CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

New Drug Application - Amendment
Complete Response to Approvable Letter
Clinical Pharmacology Review - ADDENDUM

NDA:	21-999
Submission Type:	AZ – Major Amendment Multiple Review Disciplines
Amendment Number:	14
Description:	Complete Response to Approvable Letter
Generic Name:	Paliperidone
Formulation: **Strengths:** **Route:**	Extended Release Tablets 3 mg, 6 mg, 9 mg, 12 mg, [redacted] PO
Brand Names	[redacted]
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Titusville, NJ
Date of Submission of Complete Response:	October 20, 2006
Original NDA Submission Date:	November 30, 2005
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

1 EXECUTIVE SUMMARY

This addendum addresses the sponsor's responses to the two OCP phase IV commitment requests, (FDA requests #2 and #3). OCP acknowledges the sponsor's commitment to perform request #2, and agrees with the sponsor that request #3 is not justified.

1.1 Conclusions and Recommendations

1.1.1 FDA POST-APPROVAL COMMITMENT REQUEST #2

Within 3 months of approval, you should provide information that addresses the possibility that ethanol might result in dose dumping. This should include information on the solubility of the coating materials in ethanol, and information from other similar OROS formulations. If such information cannot exclude the possibility of dose dumping and/or is not available, a dissolution experiment in ethanolic solutions should be performed and the results provided.

OCP Comment:

Sponsor agreed to post-marketing commitment #2.

1.1.2 FDA POST-APPROVAL COMMITMENT REQUEST #3:

Within 9 months of approval, results of a drug interaction study with maintenance dosing of a proton pump inhibitor should be submitted as increased gastrointestinal pH may decrease bioavailability. Depending on whether an interaction is found and the magnitude of the interaction, an additional study with antacids may be justified.

OCP Comment:

The initial OCP concern was due to the decrease in paliperidone bioavailability from paliperidone OROS with time post ingestion. Studies with a variety of different formulations administered in different ways indicated that the lower bioavailability with the OROS formulation is due to regional differences in bioavailability as the formulation progresses along the GI tract and releases drug. OCP's original thoughts were that this regional difference is likely to be at least partially due to decreasing solubility of the drug substance with increasing pH. However, the pKa of paliperidone is 8.24 and the sponsor has provided information that normal intra-duodenal pH is around 6.0, and the intra-duodenal pH doesn't vary much over a 24 hour period and is relatively unaffected by proton-pump inhibitors. A quick literature search suggests that H2 antagonists and all but extremely high doses of antacids are likely to have similar effects on duodenal pH, and meals are likely to have as large or larger effect. In addition, the sponsor provides some population PK data that Cl/F is 12% lower in subjects taking proton pump inhibitors, (PPIs), which is the opposite of what would be expected if there were an interaction. Taken together it's likely that regional differences in absorption may be more due to differences in transport than pH, and OCP agrees with the sponsor that a drug interaction study with a PPI or other pH altering agent is not justified at this time.

1.2 Comments for Sponsor

OCP agrees with the sponsor that a drug interaction study with a proton pump inhibitor, (PPI), or other pH altering agent is not justified at this time.

2 SIGNATURES

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.
Senior Reviewer, OCP DPE1

Date

Raman K. Baweja, Ph.D.
Team Leader, OCP DPE1

Date

CC:

DFS	21-999 Original Submission and Response to AE
DPP HFD-120	LaughrenT, MathisM, KhinN, BruggeK, KeidrowK
DCP1 HFD-860	KavanaghR, BawejaR, MehtaM

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

/s/

Ron Kavanagh
12/4/2006 04:37:46 PM
BIOPHARMACEUTICS

Raman Baweja
12/4/2006 05:06:02 PM
BIOPHARMACEUTICS

New Drug Application - Amendment
Complete Response to Approvable Letter
Clinical Pharmacology Review

NDA:	21-999
Submission Type:	AZ – Major Amendment Multiple Review Disciplines
Amendment Number:	14
Description:	Complete Response to Approvable Letter
Generic Name:	Paliperidone
Formulation: **Strengths:** **Route:**	Extended Release Tablets 3 mg, 6 mg, 9 mg, 12 mg, [redacted] PO
Brand Names	[redacted]
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Titusville, NJ
Date of Submission of Complete Response:	October 20, 2006
Original NDA Submission Date:	November 30, 2005
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

1 EXECUTIVE SUMMARY

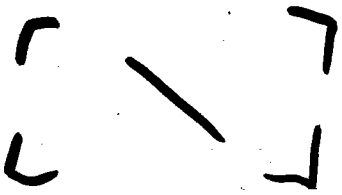
1.1 Description of Submission

The present submission contains the following two items of interest to OCP:

- Sponsor's Counter-Proposal to AE Letter Labeling
- Response to Proposed Dissolution Specifications

The proposed dissolution specifications as outlined in the September 30th, 2006 approvable letter are as follows:

2 hours
8 hours
14 hours
18 hours
24 hours



The sponsor has agreed with the 2, 8, and 24 hour specifications, but had challenged the range for the 14 hour, and the need for the 18 hour time point.

1.2 Conclusions and Recommendations

1.2.1 Dissolution Specifications

OCP has reviewed the sponsor's response and finds that the original FDA dissolution specifications as outlined in the AE letter of September 30th, 2006 are justified and should be adopted.

1.2.2 Labeling

OCP comments regarding the sponsor's response to the labeling have been previously sent to the Division of Psychiatric Drug Products for collation into a master response document. OCP changes and comments that were sent are included in APPENDIX 1 beginning on page 19, and are included here for documentation.

1.3 Comments for Sponsor

The following should be sent to the sponsor in its entirety.

The final regulatory dissolution method for all strengths of Paliperidone Extended Release tablets are shown in Table 1.

Table 1 Final Regulatory Dissolution Method and Specifications for Paliperidone Extended Release Tablets 3 mg, 6 mg, 9 mg, and 12 mg

Parameter	Dissolution Method and Specifications
Apparatus type:	USP Type VII Reciprocating Disk
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5
Volume:	50 ml
Temperature:	37 ± 0.5 °C
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)
Amplitude:	2 – 3 cm
Sampling Times:	2, 8, 14, 18, and 24 hours
Specifications (% of Label Claim)	2 hours 8 hours 14 hours 18 hours 24 hours
Acceptance Criteria:	Conforms to USP XXVIIII <724> acceptance Table 1 for extended-release articles

2 REVIEW

2.1 Pivotal Clinical Batches

The sponsor included raw data for the pivotal clinical batches and for the stability batches from hours 14 through 24 of sampling.

Scatter-plots and high-low plots with means of the percent dissolved at 14 hours and 18 hours with the proposed specification ranges are shown in Figure 1 and Figure 2 respectively for the pivotal clinical batches.

These plots demonstrate that the proposed dissolution specifications at 14 and 18 hours are appropriate.

Figure 3 includes scatter-plots and high-low plots with means of the percent dissolved at 20 hours for the pivotal clinical batches. These plots show that in some cases there is already [redacted] dissolution at 20 hours and this demonstrates the need for a dissolution sample prior to 20 hours and after 14 hours.

The 18 hour sampling time is the only time with sufficient difference in dissolution from the 14 hours sample and with less than [redacted] dissolution to be acceptable.

Figure 1 and Figure 2 also demonstrate the high intra- and inter-batch variability and the likely need to go to L2 frequently.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*1

2.2 Stability Data

The commercial scale batches and complete stability data were also examined.

The manufacturing process was developed in Mountain View, California and subsequently transferred to the commercial manufacturing facility in Vacaville, California. The manufacturing process was carried out at a batch size of [redacted] for clinical and stability batches. For the actual commercial batches produced at Vacaville, California the batch size will be [redacted]

[redacted]

Table 2 Facilities Involved in Manufacturing, Packaging, Release and Stability Testing of Paliperidone ER Tablets

Facility	Responsibility/Possibilities of the Facility
ALZA Corporation 700 Eubanks Drive Vacaville, CA 95688 Registration number 2938701	Manufacture Release and stability testing of finished product
Janssen-Ortho L.L.C. HC 02 Box 19250 State Road 933 Km 0.1 Mamey Ward Gurabo, Puerto Rico 00778-9629 Registration number: 2650104	Primary and secondary packaging
[redacted]	[redacted]
	[redacted]

One batch of each tablet strength produced on the commercial equipment in Vacaville California were used for stability testing. In addition another 2 batches each of 3 mg and [redacted] tablets produced on the development equipment at Mountain View California were also placed on stability.

For each stability line, the baseline dissolution data at 14 hours is shown in Figure 4 to Figure 6 and for 18 hours in Figure 7 to Figure 9. What's interesting is that in every case dissolution is more rapid for the tablets packaged in blisters compared with those packaged in bottles. The odds of this are [redacted]

When dissolution data over [redacted] is examined for both the 14 and 18 hour samples, (see Figure 10 to Figure 27), there is no indication of any stability problems as trend lines on average remain flat, with increases and decreases over time attributable to normal variability. However, individual tablets fall outside of the proposed specification ranges quite frequently due to the high intra- and inter-dissolution experiment variability, thereby necessitating L2 level dissolution testing. Typically whether the tablets dissolution rates are falling above or below the proposed specification ranges depends upon the average

dissolution rate at baseline. Consequently, if the average dissolution at baseline is relatively high or low that particular batch is more likely to undergo L2 dissolution testing at some point, but it may be as early as 1 month after baseline testing rather than later, (See Figure 10 to Figure 27).

Examination of manufacturing site, and time lapse between various manufacturing and packaging steps and dissolution testing failed to reveal any clear patterns as to cause. However, there were significant delays before tablets were packaged and tested that do not appear reasonable, (see Table 3 and Table 4).

Figure 28 and Figure 29 show histograms of the distributions of all stability samples at the 14 and 18 hour sampling times respectively. It's clear that only a single experiment would necessitate going to L3 testing although this experiment would pass at L3.

Although not shown the average dissolution rates for every experiment falls within the [redacted] specification range.

9 Page(s) Withheld

✓ Trade Secret / Confidential

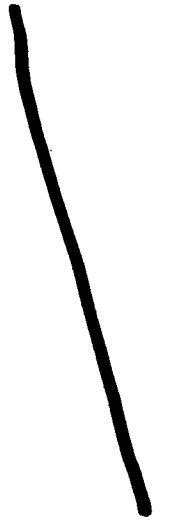
_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

Table 4 Average 14 Hour Dissolution Rates for Stability Batches Produced at Commercial Site at Release, and at Stability Experiment Baseline

Strength		3 mg	6 mg	9 mg	12 mg
Lot		406819	406946	406931	406932
Date of Manufacture		11-Mar-04	25-Mar-04	15-Mar-04	16-Apr-04
Date of Release Testing		29-Mar-04	22-Apr-04	2-Apr-04	30-Apr-04
14 hr % LC at Release		56%	52%	53.7%	56%
Blister	Date of Packaging	7-May-04	8-May-04	8-May-04	5-May-04
	Date of Baseline Stability Testing	14-Jun-04	7-Jun-04	1-Jun-04	28-Jun-06
	14 hr %LC at Baseline	55.2%	55.8%	53.4%	55.5%
75 cc Bottle	Date of Packaging	18-May-04	19-May-04	5-May-04	19-May-04
	Date of Baseline Stability Testing	7-Jun-04	28-Jun-04	25-May-04	14-Jun-06
	14 hr %LC at Baseline	53.2%	48.2%	49.7%	53.9%
160 cc Bottle	Date of Packaging	23-Apr-04	24-Apr-04	21-Apr-04	27-May-04



1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 3

3 SIGNATURES

Ronald E. Kavanagh, B.S.Pharm., Pharm.D., Ph.D.
Senior Reviewer, OCP DPE1

Date

Raman K. Baweja, Ph.D.
Team Leader, OCP DPE1

Date

CC:

DFS	21-999 Original Submission and Response to AE
DPP HFD-120	LaughrenT, MathisM, KhinN, BruggeK, KeidrowK
DCP1 HFD-860	KavanaghR, BawejaR, MehtaM
ONDQA	OliverT, TeleC

APPENDIX 1 OCP Labeling Comments

The following document is based on the labeling included in the FDA AE letter of September 30th, 2006. This text is shown in black type.

The sponsor's changes are indicated by green ink.

OCP's changes to the sponsor's counterproposal are indicated by red ink.

Deletions are indicated by single line ~~strikeouts~~, and additions are indicated by single underlines, regardless of whether from the sponsor of OCP.

