. Both patients were also taking additional antipsychotic medications, therefore it is unlikely that lack of efficacy of the RIS depot formulations would be observed in the present trial. An early release pattern of this type has not been observed in any of the single dose studies.

7.3.2 RIS-INT-32: Steady-state bioavailability in chronic schizophrenic patients comparing once daily oral administration of risperidone with IM injections of a risperidone depot microsphere formulation given every two weeks.

Study Objectives:

- To compare the steady-state bioavailability of risperidone (RIS) and the active moiety (RIS + 9-hydroxy-RIS) after oral treatment (2, 4, & 6 mg QD) to intramuscular (IM) depot injections (5 biweekly inj; 25, 50, & 75 mg RIS; Phase I/II formulation).

The secondary objective was to evaluate different oral supplement regimens during the initial 4 weeks of the RIS IM depot injections, and to assess the safety and tolerability of the RIS dosing regimens.

Study Design and Methods: This was an open, multi-center, parallel-group trial in chronic schizophrenic patients. At least 90 patients were to be enrolled (M/F, 18-65 years of age). A total of 15 investigators in Belgium, Germany, the Netherlands, Sweden and Denmark conducted the 15-week trial.

Prior to study entry, the patients had to be on 2, 4, or 6 mg oral RIS QD for at least 4 weeks. The patients were enrolled, and each oral dosing regimen of RIS was continued for 7 days, and plasma samples for pharmacokinetic (PK) evaluation collected during the last dosing interval (Day 7). Thereafter, IM depot injections were given biweekly for 10 weeks. Patients who had been treated with oral risperidone 2 mg, 4 mg, or 6 mg QD, received 5 biweekly RIS depot injections of 25 mg, 50 mg or 75 mg, respectively. The same dose of oral RIS was continued during Week 1-3 (between the 1st & 2nd IM injection) and half the previous oral dose (1, 2 or 3 mg RIS) was given during Week 4-5 (between the 2nd and 3rd IM injection). No oral RIS doses were given on the days of IM injections. The IM injections were given in the gluteal muscles (alternate sides). The Phase I/II depot formulations were used in the trial.

Other chronic medications (e.g. neuroleptics except oral RIS or newly registered antipsychotics) were continued during the trial. However, treatment of known hepatic inducers or inhibitors was not allowed (exclusion criterion). The psychopathology of the patients was assessed by the Positive and Negative Syndrome Scale for schizophrenia (PANSS, 30-item rating scale) at study start, after 1, 3, 5, 9, and 15 weeks. Safety was assessed weekly to determine tolerability and safety [blood pressure (BP), heart rate (HR), AEs, injection site reactions]. ECG, physical examination, and clinical laboratory were measured at screening & at the end of the study.

Blood samples for drug analyses were collected according to the following schedule:
Oral dose: pre-dose (days 1 & 7), 1, 2, 3, 4, 6, 8, 12 and 24 h post-dose Day 7
1st IM (Day 8): pre-dose (0), and 12 h post-injection, and pre-dose (oral) Day 15
2nd IM (Day 22): pre-dose (0), and pre-dose (oral) Day 29
3rd IM (Day 36): pre-dose (0)
4th IM (Day 50): pre-dose (0)
5th IM (Day 64): pre-dose (0), every 24 h for 14 days (Days 65-78) and weekly on Days, 85, 92, 99, and 106 (Week 13-16)

RIS and active moiety (RIS +9-hydroxy-RIS) were determined by RIA, and the limit of quantitation for RIS was [redacted] ng/mL and the active moiety was [redacted] ng/mL. Concentrations of the active metabolite, 9-hydroxy-RIS (9-OH-RIS) were calculated from RIS and active moiety concentrations (Study report RIS-INT-32 was amended to also include 9-OH-RIS). The pharmacokinetic (PK) parameters for RIS, 9-OH-RIS, and active moiety were calculated by non-compartmental methods. The calculated PK parameters were: $C_{pre\text{-}dose}$ (measured on Days 7 & 64), C_{min} (lowest concentration during the last dosing interval post-dose given on Days 7 &64), t_{min} (time to reach C_{min}), C_{max}, t_{max}, AUC_{24h}, AUC_{336h}, C_{av} (average concentration at steady state calculated as AUC_{24h}/24 h or $AUC_{336\ h}$/336 h) & %fluctuation (100 x C_{max}-C_{min}/C_{av}).

Results:

Patient disposition and demographics:

A total of 78 patients completed the trial (86 patients were enrolled, and 82 patients received at least one RIS depot injection). The majority of patients were Caucasian (94%).

The table below shows the patient disposition between treatment groups, and the number of drop-outs for each treatment:

Baseline characteristics - subject disposition	Group 1 (2 mg RIS p.o. - 25 mg depot IM)	Group 2 (4 mg RIS p.o. - 50 mg depot IM)	Group 3 (6 mg RIS p.o. - 75 mg depot IM)
Number of subjects randomized (M/F)	25 (15/10)	32 (20/12)	29 (21/8)
Age: median (min-max), yrs	40.0 (17 – 56)	41.0 (21 – 62)	39.0 (22 – 60)
Drop-outs - reason			
– adverse event	1	1	0
– subject lost to follow-up	1	0	0
– subject withdrew consent	2	0	3

The 2 patients who dropped out due to adverse events experienced anxiety (on Day 15, 25 mg IM inj, F, 39 years old) and fatigue (on Day 6, 4 mg oral RIS QD, M, 33 years old).

In total, 66% of the patients used concomitant medications. The most commonly used concomitant medications in the study were antipsychotics (about 40% of the patients), anti-Parkinson drugs (12% on 25 mg IM inj, 31% on 50 mg IM inj, 55% on 75 mg inj), and benzodiazepines (about 50% of the patients).

Pharmacokinetics:
During the oral treatment of RIS (2, 4 and 6 mg QD) and the biweekly IM injections (25, 50 and 75 mg) the plasma levels of RIS, 9-OH-RIS and the active moiety remained at steady state in all patients. The median plasma concentration-time profiles of the active moiety after the 2mg PO/25 mg IM, 4 mg PO/50 mg IM and 6 mg PO/75 mg RIS treatments are depicted in Figure 1. The median plasma concentration-time profiles of RIS and 9-OH-RIS were similar to that of the active moiety.

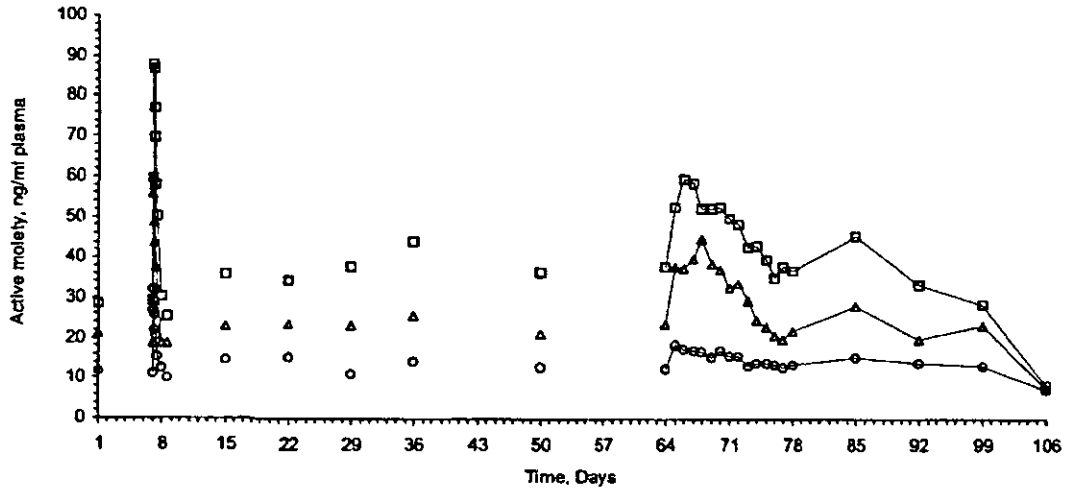


FIGURE 1. Median plasma concentration-time profiles of the active moiety after oral RIS (Day 8) and 5 biweekly IM RIS injections. Circles: 2mg PO/25 mg IM (n=21); Triangles: 4 mg PO/50 mg IM (n=31); Squares: 6 mg PO/75 mg RIS (n=25) [RIS-INT-32]

As expected, the oral once-daily administration of RIS gave higher peak concentrations (C_{max}) and larger fluctuations over the dosing interval than the IM depot injections. The C_{max} and C_{min} (lowest plasma level over the dosing interval) values and the % fluctuation are given in Table 1.

TABLE 1. Median, and mean ± SD steady-state PK parameters of the active moiety, RIS & 9-OH-RIS after oral RIS administration (2, 4 & 6 mg QD, Day 7, τ=24 h) and IM depot injections (25 50 or 75 mg biweekly, Week 8-10, τ=336 h). [RIS-INT-32]

Active moiety								
	Risperidone p.o.				Risperidone depot			
Parameters	C_{min} ng/ml	C_{max} ng/ml	C_{max}/C_{min} ratio	% fluctuation	C_{min} ng/ml	C_{max} ng/ml	C_{max}/C_{min} ratio	% fluctuation
2 mg p.o. - 25 mg depot (n = 21)	11.1 11.4 ± 3.6	32.8 32.9 ± 9.2	2.71 3.01 ± 0.79	118 118 ± 33	9.85 11.3 ± 4.5	19.2 22.7 ± 9.2	1.85 2.38 ± 1.80	56.3 69.3 ± 43.6
4 mg p.o. - 50 mg depot (n = 31)	18.1 22.3 ± 12.1	67.2 74.1 ± 31.5	3.48 3.51 ± 0.72	129 137 ± 32	17.9 24.3 ± 16.0	45.5 57.3 ± 32.3	2.08 2.87 ± 2.31	70.7 83.3 ± 45.5
6 mg p.o. - 75 mg depot (n = 25)	29.1 32.6 ± 15.7	101 107 ± 49	3.38 3.51 ± 1.24	121 130 ± 46	30.1 32.6 ± 16.5	77.2 80.6 ± 40.0	2.00 3.96 ± 6.54	66.1 87.8 ± 54.2
Risperidone								
	Risperidone p.o.				Risperidone depot			
Parameters	C_{min} ng/ml	C_{max} ng/ml	C_{max}/C_{min} ratio	% fluctuation	C_{min} ng/ml	C_{max} ng/ml	C_{max}/C_{min} ratio	% fluctuation
2 mg p.o. - 25 mg depot (n = 21)	0.39 2.24 ± 3.90	13.5 16.8 ± 10.0	24.5 28.4 ± 21.9	335 342 ± 140	2.45 3.44 ± 3.58	5.71 8.03 ± 6.31	1.85 3.29 ± 2.76	66.3 92.1 ± 63.7
4 mg p.o. - 50 mg depot (n = 31)	0.85 4.87 ± 10.5	29.1 39.8 ± 30.2	33.6 35.1 ± 21.5	384 398 ± 169	4.29 9.57 ± 14.9	12.3 21.7 ± 23.7	2.33 3.32 ± 2.41	83.5 99.8 ± 53.9
6 mg p.o. - 75 mg depot (n = 25)	2.25 7.03 ± 8.86	54.4 58.6 ± 35.3	18.5 28.0 ± 32.8	320 339 ± 188	10.3 13.5 ± 10.8	23.8 35.6 ± 28.8	1.95 4.22 ± 8.30	66.8 92.3 ± 67.2
9-hydroxy-risperidone								
	Risperidone p.o.				***Risperidone depot***			
Parameters	***C_{min} ng/ml***	***C_{max} ng/ml***	***C_{max}/C_{min} ratio***	***% fluctuation***	***C_{min} ng/ml***	***C_{max} ng/ml***	***C_{max}/C_{min} ratio***	***% fluctuation***
2 mg p.o. - 25 mg depot (n = 21)	***8.90 8.67 ± 3.38***	***18.0 18.8 ± 6.1***	***2.05 2.35 ± 0.76***	***71.6 84.7 ± 35.1***	***6.81 6.83 ± 3.20***	***14.4 16.2 ± 7.1***	***2.00 2.63 ± 1.78***	***66.9 84.1 ± 43.2***
4 mg p.o. - 50 mg depot (n = 31)	***14.3 14.8 ± 7.5***	***38.7 40.1 ± 13.6***	***2.53 2.80 ± 0.95***	***85.3 101 ± 33***	***12.4 13.5 ± 9.1***	***31.9 39.0 ± 21.4***	***2.29 3.14 ± 2.68***	***78.9 101 ± 61***
6 mg p.o. - 75 mg depot (n = 25)	***18.8 19.1 ± 13.8***	***54.9 58.1 ± 23.4***	***2.31 2.59 ± 0.78***	***94.5 111 ± 57***	***16.9 18.1 ± 12.4***	***47.3 50.1 ± 22.8***	***2.31 4.47 ± 6.19***	***75.3 106 ± 62***

The steady state values for AUC, $C_{pre\text{-}dose}$ (trough sample) and average plasma concentration over the dosing interval (C_{av}) are given in Table 2.

TABLE 2. Median, and mean ± SD steady-state PK parameters of the active moiety, RIS & 9-OH-RIS after oral RIS administration (2, 4 & 6 mg QD, Day 7, τ=24 h) and IM depot injections (25 50 or 75 mg biweekly, Week 8-10, τ=336 h).
Note: oral C_{av} = AUCτ/24 h; IM C_{av} = AUCτ/336 [RIS-INT-32]

ACTIVE MOIETY

	RIS oral doses				RIS IM injections		
Parameters	**AUC_{24h}** (ng.h/mL)	**AUC_{24h} x14** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)	**AUC_{336h}** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)
2 mg p.o.-	436	6104	18.2	11.2	4829	14.4	12.5
25 mg IM	443 ± 110	6199 ±	18.4 ±	11.9 ±	5531 ±	16.5 ±	14.4±
(n=21)		1540	4.6	4.0	1678	5.0	5.6
4 mg p.o.-	831	11634	34.6	18.7	11171	33.2	23.7
50 mg IM	944 ± 433	13217 ±	39.3 ±	23.1 ±	13210 ±	39.3 ±	32.3 ±
(n=31)		6059	18.0	12.5	7132	21.2	24.8
6 mg p.o.-	1369	19166	57.0	29.4	17054	50.8	38.0
75 mg IM	1399 ±	19583 ±	58.3 ±	33.7 ±	18144 ±	54.0 ±	40.7±
(n=25)	557	7796	23.2	16.7	6561	19.5	23.6

RISPERIDONE

	RIS oral doses				RIS IM injections		
Parameters	**AUC_{24h}** (ng.h/mL)	**AUC_{24h} x14** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)	**AUC_{336h}** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)
2 mg p.o.-	80.9	1133	3.37	0.45	1336	3.98	3.07
25 mg IM	138 ± 131	1929 ±	5.7 ± 5.5	2.3 ± 3.9	1787 ±	5.3 ± 4.2	4.3± 3.9
(n=21)		1840			1424		
4 mg p.o.-	178	2492	7.4	1.06	2621	7.8	4.9
50 mg IM	346 ± 457	4844 ±	14.4 ±	5.1 ±	4967 ±	14.8 ±	13.5 ±
(n=31)		6401	19.0	10.8	6433	19.1	21.2
6 mg p.o.-	350	4900	14.6	3.6	4918	14.6	12.4
75 mg IM	507 ± 417	7095 ±	21.1 ±	7.8 ± 9.2	7365 ±	21.9 ±	16.3±
(n=25)		5836	17.4		4700	14.0	11.6

9-HYDROXY-RISPERIDONE

	RIS oral doses				RIS IM injections		
Parameters	**AUC_{24h}** (ng.h/mL)	**AUC_{24h} x14** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)	**AUC_{336h}** (ng.h/mL)	**C_{av}** (ng/mL)	**$C_{predose}$** (ng/mL)
2 mg p.o.-	315	4410	13.1	9.5	3444	10.3	8.6
25 mg IM	305 ± 104	4267 ±	12.7 ±	9.6 ± 3.3	3751 ±	11.2 ±	10.0 ±
(n=21)		1450	4.3		1331	4.0	4.8
4 mg p.o.-	581	8134	24.2	17.1	7372	22.0	15.4
50 mg IM	626 ± 216	8760 ±	26.1 ±	18.0 ±	8448 ±	25.1 ±	18.8 ±
(n=31)		3027	9.0	6.7	4069	12.1	11.3
6 mg p.o.-	867	12138	36.1	22.4	10002	29.8	21.7
75 mg IM	903 ± 372	12648 ±	37.6 ±	25.9 ±	10786 ±	32.1 ±	25.2 ±
(n=25)		5209	15.5	11.8	4783	14.2	19.7

The sponsor also evaluated the dose proportionality of the oral and IM drug administrations, by linear regression. All PK parameters (AUC_{τ}, C_{av}, C_{min}, C_{max}, & $C_{predose}$) increased in a proportional manner over the studied dose range, and each oral dose matched the corresponding IM dose with regard to AUC and average plasma levels over the dosing intervals. As would be

expected, the IM depot injections gave 25-30% lower fluctuations between peak and through plasma levels (see Table 1) compared to the oral doses of RIS. It should be noted that no samples were collected during the initial 24-h period post-injection, when an early peak has been observed with this Phase I/II formulation). The mean trough levels were not different between the IM and oral treatments ($p>0.05$, ANOVA).