42 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 4

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

/s/

Ron Kavanagh
12/1/2006 10:57:06 AM
BIOPHARMACEUTICS

Raman Baweja
12/1/2006 05:22:33 PM
BIOPHARMACEUTICS

New Drug Application
Notes for Teleconference
Clinical Pharmacology Review

NDA:	21-999
Generic Name:	Paliperidone
Formulation: **Strengths:** **Route:**	Extended Release Tablets 3 mg, 6 mg, 9 mg, 12 mg, [redacted] PO
Brand Names	[redacted]
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Titusville, NJ
Original NDA Submission Date:	November 30, 2005
Date of Meeting Request:	October 11, 2006
Date of Teleconference:	October 13, 2006
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

1 BACKGROUND

This teleconference was to discuss the dissolution specifications outlined in the approvable letter.

The sponsor wishes to widen the proposed dissolution specifications because the wide inter-individual variability in dissolution is likely to either result in a expiry shorter than their desired expiry of [redacted] or recall of [redacted] of batches if a [redacted] expiry is granted.

The background package included a graph of clinical batch dissolution data at release, but this graph included data from both pivotal and non-pivotal clinical batches (see Figure 1). The pivotal clinical drug product batches used in the phase III efficacy and safety studies are indicated by colored boxes around the SS numbers. The multiple boxes associated with each color indicate a different packaging configuration. Consequently, the appropriate data to use is from these [redacted] dissolution experiments rather than the [redacted] experiments used by the sponsor.

Individual units with dissolution outside of [redacted] are circled. The values are highlighted by a box with red dashed lines was reported to have a mean dissolution of [redacted] in the NDA, whereas this is inconsistent with data in Figure 1.

Individual unit dissolution data for the pivotal clinical batches were not submitted in the original FDA.

2 TELECONFERENCE NOTES

The sponsor and the FDA agreed on dissolution specifications at 2 hours and 8 hours.

Discussion included the various points made by the sponsor in the background package and concerns OCP had, the problematic nature of using claims of having used [redacted] tablets in clinical trials to support a [redacted] expiry and the inability to adequately assess the nature of any clinical differences, and OCP's rationale for the dissolution specifications proposed by FDA.

1 Page(s) Withheld

✔ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 5

3 COMMENTS TO SPONSOR

The following comments should be communicated to the sponsor.

Upon reflection, OCP would like the sponsor to provide the following information in their complete response:

All individual unit dissolution data at release (and at time 0 of stability studies) for batches used in the pivotal phase III clinical efficacy and safety studies, and for batches used in study P01-1008, for samples collected at 14, and 18 through 24 hours.

Post meeting notes:

The justification should include information on statistical methods, data files, and command files used to generate calculations and simulations.

Please indicate which dissolution data was generated with encapsulated tablets.

N.B. The above comments do not include requests made by the chemistry team.

4 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Date**

Senior Reviewer
Division of Clinical Pharmacology I

Ramen Baweja, Ph.D. **Date**

Team Leader
Division of Clinical Pharmacology I

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

/s/

Ron Kavanagh
10/19/2006 10:25:12 AM
BIOPHARMACEUTICS

Raman Baweja
10/19/2006 11:46:24 AM
BIOPHARMACEUTICS

New Drug Application
Clinical Pharmacology Review

NDA:	21-999			
Generic Name:	Paliperidone			
Formulation: **Strengths:** **Route:**	Extended Release Tablets 3 mg, 6 mg, 9 mg, 12 mg, [redacted] PO			
Brand Names	[redacted]			
Sponsor:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Titusville, NJ			
Original Submission Date:	November 30, 2005			
Supplements to Original Submission	0001 0002* 0003 0004 0005 0006* 0007 0008* 0009 0010	January 12, 2006 March 29, 2006 May 4, 2006 May 26, 2006 June 15, 2006 June 15, 2006 June 27, 2006 July 27, 2006 July 31, 2006 August 29, 2006	BM SU BC BC BM BZ BM BM BC BZ	Minor Amendment – Medical 120 day Safety Update (Includes revised phase I study reports) Minor Amendment – Chemistry Minor Amendment – Chemistry Minor Amendment – Multiple Disciplines (Revised Labeling) Minor Amendment – Medical Minor Amendment – Medical (impact of investigator site) Minor Amendment – Chemistry Minor Amendment – Multiple Disciplines
Related NDAs	20-272 Risperidone IR Tablets 20-588 Risperidone Oral Solution 21-346 Risperidone IM Injection 21-444 Risperidone Orally Disintegrating Tablets			
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.			

* Amendments with information reviewed by OCP

1 TABLE OF CONTENTS

1.1 Table of Contents

1.2 List of Tables

1.3 List of Figures

2 EXECUTIVE SUMMARY

2.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed NDA #21-999 submitted January 12, 2006, March 29, 2006, May 4, 2006, May 26, 2006, June 15, 2006, June 15, 2006, June 27, 2006, June 27, 2006, July 27, 2006, July 31, 2006 and August 29, 2006.

OCPB finds this application acceptable provided that currently outstanding issues are adequately resolved, (e.g. agreement on dissolution and labeling).

Comments should be communicated to the sponsor as appropriate (see Section 2.3.3 Dissolution under Section 2.3.1 Comments to the Sponsor on page 13. Labeling comments should also be communicated to the sponsor as appropriate (see Section 2.3.4 Labeling Comments on page 14).

2.2 Summary of Major Conclusions

The information provided was close to complete, more so than is typically seen.

The major findings are as follows:

- Exposures to paliperidone and its enantiomers after maximal dosing are less than after maximal doses of risperidone.
- There are regional variations in bioavailability possibly due to pH. Consequently bioavailability may be decreased by a shortened GI system or pH changes.
- Inter and intraday variability is likely to be quite high, as peak concentrations from one day can occur on the following day.
- There is a food effect that may result in clinically observable CNS and cardiovascular side effects, as smaller changes in other studies did result in these types of side effects.
- There does not appear to be a gender effect.
- There was no indication of a difference between Japanese and Caucasians; however there was little or no data to establish this in most other racial groups.
- Exposures are higher in the elderly than young.
- Paliperidone is eliminated to a significant extent by both renal and hepatic mechanisms.
- Paliperidone dosage needs to be reduced in renal insufficiency.
- Moderate hepatic insufficiency did not affect the pharmacokinetics of paliperidone, although the possibility of a pharmacodynamic interaction for any CNS active agent should be considered.
- There are no clinically significant changes in sleep parameters.
- There is a higher incidence in side effects in the presence of trimethoprim, possibly due to protein binding changes.

- There is a measurable increase in QTc, (9.3 mSec) that is greater than with the control drug moxifloxacin, (6.1 mSec).
- There is a dose response that suggests that the maximal therapeutic index occurs at a dose of 6 mg.
- [redacted]

2.3 Comments

2.3.1 Comments to the Medical Division

From a pharmacokinetic and clinical pharmacology perspective paliperidone has very desirable properties. The side effect profile appears to be what is expected based upon the receptor binding and may well be unavoidable for the current state of knowledge and pharmacologic approach to managing psychosis. Paliperidone does not tend to possess the pharmacokinetic properties that result in the typical issues with adjusting dosage that are typical with lipophilic drugs.

2.3.2 Comments to the Sponsor

1. The proposed dissolution specifications are not acceptable. We are proposing the following specifications:

   2 hours [redacted]
   8 hours
   14 hours
   18 hours
   24 hours

2. [redacted]

3. Our review suggests that there might be some advantage in terms of side effects for the (+) enantiomer compared to the racemate when both are administered as OROS formulations and this may be of interest to you. If pursued this review finding would need to be confirmed as well as possibly whether there is similar or differential efficacy.

4. Our review of the available information and your dose response analysis lead us to believe that it may be possible to predict who may be better or worse candidates for increasing or decreasing the dose from 6 mg in the case of an inadequate therapeutic response or unacceptable side effects. This may also be useful in obtaining an adequate therapeutic response more quickly as well as assuring who is likely to obtain a fair therapeutic trial before switching to another product. Additional analysis of samples for genotype as well as pharmacodynamic modeling would be needed to investigate this. We would be amenable to discussing this in the future.

2.3.3 Dissolution

The sponsor is requested to adopt the following regulatory dissolution method and specifications for Paliperidone Modified Release Tablets, (see Table 1).

Table 1 Proposed Regulatory Dissolution Method and Specifications for Paliperidone Extended Release Tablets 3 mg, 6 mg, 9 mg, and 12 mg

Parameter	Proposed Dissolution Method and Specifications
Apparatus type:	USP Type VII Reciprocating Disk
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5
Volume:	50 ml
Temperature:	37 ± 0.5 °C
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)
Amplitude:	2 – 3 cm
Sampling Times:	2, 8, 14, and 18 hours
Specifications (% of Label Claim)	2 hours 8 hours 14 hours 18 hours 24 hours
Acceptance Criteria:	Conforms to USP XXVIIII <724> acceptance Table 1 for extended-release articles

2.3.4 Labeling Comments

The sponsor is requested to adopt OCP proposed labeling as outlined in §4.3 Appendix 3: Labeling on page 232.

2.4 Commitments to be Performed Prior to Approval

1. The sponsor should provide information that addresses the possibility that ethanol might result in dose dumping. This should include information on the solubility of the coating materials in ethanol, and information from other similar OROS formulations. If such information cannot exclude the possibility of dose dumping and/or is not available, a dissolution experiment in ethanolic solutions should be performed and the results provided.

2. We are concerned about the possibility that increases in gastrointestinal pH may increase bioavailability. Information on the distribution of efflux transporters in the GI tract, gastrointestinal pH in different regions of the GI tract associated with efflux transporters, and the effect of possible alterations of pH in these regions on paliperidone bioavailability should be submitted. If convincing information cannot be provided, a drug interaction study with maintenance dosing of a proton pump inhibitor should be considered by the sponsor. Depending on whether an interaction is found in such a study and depending on the magnitude of the interaction an additional study with antacids may need to be considered.

2.5 Phase IV Commitments to be Performed Post Approval

None are recommended.

2.6 Summary of Clinical Pharmacology and Biopharmaceutics Findings

2.6.1 Introduction and Background

Chemistry and Mechanism of Action

Paliperidone is a benzisoxazole derivative and is the racemic 9-hydroxy-metabolite of risperidone. Risperidone is an antipsychotic that is approved for the treatment of schizophrenia.

Paliperidone is a serotonergic 5HT2A and dopaminergic D2 receptor antagonist. Paliperidone also binds to α1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and α2-drenergic receptors, and belongs to the atypical antipsychotic class of psychotropic drugs.

Proposed Indication

The proposed indication is for the treatment of schizophrenia.

Proposed Formulation and Strengths

The proposed to-be-marketed formulation is an osmotically activated modified release tablet, (OROS® – Alza), that is designed to deliver drug through a semi-permeable rate controlling membrane over a 24 hour period.

Four tablets strengths are presently proposed for marketing, including 3 mg, 6 mg, 9 mg and 12 mg tablets.

Proposed Dosage Regimen

The proposed dosage regimen for paliperidone OROS MR tablets is 6 mg po daily, with dose adjustment within the range of 3 mg to 12 mg based on clinical response and tolerability.

2.6.2 Pertinent Clinical Pharmacology and Biopharmaceutic Questions

Are other indications or formulations anticipated?

[redacted]

What dosage regimens are anticipated for these indications and formulations?

[redacted]

What formulations were used in the pharmacokinetic, clinical pharmacology studies, and pivotal phase III studies?

All pivotal phase III trials as well as the majority of pharmacokinetic and clinical pharmacology studies used combinations of 3 mg and 9 mg strength Phase III Clinical Trial Formulation tablets, (CTF). For the pivotal phase III studies these tablets were over-encapsulated for blinding purposes. The to-be-marketed (TBM) formulation was used in the pivotal BE study, the single-dose dose proportionality study, [redacted]

An [redacted] release development formulations were used in early exploratory PK/PD [redacted] studies.

Solutions, IR tablets, IR capsules, and 2 ER encapsulated [redacted] formulations were used in several early PK and exploratory PK/PD studies.

Were there differences between the To-Be-Marketed, (TBM), and Clinical Trial Formulation, (CTF)?

The differences between the TBM and the CTF formulations appear to be minor.

The TBM formulation uses [redacted] in a higher percentage in the tablet [redacted] compared with use of a lower percentage of hydroxy-ethyl-cellulose in the phase III CTF formulation, [redacted]

[redacted]

Are the CTF and TBM formulations bioequivalent?