Four patients (25 mg: n=1; 50 mg: n=2; 75 mg n=1) displayed high fluctuations in active moiety plasma levels after the 5th IM injection. Their peak-to-trough ratios of the active moiety were larger than those observed in all patients following the oral treatment (Day 7, *i.e.*, a ratio $C_{max}/C_{min} > 7$). C_{max} of the active moiety after the IM injection in these 4 patients with high fluctuations were 42 to 116 % higher than after oral treatment (but all C_{max} values were within the observed range of the other patients within the specific treatment group). The peak plasma concentrations occurred 2-4 days post-injection. All 4 patients seemed to be extensive metabolizers with a RIS/active moiety AUC ratio < 0.5. No indication of dose dumping was observed in 2 of the patients, however the other 2 had about 50% lower trough plasma concentrations (active moiety) after the IM injections (50 & 75 mg) without oral RIS substitution therapy, which may indicate early release from the depot formulations. The $C_{predose}$ after IM injections without the oral RIS regimens were about 10 mg/mL in both patients.

After the 5th (last) IM injection, the steady-state plasma levels were maintained for 4-5 weeks.

Based on the statistical tests performed on the active moiety, AUC and C_{av} were comparable (confidence intervals were within acceptance criteria of 80-125%) between the biweekly depot injections (25, 50 and 75 mg) and the corresponding QD oral regimens (2, 4 and 6 mg). See the main review, Section 4.5.2, for results. The sponsor also performed the same statistical tests on RIS and 9-OH-RIS. The mean % ratio of AUC and C_{av} (depot vs. oral treatment, log-transformed data) ranged between 107 and 121 % for RIS and 84 and 94 % for 9-OH-RIS.

The $C_{predose}$ and intermittent levels (1 week post-injection) during the treatment periods after the 1st and 2nd RIS IM injections were comparable to the steady-state trough levels observed at other time-points. This indicates that the oral supplementation regimen was sufficient during the first weeks of IM depot injection treatment (see Figure 1).

Efficacy:
As a measure of efficacy, PANSS was assessed. The PANSS (total & subscale) scores remained more or less stable over the investigational period, and some improvement (>20% improvement over baseline) was observed in the 25 mg IM injection group, but not in the 50 or 75 mg RIS IM injection groups. However, no placebo control groups were included in the trials, and patients were allowed to take other oral antipsychotics, therefore, no conclusions can be made regarding the efficacy of the RIS IM injections.

Safety:
The local tolerability was good, with few, reports of redness, swelling, and indurations throughout the trial. A few patients reported mild to moderate discomfort with the injection.

No consistent changes were observed in the vital signs (both increases and decreases reported in HR, SBP & DBP), ECG or laboratory parameters.

A total of 67 of the 86 patients (78 %) reported 1 or more adverse events (AE), there was no trend in higher number of AE reports with higher doses. The AEs were mainly CNS related, except a high number of influenza-like symptoms and tachycardia. In total, 4 serious AEs were reported (4 mg PO/50 mg IM n=1; 6 mg PO/75 mg IM n=3). The serious AEs were anxiety (25 mg IM,

dropped out), fatigue in combination with anxiety (6mg PO, dropped out), hospitalizations after the 75 mg IM injections (anxiety, injury, depression: n=1; aggravated psychotic condition: n=1). Concomitant medications were taken by 48-74% of the patients throughout the 15-week trial.

Conclusions:
The oral substitution therapy (2 weeks with the full oral dose after the 1st IM injection, and half the oral dose during the following 2 weeks after the 2nd IM injection) seems adequate to maintain the steady state drug levels throughout the first month of IM therapy. This would cover the 2-3 weeks lag phase after the first IM injection until drug absorption starts, and until steady state levels have been reached.

There was a dose proportional increase in drug exposure after the IM injections over the 25-75 mg RIS dose range. The higher variability (see Table 2) in the PK parameters of RIS is expected, since about 7 patients could be classified as poor metabolizers (a RIS/active moiety AUC ratio >0.7), and another 7 patients had an RIS/active moiety AUC ratio between 0.5 and 0.7.

The fluctuations in steady state plasma drug levels over the last dosing interval were lower after the IM depot injections compared to the oral once-daily tablet regimens. However 4 of the 86 patients (4.6%) exhibited higher fluctuations between trough and peak levels after the IM injections as compared to the oral therapy. The higher peak drug concentrations after the IM injections in these patients were within the range observed after the corresponding oral treatments. No indication of dose dumping was observed in 2 of the patients, however the other 2 had about 50% lower trough plasma concentrations (active moiety) after the IM injections (50 & 75 mg) without oral RIS substitution therapy, which may indicate early drug release from the depot formulations. The $C_{predose}$ after IM injections without the oral RIS regimens were about 10 mg/mL in both patients.

AUC and C_{av} (CI of ratios within 80-125%) of the active moiety were similar between the biweekly IM depot treatment of 25, 50, and 75 mg RIS and the once-daily oral treatment of 2, 4, and 6 mg RIS, respectively.

7.3.3 RIS-GER-9: A study on the steady state pharmacokinetics and safety of lithium in adult psychotic patients taking lithium in combination with risperidone or with other antipsychotic agents. Part I: Pharmacokinetics

Study Objectives:

- To compare the steady-state pharmacokinetics (PK) and safety of lithium in adult psychotic patients receiving an oral combination therapy of lithium and other antipsychotic agents to that of oral lithium + risperidone (RIS) combination therapy

Study Design and Methods: This was an open, multi-center, two-sequential treatment pilot trial in patients diagnosed with bipolar disorder, schizophrenia or schizoaffective disorder. Thirteen patients were enrolled, and all patients completed the trial (4M/9F, 22-62 years of age). A total of 5 investigators in Germany and Sweden conducted the 9-day trial.

Prior to study entry, the patients had stabilized on individual dosing regimens of lithium BID (8 AM/8 PM dose intake) for 5 days. The BID lithium regimen was maintained throughout the trial. Chronic antipsychotic medications (and other chronic medications e.g. benzodiazepines and antidyskinetics) were administered concurrently. The pre-trial antipsychotic agents were administered up to study Day 2, and subsequently replaced by RIS from Day 3 until the end of the trial (Day 3: 1 mg BID, Day 4: 2 mg BID, Days 5-9: 3 mg BID). Blood samples for plasma analysis of lithium were collected during 0-12 h (one dosing interval) on Days 2 and 9, and trough concentrations were collected each day before dose intake. RIS and active moiety (RIS + 9-OH RIS) were also collected during the 12-h period on Day 9.

Plasma concentrations of lithium were determined by a ——— method at the local laboratories (linear in the concentration ranges — nmol/L deviation of precision——— nmol/L· ——— nmol/L deviation of precision —— nmol/L). Plasma concentrations of RIS and active moiety (RIS +9-hydroxy-RIS) were determined by RIA, and the limit of quantitation for RIS was— ng/mL and the active moiety was — ng/mL. The pharmacokinetic (PK) parameters for the analytes were calculated by non-compartmental methods. The calculated PK parameters were C_{min}, C_{max}, t_{max}, and AUC_{12h}.

Results:

A standardized, validated analytical method was used for the lithium plasma analysis. The sponsor analyzed the RIS and active moiety in-house, by use of validated RIA methods.

Following the oral RIS administration of 3 mg BID (6 mg/day), C_{max} of RIS was 23 ± 9.4 ng/mL (median peak: 26.6 ng/mL), 9-OH-RIS was 60.0 ± 22 ng/mL (median peak: 57.8 ng/mL), and C_{max} of the active moiety was 98.7 ± 40.7 ng/mL (median peak: 88.7 ng/mL). These values are in accordance with those observed in other studies (e.g. RIS-INT-32).

The average morning dose (mean ± SD) of lithium was 11.9 ± 4 mmol (range 6-18 mmol) and the total daily lithium dose was 26 ± 8.6 mmol/day (range 12-36 mmol) in the 13 patients (all patients completed the trial). The patients were treated with depot formulations of lithium carbonate (daily individual doses in the range of 800-1200 mg/day) or lithium citrate (———, used in Europe, daily individual doses in the range of 1120-3360 mg/day)

There were no statistically significant differences in the PK parameters after lithium combination therapy with other antipsychotic drugs and lithium combination therapy with risperidone. The 90% confidence intervals for C_{max} and AUC were within the acceptance criteria of 80-125%, as shown in Table 1.

TABLE 1. Pharmacokinetic parameters (upper panel) and 90% confidence intervals (CI's, lower panel) of lithium in combination with other antipsychotics (Day 2) and RIS (Day 9). The 90% CI's are based on a lithium dose normalized to 12 mmol.

Lithium parameters	Mean (± S.D.)		Wilcoxon's signed rank test
	Lithium + other antipsychotics (Treatment A) (day 2)	Lithium + risperidone (Treatment B) (day 9)	p-values (n=13)
Not dose-normalised			
t_{max}, h	2.37 ± 0.98	3.05 ± 0.94	0.15
mean trough, nmol /l	0.57 ± 0.07	0.58 ± 0.12	1.00
C_{max}, nmol/l	0.71 ± 0.12	0.80 ± 0.16	0.11
AUC_{12h}, nmol.h/l	7.05 ± 1.50	7.80 ± 1.86	0.17
Dose normalised*			
mean trough, nmol /l	0.64 ± 0.25	0.67 ± 0.34	0.85
C_{max}, nmol/l	0.79 ± 0.31	0.90 ± 0.38	0.17
AUC_{12h}, nmol.h/l	7.91 ± 3.48	8.93 ± 4.75	0.11

Lithium parameters	Least-squares means				
	Lithium + other antipsychotics (Treatment A) (day 2)	Lithium + risperidone (Treatment B) (day 9)	MSE (ANOVA) (n=9)	Relative bioavailability B/A %	90% classical confidence interval
Dose normalised*					
Original scale					
C_{max}, nmol/l	0.85	0.89	0.0104	104	93-114
AUC_{12h}, nmol.h/l	8.49	9.10	2.57	107	91-124
Log-transformed					
C_{max}, nmol/l	0.79	0.80	0.005	101	94-110
AUC_{12h}, nmol.h/l	7.75	7.99	1.08	103	92-116

*dose normalised to 12 mmole of lithium.

Four of the 13 patients (30%) had modest increases in lithium AUC_{12h} (30-40%) with the RIS combination therapy compared with the reference antipsychotic drug combination therapy.

In conclusion, there were no statistically significant differences in the PK parameters after lithium combination therapy with other antipsychotic drug or combination therapy with risperidone. The 90% confidence intervals for C_{max} and AUC were within the acceptance criteria of 80-125%, therefore the combination of lithium and risperidone does not seem to warrant special precautions.

7.3.4 RIS-CAN-27: Observational, open, parallel-group trial to document the steady state pharmacokinetics and safety of valproate in combination with risperidone or placebo in 24 adult bipolar patients

Study Objectives:

- To compare the steady-state pharmacokinetics (PK) and safety of valproate in adult psychotic patients receiving repeated oral risperidone (RIS) doses as an add-on therapy to that of placebo as add-on therapy

Study Design and Methods: This was an open, multi-center, parallel-group, observational trial in patients diagnosed with bipolar disorder. A total of 22 patients completed the trial (valproate + placebo: 7M/4F, 24-59 years of age; valproate + RIS: 5M/6F, 21-52 years of age). A total of 3 investigators in Canada conducted the 4-week trial.

Prior to study entry, the patients had stabilized on individual dosing regimens of valproate of 1000 mg/day (TID) for at least 3 days. The valproate dosing regimen was maintained throughout the trial. All 22 patients received valproate monotherapy on Days 1-14. Thereafter, 11 patients were randomized to valproate + placebo add-on, and 11 patients were randomized to valproate + RIS add-on therapy (titrated Day 15-16), that was kept constant (4 mg QD) on Days 17-28. Blood samples for plasma analysis of valproate were collected during 24 h on Days 14 and 28, and trough concentrations (before AM dose) were collected 2 days before the 24-h sampling period. Plasma samples for RIS and 9-OH-RIS analyses were collected on Day 28.

Plasma concentrations of valproate were determined by a validated GC-MS method (lower limit of quantitation—μg/mL). Plasma concentrations of RIS and 9-OH-RIS were determined by a validated LC-MS/MS method, where the lower limits of quantitation of RIS and 9-OH-RIS were — ng/mL. The pharmacokinetic (PK) parameters for the analytes were calculated by non-compartmental methods. The calculated PK parameters were $C_{pre\text{-}dose}$, C_{av}, (mean concentration over the collection interval at steady state: AUC_{24h}/24 h) C_{max}, t_{max}, and AUC_{24h} and fluctuation index (%,C_{max}- $C_{pre\text{-}dose}$x100/ C_{av})

Results:
All bioanalytical methods were validated, and are deemed acceptable.

Following the oral RIS administration of 4 mg QD, C_{max} of RIS was 41.4 ± 16.5 ng/mL (median peak: 37.7 ng/mL), 9-OH-RIS was 26.2 ± 9.7 ng/mL (median peak: 23.4 ng/mL), and C_{max} of the active moiety was 66.0 ± 21.5 ng/mL (median peak: 62.0 ng/mL). These values are in accordance with those observed in other studies (e.g. RIS-INT-32).

The PK parameters of valproate after monotherapy or add-on therapy with risperidone are depicted in Table 1. The 90% confidence intervals for $C_{pre\text{-}dose}$, C_{av}, and AUC_{24h} were within the acceptance criteria of 80-125%, but valproate C_{max} was increased by 20% during RIS combination therapy, as shown in Table 1.

TABLE 1. Pharmacokinetic parameters (upper panel) and 90% confidence intervals (CI's, lower panel) of valproate after monotherapy or in combination with 4 mg QD RIS.

Day 14 Valproate monotherapy	Placebo treatment group (N=11)	Risperidone treatment group (N=9)
$C_{predose}$, µg/ml	72.2 ± 17.1	61.9 ± 16.5
t_{max}, h	2.0 ± 3.6	3.7 ± 4.0
C_{max}, µg/ml	73.6 ± 20.2	65.5 ± 19.2
AUC_{24h}, µg.h/ml	1172 ± 284	1111 ± 281
$C_{ss,av}$, µg/ml	48.9 ± 11.8	46.3 ± 11.7
Day 28 Valproate+risperidone/placebo	Placebo treatment group (N=11)	Risperidone treatment group (N=10)
$C_{predose}$, µg/ml	67.8 ± 15.5	59.3 ± 10.3
t_{max}, h	1.3 ± 1.8	2.0 ± 1.5
C_{max}, µg/ml	70.9 ± 14.8	72.4 ± 16.3
AUC_{24h}, µg.h/ml	1157 ± 268	1019 ± 248
$C_{ss,av}$, µg/ml	48.2 ± 11.2	42.5 ± 10.4

Parameter	Ratio (risperidone *versus* placebo treatment), %	90% confidence intervals
$C_{predose}$	103.5	87.6 – 122.4
C_{max}	119.9	97.1 – 148.0
AUC_{24h}	95.6	84.0 – 108.9
$C_{ss,av}$	95.7	84.0 – 108.9

More subjects reported AEs with RIS add-on therapy compared to placebo. The most frequently reported AEs in the placebo group were headache, nausea and fatigue (n=2 each). The most frequently reported AEs in the risperidone group were headache (n=5), somnolence (n=4) and dizziness and insomnia (n=3 each). Two subjects had 3 severe AEs (asthenia on 2 mg RIS, & fatigue and somnolence on 4 mg RIS).

In conclusion, 90% confidence intervals for valproate $C_{pre\text{-}dose}$, C_{av}, and AUC_{24h} were within the acceptance criteria of 80-125%, but valproate C_{max} was increased by approximately 20% during RIS combination therapy. This observation should be described in the label, since the valproate and risperidone doses used in the study are below the maximum recommended doses of both drugs.

7.4 Pharmaceutical formulations

7.4.1 The to-be-marketed formulation

The depot IM injection will be available as a kit containing two components. The kit will include a vial of risperidone extended release (ER) microspheres for injection and a diluent in a pre-filled syringe.

The components used to manufacture the to-be-marketed (TBM) risperidone ER microspheres, the quantitative composition of the microspheres, and each component's function are shown in Table 1.

TABLE 1. Components used in the manufacturing of the risperidone ER microspheres, and the quantitative composition of the TBM risperidone ER microspheres (F109)

Component	Per gram of microsphere	Function in Formulation
Risperidone (drug substance)	[redacted]	active ingredient
Polymer: 75:25	[redacted]	
*	[redacted]	

The primary excipient of the risperidone microspheres is the polylactide-co-glycolide (PLG) polymer, and the other components are only used as processing aids. The chosen polymer, 7525 JN1 (PLG) is a high molecular weight polymer (MW 130-155 kD).

The components used to manufacture the diluent and the quantitative composition of the TBM diluent (F101) are shown in Table 2. The diluent has a neutral pH of 7 ± 0.3.

TABLE 2. Components, their function, and the quantitative composition of the TBM diluent.

Ingredient	Purpose	F101
Carboxymethylcellulose sodium 40 mPa.s	[redacted]	
Polysorbate 20		
Disodium hydrogen phosphate dihydrate		
Citric Acid anhydrous		
Sodium Chloride		
Sodium Hydroxide		
Water for Injection		

1) The exact amount of Carboxymethylcellulose sodium [redacted] which is needed to achieve a [redacted] in the final product, is calculated based on [redacted]

Handling instructions for the *ex tempore* suspension of the risperidone microspheres in the diluent prior to the deep (gluteal) intramuscular injection are provided in the package insert. The dose pack consists of a vial containing the microspheres (dosage strengths of 25, 37.5, or 50 mg

risperidone per vial), a pre-filled syringe containing the diluent. [redacted]
and one NeedlePro® 20 G TW safety needle.

7.4.2 Development history and formulations used in clinical trials

Microspheres

The sponsor has thoroughly investigated the three main factors that may influence the risperidone microsphere drug release:

PLG monomer ratio (mole ratio of lactide content to glycolide content):

[redacted] The selected PLG ratio (75:25) has an *in vitro* drug release pattern of about 50 days.

1. PLG molecular weight:
   PLG molecular weight had a limited effect on drug release behavior. Data showed that changes in final product molecular weight using 75:25 PLG from about [redacted] did not have significant effect on drug release [redacted]
2. Drug content:
   Risperidone drug content (or coreload) had some effect on drug release behavior. Drug content above [redacted] led to higher initial release. At a coreload of [redacted], the initial risperidone release was about [redacted] of the total, at a [redacted] coreload the initial risperidone release was about [redacted] of the total, and at a [redacted] coreload the initial risperidone release was about [redacted] of the total load. A theoretical drug content of [redacted] was chosen for the formulation and was used throughout clinical development of the product.

Diluent

The development of the diluent for the suspension of the drug-containing microspheres focused on fulfillment of the following criteria:

1. Fast/complete wetting of microspheres and good suspension of the latter

2. Easy to pull up in and inject from syringe

3. Physical and chemical stability

Formulations used in the clinical trials

Risperidone ER microspheres produced from the [redacted] clinical process was designated F066 and was used in Phase I and Phase II clinical trials. After [redacted], to the [redacted] commercial process, encapsulation efficiency of the drug improved, which resulted in a slightly higher drug content. This material is designated F109 and was used in Phase III clinical trials. A summary table of the formulations used in the clinical trials is shown in the main review (section 4.1.2). The quantitative compositions of F066 (phase I/II formulation) and F109 (TBM formulation) are shown in Table 1.

TABLE 1. Composition of risperidone ER microspheres per gram of microsphere used in the clinical trials

Component	F066	F109
Risperidone Drug Substance	[redacted]	[redacted]
Polymer: 75:25 poly-(d,l-lactide-co-glycolide)[1]	[redacted]	[redacted]

At [redacted] manufacturing of the Phase I/II [redacted] batches. [redacted]

The PLG in formulation F066 had a MW [redacted], and the PLG used in formulation F109 has a MW [redacted] The change in molecular weight of PLG was due to the need to [redacted]. An *in vivo* bridging study was performed with the two formulations (RIS-INT-54).

The compositions of the different diluents used in the human clinical trials are depicted in Table 2. The diluent (F065) used in the phase I/II trials differs only slightly from the TBM diluent (F101) used in the phase III trials.

TABLE 2. Compositions of the diluents used in the clinical trials (F065: Phase I/II trials, F101: Phase III trials).

Ingredient	Purpose	F065	F101-1	F101-2
Polysorbate 20				
Disodium hydrogen phosphate dihydrate				
Citric acid anhydrous				
Water for Injection				

In conclusion, the sponsor has adequately investigated the release controlling factors of the risperidone ER microspheres in terms of composition and optimized the diluent used for suspension of the microspheres prior to injection.

7.5 IN VITRO DRUG RELEASE METHODS

The sponsor proposes a combination of two *in vitro* dissolution methods (37°C-water bath and 45°C-water bath) for the *in vitro* drug release of risperidone from the microspheres into a pH 7.4 medium o[illegible] (triplicate samples [illegible] sampling volume). The use of the combined approach allows a shortened test period, since the initial method, the 37°C-water bath, requires a test period of [illegible] to characterize the full release profile of risperidone from the microspheres. The accelerated method (45°C-water bath) allows this period to be shortened to 8 days. The 37°C-water bath test method ensures that the drug product does not erode and release drug prematurely, i.e. that the intended extended release properties are maintained during the 14-day lag period.

The following four parameters will be determined within a total duration of 15 days:

- Burst, or amount of drug released in the first 24 hours (37°C)
- Drug release at Day 15, which represents the lag phase (37°C)

- Day for 50% release (or $T_{50\%}$) which is determined by linear interpolation of the 2 time points that brackets the 50% drug release. This measure represents the polymer erosion phase (45°C)
- Drug release at Day 8, which monitors the endpoint (45°C)

The sponsor's proposed *in vitro* dissolution specifications are given in the table below (triplicate samples at each time point).

Test Method	Test Point	Proposed Specification
In vitro release (37°C-water bath) [redacted]	Day 1 (burst) Day 15	[redacted]
In vitro release (45°C-water bath) [redacted]	T50% Day 8	[redacted]

The risperidone concentrations are analyzed by HPLC (37°C method) or UV detection (45°C method).

The combination of the two test methods has been discussed at the pre-NDA stage (see OCPB reviews of IND 52,982 dated 05/11/01 & 07/03/01). The sponsor has shown that the 37°C and 45°C test methods have a reasonable correlation (Figures 1 & 2). The correlation of the time to 50% drug release indicates that the accelerated 45°C method is an acceptable substitution for the [redacted] period required for the 37°C method, as shown in Figure 1.

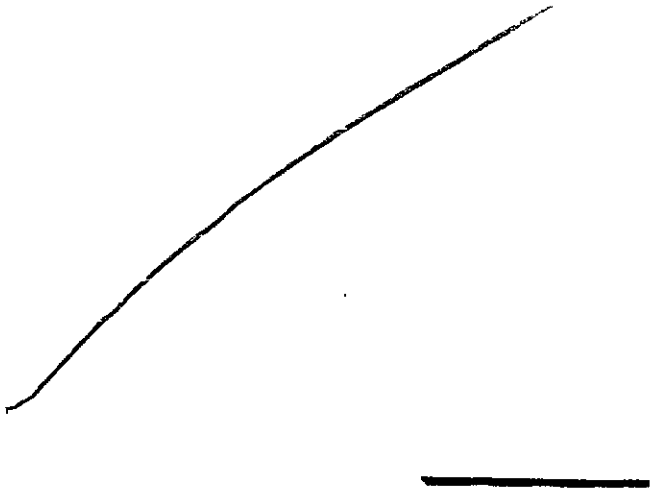


FIGURE 1. The time of 50 % drug release (T50%, days) of the 37°C test method *vs.* T50% (days) of the 45°C test methods (data represents [redacted] stability data of each batch).

The sponsor and the OCPB representatives also discussed potential value of an additional early test point for the accelerated method. The sponsor has also provided data that establishes a link between the two *in vitro* dissolution methods between Day 15 of 37°C method and [redacted] of the accelerated 45°C method, as shown in Figure 2. The sponsor presents the data as evidence that both data points ensures a quality control of a lag phase of drug release, but that the proposed specification is preferred for the lag phase (Day 15, 37°C), since more data is available for this method.

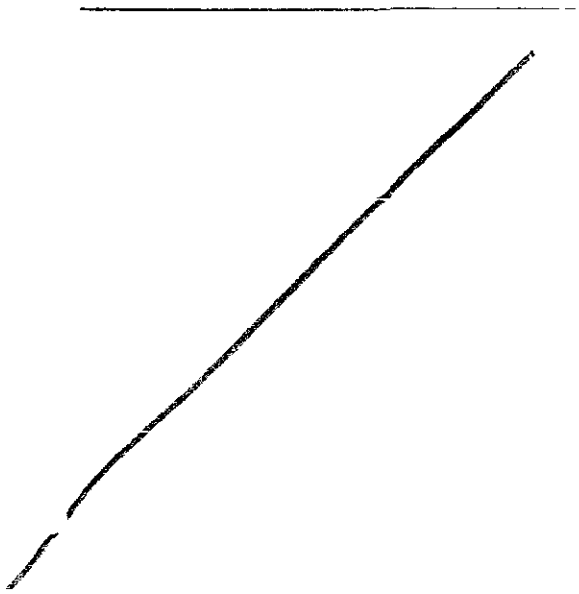


FIGURE 2. Correlation of *in vitro* percent released at Day 15 (37°C) with Day 4 (45°C).

In addition, the sponsor showed that the 37°C test method adequately detects product failure, and that an additional early test point in the 45°C test method is redundant. Table 2 summarizes the ability of the different time points and specifications to fail poor performing lots. Lots 164-0740 and 164-1430 manufactured at the ' ' scale had a shortened lag phase compared to average process lots. Lot 147-1197 was a lot manufactured with a ' ' (to change the *in vitro* profile) which produced a large *in vitro* burst (altered *in vivo* performance with high initial C_{max} values was confirmed in Study RIS-INT-54, see main review, section 4.5.5).

TABLE 2. Rejection of poor performing lots, (p=pass, f=fail), against potential specification points of the accelerated method.

Lot number	Day 1 37° C	Day 15 37° C	T50% 45° C 5.4 to 6.9 days	T80% 45° C	45° C	45° C	45° C
164-0740 bulk							
164-0740AA							
164-0740BA							
164-0740BB							
164-1430 bulk							
164-1430AA							
164-1430AB							
147-1197							

The sponsor provided information (Table 2) that compares the use of a more traditional approach with three specific time points to the proposed specifications (T50% and on Day 8). The data indicate that the use of a single time point has less precision than T50% parameter. The last time point (Day 8) covers total drug release.

In the pre-NDA discussions, the sponsor was requested to include the values of single observations (% release on each of the day) in the NDA. The reason for the request was that the data is not quite in the linear portion of the release profile (see Figure 7 in the main review, section 4.5.4). Hence, this raises a question if the composite properties of T50% could potentially obscure a relevant decrease or increase in release rate of a test batch. The T50% value for the 45°C *in vitro* method is calculated by linear interpolation of the two time points bracketing 50% release.

The sponsor has included the requested data, that showed that only samples that have been stored at room temperature for s, or for lots with very rapid release have T50% values that lie between This data is not included in this Appendix (data in Item 4, CMC Section 4.3.6.3.4, Amended Report *In vitro* release 45°C water bath of this NDA). The product label states that the product must be stored refrigerated, and can only be kept at room temperature for a maximal period of 7 days. For the product, this means that the time points usually determine the T50% value for the accelerated test. Data from has only been used in T50% calculations when the stability tests were performed at temperatures that are not according to recommended storage conditions (i.e. tests at room temperature instead of refrigerated).

The sponsor was contacted in June 2002, and asked to submit individual data, in addition to the mean data that was included in the original submission. This request encompassed data for the TBM biobatches used in two studies (RIS-USA-121, -INT-72) and the validation stability batches (accelerated: 25°C/60% RH and real time: 5°C conditions), and the requested data is shown in Tables 3, 4, and 5.