A single [redacted] TBM formulation tablet was bioequivalent to a [redacted] 9 mg and two 3 mg CTF formulation tablets.

Does paliperidone OROS exhibit linear kinetics over the dosage range?

In two separate studies Paliperidone OROS MR CTF and TBM tablets were shown to exhibit linear kinetics for single doses ranging from 3 mg to [redacted]

What is the effect of food on the bioavailability of paliperidone?

When a single 12 mg or 15 mg dose of the [redacted] OROS formulation was administered with food there was approximately a 50% - 60% average increase in both Cmax and AUC with little change in Tmax. Increases in bioavailability in individuals subjects ranged up to >10 fold, (studies P01-1012 and P01-1008).

There was no effect on the extent of absorption of paliperidone drug substance when administered as an IR tablet and only a small change in the rate of absorption as indicated by a 15 minute delay in the median lag time and a 1 hour delay in the median Tmax. (Study BEL-1)

* **What is the exposure to paliperidone and its' enantiomers compared to exposures from risperidone?**

The exposure to paliperidone after administration of paliperidone OROS 15 mg daily, (proposed maximum daily dose 12 mg), is approximately 1/3 the exposure to total 'active' moieties, (i.e. risperidone and paliperidone), after the approved maximum daily dose of risperidone IR tablets 8 mg BID, (i.e. 16 mg daily). Of the total active moieties after dosing with risperidone, 2/3's are due to paliperidone, so even if paliperidone alone is compared, the exposure after dosing of risperidone is still twice as high as after dosing with paliperidone OROS. After dosing with both risperidone and paliperidone OROS 2/3 of the paliperidone in plasma is composed of the (+) enantiomer and 1/3 of the exposure is due to the (-) enantiomer, (study SCH-102). Consequently, even accounting for increases in bioavailability due to food, etc. exposures to paliperidone with paliperidone OROS are still probably less than after maximal exposures with risperidone. If we consider more typical clinical dosages of 6 mg daily of paliperidone OROS and 6 mg daily of risperidone the exposure ratios are only about 10% less, consequently there is still an adequate margin.

Are there pharmacokinetics differences by Race or Ethnicity?

There was no indication that the single dose pharmacokinetics of paliperidone differ between Japanese and Caucasians. Other races/ethnic groups were not formally studies and there were insufficient numbers of subjects for an independent analysis.

Does paliperidone's pharmacokinetics change with increasing age?

There is a trend for increasing exposures as age increases, such that exposures are around 1/3 higher in subjects around 75 years of age compared with those around 25 years of age. No 'old' elderly, (i.e. > 85 yo), were included in the studies so the pharmacokinetics in this age group are unknown, although trends suggest they may have even higher exposures. In addition, to increases in half-life and both total and unbound Cmax and AUC with age there are also decreases in Cl/F and Vdss/F. In addition to the change in Cl/F probably being partially due to decreasing renal function, and possibly hepatic function with age, the decrease in Vdss/F and Cl/F might also be partially due to an increase in F due to slower GI transit in the elderly. (Study SCH-1011)

What are the pharmacokinetic characteristics in children?

No studies were conducted in children or adolescents less than 18 years of age.

Are there pharmacokinetics differences by gender?

No specific gender effect study was performed, however inspection of the data from the age effect study, (SCH-1011), indicates that there is unlikely to be a significant gender effect on pharmacokinetics.

What is the metabolic profile of paliperidone?

The plasma concentration profiles of total radioactivity and unchanged paliperidone are very similar. Although terminal elimination of unchanged paliperidone appears to be paradoxically slower than for ^{14}C moieties this is probably due to a lack of assay sensitivity. Concentration profiles indicate formation rate limited metabolite kinetics and little exposure to metabolites, as ^{14}C to unchanged paliperidone ratios for Cmax and AUC are 1.1 or less. Based upon these low exposures to metabolites, the metabolites probably don't contribute much to efficacy or to toxicities due to binding at serotonergic, dopaminergic, adrenergic, or histamine receptors, however without receptor binding and transporter data for the metabolites we can't be certain.

What is the metabolic scheme of paliperidone and how are paliperidone and its metabolites eliminated from the body?

Just under 60% of an oral dose of paliperidone solution is eliminated unchanged in the urine, with about slightly more than 30% eliminated as metabolites in urine and feces and less than 10% of the dose was not recovered. This indicates that paliperidone is well absorbed and that both renal elimination and hepatic metabolism contribute significantly to elimination. Of the 30% of the dose that is metabolized approximately 1/3 is eliminated in the feces (range 25% - 50%), and the 2/3's is eliminated renally.

There are four primary metabolic pathways for paliperidone metabolism in humans:

(See Figure 14 on page 73 for a schematic of the metabolic scheme.)

- Dehydrogenation of a hydroxyl group to form paliperidone ketone
- Oxidation to form 1 or possibly 2 hydroxy-paliperidone products possibly mediated by CYP2D6
- Oxidative metabolism to form a benzisoxazole scission product possibly mediated by both CYP2D6 and CYP3A4
- N-dealkylation to form an acid and amine cleavage products.

Each of these primary pathways appears to mediate 12% or less of total elimination.

Secondary metabolism appears to include benzisoxazole scission of hydroxy-paliperidone and/or hydroxylation of the benzisoxazole scission product to yield a hydroxyl-benzisoxazole scission product, and glucuronidation of the benzisoxazole scission product.

Although 60% of the dose on average is eliminated unchanged in urine in CYP2D6 extensive metabolizers the average is 55% and in poor metabolizers it's 65%.

No single metabolic pathway can be singled out as being particularly significant, but both renal and total hepatic elimination and function are clinically important.

What is the receptor and monoamine transporter binding of paliperidone and its metabolites?

In vitro receptor binding experiments indicate that paliperidone and its' enantiomers bind to 5-HT_{1A}, 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$, 5-HT_{2A} serotonin receptors, dopamine D_{2L}, D_3, $D_{4.2}$ receptors, adrenergic α_{2A}, α_{2B}, α_{2C} receptors, and histamine H_1 receptors at clinically relevant concentrations, with relatively similar affinities for each receptor to both enantiomers. Paliperidone does not appear to inhibit any of the monoamine reuptake transporters at clinically relevant concentrations.

What transporters are involved in paliperidone's disposition?

Cell transport experiments in Caco-2 cells indicate that there is facilitated absorption of racemic paliperidone at *in vivo* plasma concentrations. In addition, there is net active renal tubular secretion that comprises about 30% of total body clearance or 50% of renal clearance. As paliperidone has a pKa of 8.24, alterations in pH in the GI tract could effect absorption due to decreased facilitated absorption with

increasing pH, as well as due to decreased solubility. In addition, if there is any active renal tubular reabsorption, alterations in renal tubular pH could alter renal elimination.

At clinically achieved concentrations paliperidone has little ability to inhibit pGP transport. However, if paliperidone is concentrated in the GI tract, bile tract, renal tubules, or other tissues, concentrations might be sufficiently high to inhibit pGP transport.

Does paliperidone induce or inhibit any disposition pathways?

Little to no inhibition of P450 isozymes examined *in vitro* was detected when incubated with a 50:50 mixture of racemic paliperidone at claimed clinically relevant concentrations, (Cmax < 150 ng/ml). However, concentrations *in vivo* are not at a 1:1 molar ratio of the (+) and (–) enantiomers so the *in vitro* data must be interpreted cautiously. In addition all inhibition experiments included a pre-incubation period of only 5 minutes, and no experiments were conducted without pre-incubation. Due to the lack of experiments without pre-incubation, the limited duration of the pre-incubations used, and the low absolute quantities of the incubation experiments thereby limiting the ability to detect metabolism, we need to conclude that the potential for mechanism based inhibition by paliperidone metabolites or suicide substrate inhibition was not adequately tested for *in vitro*.

The interaction of paliperidone with the metabolism of a number of specific cytochrome P-450 substrates was investigated *in vitro* in a batch of human liver microsomes, (H-INT-1), by examining the inhibitory effect on the overall metabolism of specific substrates and/or on the formation of their major metabolites at concentrations well in excess of clinically relevant concentrations. Except for possibly some inhibition of CYP2D6 no significant inhibition was detected for CYPs 1A2, 2A6, 2C8,9,10, 2E1, 3A4 and 4A.

Further examination of the inhibition by paliperidone of CYP2D6 and of CYP3A4, using various substrates of CYP3A4 that may represent different binding sites, also failed to show any significant inhibition *in vitro* at clinically relevant concentrations.

What is paliperidone's protein binding and the effects of changes in protein binding?

There is little likelihood of a clinically significant protein binding interaction. At concentrations achieved with clinical usage, (<250 ng/ml), the overall binding of paliperidone and its enantiomers to plasma protein were concentration independent, with free fractions of 27%, 18% and 37% for paliperidone, (+)-paliperidone, and (-)-paliperidone respectively. However, when protein binding to purified protein solutions of human serum albumin and α1-acid glycoprotein were examined at a paliperidone concentration of 50 ng/ml; there were clear relationships for free fraction to protein concentration for each type of protein, and these relationships were different for protein and for each enantiomer. For a decrease in albumin concentration from 4.3 gm% to 2.0 gm%, the free fraction of (+)-paliperidone was unchanged at 61.5% and 62.9% respectively, whereas for (-)-paliperidone the free fraction increased from 53.5% to 66.7%. For α1-acid glycoprotein the free fraction of (+)-paliperidone decreased from 14.9% at 0.1 gm% to 10.1% at 0.15 gm%, whereas for (-)-paliperidone the free fraction decreased from 24.6% to 20.7%. Changes in albumin will typically occur slowly and even if they didn't total free concentrations would quickly re-equilibrate. However, α1-acid glycoprotein is an acute phase reactant that increases in the presence of physiologically stressful conditions, (e.g. MI). Consequently, a rapid rise in α1-acid glycoprotein might result in a decrease in free concentrations and there might be some temporary clinical consequences to the differential change in binding, however the risks are difficult to predict and considering the relative safety profile are not likely to be significant.

What is the degree of interconversion for the enantiomers and are there any significant clinical differences between them?

There is preferential conversion from the (-) to the (+) enantiomer *in vivo*. Specifically, after administration of the (+) R078543 enantiomer there is about 28% *in vivo* interconversion from the (+) R078543 to the (−) R078544 enantiomer as assessed by AUC ratios, whereas after administration of the (-) R078544enantiomer there is about 55% *in vivo* interconversion from the R078544 (−) to the enantiomer

R078543 (+). After administration of paliperidone as a racemate, the (+):(−) paliperidone AUC∞ ratio is about 1.6, irrespective of the route of administration and type of formulation, Although when unbound drug is examined the AUC for (-)-paliperidone is higher. Cmax +:- ratios are 1.9 after administration of the racemate, 8:1 after administration of (+)-paliperidone and 0.5 after administration of (-)-paliperidone.

For racemic paliperidone the incidence of somnolence and orthostatic hypotension was related to the rate of absorption and the Cmax, with the incidence by formulation in the following order: IV > IR > OROS.

In contrast the incidence of somnolence is lower after administration of (+)-paliperidone compared with after administration of (-)-paliperidone or the racemate. The incidence of hypotension, fatigue, and headache is slightly higher after administration of (+)-paliperidone compared with the racemic solution, the (-)-enantiomer and the OROS formulation. Although the Cmax for each individual enantiomer is higher when the enantiomer is given by itself, for the (+) enantiomer the Cmax is much higher than after administration of the racemate. When the incidence of AEs and the exposures by treatment are examined, there appears that there may be some advantage in terms of side effects for the (+) enantiomer compared to the racemate when both are administered as OROS formulations. This would need to be confirmed as well as whether there is similar or differential efficacy.

What are the pharmacokinetic / pharmacodynamic characteristics of paliperidone with respect to efficacy and extrapyramidal system toxicities?

The three Phase 3 studies (Studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305) in subjects with schizophrenia or schizoaffective disorder were included in the sponsor's PK/PD and PD analysis of PANSS and responder rates, where response is defined as a drop in PANSS of ≥30%. In addition, the sponsor also performed a PK/PD and PD analysis of the risk of developing an EPS-related adverse event. These studies employed either fixed doses of oral ER OROS Paliperidone, placebo or olanzapine for 6 weeks.

For both efficacy and safety measures of EPS, both dose and model-predicted average steady-state concentrations at endpoint were tested as drivers of the response.