The batch analysis data for biobatches used in study RIS-INT-72 (Phase I, TBM strengths mg) and the pivotal placebo-controlled study RIS-USA-121 (Phase III, TBM strengths) are depicted in Table 3.

TABLE 3. *In vitro* release data: Biobatches of the TBM microspheres used in the *in vivo* studies.

Study	Strength	*In vitro* release (water bath)			
Batch/Lot No.	(mg)	37°C		45°C	
		Day 1 (%) Individual **mean ± SD**	Day 15 (%) Individual **mean ± SD**	T50% (days) Individual **mean ± SD**	Day 8 (%) Individual **mean ±S D**
RIS-USA-121					
164-0100AB	25	0.36; 0.40; 0.37; **0.38 ± 0.02**	2.33; 2.46; 2.27; **2.35 ± 0.10**	6.49; 6.36; 6.52; **6.46 ± 0.09**	101.6; 103.6; 101.4; **102.20 ± 1.23**
164-0100AA	50	0.43; 0.42; 0.37; **0.41 ± 0.04**	2.21; 2.38; 2.32; **2.30 ± 0.08**	6.54; N/A; 6.5; **6.52 ± 0.03**	102.9; N/A; 105.9; **104.41 ± 2.16**
164-0100CB	75	0.37; 0.39; 0.41; **0.39 ± 0.02**	2.21; 2.31; 2.43; **2.32 ± 0.11**	6.44; N/A; 6.44; **6.44 ± 0.00**	103.6; N/A; 101.9; **102.75 ± 1.20**
RIS-INT-72					
164-0240DA	37.5	0.24; 0.27; 0.23; **0.25 ± 0.02**	2.20; 2.54; 2.36; **2.37 ± 0.17**	6.40; N/A; 6.43; **6.41 ± 0.02**	103.1; N/A; 100.2; **101.60 ± 2.05**
164-0240DC	50	0.26; 0.24; 0.22; **0.24 ± 0.02**	2.51; 2.62; 2.45; **2.52 ± 0.09**	6.40; N/A; 6.39; **6.39 ± 0.01**	102.5; N/A; 102.9; **102.70 ± 0.32**
164-0240CA	62.5	0.29; 0.29; 0.27; **0.29 ± 0.01**	2.49; 2.65; 2.52; **2.56 ± 0.09**	6.57; N/A; 6.53; **6.55 ± 0.03**	100.8; N/A; 102.6; **101.74 ± 1.28**

* Sponsor's proposed *in vitro* release specifications, based on mean data; sponsor's internal SOPs require (N/A in the table indicates instrument error)

Tables 4 and 5 depict the individual, mean, and standard deviation (SD) *in vitro* release data for the primary registration stability lots reported in the NDA (CMC, Consolidated Drug Product Stability Report; Appendix 1 & 2). Table 4 (next page) contains the *in vitro* release tests results for Days 1 and 15 (37°C water bath method) and Table 5 (following page) contains the results for the T50% and Day 8 (45°C water bath method). Stability data for up tc s (shelf-life storage condition of 5 ± 3°C; refrigerated or Refrig) and up to (accelerated conditions of RH; controlled room temperature or CRT) are shown. The tables contain additional significant numbers compared to those previously submitted in the NDA and specifications.

The sponsor was also requested to submit the internal procedures for acceptance criteria for batch release (information request in June 2002). The sponsor has internal procedures in place where an investigation is initiated if any of the replicates is outside of the mean specification or out-of-trend. According to the sponsor, these procedures are consistent with industry practices and the draft FDA Guidance for Industry, Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production (FDA/CDER, Sept. 1998). These procedures were also reviewed by the Agency during the pre-approval inspection of the Alkermes facility in March 2002.

The sponsor uses the following definitions: Out-of-Trend is defined as a situation where the

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

The proposed combination of two *in vitro* dissolution methods (37°C & 45°C water baths) is deemed acceptable. However, based on the data in Tables 3, 4, and 5, we recommend a tightening of the release specifications (T50%, 45°C water bath), as well as introducing formal specifications for the individual samples. These revisions are described in the main review (Section 4.5.3).

In addition, we recommend that the proposed *in vitro* release specifications are only used in an interim period, until data from the on-going stability tests is available. As a Phase IV commitment, the sponsor is requested to submit data for the TBM formulations from the on-going stability tests, and final specifications will be set after review of the data. The submission should include potentially revised specifications for in vitro drug release, and should be submitted within 4 months after the 24-month stability data is available (see Section 4.5.3 in the main review).

7.6 BIO-ANALYTICAL METHODS

The sponsor used two different methods, RIA (used in previous NDAs) and LC-MS/MS (new method), to determine risperidone (RIS), the active metabolite 9-hydroxy-risperidone (9-OH-RIS) and active moiety.

RIA: The RIA (radioimmunoassay) methods were used in all Phase I/II trials, except one. The RIA method was used in RIS-BEL-34, -INT-25, -INT-38, -NED-13, -USA-111, -INT-54, -INT-31, -SWE-17, and RIS-INT-32. All RIA analyses were performed at the same laboratory (Janssen Pharmaceutica, Beerse, Belgium). One RIA method measured specifically RIS. The other RIA method measured the active moiety (RIA + 9-OH-RIS). The plasma concentrations of 9-OH-RIS were calculated as the difference between the values of the active moiety and RIS.

The long-term stability of frozen plasma samples [redacted], has been determined to [redacted] In study RIS-INT-54, the samples were stored up to [redacted], but according to the sponsor, data from frozen quality control (QC) samples stored up to [redacted] in the study, showed that the analytes were stable in the QC samples for this period of time.

A summary of the study specific details regarding the RIA performance is shown in Table 1.

The RIA methods are considered to be adequately validated, and are also deemed to be adequately sensitive. In addition, the RIA methods (shown to be specific with no interference) have been used throughout the different development programs of risperidone. The sponsor analyzed samples from all studies at the same in-house laboratory.

TABLE 1. RIA analytical method summary (Phase I/II studies)

Study	Analyte	LLOQ* (ng/mL)	Range STD curve (ng/mL)	Study specific validation Accuracy % / Precision % (CV)
RIS-BEL-34** (50 mg RIS)	Active moiety			
	RIS			
RIS-INT-25** (50 mg RIS)	Active moiety			
	RIS			
RIS-INT-38** (100 mg RIS)	Active moiety			
	RIS			
RIS-NED-13** (25 mg RIS)	Active moiety			
	RIS			
RIS-USA-111** (25 mg RIS)	Active moiety			
	RIS			
RIS-INT-31 (25, 50, 75 mg RIS)	Active moiety			
	RIS			
RIS-SWE-17 (25, 50, 75 mg RIS)	Active moiety			
	RIS			
RIS-INT-32 (25, 50, 75 mg RIS)	Active moiety			
	RIS			
RIS-INT-54 (25, 50, 75 mg RIS)	Active moiety			
	RIS			

STD = standard; *LLOQ = Lower limit of quantitation; ** Values from few QC samples (n=1-3)/ concentration

LC-MS/MS: The LC-MS/MS (liquid chromatography-mass spectrometry/ mass spectrometry) method was used in all Phase III trials (RIS-USA-121, RIS-INT-61, & RIS-INT-57), and also in one Phase I/II trial (RIS-INT-72). One study (RIS-INT-72) was analyzed by the sponsor (Janssen Pharmaceutica, Beerse, Belgium), the other LC-MS/MS analyses were performed by a contract laboratory (. The reliability of the LC-MS/MS analysis between laboratories was established through a study where quality control (QC) samples of concentrations unknown to the contract laboratory were provided by the sponsor (contract laboratory results of blind QC samples: Accuracy RIS , Accuracy 9-OH-RIS).

The LC-MS/MS method simultaneously quantifies the plasma concentrations of RIS and 9-OH-RIS. The plasma concentrations of the active moiety were calculated as the sum of the values of RIS and 9-OH-RIS. Labeled RIS ($^{13}C_2$-$^2H_3$-RIS, R215640) and 9-OH-RIS RIS ($^{13}C_2$-$^2H_3$-9-OH-RIS, R215639) are used as internal standards (co-eludes with RIS & 9-OH-RIS), which makes the method more robust with regard to co-eluding endogenous compounds or other co-medications according to the sponsor. The plasma samples are extracted, and analyzed by LC (column) with MS/MS detection .

The LC-MS/MS method was validated in regard to accuracy, precision, selectivity, upper & lower limits of quantitation, linearity, extraction recovery, robustness, and stability. Accuracy and precision were satisfactory. Linearity ($r>0.999$) was established for both RIS and 9-OH-RIS between g/mL (LLOQ) and ng/mL (ULOQ), and back extraction for calibration standards were within of spiked concentrations. The extraction recovery of RIS and 9-OH-RIS was consistently over the calibration range. The robustness was evaluated, and was found to be satisfactory. Stability of RIS and 9-OH-RIS in plasma was shown to be stable at room temperature (and after 4 freeze-thaw cycles (whole blood: stable for). Stored, frozen , plasma samples of RIS and 9-OH-RIS are stable up

to — (tests ongoing). — samples (— were shown to be stable for — at room temperature for both moieties.

A summary of the study specific details regarding the LC-MS/MS method performance is shown in Table 2.

TABLE 2. LC-MS/MS analytical method summary (Phase III studies + RIS-INT-72)

Study	Analytes	LLOQ* (ng/mL)	Range STD curve (ng/mL)	Study specific validation Accuracy % / Precision % (CV)
RIS-INT-72; (37.5, 50, 62.5 mg RIS)	RIS 9-OH-RIS	٢		٧
RIS-INT-61 (25, 50, 75 mg RIS) (2, 4, 6 mg RIS PO)	RIS 9-OH-RIS			
RIS-USA-121 (100 mg RIS)	RIS 9-OH-RIS			
RIS-INT-57 (25, 50, 75 mg RIS)	RIS 9-OH-RIS	٢		٤

STD = standard; *LLOQ = Lower limit of quantitation

A cross-validation between the RIA and the LC-MS/MS methods was conducted with subject samples. This cross-validation showed that the results for the active moiety were comparable between the LC-MS/MS and the RIA methods. It was shown that RIS concentrations measured by the RIA method were slightly overestimated in the lower concentration range (samples contained a portion equal to — of the 9-OH-RIS concentrations).

In conclusion, the bioanalytical methods used for the clinical studies in this NDA are considered adequately documented and validated.

7.7 PHARMACOMETRICS REVIEW

Pharmacometrics Review

NDA :	**21346, Volume 33 of 65**
Compound:	**Risperdal Depot**
Submission Dates:	**8/31/01, 4/30/02**
Review Date:	**May 29, 2002**
Sponsor:	**Janssen Pharmaceuticals**
Pharmacometrics Reviewer:	**Vanitha J. Sekar, PhD**
Pharmacometrics Team Leader:	**Jogarao Gobburu, PhD**

Background: Risperidone (RO64766) has been formulated as a depot formulation for (gluteal) intramuscular (i.m.) injection, that is expected to improve patient compliance and to further ameliorate treatment of patients with psychotic disorders. Risperidone, a benzisoxazole derivative, is an antipsychotic agent with combined serotonin 5HT2A- and dopamine D2 antagonistic properties. Most patients that are adequately treated with risperidone receive a daily oral dose between 2 and 6 mg. The in-vivo release profile is characterized by a small initial release, a lag phase of about 3 weeks with almost no release and a main gradual, relatively fast release over a period of nearly 3-weeks; including a 2-week period of zero-order release.
The pharmacokinetic results of the Phase I and II repeated-dose trials in schizophrenic patients show that sustained, therapeutic plasma drug-concentrations are reached when risperidone (depot microspheres) is injected every two weeks. Therapeutic concentrations emerge from Week 3-4 onwards after the first injection. Supplementation with a full oral dose-equivalent during the first three weeks of treatment (lag-period) was recommended in the Phase III trials.

Sponsor's Objectives: The main objectives of the population pharmacokinetic analysis were to:
1) model risperidone and active moiety pharmacokinetics after i.m. administration of the depot formulation,
2) get estimates of basic pharmacokinetic parameters in healthy subjects and in the target population of schizophrenic patients,
3) evaluate effects of patients' demographic characteristics and other covariates on risperidone and active moiety clearance.

Review Objectives (based on requested pharmacometrics consult by primary reviewer):

1. Is the PPK/PPD analysis correctly performed?
2. Does the PPK analysis support the dosing recommendations for the elderly (is an adequate number of patients included in the analysis?)?
3. Does the label adequately describe the drug-drug interactions determined from the PPK analysis?

Methods:

Clinical Studies used in Population PK analysis (see Table 1)

Table 1

Acc. No.	Investigator Trial No.	Subjects (M/F)	Age (years) Median (range)	Weight (kg) Median (range)	Dosage and objectives
BEBE-1371887	RIS-INT-54	56 (38/18)	40 (23-65)	79.0 (48.0-125.0)	Risperidone microspheres i.m.; Single dose, 25, 50 and 75 mg; bio-equivalence between Phase-II and Phase-III microspheres and dose-proportionality for Phase-II microspheres (25-75 mg)
N137257	Multi-investigator RIS-INT-32	86 (56/30)	39 (17-62)	78 (49-129)	Risperidone microspheres i.m.; repeated dose, 25, 50 and 75 mg; comparison of the steady-state bioavailability following oral and i.m. depot treatment.
USTI-2673722	Multicenter RIS-INT-61	640 (414/226)	18-66 (40.0)	80.4 (43.0-166.0)	non-inferiority trial risperidone microspheres i.m. versus oral risperidone tablets o.d.
USTI-2714267	Multicenter RIS-USA-121	400 (300-100)	18-55 (37.7)	86.9 (49-159)	Risperidone microspheres i.m.; repeated dose, placebo-controlled, 25, 50 and 75 mg.
USTI-2738147	Multicenter RIS-INT-57	725 (474/251)	18-84 (42.2)	81.2 (39.9-155)	Risperidone microspheres i.m.; repeated dose, 25, 50 and 75 mg; long-term safety trial.

Study designs are described in greater detail in Appendix I.

Data

The database available for the population pharmacokinetic analysis of risperidone and active moiety was composed of approximately 1518 patients with schizophrenic or schizo-affective disorder. Except for a subset of 57 elderly patients (≥ 65 years, n=57) recruited in RIS-INT-57, most patients in the other trials were between 18 and 65 years of age. Patients randomized to the oral treatment groups in RIS-INT-61 or to the placebo treatment group in RIS-USA121 were not taken into account for the population PK-database.

RIS-INT-54 and RIS-INT-32 were 'data-rich' pharmacokinetic trials with complete characterization of single dose and steady-state pharmacokinetic profiles, respectively. In the clinical efficacy and safety trials, pharmacokinetic information was obtained by limited blood draws at several "predose" and "intermittent" time-points throughout the trial. A maximum of 7 plasma samples (RIS-INT-61) or 11 plasma samples (USA-121, RIS-INT-57) could be obtained per-patient under active treatment. The total number of subjects available in the database and the number of subjects included in the analysis are summarized in Table 2.

Table 2: Population Pharmacokinetics database

Trial	Total number of subjects in the available data base	Number of subjects included in the analysis	Subjects excluded	Explanation
RIS-INT-54	56	54	## 20 and 28	Insufficient duration of observation period; individual parameters are not estimable
RIS-INT-32	86	76	## 141, 160, 167, 199	No plasma samples
			## 1, 25, 77, 83, 118, 878	Insufficient number of plasma samples or aberrant concentration-time profile
RIS-INT-57	725	647	20052 20404 20487 20730 20927 20934 20975 20987 21197 21206 21587 21641 22196 50010 50022 50051 50123 50179 50476 50648 50849 50892 50931 50944 51293 51485 51734 51735 51736 51746 51748 51749 51751 51754 52031 52046 52181 52282 52283 52295 52301 52670 52809 53372 53379 53484 70045 70174 70181 70484 70640 70646 70848 70892 70897 70945 70953 70954 70959 70961 71307 71604 71709 71734 71738 71751 71753 71779 72304 72633 73178 73467 73472 73496 73906 73917 73937 74793	Lack or insufficient number of plasma samples during the period of depot administration; all or most of risperidone and/or active moiety concentrations below limit of quantification;
RIS-INT-61	319 (depot group)	299	6 86 176 179 206 216 289 301 523 597 680 743 823 976 1058 1075 1223 1237 1272 1534	same as above
RIS-USA-121	332	294	8 34 104 122 130 133 137 203 209 246 267 269 273 274 278 279 324 351 365 373 380 490 506 583 610 614 622 633 659 667 672 688 710 712 731 734 737 739	same as above

Software

The NONMEM V level 1.1 was used by the sponsor for all model fittings. The package was installed on a PC platform using MS Fortran Powerstation version 4.0 under MS Windows 2000. Data set preparation, exploration and visualization was performed using S-PLUS 2000 release 3 for Windows.

Models

Structural Model: The structural model developed by the sponsor was based on dense data from a single-dose RIS-INT-54 trial. A compartmental model was developed which included a one-compartment disposition submodel characterized by clearance and volume of distribution and three parallel absorption pathways:an immediate pathway describing the absorption of non-encapsulated risperidone, and a fast and a slow sustained-release pathway. To get an appropriate fit, a transform-both-sides approach was used: natural logarithms of observed concentrations served as the dependent variable. Following the development of the structural model, individual estimates of risperidone and active moiety clearance together with other model parameters were obtained using RIS-INT-54 and RIS-INT-32 using a two-stage approach. These estimates were summarized, and typical values and inter-individual variances were derived and further used as priors to obtain individual posterior clearance estimates for patients of RIS-INT-57, RIS-INT-61 and RIS-USA-12l trials via a Bayesian procedure.

Covariate Model: A regression model was then developed to relate risperidone and active moiety clearance to patient covariates. Two independent regression models for covariate effects were built: one for active moiety clearance, and another one for risperidone clearance. Other pharmacokinetic parameters were not considered as they could not be estimated with sufficient precision from the sparse data of Phase 3 trials. Table 3 summarizes covariates available for the analysis. Table 4 gives the summary of covariates derived using the basic covariates.

Table 3

Trial	Gender (M/F)	Race (Caucasian/ Others)		Age, yr	Body weight, kg	Height, cm	Serum creatinine, µmol/L	Total protein, g/dL	Alanine transaminase, IU	Aspartate transaminase, IU	Total bilirubine, µmol/L	Lactate dehydrogenase, IU	Alcaline phosphatase, IU
RIS-INT-54	36/18	52/2	Min	23	44	153	57	62	8	12	6	107	36
			Median	40	79	175	75.5	72.25	19	18.75	8.5	137.5	74.25
			Max	65	125	192	179.5	97	92	49.5	12	185.5	132
RIS-INT-32	50/26	71/5	Min	17	49	152	70.8	66	5	11	0.513	205	74
			Median	40	67	172.5	100	73	21.5	19	6.84	368.2	189
			Max	62	129	192	129.2	86	80	64	15.39	657	689
RIS-INT-57	427/220	596/51	Min	18	40	112	62.83	60.5	6	8	1.71	70	35
			Median	41	80	172	94.7	72	21	19	6.84	144	82
			Max	84	155	200	150.9	88	166	148.5	250.5	503	222.5
			Missing		7 patients	6 patients							
RIS-INT-61	194/105	263/36	Min	18	44	138	64.07	62	5	10	2.565	69	41
			Median	40	78	173	93.81	72	14	19	6.84	146.6	80
			Max	65	129	197	127.4	83	90	60	27.36	288	142
			Missing		2 patients								
RIS-USA-121	204/90	125/169	Min	18	52	145	39.5	58.5	7.5	8	3	71	31
			Median	40	74	173	71	73.5	22.5	20.5	6	149	77.5
			Max	55	159	198	119.5	88.5	148	96	31	296	186
			Missing								18 patients		

Table 4

Trial		Lean body mass, kg [a]	Body mass index, kg/m² [b]	Creatinine clearance, mL/min [c]
RIS-INT-54	Min	37.53	17.09	36.81
	Median	55.62	26.06	116.6
	Max	77.78	39.92	190
RIS-INT-32	Min	37.64	18.37	50.17
	Median	56.29	26.53	88.61
	Max	80.4	44.12	149.4
RIS-INT-57	Min	29.4	14.52	25.81
	Median	56.82	26.53	97.36
	Max	83.91	48.54	213.7
	Missing	7 patients	7 patients	7 patients
RIS-INT-61	Min	36.43	15.36	46.2
	Median	56.9	26.39	97.39
	Max	81.66	48.77	184.3
	Missing	2 patients	2 patients	2 patients
RIS-USA-121	Min	23.84	17.44	74.54
	Median	58.7	28.15	137.6
	Max	87.31	61.51	430.7

[a] Calculated using the following formulas
For females: 1.07*WT-(148*(WT²/HT²)))
For males: 1.10*WT-(128*(WT²/HT²))
[b] Calculated using the following formula
WT/(HT/100)²
[c] Calculated using the following formulas
For females: 0.85*WT*(140-AGE)/72/(SCR/88.4)
For males: WT*(140-AGE)/72/(SCR/88.4)

A trimodal distribution of active moiety-to-risperidone clearance ratio was identified in accordance with the known polymorphic nature of risperidone metabolism, and each patient was assigned to one of three metabolic phenotypes: extensive, intermediate and poor metabolizers. As the distribution of clearances follows the log-normal distribution rather than the normal one, clearance values were converted into natural logarithms which were then used as a dependent variable. Continuous covariates were also log-transformed before fitting models. In order to obtain a reference objective function value, a model without covariate effects was fitted to active moiety and risperidone clearances. The residual error model was assumed to be additive. Effects of phenotype, study, demographic and biochemical covariates were tested and the significance was assessed using (i) the likelihood ratio test and (ii) 95-% confidence intervals based on asymptotic standard errors calculated by the NONMEM program after convergence. Effects which had P-values associated with the likelihood ratio test < 0.01, and whose confidence intervals did not include zero (or unity for the effects expressed as a fraction) were considered as statistically significant.

Analysis of potential interactions of active moiety and risperidone with co-medicated drugs was carried out. For this analysis, dose-normalized plasma concentrations measured at the time when patients of Phase 3 trials received known inducers or inhibitors of drug-metabolizing enzymes were used. The co-medicated drugs in RIS-INT-57, RIS-INT-6I and RIS-USA-12I trials were examined and the following drugs known as inducers or inhibitors of drug-metabolizing enzymes were identified by the sponsor: Amitriptyline (n=105), Carbamazepine (n=139), Erythromycin (n=6), Fluoxetine (n=199), Fluvoxamine (n=44), Ketoconazole (n=2), Metoprolol (n=64), Omeprazole (n=161), Paroxetine (n=125), Propranolol (n=227), Valproate (n=240), Valpromide (n=43) and Verapamil (n=39). Only active moiety and risperidone plasma concentrations measured after i.m. injection were taken into account. Concentrations of risperidone and active moiety measured within the time intervals when the above listed drugs were administered were identified, normalized to the common dose of 50 mg and summarized. Medians related to co-medicated drugs were compared with the overall median (without the comedicated drug). Deviations exceeding + 100% or lower than -50% were considered as substantial by the sponsor.

Results and Discussion

Data

From the 1518 patients in the database, only 1370 were included in the population pharmacokinetic analysis. Reasons stated by the sponsor for exclusion of data were lack or insufficient number of plasma samples during the period of depot administration, aberrant concentration-time profiles, insufficient duration of the observation period, individual parameters not estimable.

Model

Pharmacokinetic modeling of risperidone and active moiety following administration of risperidone depot microsphere included an immediate-release of a small amount of non-encapsulated risperidone followed by two sustained-release processes differing in the rate of release. A compartmental model was developed by the sponsor to describe individual risperidone and active moiety concentration-time profiles after both single-dose (RIS-INT -54) and multiple-dose (RIS-INT -32) administration. The model included a one-compartment disposition sub-model characterized by clearance and volume of distribution and three parallel absorption pathways: an immediate pathway describing the absorption of non-encapsulated risperidone, and fast and slow sustained-release pathways. The sponsor was unable to fit a population version of the model due to numerical problems with the NONMEM software. The two-stage approach was thus used to quantify inter-individual variability. Figures 1 and 2 show examples of the individual fitted concentration-time profiles for subjects in study RIS-INT-54 and RIS-INT-32. The structural model used by the sponsor adequately described the data from these two studies. The median risperidone and active moiety clearance for study RIS-INT-54 were10.4 L/h (range: [redacted], and

4.3 L/h (range: ——— respectively. and for RIS-INT-32 the median risperidone and active moiety clearance were 15.3 L/h (range: ——— and 4.3 L/h (——— respectively. As these values suggest, there was a high inter-individual variability in the risperidone as well as active moiety clearance.

Figure 1 Examples of the individual fitted concentration-time profiles for subjects in study RIS-INT-54

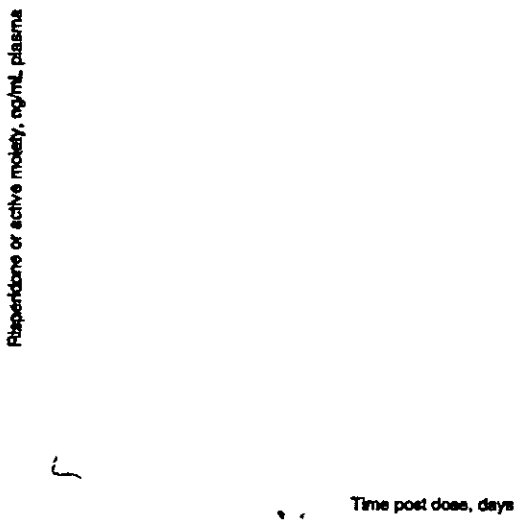
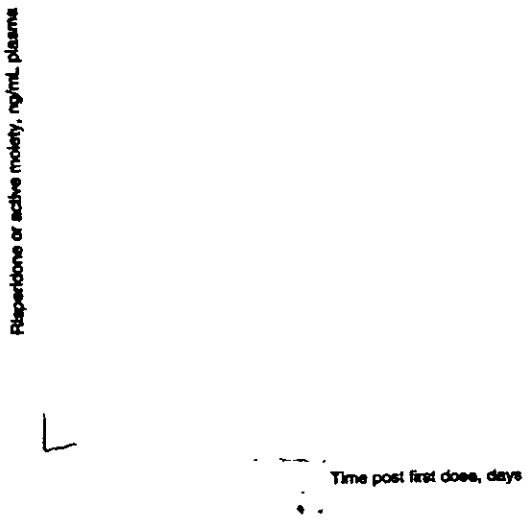


Figure 2 Examples of the individual fitted concentration-time profiles for subjects in study RIS-INT-32



Individual parameter estimates obtained from the data of RIS-INT-54 and RIS-INT-32 were summarized and typical values and variances were used as priors to estimate pharmacokinetic parameters of active moiety and risperidone in patients participating in Phase 3 trials (RIS-INT - 57, RIS-INT-6I and RIS-USA-12I) where only a few samples per patient were available. As risperidone is known to be biotransformed mainly by CYP 2D6 isozymes, the distribution of active moiety-to-risperidone clearance ratios were examined and revealed a trimodality for studies RIS-INT 54 and RIS-INT-32. Therefore, three metabolic phenotypes were considered: extensive, intermediate and poor metabolizers, and each subject was assigned to a certain phenotype which was considered as a covariate affecting clearance for these 2 studies. However, for the population pharmacokinetic analysis, a cut-off clearance ratio value of 0.35 was used to classify patients with ratio of less than 0.35 as extensive metabolizers and those with a ratio of greater than 0.35 as poor metabolizers. Plots of measured concentrations versus individual predictions for each of these Phase 3 studies are shown in Figures 3-5. These plots suggest that the sponsor's model adequately predicted the active moiety and risperidone concentrations at all doses (25, 50 and 75 mg), suggesting lack of non dose-proportionality.

Figure 3 Measured concentrations versus individual predictions (study RIS-INT-57)

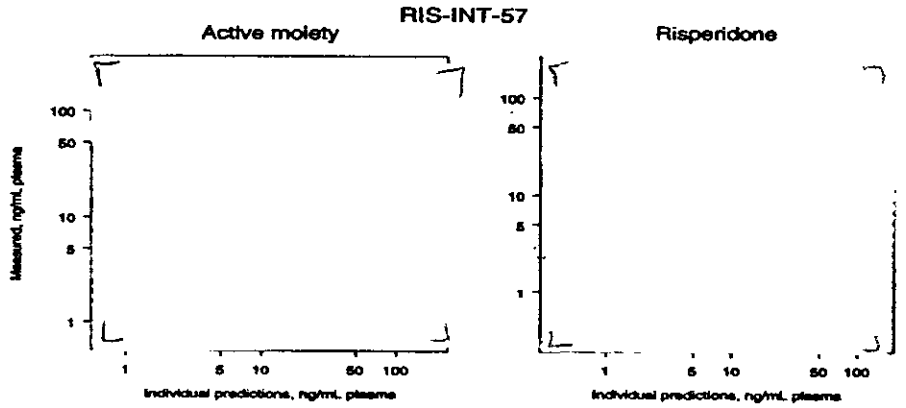


Figure 4 Measured concentrations versus individual predictions (study RIS-INT-61)

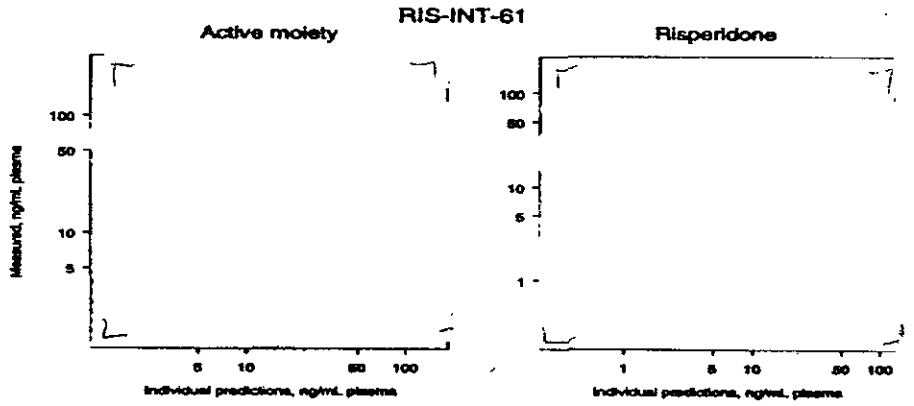
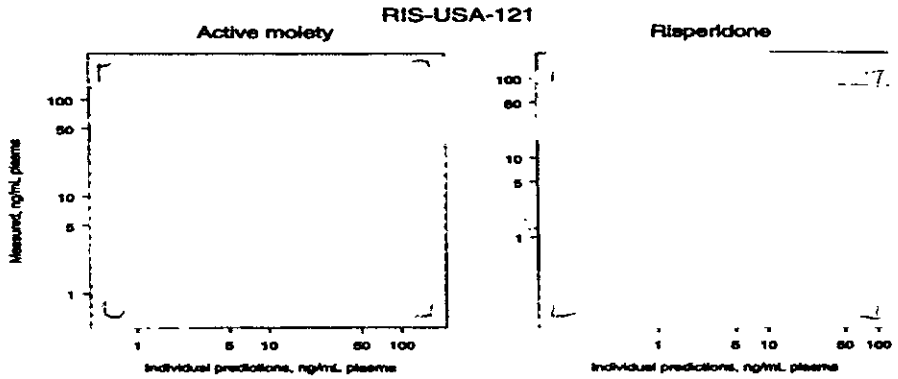


Figure 5 Measured concentrations versus individual predictions (study RIS-INT-121)



Two independent regression models for covariate effects were used by the sponsor for the covariate analysis - one for active moiety clearance, and another one for risperidone clearance. Other pharmacokinetic parameters were not considered as they could not be estimated with sufficient precision from the sparse data of Phase 3 trials. Covariates were included in the models one after another. Graphical exploration was used by the sponsor to select potentially influential covariates. (Figures 6-8). A summary of the covariate model building process for the active moiety and risperidone clearance is shown in Tables 5 and 6. The statistical criteria used by the sponsor to evaluate the significance of covariate effects included a p-value of less than 0.01 and that the 95-% confidence interval should not include zero.