The sponsor claims that the dose –response relationship was less variable than the concentration response relationship. This is not surprising as the sponsor used estimated individual average steady-state concentrations based on a post-hoc NONMEM analysis and due to the sparse sampling and the extreme variability in Tmax it's expected that these Css estimates would not be very accurate. Specifically, the intraday variability on multiple dosing with superpositioning of two peaks or two troughs from different days means that average concentration estimates in a particular patient may be way off, resulting in any model having poor predictability.

For the dose-response the sponsor claims that the mean maximal response rate after correction for a placebo response is 26.6% and the sponsor provides simulations with this degree of maximal corrected response. However, responses for both placebo and drug as stated by the sponsor in the text, in tables, and in the computer output does not match this and instead suggests a maximum response rate of only around 17.5%. NONMEM data sets were not provided by the sponsor.

Based on the sponsor's simulations for doses above 6 mg – 9 mg, there is no major increase in response rate, and at 9 mg there is no significant increase in the precision of the prediction. With the sponsor's claimed dose response relationships for EPS it's clear that there is a major increase in EPS at a dose of 9 mg compared to 6 mg. Although, the percentage increase is large (81.5%), the absolute increase is small, (9.8% vs. 5.4%). In spite of this, if the dose-response relationship for EPS in these short term studies is predictive of permanent tardive dyskinesia after long term treatment, the risk to benefit ratio may not be acceptable at a dose of 9 mg for patients who are obtaining a response at 6 mg. Thus doses of 9 mg and 12 mg should probably be reserved for patients who don't respond at lower doses.

It may be possible to predict who would be a candidate for a higher dose based on estimated creatinine clearance, drug metabolizing genotyping, and other factors. No recommendations are being made

presently as additional data analysis including additional genotyping data from the sponsor would be needed in order to make recommendations.

What is the effect of the food effect on the incidence of EPS?

As a secondary objective, the EPS PK/PD-model was used to predict the impact of the food effect on the dose response of the EPS incidence. Based on an average increase in bioavailability of 60% and using the PK/PD model the sponsor's estimated percentage increase in EPS is 74% at a dose of 6 mg and 30% at the maximum dose of 12 mg. However, as stated above the absolute increase is predicted to be small, i.e. 9.4% vs. 5.4% at 6 mg and 17.1% vs. 13.2% at 12 mg. However, the poor estimate of average steady-state concentrations mentioned previously raise significant concerns about the accuracy of concentration predictions and there would be even greater errors in predictions in the presence of a food effect. In addition, the range of increased concentrations in the presence of food may vary up to > 10 fold which was not taken into account by the sponsor. These factors may be especially important early in treatment where this could precipitate an acute dystonic reaction, or where interday variability might result in hypotension.

What was the effect of paliperidone on hormones?

The effect of paliperidone on prolactin levels was examined in 5 studies, Alza-039, Alza-019, INT-1, SCH-101, and SCH-1008.

All studies used immediate release paliperidone or oral solutions, except for study SCH-101 that examined the steady-state dosing of the OROS formulation at a dose of 12 mg. Examination of prolactin exposures after placebo, risperidone, and paliperidone immediate release formulations at various doses and regimens suggests that the maximum effect for elevating prolactin exposures may be close to being achieved with around the 15 mg OROS dose or less. In addition, after slow administration of both risperidone and paliperidone the plasma drug concentrations for active moiety peaked at 22 to 23 hours however the prolactin peak occurred much earlier (from 2.5 to 5.5 h).

Also of note, is that in one study two subjects reporting early menses had the highest peak prolactin levels.

No specific clinical pharmacology studies examined the potential for effects on ADH secretion.

What was the effect of paliperidone on cardiovascular vital signs?

When diastolic blood pressure is examined after single or multiple dosing of paliperidone there does not appear to be any obvious dose response relationship. However when systolic blood pressure is examined after single doses of paliperidone in the same studies there appears to be a small signal for a dose response relationship, although this isn't apparent in the multiple dosing study. In addition, when the incidence of potentially orthostatic changes in SBP or symptoms consistent with orthostasis is examined, the incidence appears to track with expected changes in dose, rate, and extent of absorption and this is observed in several studies.

As with changes in blood pressure there appears to be a diurnal pattern to changes in heart rate after single doses of paliperidone OROS with a decrease in HR during sleep with rebound tachycardia the day after dosing which appears to be dose related.

* **What was the PK/PD relationship of paliperidone to QTc?**

The sponsor conducted a multiple dose QT study using immediate release paliperidone and moxifloxacin as the active control. A day averaged linearly corrected QT based on QT vs. RR for the study populations examined was the primary comparison. This type of comparison is inappropriate as these are averaged values across the entire dosage interval. Thus these QTcLD values are lower than the actual changes in

QTcLD observed around the concentration peak. In addition correction of QT by other methods may be larger.

The sponsor's assessment criteria for a 'negative' effect on QTc were if the upper limit of the 2-sided 90% confidence interval excluded 10 milliseconds. However, the criteria used for the positive control, (moxifloxacin 400 mg), were if the lower limit of the 2-sided 90% confidence interval was greater than 0 milliseconds. Thus the assessment criteria for determining if there were QT effects were inconsistent between the test and control groups. Even using the sponsor's inappropriate assessment method, although the upper limit of the 90% CI for QTcLD at steady-state dosing of paliperidone 8 mg IR is less than 10 mSec, the change in QTcLD is still greater for paliperidone than for the active control moxifloxacin, albeit the difference is small (1 mSec).

When change from baseline in QTcLD is examined by time post dose it clearly occurs around the peak concentration, and there appears to be a dose response with QTcLD prolongation, which is confirmed by hysteresis plots. The QTc prolongation is apparent even at the lowest dose studied and even at this dose is greater than for the active control, In addition, it appears that the QTc changes in the control group is driven by QTc effects in fewer individuals and that the relative degree of effect varies by the correction method used. In addition, the effect on QTc is seen not only with the QTcLD correction, but also with Fridericia's and Bazett's methods.

According to the sponsor none of the subjects in either the IR paliperidone or moxifloxacin treatment group had a QTcLD increase >60 mSec, although nineteen (26%) of 72 subjects in the IR paliperidone group and 12 (17%) of 69 subjects in the moxifloxacin group had a 30-60 ms increase in QTcLD. Yet the sponsor claimed that no subject in either treatment group had a QTcLD, QTcF, or QTlc interval ≥450 ms at any time during the study.

The present study was conducted with an IR formulation however; the proposed ER OROS formulation has lower bioavailability and a lower Cmax. In spite of this, there does appear to be overlap of the concentrations associated with a QT effect in the controlled QT study and the peak concentrations likely to be seen with clinical dosing of the Paliperidone OROS formulation, even without accounting for slightly higher peak concentrations in the elderly, with any food effect, or in patients with organ dysfunction that might result in higher exposures than is typical.

The sponsor claims that the increase in QTcLD interval exceeds the 5 mSec threshold for regulatory concern but is considerably less than the >20 mSec increase associated with a substantially increased risk for arrhythmia. There were also a number of changes in ECG morphology that are not addressed in this review.

Several other studies also mentioned potential cardiac findings.

In study Alza-039 there was one report of syncope during Ascend treatment, two subjects each experienced tachycardia, another subject experienced bradycardia, and there was a case of tachycardia and presumed arrhythmia that was described as an irregular pulse lasting eight minutes, One subject, a 55 year-old male, had ectopic beats on his ECG first during IR treatment and again during both slow paliperidone administration and placebo treatments.

In study Alza-034 a higher incidence of palpitations was noted with a more rapidly absorbed paliperidone OROS development formulation.

Also in study SCH-1011 there were a number subjects who had prolongations of QTcF between 30 – 60 milliseconds while receiving paliperidone OROS 3 mg qd, with more instances in elderly subjects than in young subjects.

The possibility of increased bioavailability in the presence of potent pGP efflux transporter inhibitors needs to be considered as a risk factor. Especially with drugs that may both increase bioavailability and also have effects on QT, such as quinidine.

A cardiology consult has been requested by the medical review team to assess the potential clinical significance of these observations.

What was the effect of paliperidone on sleep?

The sponsor was unable to show any improvement in sleep parameters when paliperidone was administered to schizophrenic patients. The effects of paliperidone OROS 9 mg compared to placebo on sleep parameters was examined in schizophrenic patients after 2 weeks of therapy and included a comparison of the duration and proportion of sleep stages as measured by polysomnography.

The time to onset of sleep is decreased by 10 minutes and stage 2 sleep is increased by 30 minutes, however the sponsor indicates that these differences are not clinically relevant as the differences could be due to differences between the two groups at baseline with the lack of difference between groups at 2 weeks due to normal variability.

There were no clinically significant differences between groups in measures of sleep continuity, including the duration of uninterrupted sleep, sleep duration, latency to sleep onset or persistent sleep, sleep efficiency index, awakenings, microarousals, and time awake.

What is the effect of renal insufficiency on paliperidone?

After single doses average exposure to paliperidone increases 1.5, 2.6, and 4.8 fold in patients with mild (Clcr ≥50 - <80 ml/min), moderate (Clcr ≥30 - <50 ml/min), and severe (Clcr 9.5 - <30 ml/min), renal insufficiency respectively compared to subjects with normal renal function (Clcr ≥80 ml/min). Subjects on dialysis were not studied. Based on changes in total paliperidone clearances average dosages should probably be decreased by approximately 1/3 in mild renal insufficiency, at least ½ in moderate insufficiency, and by 75 – 80% in severe insufficiency. Using the sponsor's proposed dose range of 3 mg to 12 mg dose and a typical recommended dose of 6 mg, this translates into dosages of 4 - 8 mg in mild renal insufficiency, 1.5 - 3 mg in moderate insufficiency, and 1.2 – 2.4 mg severe renal insufficiency. Since, the OROS tablet only comes in dose increments of 3 mg and cannot be divided, the maximum allowable dose would be 6 mg in mild renal insufficiency and 3 mg in moderate and severe insufficiency.

What's interesting is that the enantiomer ratio changes as renal function decreases and is a proportionately greater change for the unbound ratio. This appears to be due to differences in the elimination of the enantiomers, as evidenced by the fact that the enantiomer ratio changes to a greater extent as the time post dosing increases. Thus the ultimate exposure to each enantiomer is difficult to predict. Since the enantiomer pharmacokinetic studies indicated that there may be a pharmacodynamic difference between the enantiomers in their propensity to cause toxicity even at the same exposures, we are unable to predict the risk benefit ratio with higher steady-state dosing of paliperidone in patients with renal insufficiency. Consequently, clinicians should be aware that the toxicity to efficacy profile in renally impaired patients may be different than in patients with normal renal function.

What is the effect of hepatic insufficiency on paliperidone?

In subjects with moderate hepatic impairment the free fraction of (+)-paliperidone increases on average by almost 50% and of (-)-paliperidone by almost 20%. Because of this the total paliperidone exposure decreases in patients with moderate hepatic impairment, (mean AUC_{∞} 128 vs. 176 ng/ml x hr^{-1}). However the exposure to unbound racemic paliperidone as well as to the unbound paliperidone enantiomers remains essentially unchanged, (mean $AUCu,_{\infty}$ 45.8 vs. 45.7 ng/ml x hr^{-1}), (study SCH-1008). Although pharmacokinetically there does not appear to be a reason to alter dosing in moderate hepatic impairment, pharmacodynamically paliperidone as a CNS active agent might induce a hepatic encephalopathy in patients with hepatic impairment. The effect of severe hepatic insufficiency on paliperidone kinetics is unknown.

What are the results of the drug / drug interactions studies?

When paliperidone was administered together with trimethoprim the significant changes for paliperidone included a 25% – 30% increase in the total and unbound Cmax of the paliperidone enantiomers with a decrease in total drug AUC. The average free fraction also increased by 15.5% for racemic paliperidone, 20.8% for (+)-paliperidone, and 9.4% for (-)-paliperidone. There was also a decrease in average half-life for each paliperidone species of about 5 hours. There was little change in other metrics including unbound AUC and no difference in unbound oral clearance (Clu/F).

These observations are consistent with a protein binding displacement interaction without a change in active renal secretion. With a first dose of paliperidone or of trimethoprim or other displacers, there may be transient clinical consequences such as hypotension, somnolence ,or other cardiovascular side effects as was seen in this study, but this is likely to be less than with the food effect.