Figure 6

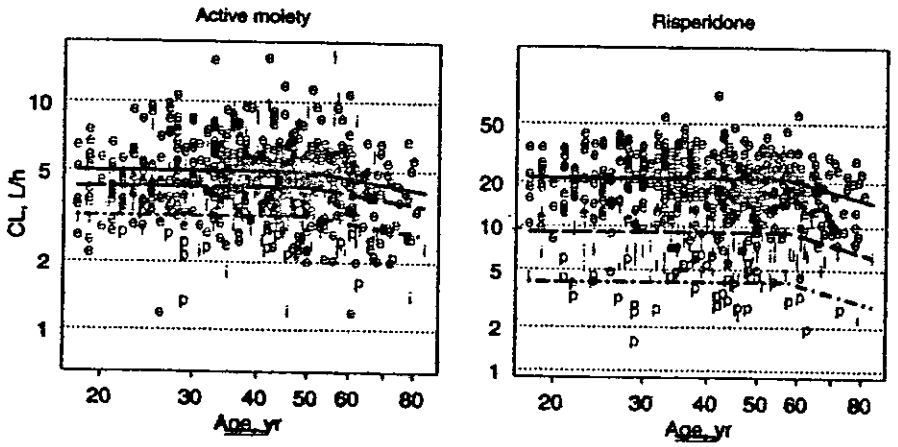


Figure 7

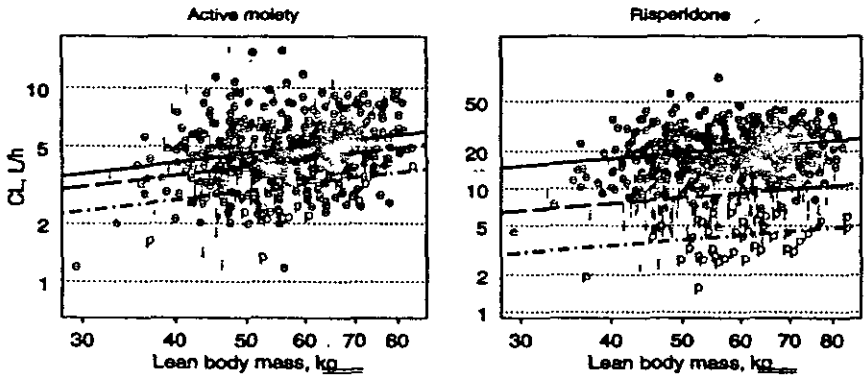


Figure 8a

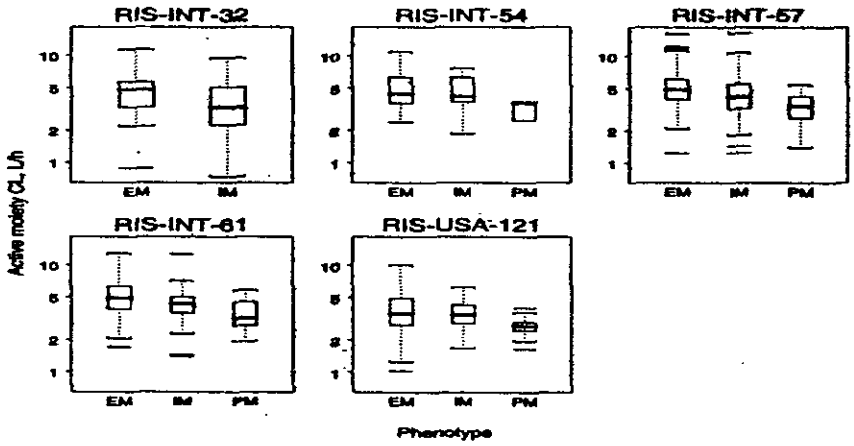


Figure 8b

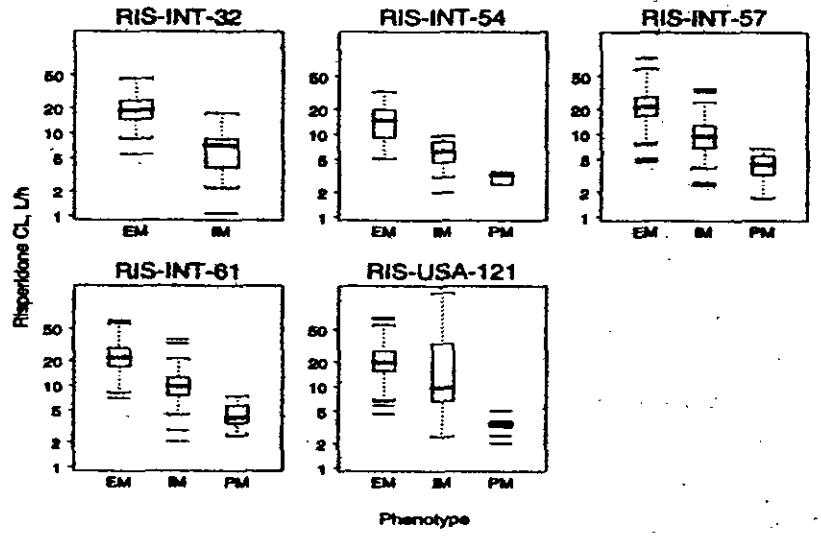


Table 5 Covariate model building for active moiety (accepted models are shown in bold)

#	Model description	MOF [1]	ΔMOF [2]	P-value [3]	95% CI (lower or upper bound)	Comments
1	Base model, no covariate effects	-1110.314	-	-		-
2	Phenotype and study effects: full model	-1309.533	-199.219	2 vs. 1 <0.001 (13)		Many fixed effects negligible
3	Phenotype and study effects: reduced model	-1293.133	-182.819	3 vs. 1 <0.001 (4)		All fixed effects significant
4	Body weight effect	-1326.700	- 33.567	4 vs. 3 <0.001 (1)	0.1378	
5	Lean body mass effect	-1365.722	- 72.589	5 vs. 3 <0.001 (1)	0.3568	Effect is more significant than that of body weight
6	Body mass index effect	-1293.133	0	6 vs. 3 > 0.05 (1)	-0.106	Body mass index has no effect
7	Age effect	-1375.337	- 9.615	7 vs. 5 0.0082 (2)	-0.042	As the slope is negative, upper CI bound is applied
8	Creatinine clearance effect	-1380.161	-4.824	8 vs. 7 0.028 (1)	-0.0597	
9	Lactate dehydrogenase effect	-1393.062	-17.725	9 vs. 7 < 0.001 (1)	-0.0438	As the slope is negative, upper CI bound is applied
10	Gender effect	-1393.123	-0.061	10 vs. 7 >0.05 (1)	1.037	As the effect is less than 1, upper CI bound is applied
11	Race effect	-1393.732	-0.67	11 vs. 7 >0.05 (1)		Covariance step failed; standard errors not available

[1] Minimum objective function value
[2] Change in MOF compared to the latest accepted model
[3] Models in comparison, asymptotic likelihood ratio test P-value (χ^2), number of degrees of freedom is given in parenthesis

Table 6 Covariate model building for risperidone (accepted models are shown in bold)

#	Model description	MOF [1]	ΔMOF [2]	P value [3]	95% CI (lower or upper bound)	Comments
1	Base model, no covariate effects	310.400	-	-	-	-
2	Phenotype and study effect: full model	-853.075	-1163.47	<0.001 (13)	-	Many dose effects negligible
3	Phenotype and study effects: reduced model	-850.139	-1160.54	3 vs. 1 <0.001 (10)	-	All fixed effects significant
4	Body weight effect	-880.369	-30.23	4 vs. 3 <0.001 (1)	0.1888	
5	Lean body mass effect	-903.439	-53.30	5 vs. 3 <0.001 (1)	0.3398	Effect is more significant than that of body weight
6	Body mass index effect	-852.567	-2.428	6 vs. 3 >0.05 (1)	-0.0352	Body mass index has no effect
7	Age effect	-916.746	-13.307	7 vs. 5 0.0013 (2)	-0.139	As the slope is negative, upper CI bound is applied
8	Lactate dehydrogenase effect	-917.767	-1.021	8 vs. 7 >0.05 (1)	0.0694	As the slope is negative, upper CI bound is applied
9	Gender effect	-916.920	-0.174	9 vs. 7 >0.05 (1)	0.983	
10	Race effect	-922.493	-5.747	10 vs. 7 0.0165 (1)	1.0054	Despite CI does not include 1 the race effect was not included based on LRT and low magnitude

[1] Minimum objective function value
[2] Change in MOF compared to the latest accepted model
[3] Models in comparison, asymptotic P value, χ^2, number of degrees of freedom (in parenthesis)

The sponsor's final model for the active moiety included effects of lean body mass, age, phenotype and lactate dehydrogenase concentrations. The effect of age was not evaluated as a continuous variable – instead the sponsor assumed that clearance would be lower in older patients aged 50-60 years. A threshold age was estimated at 50 and 57 years, for the active moiety and risperidone, respectively. Active moiety clearance estimated in RIS-USA-121 was somewhat lower than in other trials. The sponsor's final model for risperidone included effects of phenotype, lean body mass and age. No effect of lactate dehydrogenase or other biochemical variables reflecting the liver function was detected. The sponsor therefore concludes that the lactate dehydrogenase effect on active moiety clearance is accidental and will have no clinical implications. This conclusion is reasonable. Among body size variables (body weight, lean body mass and body mass index), the sponsor concludes that lean body mass was a covariate affecting active moiety and risperidone clearances. However, the overall magnitude of the effect was small and probably not clinically relevant due to the high residual inter-individual scatter of clearance values. It should be noted that no patients with renal insufficiency participated the trials under analysis, hence the conclusion of the lack of creatinine clearance effect can not be extrapolated to the cases with true renal insufficiency.

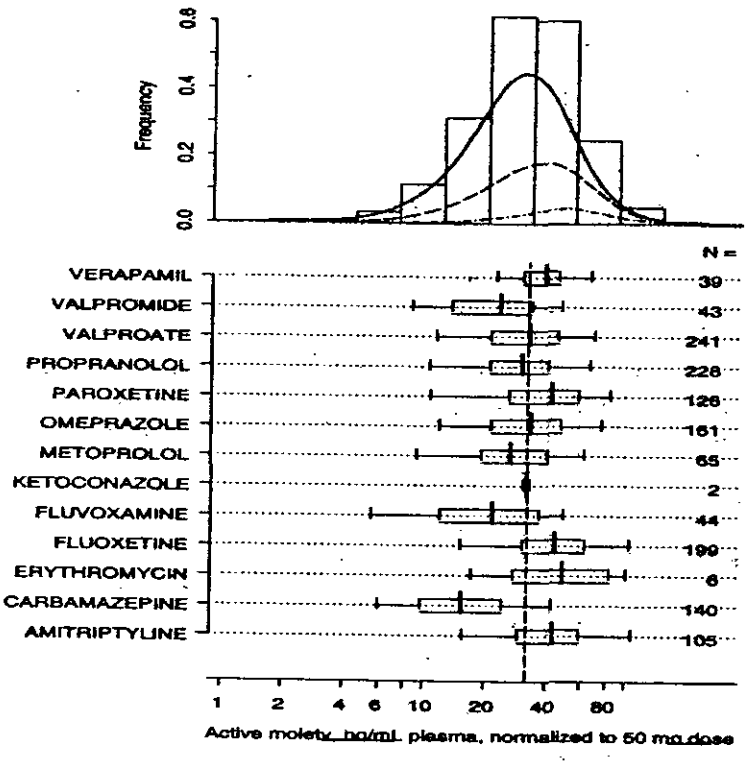
The effect of comedications on active moiety and risperidone clearances is summarized in Table 7 and Figure 9. The upper part of the figure displays the histogram of all active moiety plasma concentrations collected in Phase 3 trials (RIS-INT-57, RIS-INT-61 and RIS-USA-121) normalized to 50 mg dose. Continuous, dashed and dotted lines show the distribution densities of concentrations for extensive, intermediate and poor metabolizers, respectively. The lower part of the figure presents the box-plots of normalized concentrations measured within the time intervals patients took the drugs listed on the left side. The bold bars show medians, boxes correspond to interquartile ranges and whiskers show 5 and 95 percentiles. The numbers at the right side give the total number of plasma samples taken when patients received specific comedications. The vertical dashed line shows the overall median dose-adjusted active moiety plasma concentration.

The cytochrome-P450 (3A4) enzyme inducer carbamazepine reduced the active moiety concentrations by 54%, while its effect on risperidone plasma concentrations was a 44 % decrease. Cytochrome-P450 (2D6) enzyme inhibitor, fluoxetine increased risperidone concentrations by more than 100 %suggesting a potential interaction when these two drugs are coadministered. Coadministration of risperidone and amitriptyline resulted in an increase of active moiety concentrations by 123%. Both risperidone and amitriptyline are CYP2D6 substrates. However, as can be seen from figure 9, in all cases except for coadministration with carbamazepine, there is a considerable overlap of active moiety concentrations with and without concomitant medication.

Table 7

Comedication	Per cent change from the overall median	
	Active moiety	Risperidone
AMITRIPTYLINE	59.00	**123.00**
CARBAMAZEPINE	**-54.00**	-44.00
ERYTHROMYCIN	6.00	3.00
FLUOXETINE	31.00	**156.00**
FLUVOXAMINE	-19.00	-38.00
KETOCONAZOLE	35.00	-5.00
METOPROLOL	-27.00	-39.00
OMEPRAZOLE	23.00	23.00
PAROXETINE	-15.00	62.00
PROPRANOLOL	-2.00	-13.00
VALPROATE	3.00	-16.00
VALPROMIDE	-36.00	**-56.00**
VERAPAMIL	14.00	-23.00

Figure 9 Analysis of comedication effects on active moiety concentrations



Proposed Labeling: The sponsor's proposed label is attached as part of the primary review in the Appendix, Section 7.8.

Reviewer's Comments

1. Adequateness of the sponsor's analysis: The population pharmacokinetic analysis performed by the sponsor is acceptable based on evaluation of the goodness-of-fit of the sponsor's proposed models (in terms of the change in objective function, p-values, standard errors of parameter estimates, plots of predicted versus observed concentrations). (Refer Tables 5-6 and Figures 1-4). The clearance values obtained for risperidone and the active moiety following intramuscular injection are in the range of those following oral administration (original NDA review for oral Risperdal). In addition the number of patients included in the population pharmacokinetic analysis was adequate and covered the relevant age range, 18-84 years of age (with adequate number of patients across the age range (as described in review).
2. Comparison of the Young versus the Elderly: The data analyzed from the Phase 3 trials suggest that risperidone and active moiety clearances following the i.m injection of Risperdal are not significantly influenced by age. Elderly patients (65 years of age) had approximately 10% mean lower clearance of active moiety when compared to young patients. When corrected for lean body mass, this age effect was reduced by 5%, suggesting that body size explains some of the variability seen in active moiety clearance with increasing age. The unexplained variability for the sponsor's model incorporating the effects of lean body mass was fairly high, approximately 36%. Based on these results, dose adjustment in the elderly

following risperdal i.m. injection is probably not warranted. However, any specific safety concerns in the elderly population that may be warrant a dose adjustment in the elderly need to be discussed with the medical officer.

3. Effect of Comedications: The proposed label language regarding coadministration with carbamazepine and fluoxetine is consistent with results seen in the present analysis.
4. Documentation of Analysis: The results obtained by the sponsor for individual subjects in study INT54 using NM control Stream differed from our results significantly (see Appendix 2); this may be due to the different compilers being used to perform these analyses. The population pharmacokinetic analyses for risperidone depot were performed by the sponsor using the MS Fortran Powerstation version 4 compiler. However, we at the Agency use Compaq Visual Fortran Compiler version 6.1 to perform population pharmacokinetic analysis/reanalysis. This was communicated to the sponsor via e-mail and telecon. To facilitate the review of this application, we requested the sponsor to: a) provide us with a computer with the versions of the Fortran compiler and NONMEM used in their analysis, b) control streams (no control streams were submitted electronically) and c) data sets (not submitted in the format used for the final models). The sponsor was unable to provide us with a) and b). Data sets that were re-submitted were again not in the format that was used in the final model.

Comments to Sponsor:

1. Data sets submitted to the FDA were different from those used by the sponsor in the population pharmacokinetic analysis. The sponsor used one combined file which consisted of data from all of the 3 Phase 3 trials. However, the files submitted to the Agency were data for each study. No control streams were submitted. In order for the Agency to evaluate the appropriateness of the sponsor's analysis, exact control streams as well as data sets with identically matching file names should be submitted in all future submissions. In addition, the individual two-stage analysis was not documented at all – only final results were displayed. Lack of submission of appropriate documentation of the analysis to the Agency can lead to duplication of efforts, burdensome reanalysis by the Agency as well as suboptimal use of resources.

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

Jogarao Gobburu, Ph.D.
Team Leader, Pharmacometrics Group,
DPE I, OCPB

cc: HFD-120 NDA 21-346
/MO/ E. Hearst
/CSO/S. Hardeman
/Biopharm/V. Sekar/M.Sunzel
/TL Biopharm/R. Uppoor, J. Gobburu
HFD-860 /DD DPE1/M. Mehta

APPENDIX I

Study Designs

RIS-INT-54: A comparative single-dose bridging bioavailability trial was carried out with risperidone depot microspheres originating from two different manufacturing scales: the ——— manufacturing scale in support of the Phase-I and II trials, and the final —— scale used in Phase-III trials and "to be marketed". Five single-dose treatments were tested: Treatments A (25 mg risperidone), B (50 mg) and C (75 mg) from the ——scale, and treatment D was the 50-mg reference batch from the ——process. An experimental batch (Treatment E) was also included for explorative purposes, but was not included in the population pharmacokinetic modeling. The trial consisted of two parts, each of 1 week duration, separated by a wash-out period of 3 weeks. Twenty-eight of the 56 chronic schizophrenic subjects received treatments Band D in a randomized, cross-over order. The other 28 subjects received treatment A or C in part I of the trial, and treatment E in part II.

RIS-INT-32: An open, comparative pharmacokinetic trial in 86 subjects with schizophrenic disorder was conducted to investigate the steady-state dose-proportionality of the risperidone microspheres formulation, and to compare the steady-state bioavailability between oral and depot treatment (2, 4 and 6 mg once daily versus 25, 50 and 75 mg biweekly) 6. One goal was to provide a guideline for switching from oral risperidone therapy to depot therapy. In addition, an exploratory oral supplement scheme was evaluated during the first two injection cycles. Subjects entering the trial were treated with oral risperidone until they reached steady state. They continued the oral therapy at the same dosage during Weeks1-3, and at half the dosage during weeks 4-5. Starting from Week 2 (Day 8), subjects who had been treated with oral risperidone 2 mg, 4 mg or 6 mg oral dose received risperidone depot injections of 25 mg, 50 mg or 75 mg, respectively, every 2 weeks.

RIS-INT-61: A double-blind efficacy and safety trial was conducted in 640 schizophrenic subjects, comparing the daily oral intake of risperidone tablets (2, 4 and 6 mg) with i.m. injections of the risperidone depot formulation (25, 50 and 75 mg) every two weeks. Once subjects had been stabilized on oral risperidone (2, 4 or 6 mg) for 8 weeks, they were randomly allocated to one of the two treatment groups. One group was treated with risperidone depot injection (25, 50 or 75 mg) every two weeks and placebo tablets once daily. The other group received placebo injections every two weeks and risperidone tablets (2, 4 or 6 mg) once daily: All active depot patients received oral supplementation with risperidone tablets during the first three weeks of the double-blind period (i.e., from the first injection until one week after the second injection).

RIS-USA-121: The efficacy of risperidone microspheres 25 mg, 50 mg and 75 mg was compared with placebo in a randomized, double-blind, parallel-group trial. The trial consisted of a 1-week run-in period during which subjects started on oral risperidone (2 mg for the first 4 days and 4 mg for the last 3 days), followed by a 12-week double-blind period during which subjects received i.m. injections of placebo; 25, 50, or 75 mg risperidone depot microspheres every 2 weeks. In addition, during the first 3 weeks of double-blind treatment, patients received placebo, 2, 4, or 6 mg of oral risperidone per day.

RIS-INT-57: In an open-label, long-term safety trial, 725 subjects with schizophrenia or schizo-affective disorder were administered biweekly i.m. injections of risperidone depot microspheres (25, 50 or 75 mg) over a period of 12 months. Elderly subjects (≥ 65 years, n=57) received the same treatment for a period of at least 6 months and up to 12 months. Risperidone oral supplementation was given during the first 2-3 weeks of the treatment period.