The effect on trimethoprim pharmacokinetics was not fully examined. Pre-dose concentrations were obtained prior to trimethoprim on all days, and 2 hour post-dose concentrations were obtained on day 6 and day 8, i.e. 26 and 74 hours after dosing with paliperidone. For each subject, 2 hour trimethoprim concentrations were lower on day 6 than on day 8. Although this possibly suggests a lack of an effect of paliperidone on trimethoprim pharmacokinetics, it is also consistent with a protein binding displacement of trimethoprim, prevention of reabsorption, some other mechanism, or assay interference

Is there any potential for other drug / drug interactions?

In vitro data suggests that quinidine and verapamil may inhibit gastrointestinal transporter efflux and increase bioavailability.

Since paliperidone's bioavailability varies with time post administration it's reasonable to presume that there're regional differences in absorption. This might be due to regional differences in pH or transporters, or a combination of these factors. Since the OROS formulation releases drug at a relatively consistent rate differences in GI transit time may affect bioavailability. Since bioavailability is complete in the upper GI tract and decreases as the tablet presumably travels down the intestines, drugs with anticholinergic properties such as tricyclic antidepressants are expected to decrease bioavailability, and drugs that increase motility such as laxatives are expected to decrease bioavailability.

3 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 6

2.7 Signatures

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D. **Senior Reviewer** **Division of Clinical Pharmacology I**	**Date**
Ramen Baweja, Ph.D. **Team Leader** **Division of Clinical Pharmacology I**	**Date**

OCP Briefing Meeting:

Date:	Friday, September 8, 2006
Time:	2:00 PM – 3:00 PM
Location:	White Oak Buiding 21 Conference Room 1539
Level:	Optional Inter-Division
Attendees:	***Psychiatry*** Tom Laughren Mitch Mathis Nhi Khin Keith Kudrow ***Cardiology*** Shari Targum ***Chemistry*** Chagan Tele ***Pharmacology*** Barry Rosloff ***Office of Clinical Pharmacology*** Mehul Mehta Ray Baweja Ron Kavanagh Kofi Kumi ***Pharmacometrics*** Rajnikanth Madabushi Christoffer Tornoe ***Pharmacogenomics*** Felix Frueh Shashi Amur

cc: NDA 21-999 0000, [redacted] (DFS)
HFD-120 (LaughrenT, KhinN, BruggeK, Chalecka-FranaszekE, RosloffB, HardemanS, KiedrowK, TeleC, OliverT)
HFD-860 (KavanaghR, BawejaR, MehtaM)

3 DETAILED REVIEW

3.1 Overview of Clinical Development Program

3.1.1 Description of Clinical Development Program

The clinical development program consists of the typical Phase I / II Pharmacokinetic and Clinical Pharmacology and Phase III Efficacy / Safety studies for which the OROS Clinical Trial formulation was used, (except for the pivotal BE study where the TBM formulation was also used). The CTF is essentially identical to the To-Be-Marketed formulation.

Prior to conducting the typical Phase I/II Pharmacokinetic and Clinical Pharmacology program, a preliminary program of 9 formulation development studies was conducted. Initial review plans were to skip review of these studies. However upon examination virtually every study provided useful information on the pharmacokinetic and pharmacodynamics related to delivery rate often in comparison to risperidone or information on the properties of the drug substance itself. Since this information could be critical in evaluating delivery rate related adverse effects these studies were also reviewed. See Table 5 for an overview of these studies.

Table 3 on the following page shows a list of all *in vivo* studies and reports that includes study report numbers and titles. Following this Table 4 lists the *in vitro* studies conducted with human biomaterials.

3.1.2 Lists of Studies

3.1.2.1 Study Titles by Primary Goal

Table 3 Phase I, II, and III Clinical Studies and Study Reports

N	Protocol Number	Protocol Title
Formulation Development Bioavailability Studies		
1	RIS-BEL-28	Comparative Trial on the Pharmacokinetics, Pharmacodynamic Effects, Tolerability, Cardiovascular and Laboratory Safety of 9-Hydroxy-Risperidone and Risperidone in Healthy Subjects After Single Oral Dosing of 1 mg. A Randomized, Double-Blind and Placebo-Controlled Cross-Over Study
2	R076477-BEL-1	A Comparative Trial in Healthy Volunteers to Assess the Relative Oral Bioavailability of a Single Oral Dose of 0.5 mg R076477 (9-hydroxy-risperidone) Taken Either as a Solution When Fasting, as a Tablet When Fasting or as a Tablet Immediately After the Intake of Food
3	ALZA-C-2001-032	Pharmacokinetics of Paliperidone and Risperidone when Administered as Osmotic Modules and Oral Solutions in Healthy Volunteers
4	ALZA-C-2001-039	A Pharmacokinetic-Pharmacodynamic Study to Evaluate Various Dosing Regimens of Paliperidone
5	ALZA-C-2002-019	A Comparison of Pharmacodynamic Effects of Risperidone and Paliperidone
6	ALZA-C-2002-034	Evaluation of OROS® (paliperidone) Pharmacokinetics and Pharmacodynamics
7	R076477-P01-101	A Comparative Evaluation of the Pharmacokinetics and Pharmacodynamics Under Fasting and Fed Conditions of 2 Paliperidone Extended-Release Formulations With Paliperidone Oral Solution in Healthy Adults
8	R076477-P01-102	A Comparative Evaluation of the Pharmacokinetics and Pharmacodynamics under Fasting and Fed Conditions of 2 Paliperidone Extended-Release [redacted] Formulations with Paliperidone Oral Solution in Healthy Adults
9	PAL-SCH-101	A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Phase 1 Study to Compare the Tolerability of OROS® Paliperidone (Extended-Release) With Immediate-Release (IR) Risperidone in Subjects With Schizophrenia
Single Dose Pharmacokinetics		
10	R076477-P01-1007	Disposition of Paliperidone Enantiomers After Treatment With Different Formulations of the Racemate and the Separate Enantiomers and the Determination of the Absolute Bioavailability of IR and ER OROS Paliperidone
11	ALZA-C-2003-044	A Study To Evaluate the Pharmacokinetics of Four OROS®(Paliperidone) Doses (6 mg, 9 mg, 12 mg, and 15 mg) in Healthy Subjects
12	R076477-P01-1010	Dose-Proportionality Study of the Five ER OROS Paliperidone [redacted] Tablet Strengths (3, 6, 9, 12, and 15 mg) in Healthy Male Subjects
Multiple Dose Safety/Tolerability and Pharmacokinetics		
13	R076477-INT-1	Steady-State Pharmacokinetics of R076477 in Chronic Schizophrenic Patients Following Repeated Oral Administration of 1, 4, and 8 mg R076477

14	R076477-SCH-102	Comparison of Steady–State Pharmacokinetics of Paliperidone After Extended-Release OROS® Paliperidone 15 mg and Immediate-Release Oral Risperidone 8 mg b.i.d. in Subjects With Schizophrenia or Schizoaffective Disorder
Pivotal Bioequivalence Studies		
15	R076477-P01-1008	Pivotal Bioequivalence Study With 15 mg ER OROS Paliperidone Comparing the Phase 3 Formulation With [redacted] Formulation and Evaluation of Food Effect on the [redacted] Formulation in Healthy Male Subject
[redacted]		
Metabolism		
17	R076477-P01-103	Plasma Concentrations, Metabolism and Excretion of 14C-Paliperidone After a Single Oral Dose in Healthy Male Subjects
PK/PD		
18	R076477-SWE-1	PET study of D_2 and 5-HT2A receptor occupancy induced by R076477 (9-hydroxy-risperidone) in three healthy volunteers
19	R076477-SIV-101	Open-Label Positron Emission Tomography (PET) Study of Central D_2-Receptor Occupancy in Healthy Subjects Following a Single Oral Dose of OROS Paliperidone
20	R076477-SCH-1009	A Placebo- and Positive-Controlled, Randomized Study Evaluating QT and QTc Intervals Following Administration of Immediate-Release Paliperidone in Subjects With Schizophrenia or Schizoaffective Disorder
21	R076477-SCH-1010	A Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Effect of ER OROS® Paliperidone Compared With Placebo on Sleep Architecture in Subjects With Schizophrenia
Pop PK & PK/PD		
22	psdb-4647364 [a]	Population Pharmacokinetic Analysis of ER OROS® Paliperidone
23	psdb-4855692 [a]	Dose- and Concentration-Response Modeling of Endpoint PANSS Scores and Responder Analysis
Effect of Intrinsic Factors		
24	R076477-P01-1005	A Randomized, Double-Blind, Placebo-Controlled, Single and Multiple Dose Study to Evaluate and Compare the Pharmacokinetics of ER OROS® Paliperidone in Healthy Japanese and Caucasian Subjects
25	R076477-SCH-1008 [b]	Pharmacokinetics of Paliperidone in Subjects With Moderate Hepatic Impairment as Compared to Subjects With Normal Hepatic Function
26	R076477-REI-1001	The Pharmacokinetics of ER OROS® Paliperidone in Subjects With Varying Degrees of Impaired Renal Function (Mild, Moderate, and Severe) as Compared to Subjects With Normal Renal Function
27	PALIOROS-SCH-1011	An Open-Label, Single- and Multiple-Dose Study to Evaluate the Pharmacokinetics of ER OROS® Paliperidone in Healthy Elderly and Young Subjects
Effect of Extrinsic Factors		
28	ALZA C-2004-006	A Study To Evaluate Tolerability and Pharmacokinetics of ER OROS®(Paliperidone) 12 mg and 15 mg and ER OROS® (Paliperidone) 15 mg with Food in Healthy Subjects

29	R076477-P01-1006	A Randomized, Open-Label, Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of ER OROS® Paliperidone in Healthy Japanese Subjects
30	Palioros-P01-1012	Evaluation of the Effect of Food and Posture on the Pharmacokinetics of Paliperidone After a Single Administration of 12 mg ER OROS Paliperidone to Healthy Men
31	R076477-P01-1004	Investigation of the Potential Effects of Trimethoprim on the Pharmacokinetics of ER OROS® Paliperidone in Healthy Male Subjects
Pivotal Efficacy and Safety Studies		
32	R076477-SCH-303/703	A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS® Paliperidone (6, 9, and 12 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia
33		OL extension
34	R076477-SCH-304/704	A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 2 Fixed Dosages of Extended Release OROS□ Paliperidone (6 and 12 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia
35		OL extension
36	R076477-SCH-305/705	A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Dose-Response Study to Evaluate the Efficacy and Safety of 3 Fixed Dosages of Extended Release OROS® Paliperidone (3, 9, and 15 mg/day) and Olanzapine (10 mg/day), With Open-Label Extension, in the Treatment of Subjects With Schizophrenia
37		OL extension
38	R076477-SCH-302/702	A Randomized, 6-Week Double-Blind, Placebo-Controlled Study With an Optional 24-Week Open-Label Extension to Evaluate the Safety and Tolerability of Flexible Doses of Extended Release OROS® Paliperidone in the Treatment of Geriatric Subjects With Schizophrenia
39		OL extension

a - Reports of analyses from more than one study or study(ies) and experiments(s).
b - The study title associated with this study number in the global summit review tree structure of the FDA electronic document room is erroneously listed as the title for the pivotal bioequivalence study for the15 mg dose. However, the link does correctly go to the hepatic impairment study.

Table 4 *In Vitro* Studies with Human Biomaterials

Protein Binding	
FK3009	Plasma protein binding of Paliperidone enantiomers
FK5209	Plasma protein binding of Paliperidone and its enantiomers
Cell Transport	
FK4856	*In vitro* study on mechanisms of transepithelial transport of paliperidone across monolayers
***In Vitro* Metabolism**	
FK2995	*In vitro* metabolism of paliperidone and individual enantiomers in human liver cells and subcellular fractions
FK3103	*In vitro* pooled human microsomal CYP450 metabolism of Paliperidone Effect of paliperidone on human CYP450 probe substrates
FK5304	*In vitro* study of the inhibition of paliperidone on CYP450 3A4/5 and 2D6 probe substrates in pooled human microsomes

3.1.2.2 *Summary of Study Design, Populations, Treatments and Formulations Used Arranged by Primary Study Goal*

Table 5 on the following page shows a summary of study designs, study population demographics, treatments and formulations used for each study. The studies themselves are grouped and arranged by the primary study goal as shown by the sub-headers in the table.

Significant objectives as well as multiple dose clinical pharmacology studies are indicated by [redacted]. Use of phase III clinical trial formulations, (Ph III CTF), are indicated by yellow highlighting and use of the to-be-marketed, (TBM), formulations are indicated by blue highlighting. Significant other formulations or facts are highlighted by use of different colored text, e.g. red or violet.