APPENDIX 2

Results obtained by the sponsor for individual subjects in study INT54 using NM control Stream displayed in the submission (refer to display 5 and Table 4 of Volume 33) differ from our results (please see below for results for subject ID 1 from study INT 54). This may be due to the different compilers being used to perform these analyses. We note that the population pharmacokinetic analyses for risperidone depot were performed by the sponsor using the MS Fortran Powerstation version 4 compiler. However, we at the Agency use Compaq Visual Fortran Compiler version 6.1 to perform population pharmacokinetic analysis/reanalysis.

```
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NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM)     DOUBLE PRECISION
NONMEM    VERSION V LEVEL 1.1
 DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

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 NO. OF DATA ITEMS IN DATA SET:  15
 ID DATA ITEM IS DATA ITEM NO.:  15
 DEP VARIABLE IS DATA ITEM NO.:  13
 MDV DATA ITEM IS DATA ITEM NO.: 14
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  0  0
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 RATE     EVID     INDX     LOGC      MDV     .ID.
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 ALG2     ALG3       D2       D3       F3    IPRE     SIGR     SIGA
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  0.1000E+01     0.2000E+03     0.5000E+04
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 ESTIMATE OUTPUT TO MSF:            NO
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 EIGENVLS. PRINTED:    NO
 SPECIAL COMPUTATION: YES
 COMPRESSED FORMAT:    NO
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 FILE TO BE FORWARDED:   NO
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0-- TABLE  2 --
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 PRINTED:                NO
 HEADER:                 YES
 FILE TO BE FORWARDED:   NO
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F2    ALG2    ALG3      D2      D3    SIGR
 SIGA      F3
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             TO COMPT.
  FROM       1    2    3    4    5    6    7
  COMPT.
    1        *    -    -    -    -    1    -
    2        -    *    -    2    -    -    -
    3        -    -    *    -    4    -    -
    4        -    -    -    *    -    3    -
    5        -    -    -    -    *    5    -
    6        -    -    -    -    -    *    6
             * LINK FROM A COMPARTMENT TO ITSELF IS NOT POSSIBLE
             - LINK BETWEEN THESE COMPARTMENTS IS NOT DEFINED FOR THIS
MODEL
0COMPARTMENT ATTRIBUTES—
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 COMPT. NO.    FUNCTION    INITIAL     ON/OFF       DOSE       DEFAULT
DEFAULT
                          STATUS      ALLOWED     ALLOWED     FOR DOSE
FOR OBS.
     1          DOSE1         ON          YES         YES         YES
NO
     2          DOSE2         ON          YES         YES         NO
NO
     3          DOSE3         ON          YES         YES         NO
NO
     4          INTER1        ON          YES         YES         NO
NO
     5          INTER2        ON          YES         YES         NO
NO
     6          CENTRAL       ON          YES         YES         NO
YES
     7          OUTPUT        OFF         YES         NO          NO
NO
1
 ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
 COMPT. NO.                                  INDICES
               SCALE       BIOAVAIL.    ZERO-ORDER   ZERO-ORDER   ABSORB
                           FRACTION     RATE         DURATION     LAG
     1           *             7           *            *           *
     2           *             8           *           11           9
     3           *            13           *           12          10
     4           *             *           *            *           *
     5           *             *           *            *           *
     6          14             *           *            *           *
     7           *             -           -            -           -
            - PARAMETER IS NOT ALLOWED FOR THIS MODEL
            * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
              WILL DEFAULT TO ONE IF APPLICABLE
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   TIME DATA ITEM IS DATA ITEM NO.:           5
   DOSE AMOUNT DATA ITEM IS DATA ITEM NO.:    7
   DOSE RATE DATA ITEM IS DATA ITEM NO.:     10
   COMPT. NO. DATA ITEM IS DATA ITEM NO.:     9

0PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE
TIMES.
0DURING SIMULATION, ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.
 OTHERWISE, ERROR SUBROUTINE CALLED ONLY WITH OBSERVATION EVENTS.
1
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EVALS.:16
 CUMULATIVE NO. OF FUNC. EVALS.:    16
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             0.1000E+00  0.1000E+00  0.1000E+00  0.1000E+00  0.1000E+00
```

```
 GRADIENT:    0.9066E+04  0.0000E+00 -0.4320E+05  0.0000E+00  0.5966E+03
0.6435E+04  0.1570E+05  0.4906E+04 -0.2678E+05 -0.1167E+05
            -0.2458E+04 -0.6541E+04 -0.9816E+05 -0.1422E+06  0.0000E+00
0ITERATION NO.:    10      OBJECTIVE VALUE:  0.5290E+01      NO. OF FUNC.
EVALS.:18
 CUMULATIVE NO. OF FUNC. EVALS.:  193
 PARAMETER: -0.3726E+00  0.1000E+00  0.1416E+00  0.1000E+00  0.4746E+00
0.1581E+00 -0.1354E-02  0.8230E-01 -0.6161E-02  0.1287E+00
             0.9809E-01  0.9611E-01  0.2320E+00  0.4713E+00  0.1000E+00
 GRADIENT:    0.2452E+00  0.0000E+00 -0.6775E+02  0.0000E+00  0.4992E+02
0.2988E+02 -0.1336E+03 -0.1760E+02 -0.8036E+01 -0.1304E+03
             0.1347E+02 -0.1117E+03  0.1168E+02  0.2135E+02  0.0000E+00
0ITERATION NO.:    20      OBJECTIVE VALUE: -0.1167E+01      NO. OF FUNC.
EVALS.:17
 CUMULATIVE NO. OF FUNC. EVALS.:  367
 PARAMETER: -0.3488E+00  0.1000E+00  0.1717E+00  0.1000E+00  0.2554E+00
0.1473E+00 -0.4639E-02  0.8456E-01  0.3300E-02  0.1934E+00
            -0.1602E-01  0.7580E-01  0.1926E+00  0.4862E+00  0.1000E+00
 GRADIENT:   -0.1226E+02  0.0000E+00  0.2215E+02  0.0000E+00 -0.5222E+01
0.2132E+01 -0.1932E+03  0.1319E+01 -0.1240E+02 -0.8024E+01
            -0.2292E+01 -0.7731E+01  0.1755E+01 -0.1275E+02  0.0000E+00
0ITERATION NO.:    30      OBJECTIVE VALUE: -0.3025E+01      NO. OF FUNC.
EVALS.:17
 CUMULATIVE NO. OF FUNC. EVALS.:  538
 PARAMETER: -0.2955E+00  0.1000E+00  0.1702E+00  0.1000E+00  0.3021E+00
0.1223E+00 -0.8587E-02  0.8524E-01  0.6135E-01  0.2006E+00
             0.8571E-02  0.9505E-01  0.1656E+00  0.4964E+00  0.1000E+00
 GRADIENT:    0.1655E+01  0.0000E+00  0.1116E+02  0.0000E+00  0.9930E-01
-0.3956E+01  0.1769E+03 -0.8255E+01  0.4083E+01  0.1098E+01
             0.1576E+01  0.1061E+02 -0.3907E+00  0.6341E+01  0.0000E+00
0ITERATION NO.:    40      OBJECTIVE VALUE: -0.4802E+01      NO. OF FUNC.
EVALS.:17
 CUMULATIVE NO. OF FUNC. EVALS.:  712
 PARAMETER: -0.2927E+00  0.1000E+00  0.1626E+00  0.1000E+00  0.2863E+00
0.1170E+00 -0.1817E-01  0.8378E-01  0.1037E+00  0.1968E+00
             0.3071E-02  0.9642E-01  0.1487E+00  0.5006E+00  0.1000E+00
 GRADIENT:    0.3549E+01  0.0000E+00 -0.7007E+01  0.0000E+00 -0.1716E+01
0.8120E-01  0.1428E+03  0.4041E+01  0.5747E+02 -0.7557E+01
             0.3446E+00 -0.9193E+01 -0.3044E+01 -0.8376E+00  0.0000E+00
0ITERATION NO.:    50      OBJECTIVE VALUE: -0.4883E+01      NO. OF FUNC.
EVALS.:18
 CUMULATIVE NO. OF FUNC. EVALS.:  883
 PARAMETER: -0.3016E+00  0.1000E+00  0.1632E+00  0.1000E+00  0.3050E+00
0.1190E+00 -0.1857E-01  0.8354E-01  0.1040E+00  0.1991E+00
            -0.1239E-02  0.9830E-01  0.1510E+00  0.5002E+00  0.1000E+00
 GRADIENT:   -0.8709E+00  0.0000E+00 -0.4994E+00  0.0000E+00  0.4326E+00
-0.2507E+01  0.2470E+02 -0.3025E+01  0.1072E+02 -0.1903E+01
            -0.1254E+00  0.1089E+01 -0.5234E+01 -0.4129E+01  0.0000E+00
0ITERATION NO.:    60      OBJECTIVE VALUE: -0.4927E+01      NO. OF FUNC.
EVALS.:32
 CUMULATIVE NO. OF FUNC. EVALS.: 1070
 PARAMETER: -0.3000E+00  0.1000E+00  0.1633E+00  0.1000E+00  0.3013E+00
0.1197E+00 -0.1885E-01  0.8367E-01  0.1042E+00  0.2000E+00
             0.3853E-05  0.9872E-01  0.1644E+00  0.5011E+00  0.1000E+00
```

```
 GRADIENT:  -0.1677E-02  0.0000E+00 -0.3862E-02  0.0000E+00  0.6024E-03
0.4357E-02 -0.1488E+00  0.3274E-02 -0.4082E-01  0.5186E-02
            0.3834E-03 -0.1952E-01 -0.8309E-04 -0.1333E-01  0.0000E+00
0ITERATION NO.:   63      OBJECTIVE VALUE: -0.4927E+01      NO. OF FUNC.
EVALS.: 0
 CUMULATIVE NO. OF FUNC. EVALS.: 1134
 PARAMETER: -0.3000E+00  0.1000E+00  0.1633E+00  0.1000E+00  0.3013E+00
0.1197E+00 -0.1885E-01  0.8367E-01  0.1041E+00  0.2000E+00
           -0.1641E-06  0.9872E-01  0.1644E+00  0.5011E+00  0.1000E+00
 GRADIENT:  -0.2899E-05  0.0000E+00  0.1011E-04  0.0000E+00 -0.4016E-05
0.7755E-04 -0.1286E-02  0.4216E-03 -0.7016E-03  0.8627E-04
           -0.1633E-04 -0.7570E-04 -0.7085E-04  0.9027E-04  0.0000E+00
0MINIMIZATION SUCCESSFUL
 NO. OF FUNCTION EVALUATIONS USED: 1134
 NO. OF SIG. DIGITS IN FINAL EST.:  5.9
0ESTIMATE OF THETA IS NEAR THE BOUNDARY AND IS PROBABLY UNINTERPRETABLE
0R MATRIX ALGORITHMICALLY SINGULAR
 AND ALGORITHMICALLY NON-POSITIVE-SEMIDEFINITE
0COVARIANCE STEP ABORTED

************************************************************************
**************************************************
 **********************
**********************
 **********************        MINIMUM VALUE OF OBJECTIVE FUNCTION
**********************
************************************************************************

****************************          -4.927
**************************************************
************************************************************************
**************************************************
 **********************
**********************
 **********************           FINAL PARAMETER ESTIMATE
**********************
 **********************
**********************

 THETA - VECTOR OF FIXED EFFECTS PARAMETERS    *********

            TH 1      TH 2      TH 3      TH 4      TH 5      TH 6
TH 7       TH 8      TH 9      TH10      TH11      TH12
              TH13      TH14      TH15

          4.00E+01  5.00E+00  5.20E+02  2.00E+02  4.00E+01  1.39E-02
4.53E-03  9.18E-03  8.31E-01  8.00E+02  1.37E-11  2.93E+02
          6.00E+02  5.33E-01  2.00E-01


 OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

             ETA1      ETA2
```

```
 ETA1
+         1.00E+00

 ETA2
+         0.00E+00  1.00E+00

**********************
**********************
 **********************        TABLES OF DATA AND PREDICTIONS
**********************
 **********************
**********************


1TABLE NO.  1


 LINE NO.     TID       TIME       IPRE       DOSE       CONC        AMT
CMT       INDX       LOGC       PRED       RES        WRES

    1
+         1.00E+00  0.00E+00  0.00E+00  5.00E+01  0.00E+00  5.00E+01
2.00E+00  1.00E+00  0.00E+00  0.00E+00  0.00E+00  0.00E+00

    2
+         1.00E+00  0.00E+00  0.00E+00  5.00E+01  0.00E+00  5.00E+01
3.00E+00  1.00E+00  0.00E+00  0.00E+00  0.00E+00  0.00E+00

    3
+         1.00E+00  0.00E+00  0.00E+00  5.00E+01  0.00E+00  5.00E+01
1.00E+00  1.00E+00  0.00E+00  0.00E+00  0.00E+00  0.00E+00

    4
+         1.00E+00  5.00E-02 -2.72E-01  5.00E+01  4.70E+00  0.00E+00
6.00E+00  1.00E+00  1.55E+00  7.28E-01  8.19E-01  1.54E+00

    5
+         1.00E+00  9.00E-02 -1.57E-01  5.00E+01  3.65E+00  0.00E+00
6.00E+00  1.00E+00  1.29E+00  8.43E-01  4.51E-01  8.47E-01

    6
+         1.00E+00  1.70E-01 -1.36E-01  5.00E+01  2.25E+00  0.00E+00
6.00E+00  1.00E+00  8.11E-01  8.64E-01 -5.31E-02 -9.97E-02

    7
+         1.00E+00  3.40E-01 -1.48E-01  5.00E+01  9.50E-01  0.00E+00
6.00E+00  1.00E+00 -5.13E-02  8.52E-01 -9.03E-01 -1.70E+00

    8
+         1.00E+00  2.40E+01 -1.96E+00  5.00E+01  2.00E-01  0.00E+00
6.00E+00  1.00E+00 -1.61E+00 -9.64E-01 -6.45E-01 -1.21E+00

    9
```

```
+        1.00E+00  4.80E+01 -3.64E+00  5.00E+01  1.00E-01  0.00E+00
6.00E+00  1.00E+00 -2.30E+00 -2.64E+00  3.40E-01  6.39E-01

   10
+        1.00E+00  9.60E+01 -3.95E+00  5.00E+01  1.40E-01  0.00E+00
6.00E+00  1.00E+00 -1.97E+00 -2.95E+00  9.88E-01  1.85E+00

   11
+        1.00E+00  1.68E+02 -2.95E+00  5.00E+01  1.30E-01  0.00E+00
6.00E+00  1.00E+00 -2.04E+00 -1.95E+00 -8.61E-02 -1.62E-01

   12
+        1.00E+00  2.40E+02 -2.39E+00  5.00E+01  1.20E-01  0.00E+00
6.00E+00  1.00E+00 -2.12E+00 -1.39E+00 -7.26E-01 -1.36E+00

   13
+        1.00E+00  3.36E+02 -1.95E+00  5.00E+01  1.70E-01  0.00E+00
6.00E+00  1.00E+00 -1.77E+00 -9.47E-01 -8.25E-01 -1.55E+00

   14
+        1.00E+00  4.08E+02 -1.73E+00  5.00E+01  3.40E-01  0.00E+00
6.00E+00  1.00E+00 -1.08E+00 -7.30E-01 -3.49E-01 -6.56E-01

   15
+        1.00E+00  5.04E+02 -1.53E+00  5.00E+01  7.90E-01  0.00E+00
6.00E+00  1.00E+00 -2.36E-01 -5.31E-01  2.95E-01  5.54E-01

   16
+        1.00E+00  5.76E+02 -1.43E+00  5.00E+01  8.20E-01  0.00E+00
6.00E+00  1.00E+00 -1.98E-01 -4.27E-01  2.28E-01  4.28E-01

   17
+        1.00E+00  6.72E+02 -1.37E+00  5.00E+01  8.10E-01  0.00E+00
6.00E+00  1.00E+00 -2.11E-01 -3.66E-01  1.56E-01  2.92E-01

   18
+        1.00E+00  7.44E+02 -1.43E+00  5.00E+01  8.20E-01  0.00E+00
6.00E+00  1.00E+00 -1.98E-01 -4.27E-01  2.28E-01  4.29E-01

   19
+        1.00E+00  8.40E+02 -8.51E-01  5.00E+01  1.03E+00  0.00E+00
6.00E+00  1.00E+00  2.96E-02  1.49E-01 -1.20E-01 -2.24E-01

   20
+        1.00E+00  9.12E+02  4.62E-01  5.00E+01  2.33E+00  0.00E+00
6.00E+00  1.00E+00  8.46E-01  1.46E+00 -6.16E-01 -1.16E+00

   21
+        1.00E+00  1.01E+03  1.03E+00  5.00E+01  5.86E+00  0.00E+00
6.00E+00  1.00E+00  1.77E+00  2.03E+00 -2.61E-01 -4.89E-01

   22
+        1.00E+00  1.34E+03 -5.23E-01  5.00E+01  1.06E+00  0.00E+00
6.00E+00  1.00E+00  5.83E-02  4.77E-01 -4.19E-01 -7.86E-01
```

```
start 04-18-2002
end   04-18-2002
exe  nmtcl
user 0:1.76
real 0:1.76
sys  0:0
start 04-18-2002
end   04-18-2002
exe  nonmem
user 0:5.05
real 0:5.05
sys  0:0
```

25 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

7.9 FILING MEMO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	NDA 21-346	Brand Name	Risperdal Consta
OCPB Division I	HFD-860	Generic Name	risperidone
Medical Division	HFD-120	Drug Class	Benzisoxazole derivatives
OCPB Reviewer	Maria Sunzel, Ph.D.	Indication(s)	Treatment of schizophrenia
OCPB Team Leader	Ramana Uppoor, Ph.D.	Dosage Form	Depot injection (microspheres)
Date of Submission	August 31, 2001	Dosing Regimen	25 mg every 2 weeks (max 50 mg biweekly)
Estimated Due Date of OCPB Review	Early May, 2002	Route of Administration	Parenteral (deep IM)
PDUFA Due Date	June 30, 2002	Sponsor	Janssen Research Foundation
Division Due Date	Mid-May, 2002	Priority Classification	3S (new formulation)

BACKGROUND: The Agency has approved two oral formulations (IR tablets & solution) of risperidone. The sponsor has developed a depot injection intended for the treatment of schizophrenia in adult patients (≥18 years of age). In the new formulation, risperidone is encapsulated in microspheres ——————. The product package consists of a vial with microspheres, a pre-filled syringe containing the diluent (2 mL) and needles. The vial content will be mixed with the diluent immediately before administration. The sponsor intends to market three dosage strengths (25 mg, 37.5 mg, and 50 mg risperidone per vial). After the IM injection, the drug is slowly released over 4-6 weeks as the microspheres erode (3-week lag phase until drug absorption starts).

The sponsor has performed 13 studies in total (6 single dose, 7 repeated dose studies). All studies were performed in the target population. Risperidone was studied in the dose range 25-100 mg, but the sponsor concludes that maximal effect is achieved after a 50-mg dose. Therefore, an intermediate dosage strength of 37.5 mg was developed late in the program, and was only tested in one single dose trial.

PK information from the submitted trials covers the following items:

- Pharmacokinetics after single doses & repeated doses of risperidone (IM injection)
- Relative bioavailability (clinical trial vs. to-be-marketed formulations & tablets given PO)
- Dose proportionality (25-50-75 mg & 37.5-50-62.5 mg)
- Population exposure-response analysis (PK/PD, Phase III trials)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	No. studies submitted	No. studies reviewed	Comments
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Electronic submission
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	Incomplete		Reviewed bioanalytical methods	Need to contact sponsor for method documentation (study validation reports OK, but one method validation report missing)
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-			
multiple dose:	-			
Patients-				
single dose:	X	7	7	5 studies w/clin. trial formulation, 2 w/TBM formulation
multiple dose:	X	6	6	3 Phase III studies w/TBM formulation (PPK)

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	(X)		X	PPK analysis
In-vivo effects of primary drug:	-		2 (Phase 1 studies)	Lithium, valporate
In-vitro:	-			
Subpopulation studies -				
ethnicity:	(X)		x	PPK analysis
gender:	(X)		x	PPK analysis
pediatrics:	-			
geriatrics:	(X)		x	PPK analysis
renal impairment:	-			
hepatic impairment:	-			
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X		x	PPK analysis
Population Analyses -				
Data rich:	X		x	PPK: Combined 2 PK studies &
Data sparse:	X		x	the 3 Phase III studies
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X		x	
Bioequivalence studies -				
traditional design; single / multi dose:	(X)		x	Rel. BA pilot &TBM formulations
replicate design; single / multi dose:	-			
Food-drug interaction studies:	**Not applicable**			
Dissolution:	X		x	In CMC section (Item 4)
(IVIVC):	-			
Bio-waiver request based on BCS	**Not applicable**			
BCS class	**Not applicable**			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Deferral, proposal sent to FDA May 2000
Literature References	?		x	Not available on paper or electronically, but referred to in text
Total Number of Studies	13		15	See attachment

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	Considered 'filable' although sponsor did not structure item 6 according to the Guidance for electronic submissions
Comments sent to firm?	X	• The sponsor is asked to provide 1 bioanalytical method report (Item 6 summary: ref PK 3, electronic version is not linked to any document, and has not been located in any of the study reports) • The sponsor is asked to identify the volume (referred to on top of page 93, Item 6) that contains the literature references (ref L 1 – L 22) in Item 6, since the electronic version does not contain links. • Please provide data sets (as SAS transport files) for the pharmacokinetic parameters from the studies (individual values). • Please provide the data sets (final & for the different steps in the model building) that were used for the NONMEM analysis electronically as SAS transport files. • At the pre-NDA meeting the sponsor was asked to provide data regarding the effects on the dissolution profile (e.g. *in vitro*) of the drug product of different temperatures, mimicking body temperatures seen at a high fever. Please address this question, or give directions to where this issue is addressed in the NDA.
QBR questions (key issues to be considered)	• Does the depot injection truly have an extended release profile *in vivo*? • Is there a potential for dose dumping at higher temperatures, e.g. fever? • Is the inter- & intra-individual variability calculated for the PK parameters of risperidone after administration of the depot injection? • Is the PPK analysis appropriate? • Are the proposed *in vitro* dissolution methods acceptable? • Does the submitted data support the proposed label text? • Is the proposed label text (including drug-drug interactions, special populations & dosing recommendations) appropriate?	
Other comments or information not included above	The sponsor has also provided background information on the pharmacokinetics of risperidone (basic properties, DDIs, special populations) from earlier risperidone NDAs (oral formulations: solution & tablets)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

cc: NDA 21-346, HFD-850 (Electronic Entry /Lee), HFD-120 (Hardeman), HFD-860 (Mehta, Uppoor, Sahajwalla, Sunzel)

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Maria Sunzel
6/21/02 06:44:33 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
6/21/02 06:58:51 PM
BIOPHARMACEUTICS