Light yellow shaded cells indicate pivotal bioequivalence and pharmacokinetic studies.

[redacted]

Light blue shaded cells indicate studies that compared exposures after dosing of both Risperidone and Paliperidone.

Light green shaded cells indicate studies that included PK/PD information that are not highlighted elsewhere.

Table 6 contains a guide to formulation codes for paliperidone and its associated formulations and may be useful to the reader when examining Table 5. (Risperidone codes are not included in Table 6 but may be found in §4.2.

Table 5 Summary of Study Design, Population Demographics, Treatments and Formulations Used Arranged by Primary Study Goal[a]

N	Number	Country	FPI	LPO	Study Description/Design	Vol /Pxt	N	Sex M / F	Age[b]	Race W/B/O[c]	SD/ MD	Rx	Formulation[d]
Formulation Development Studies													
1	RIS-BEL-28	Belgium	10 May 93	25 Jul 93	DB, PC, SD, Rand, 3-way XO of the [redacted] (serum [redacted]), [redacted] of [redacted]		9	9 / 0	34 (25-40)	Race data not available	SD	A) RIS IR 1 mg Soln B) PAL IR 1 mg Soln C) Placebo	F029 F001
2	R076477-BEL-1	Belgium	17 Sep 98	23 Oct 98	OL, SD, 3-way XO of the [redacted] of PAL IR tablet vs. oral solution and [redacted] on PAL IR tablet.		12	6 / 6	33.5 (24 – 51)	12/0/0	SD	A) PAL 0.5 mg solution (fasted) B) PAL 0.5 mg IR tablet (fasted) C) PAL 0.5 mg IR tablet (fed)	F008 F003
3	ALZA-C-2001-032	UK	19 Nov 01	13 Dec 01	[redacted], OL, SD, 4x XO of the [redacted] of [redacted] and oral solution.		16	8 / 8	(19 – 36) [25.2]	15/0/1	SD	A) RIS 2 mg osmotic module B) RIS 2 mg oral solution C) PAL 2 mg osmotic module D) PAL 2 mg oral solution	? not mentioned
4	ALZA-C-2001-039	UK	08 Jan 02	21 Feb 02	[redacted], DB, PC, 4-way XO of the [redacted] after [redacted] of PAL		27	18 / 9	52.2 (40 – 65)	22/3/2	?	Oral doses over 2 days: A) PAL 5.5 mg (Ascend profile) B) PAL 4.5 mg (Flat profile) C) PAL 4 mg (IR) D) placebo solution	? no code or not mentioned
5	ALZA-C-2002-019	UK	01 May 02	08 Jul 02	[redacted], DB, PC, 5-way XO of the [redacted] after [redacted]		30	21 / 9	(40 – 64) [50.5]	25/3/2	?	Oral doses over 2 days: A) RIS 6 mg (RIS Ascend-4) B) PAL 6 mg (PAL Ascend-4) C) PAL 4 mg (PAL Ascend-2) D) RIS 4 mg (IR-2) E) placebo solution	? no code or not mentioned
6	ALZA-C-2002-034	UK	27 Sep 02	29 Oct 02	OL, SD, 4-way XO of the [redacted] of 2 different formulations of [redacted]		32	18 / 14	(19 – 39) [24.3]	29/1/2	SD	A) [redacted] ROS 4 mg, fasted B) SLOW OROS 4 mg, fasted C) SLOW OROS 4 mg, fed D) PAL oral solution (IR) 2 mg, fasted	[redacted] SLOW SLOW
7	R076477-P01-101	Belgium	26 Jun 03	12 Aug 03	Rand, OL, SD, 5-way XO study of the PK & [redacted] of 2 [redacted] of 2 mg-eq PAL vs. 2 mg PAL oral solution; [redacted] on ER [redacted] formulations; [redacted]); safety, and tolerability.		35	19 / 16	39.0 (19 – 54)	35/0/0	SD	PAL PO A) ER [redacted] (2.5 mg cap) 2 mg-eq fasted B) ER [redacted] (2.5 mg cap) 2 mg-eq fed C) Coated PAL OROS ER (2x2 mg tablets), 2 mg-eq fasted D) Coated PAL OROS ER (2x2 mg tablets), 2 mg eq fed E) PAL PO Soln, 2 mg fasted (1 mg/ml).	F025 F026 [redacted] F021
8	R076477-P01-102	Belgium	09 Sep 03	25 Nov 03	5-way XO study of the PK, [redacted], [redacted] ([redacted]), safety, and tolerability of 2 ER PAL [redacted] formulations (2 mg-eq PAL) vs. IR PAL oral solution		35	19 / 16	37 (20 – 55)	35/0/0	SD	A) ER PAL [redacted] formulation 1, 2.5 mg capsule, fasted B) ER PAL [redacted] formulation 1, 2.5 mg capsule, with food C) ER PAL [redacted] formulation 2, 2.5 mg capsule, fasted D) ER PAL [redacted] formulation 2, 2.5 mg capsule, with food E) IR PAL oral solution, 2 mg (1 mg/ml), fasted	F036 F037 F021

N	Number	Country	FPI	LPO	Study Description/Design	Vol /Pat	N	Sex M / F	Age[b]	Race W/B/O[c]	SD/ MD	Rx	Formulation[d]
9	PAL-SCH-101	Austria, Belgium, Croatia, Lithuania, Poland, Ukraine	13 Mar 03	18 Jun 03	Rand, DB, PBO and Active Control non-inferiority study [redacted] Also evaluated PK/PD ([redacted]), & S/T	[redacted]	113	83 / 30	37 (20-63)	111/0/2	[redacted]	PAL OROS PO after a standard meal, A) Day 1 PBO Days 2-6 PAL OROS 12 mg B) Days 1-6 PAL OROS 12 mg C) Day 1 RIS IR 2 mg Days 2- 6 RIS IR 4 mg	PAL 2mg: MV02225527
Single Dose Pharmacokinetics													
10	R076477-P01-1007	Belgium	28 Jun 04	27 Aug 04	SD, Rand, OL, 5-way XO study of the [redacted]		20	10 / 10	41 (23 - 55)	20/0/0	SD	A) PAL oral solution 1 mg B) PAL OROS 3 mg C) PAL I.V. 1 mg over 30 min D) + enantiomer (R078543) oral soln 1 mg E) - enantiomer (R078544) oral soln 1 mg	F044 F016 F044 F001 F001
11	ALZA-C-2003-044	UK	09 Oct 03	27 Nov 03	OL, SD, 4 period, 4 treatment, sequential study evaluating the [redacted] and tolerability of 6, 9, 12, and 15 mg PAL OROS		30	30 / 0	[24.1] (18 – 41)	29/0/1	SD	PAL OROS, (Ph 3 formulation) fasted 6 mg (2 x 3 mg tablets) 9 mg (1 x 9 mg tablet) 12 mg (1 x 9 mg and 1 x 3 mg tablets) 15 mg (1 x 9 mg and 2 x 3 mg tablets) 6 - 30 day WO between treatments	F016 (3 mg) F017 (9 mg)
12	R076477-P01-1010	UK	19 Jul 04	01 Oct 04	Rand, SD, 5-way XO to evaluate the [redacted] of 3, 6, 9, 12, and 15 mg PAL OROS		50	50 / 0	27.1 (18-50)	41/5/4	SD	PAL OROS po fasted 3 mg 6 mg 9 mg 12 mg 15 mg	F016 [redacted]
Multiple Dose Safety/Tolerability and Pharmacokinetics													
13	R076477-INT-1	Belgium, S. Africa	09 Nov 98	10 Mar 99	Rand, OL, [redacted] parallel group study of the steady-state PK, [redacted], safety and tolerability of 1 mg, 4 mg and 8 mg PAL.	[redacted]	34	28 / 6	41.5 (24-61)	29/3/2	[redacted]	PAL IR tabs qd: A) PAL 1 mg IR (Days 1-14) B) PAL 4 mg: 2 mg IR (Days 1-2) 4 mg IR (Days 3-14) C) PAL 8 mg: 2 mg IR (Days 1-2) 4 mg IR (Days 3-4) 6 mg IR (Days 5-6) 8 mg IR (Days 7-14)	F004 F006 F007
14	R076477-SCH-102	US	08 Sep 03	17 Jan 04	Rand, OL, MD, parallel group study of: the [redacted]		53	43 / 10	39 (25–50)	28/16/9	[redacted]	Days 1-7: washout and taper PAL group: Days 8-14: PAL OROS 9 mg q.d. (1 x 9 mg tablet) Days 15-21: PAL OROS 15 mg q.d. (1 x 9 mg + 2 x 3 mg tablets) RIS group: Day 8: RIS IR 1 mg q12h Days 9-14: increase dose by 1 mg q12h to achieve 7 mg q12h Days 15-21: RIS 8 mg IR q12h	F017 (9 mg) F016 (3 mg)

N	Number	Country	FPI	LPO	Study Description/Design	Vol /Pxt	N	Sex M / F	Age[b]	Race W/B/O[c]	SD/ MD	Rx	Formulation[d]
Pivotal Bioequivalence Studies													
15	R076477-P01-1008	United Kingdom	29 Jul 04	18 Dec 04	Rand, OL, 3-way XO to evaluate the [redacted] of the PAL OROS [redacted]; assess [redacted] on 15 mg [redacted] tablet strength		80	80 / 0	24 (18-43)	67/7/6	SD	A: 15 mg PAL OROS, Ph 3 form, fasted 2x 3 mg tablets + 1x 9 mg tablet B: 15 mg PAL OROS, [redacted] fasted 1x 15 mg tablet C: 15 mg PAL OROS, [redacted] fed 1x 15 mg tablet	F016 (3 mg) F017 (9 mg) [redacted]
Metabolism													
16	R076477-P01-103	Belgium	07 Jul 03	23 Jul 03	OL, SD, absorption, metabolism, elimination, safety, and tolerability of [redacted]		5	5 / 0	52 (40-63)	5/0/0	SD	1 mg 14C PAL IR, fasted	0.1 mg/ml 14C Soln
PK/PD													
17	R076477-SWE-1	Sweden	08 Apr 99	25 Nov 99	OL, SD, [redacted] study of PK/PD of D_2 and 5HT2A receptor occupancy of PAL.		3	3 /0	23 (23-26)	3/0/0	SD	PAL IR 1 mg fasted	F004 (Tab) F008 (Soln)
18	R076477-SIV-101	Sweden	28 Mar 03	06 Jun 03	OL, SD, [redacted] study of PK/PD of D_2 receptor occupancy of PAL.		4	2 / 2	24 (23-24)	4/0/0	SD	Paliperidone OROS 6 mg fasted (3 x 2-mg OROS)	[redacted]
19	R076477-SCH-1009	US	02 Feb 05	26 May 05	Rand, DB, PC, AC study to evaluate the cardiovascular effect of PAL, in particular, potential effect of PAL on [redacted] Also evaluated relationship between PK parameters and ECG results.	pxt	141	111 / 30	41 (18-51)	48/78/15	[redacted]	PAL Treatment Group: Day 1: placebo Day 2: PAL IR 4 mg Day 3: PAL IR 6 mg Days 4-8: PAL IR 8 mg Moxifloxacin Treatment Group: Days 1-7: placebo Day 8: moxifloxacin 400 mg	F052 (2 mg Capsule)
20	R076477-SCH-1010	France, Poland, Romania	01 Mar 05	18 Aug 05	Rand, DB, PC, parallel group study to evaluate effect of PAL OROS on [redacted] measured by [redacted]	pxt	42	28 / 14	32 (20-46)	42/1/0	[redacted]	Placebo Group: Days 1-14: Placebo q.d. PAL Group: Days 1-14: PAL OROS 9 mg q.d.	F023 [redacted]
Effect of Intrinsic Factors													
21	R076477-P01-1005	UK	11 Mar 04	02 Jul 04	Rand, DB, PC, SD & MD study of the [redacted] of PAL OROS in [redacted] adults; safety & tolerability	vol	60	34 / 26	26.0-27.5 (21-39)	30/0/30	[redacted]	PAL OROS or placebo (4:1 ratio) Day 1: PAL OROS 3 mg or PBO Days 3-5: washout Days 5-11: PAL OROS 3 mg or PBO qd Days 12-18: washout Day 19: PAL OROS 6 mg or PBO	F022
22	R076477-SCH-1008	Germany	23 Aug 04	03 Dec 04	SD, OL, parallel-group study to evaluate the [redacted] of IR PAL in moderate [redacted] plasma protein binding; disposition of [redacted] of PAL; safety & tolerability.		20	16 / 4	60 (44-68)	20/0/0	SD	PAL 1 mg oral solution	F044
23	R076477-REI-1001	Germany	19 Aug 04	11 Feb 05	SD, parallel-group, OL study of [redacted] of PAL OROS in [redacted]; plasma protein binding; disposition of [redacted] of PAL; safety & tolerability.		47	32 / 15	60 (31-74)	47/0/0	SD	PAL OROS 3 mg	F016
24	PALIOROS-SCH-1011	The Netherlands	03 Feb 05	20 May 05	Open-label, SD and MD study to evaluate the [redacted] of PAL OROS in [redacted]		60	32 / 28	55 (18-85)	52/6/2	[redacted]	Day 1: PAL OROS 3mg Day 6 to 12: PAL OROS 3 mg q.d.	F016

N	Number	Country	FPI	LPO	Study Description/Design	Vol /Pxt	N	Sex M / F	Age[b]	Race W/B/O[c]	SD/ MD	Rx	Formulation[a]
Effect of Extrinsic Factors													
25	ALZA C-2004-006	UK	22 Mar 04	29 Apr 04	OL, SD [redacted] PK and max [redacted] study		40	40 / 0	[25.7] (18-41)	39/0/1	SD	PAL OROS: Group 1 (n=20): 12 mg, fasted (1 x 9 mg + 1 x 3 mg) 15 mg, fasted (1 x 9 mg + 2 x 3 mg) Group 2 (n=20): 15 mg, fasted (1 x 9 mg + 2 x 3 mg) 15 mg, fed (1 x 9 mg + 2 x 3 mg)	F016 (3 mg) F017 (9 mg)
26	R076477-P01-1006	US	15 Mar 04	18 May 04	Single-dose, Rand, OL, 2x-XO [redacted] S/T study of PAL OROS in [redacted]		20	12 / 8	26 (20-41)	0/0/35	SD	ER OROS PAL 3 mg, fasted ER OROS PAL 3 mg, fed	F016
27	Palioros-P01-1012	US	30-Aug-05	1-Dec-05	SD, Rand, OL, 3x XO [redacted] in healthy males	Vol	74	74 / 0	28.6 (18-55)	64/8/0	SD	ER OROS Pal 12 mg fasted supine ER OROS Pal 12 mg fasted ambulatory ER OROS Pal 12 mg fed ambulatory	F049
28	R076477-P01-1004	Belgium	06 Oct 04	07 Nov 04	Rand, SD, OL, 2x-XO study to evaluate the effect of [redacted] on the PK of PAL OROS		30	30 / 0	39 (19-51)	30/0/0	SD	A: Day 1: PAL OROS 6 mg B: Days 1 – 8: trimethoprim 200 mg b.i.d. Day 5: PAL OROS 6 mg	F047
Pivotal Efficacy and Safety Trials													
29	R076477-SCH-303	International	29 Mar 04	25 Jan 05	Rand, DB, PC, AC, parallel-group, [redacted] study of [redacted], with OL extension OL extension (52 wk): PAL OROS flexible dosing 3 - 12 mg/day		629	329 / 300	37 (18-71)	539/--c/89	MD	6 wk DB treatment A) PAL OROS 6 mg B) PAL OROS 9 mg C) PAL OROS 12 mg D) Olanzapine 10 mg E) Placebo	F022 (3 mg) F023 (9 mg)
30	R076477-SCH-703				[redacted] OL phase ongoing						MD		
31	R076477-SCH-304	International	17 Feb 04	22 Dec 04	Rand, DB, PC, AC, parallel-group, [redacted] study of [redacted], with OL extension		439	325 / 114	43 (19-76)	188/242/9	MD	6 wk DB treatment A) PAL OROS 6 mg B) PAL OROS 12 mg C) Olanzapine 10 mg D) Placebo	F022 (3 mg) F023 (9 mg)
32	R076477-SCH-704				[redacted] OL phase ongoing						MD	52 wk PAL OROS 3-12 mg/day flexible dosing	
33	R076477-SCH-305	International	13 May 04	24 May 05	Rand, DB, PC, AC, parallel-group, [redacted] study of [redacted], with OL extension		614	417 / 197	36 (18-64)	301/132/18 1	MD	6 wk DB treatment A) PAL OROS 3 mg B) PAL OROS 9 mg C) PAL OROS 15 mg D) Olanzapine 10 mg E) Placebo	F022 (3 mg) F023 (9 mg)
34	R076477-SCH-705				OL extension OL phase ongoing						MD	24 wk OL extension PAL OROS 3 -12 mg/day flexible dosing	
35	R076477-SCH-302	International	04 Aug 04	24 May 05	Randomized, DB, PC, parallel group [redacted] in [redacted] subjects with OL extension		114	31 / 83	68 (64-81)	113/-c/1	MD	6 wk DB treatment Placebo, *or* PAL OROS 3 - 12 mg/day flexible dosing	F022 (3 mg) F023 (9 mg)
36	R076477-SCH-702				[redacted] OL phase ongoing						MD	OL extension (24 wk): PAL OROS 3 - 12 mg/day flexible dosing	

a See text at the beginning of this section for mean of highlighting and shading colors. b Age: Mean (Range); [Median] c W/B/O c

3.2 Pharmacology

Paliperidone is the active 9-hydroxy-metabolite of the antipsychotic risperidone that is approved for the treatment of schizophrenia.

The following description of the pharmacology of paliperidone is quoted directly from the sponsor's submission:

"Paliperidone is a monoaminergic antagonist with a high affinity for serotoninergic (5-hydroxytryptamine [5-HT] type 2A [5HT2A]) and dopaminergic D2 receptors. Paliperidone binds also to α1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and α2-drenergic receptors. Paliperidone has no affinity for cholinergic, muscarinic, or β1- and β2-adrenergic receptors. Paliperidone is a new chemical entity belonging to the atypical antipsychotic class of psychotropic drugs. It is the major active metabolite of risperidone that is registered worldwide for the treatment of schizophrenia. Paliperidone is a racemate comprised of enantiomers R078543 (+) and R078544 (-). The pharmacological profiles of the racemate and the 2 enantiomers are similar in in vitro binding assays, in vivo receptor occupancy studies, and in in vivo functional interaction studies."

The sponsor's findings and conclusions regarding *in vivo* and *in vitro* pharmacology of paliperidone include the following:

1) *shared nearly the same binding affinity for 5-HT_{2A}, D_2, α_1, and α_2 receptors*

2) *reversed dopamine-induced suppression of PRL release from anterior pituitary cells*

3) *reduced 5-HT-induced human platelet aggregation. In a series of standard in vivo pharmacology tests, paliperidone, its enantiomers and risperidone showed similar effects at closely related doses.*

"Paliperidone was shown to distribute to specific brain regions with high density of 5-HT_{2A}- and D_2-receptors and achieve exposure (AUC) that was in excess of that in plasma. There was no undue tissue retention of paliperidone except in melanin-containing tissues of pigmented rats. The melanin binding of paliperidone was shown to be reversible.

The major biotransformation routes of paliperidone were similar in laboratory animals and in humans. All metabolites identified in the human mass balance study were also observed in at least one laboratory animal species. All the metabolites that were identified following paliperidone administration in humans were also observed following risperidone administration in humans.

Paliperidone at relevant clinical concentrations had no or only a marginal inhibitory effect on the major CYP450's. Paliperidone was shown to be a P-gp substrate but the influence of any drug-drug interaction with P-gp at the level of the blood-brain barrier is likely to be modest."

3.3 Chemistry

3.3.1 Drug Substance

Paliperidone is a 50:50 racemic mixture of (+) and (-) paliperidone. It is the 9-hydroxy- metabolite of risperidone.

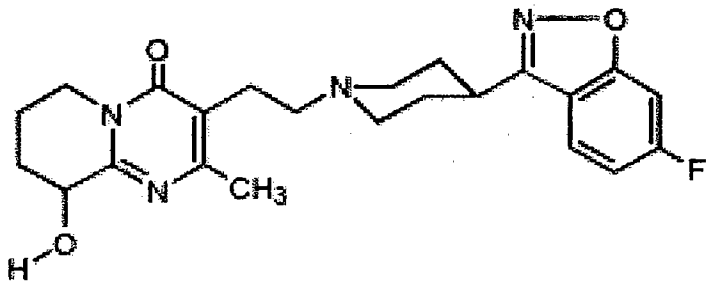
3.3.1.1 Chemical Name

(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2a]pyrimidin-4-one

3.3.1.2 Code Names and Numbers

Paliperidone:	R076477
(+)-paliperidone:	R076473
(—)-paliperidone:	R076474

3.3.1.3 Structural Formula



3.3.1.4 Molecular Formula

$C_{23}H_{27}FN_4O_3$

3.3.1.5 Molecular Weight

426.49

3.3.1.6 Polymorphs

[redacted]

3.3.1.7 pKa

8.24

3.3.1.8 Solubility

Solvent	Solubility (mg%)
Water	3

3.3.1.9 Particle Size

D_{50} Mean [redacted]
Range [redacted]

Appears This Way
On Original

3.3.2 Drug Product

3.3.2.1 Formulation Descriptions

Five OROS formulations are described in the NDA, including three development formulations, the pivotal phase III clinical trial formulation (Ph III CTF), [redacted]. The three OROS development formulations include 'slow' [redacted] formulation that also contains an immediate release coating on the outside of the tablet, resulting in a [redacted] drug release pattern.

In addition to the OROS formulations oral solutions, immediate release encapsulated [redacted], immediate release tablets, and extended release encapsulated [redacted] formulations were also used.

As many of the tables and documents submitted only referred to the formulations that were used by code number some of the tables in this review also had to be generated in the same manner. A guide to these codes and their associated formulations are shown in Table 6. Note that the OROS Ph III CTF [redacted] formulations also have second codes that were used when the dosage units were over-encapsulated for blinding purposes or were also imprinted with identifying codes.

Table 6 Codes for Paliperidone Formulations Used in NDA 21-999

Primary Descriptor	Secondary Descriptor	Strength	Code	Over encapsulated	Imprinted
OROS Formulations	Slow	2 mg	[redacted]		
	[redacted]		[redacted]		
	[redacted]		F026		
	Ph III CTF	3 mg	F016	F022	
		9 mg	F017	F023	
	[redacted]	3 mg	F046		F039
		6 mg	F047		F040
		9 mg	F048		F041
		12 mg	F049		F045
		15 mg	F050		F043
Oral Solutions	Includes single enantiomer solutions	0.1 mg/ml	F001		
		0.05 mg/ml	F008		
	Also used for IV	0.1 mg/ml	F044		
		1 mg/ml	F021		
IR Bul[redacted]		[redacted]	F028		
IR Capsules		2 mg	F052		
IR Tablets		0.5 mg	F003		
		1 mg	F004		
		4 mg	F006		
		8 mg	F007		
ER Encapsulated [redacted]		2.5 mg	F025		
	pH 5.5		F036		
	pH 6.5		F037		

3.3.2.2 *Qualitative / Quantitative Composition of MR OROS Formulations*

The qualitative /quantitative compositions of the paliperidone modified release OROS formulations are shown in Table 7, along with the studies that they were used in.

Differences in the qualitative composition of the formulations are highlighted by differential coloring of table cells.

The major differences between formulations follow and are best reviewed while simultaneously examining Table 7.

For the TBM and the Phase III CTF formulations the differences: include

[redacted] in a higher percentage in the TBM formulation compared with use of [redacted] at a lower percentage the phase III CTF formulation. [redacted]

Rate Controlling Membrane: [redacted] rate controlling membrane was also used in the TBM formulation compared with the phase III formulation.

Except for colorants, imprinting ink, probable use of slightly different descriptors for certain ingredients and use of over-encapsulation for blinding purposes there does not appear to be any other differences between the Ph III CTF and TBM formulations. In addition, the differences mentioned are unlikely to alter the drug release properties of the formulations.

Best Possible Copy

For the [redacted] formulation the differences compared to the Phase III CTF formulation include:

Rate Controlling Membrane: [redacted] tablets not indicated.

[redacted]

3 Page(s) Withheld

✔ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*7

3.3.2.3 Manufacturing, QC, Stability Testing and Packaging Sites

3.3.2.4 Commercial Batch Sizes

3.3.2.4.1 Manufacturing Formulae

3.3.2.4.2 Capsule Batch Qualitative Quantitative Composition

[redacted]

3.4 Bioanalytic Methods

3.4.1 Methods Used and Assay Validations

3.4.2 Sample Handling and Storage

3.4.3 In-Process Quality Controls

3.5 Dissolution

3.5.1 Sponsor's Proposed Dissolution Method and Acceptance Criteria

Table 8 Sponsor's Proposed Paliperidone MR Tablets Dissolution Method and Specifications

Parameter	Proposed Dissolution Method and Specifications
Apparatus type:	USP Type VII Reciprocating Disk
Media:	NaCl 2 gm/L (0.2% w/w) in 0.0825 N HCl pH 1.0 ± 0.5*
Volume:	50 ml
Temperature:	37 ± 0.5 °C
Frequency:	Agitation by Reciprocating Arm 30 cycles per minute (cpm)
Amplitude:	2 – 3 cm
Sampling Times:	2 hour intervals for a duration of 24 hours
Acceptance Criteria:	Conforms to USP <724> acceptance Table 1 for extended-release articles 2 hours Q 8 hours Q 14 hours Q 24 hours Q
Analysis	HPLC UV Analytical Method

* The sponsor is calling this media 'Modified Artificial Gastrointestinal Fluid, (AGF). The sponsor claims that this is the same as USP Simulated Gastric Fluid (SGF) without enzyme. The USP's description of SGF follows, and a comparison the varying methods used to acidify the solution and ballpark verification of the pH may be found in Table 9.

"Gastric Fluid, Simulated, TS —Dissolve 2.0 g of sodium chloride and 3.2 g of purified pepsin, that is derived from porcine stomach mucosa, with an activity of 800 to 2500 units per mg of protein, in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. [NOTE—Pepsin activity is described in the Food Chemicals Codex specifications under General Tests and Assays.*] This test solution has a pH of about 1.2."*

3.5.2 Dissolution Data

3.5.2.1 Dissolution Data

Table 10 shows dissolution data as reported in the COAs for development, clinical trial, and To-Be-Marketed formulation batches and also which studies they were used in. Except for batch MV0301019 no additional dissolution data was found for any batches used in the pivotal phase III studies. For batch MV03011019 full dissolution profile data in shown in Table 11, as it was used for external validation of the

In Table 10 light yellow shaded rows indicate the primary batch and unshaded rows indicate over-encapsulated sub-batches used for blinding purposed in the phase III pivotal efficacy studies, these studies are also indicated by red text and light blue text. Orange, green, and royal blue text highlight different batches that were used in a single study. Light turquoise shaded rows with violet text highlight overall mean dissolution rates and ranges for clinical and to-be-marketed formulation batches.

Appears This Way
On Original

Appears This Way
On Original

Table 10 Reported Dissolution Data for Paliperidone Development, Clinical Trial, and [redacted] Formulation Batches

Tablet Strength (mg)	Form Code	Study	Type of Study	Drug Substance Batch	Drug Product Batch	Encapsulated Drug Product Batch	Manufacturing Site	Date of Manufacture	Batch Size	Batch Size	Mean Cumulative Release (% of LC) Sampling Time 2 hr	8 hr	14 hr	24 hr
											Proposed Acceptance Range			
Development Formulations														
2	[redacted] OROS	P01-101		PUA081	MV0311255		Mountain View	03 Jun 2003			20.5		59.5	103.0
2	OROS slow	Alza-034 SCH-101 SIV-101		PUA031	MV0214352		Mountain View	09 Aug 2002			1.0		47.5	100.5
											Sampling Times for OROS Formulation			
2	OROS fast	Alza-034		PUA031	MV0214353		Mountain View	19 Aug 2003			*2 hr*		*6 hr*	*16 hr*
											4.0		38.0	1.05
Clinical Trial Formulation														
3	F016	Alza-044 Alza-006 P01-1008 P01-1010 SCH-102	Dose Proportionality Food Effect Pivotal BE Dose Proportionality MD PK	PUA051	MV0301019		Mountain View	25 Apr 2003			2.0	18.1	54.0	101.0
3	F022	SCH-303 SCH-304 SCH-305	Ph III Ph III Ph III		MV0301019	03G09/F022	Mountain View	9 Jul 2003						
3	F016	P01-1006 P01-1007	Food Japanese Enantiomer	PUA051	MV0307085		Mountain View	25 Apr 2003			1.7	17.7	52.7	99.3
3	F022	SCH-305	Ph III		MV0307085	03I10/F022	Mountain View	15 Sep 2003						
3	F022	P01-1005 SCH-302 SCH-305	Ethnicity Ph III Elderly Ph III		MV0307085	03J01/F022	Mountain View	01 Oct 2003						
3	F016	REI-1001	Renal Failure	EIA081	MV0332871		Mountain View	19 Feb 2004			1.7	20.5	56.7	96.0
3	F016	SCH-1011	Young/Elderly	EIA131	MV0332891		Mountain View	15 Mar 2004			2.0	21.3	59.7	99.0
3	F022	SCH-303 SCH-304	Ph III Ph III		MV0332891	04C29/F022	Mountain View	29 Mar 2004						
3	F022	SCH-302 SCH-305	Ph III Elderly Ph III		MV0332891	04D05/F022	Mountain View	19 Apr 2004						
3	F022	SCH-303 SCH-304 SCH-305	Ph III Ph III Ph III		MV0332891	04D13/F022	Mountain View	26 Apr 2004						

9	F017	Alza-044 Alza-006 P01-1008 SCH-102	Dose Proportionality Food Effect Pivotal BE MD PK	PUA051 PUA061 PUA081	MV0301025		Mountain View	25 Apr 2003			1.9	20.6	57.6	102.4
9	F023	SCH-303 SCH-304 SCH-305	Ph III Ph III Ph III		MV0301025	03G14/F023	Mountain View	14 Jul 2003						
9	F023	SCH-302 SCH-305	Ph III Elderly Ph III		MV0301025	03J13/F023	Mountain View	13 Oct 2003						
9	F023	SCH-305	Ph III		MV0301025	03123/F023	Mountain View	23 Sep 2003						
9	F017	NA		EIA071	0406657c		Vacaville	10 Mar 2004			1.8	17.2	49.9	97.8
9	F023	SCH-1010 SCH-303 SCH-304 SCH-305	PK/PD Sleep Ph III Ph III Ph III		0406657	04D26/F023	Vacaville	05 Apr 2004						
9	F023	SCH-1010 SCH-302 SCH-305	PK/PD Sleep Ph III Elderly Ph III		0406657	04E04/F023	Vacaville	03 May 2004						
Global Mean and Range of Means for Clinical Trial Formulation Batches											1.9 1.7 - 2.0	19.2 17.2 - 21.3	55.1 49.9 - 59.7	99.3 96.0 - 102.4
[redacted] Formulation														
3	F046	NA		EIA081	MV0332868		Mountain View	08 Mar 2004						
6	F047	P01-1004 P01-1010	Trimethoprim DDI Dose Proportionality	EIA111	0406837		Vacaville	22 Mar 2004			1.63		56.0	99.3
9	F048	P01-1010	Dose Proportionality	EIA071	0406836		Vacaville	12 Mar 2004			2.0		52.0	95.0
12	F049	P01-1010	Dose Proportionality	EIA071	0406838		Vacaville	14 Apr 2004			1.5		53.7	97.6
15	F050	P01-1008 P01-1010	Pivotal BE Dose Proportionality	EIA111	0406659		Vacaville	08 Mar 2004			2.0		56.0	96.0
15	F050	NA		EIA081	MV0332881		Mountain View	02 Mar 2004			1.3		52.5	97.3
[redacted] Formulation Used in Stability Studies											1.6		54.5	98.0
3	F039	—	Stability Study	EIA081	0406817		Mountain View	11 Mar 2004			1.63	21.0	56.0	99.3
3	F039	—	Stability Study	EIA131	0406819		Mountain View	11 Mar 2004			2.0	20.9	56.0	98.0
3	F039	—	Stability Study	EIA111	0415156		Vacaville	22 Jun 2004			2.0	17.2	51.0	103.0
6	F040	—	Stability Study	EIA111	0406946		Vacaville	25-Mar-2004			2.0	17.8	52.0	95.0
9	F041	—	Stability Study	EIA071	0406931		Vacaville	15-Mar-2004			1.5	18.4	53.7	97.6
12	F045	—	Stability Study	EIA071	0406932		Vacaville	16-Apr-2004			2.0	19.7	56.0	96.0
15	F043	—	Stability Study	EIA081	0406835		Mountain View	09-Mar-2004			1.6	19.5	54.5	98.0
15	F043	—	Stability Study	EIA101	0417060		Mountain View	22-Jun-2004			2.0	20.3	55.0	100.0
15	F043	—	Stability Study	EIA111	0406929		Vacaville	10-Mar-2004			1.3	18.3	52.5	97.3
Global Mean and Range of Means for [redacted] Formulation Batches											1.7 1.3 - 2.0	19.2 17.2 - 21.0	54.1 51.0 – 56.0	97.8 95.0 – 103.0

13 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 8

3.6 Receptor Binding and Neurotransmitter Transporter Uptake

In vitro data indicates that paliperidone and both metabolites bind to histamine H_1, and a variety of serotonergic, dopaminergic, and alpha adrenergic receptors at low nanomolar concentrations, (see Table 22 and Table 23). Experimental details were not provided in report cns-as-psdb-2532160 for the data in Table 22, however for the experiments for these particular receptors were conducted in a variety of buffers without added protein, in contrast for a few other experiments, such as for substance P receptor binding, that were conducted in the presence of BSA according to Report N79120 for Table 23. Consequently, we can assume that Ki values for the pertinent receptors are for free concentrations.

With maximal clinical dosing of Paliperidone OROS 12 mg daily the maximum concentrations observed in two different studies, (SCH-101 and SCH-102), were upwards of 175 ng/ml. Assuming a 2 fold increase with food, concentrations of up to 350 ng/ml or 821 nM/L may be expected clinically. With a 25% free fraction for racemic paliperidone, free concentrations up to 205 nM/L are expected, in contrast, with typical dosing of 6 mg qd, average Cmax's of 23 ng/ml are expected with free concentrations of 12.2 nM. Based on these values the percent inhibition of each receptor has been estimated and is also shown in Table 22. The typical percent inhibition appears to be low compared to what is observed *in vivo* (i.e. ~ 70% - 80%) but is within 1 order of magnitude and so is very good estimate.

Table 22 *In Vitro* Binding of Paliperidone and its Enantiomers to Cloned Human Receptors – Report cns-as-psdb-2532160

Receptor Class	Receptor	Cell Line Expressed In	Ki-values (nM), n = 2-5				Estimated Approximate % Inhibition with a Maximum Expected Cmax of Racemic Paliperidone of	
							20 ng/ml or 47 nM (i.e. 12.2 nM free)	350 ng/ml or 821 nM (i.e. 205 nM free)
			Risperidone	at a Dose of 6 mg qd	at a Dose of 12 mg qd	(-)-Paliperidone	6 mg OROS qd	12 mg OROS qd
Serotonergic	$5\text{-}HT_{1A}$	Ha-6 cells	420	590	412	N/A	2.0	25.8
	$5\text{-}HT_{1D\alpha}$	C6-glioma	9.8	12	15	25	50.4	94.5
	$5\text{-}HT_{1D\beta}$	L929	140	170	N/A	N/A	6.7	54.7
	$5\text{-}HT_{2A}$	L929	0.52	1.0	0.60	1.1	92.4	99.5
Dopaminergic	D_{2L}	CHO cells	5.9	4.8	10	14	71.8	97.7
	D_3	CHO cells	14	6.4	8.1	7.9	65.6	97.0
	$D_{4.2}$	CHO cells	16	30	21	12	28.9	87.2
Adrenergic	α_{2A}	CHO-1E5 cells	23	30	45	25	28.9	87.2
	α_{2B}	CHO-3B3 cells	8.5	9.5	12	11	56.2	95.6
	α_{2C}	CHO-11A9 cells	9.1	11	19	15	52.6	94.9
	β_1	E. Coli	>5000	>5000	>5000	>5000		
	β_2	E. Coli	>5000	>5000	>5000	>5000		
Histaminergic	H_1	CHO cells	27	32	N/A	N/A	27.6	86.5

N/A: Not available

			R 64766 risperidone			R 76477 (±)9OH-risperidone			R 78543 (+)9OH-risperidone			R 78544 (-)9OH-risperidone		
			Ki nM	SD	n	Ki nM	SD	n	Ki nM	SD	n	Ki nM	SD	n
Neurotransmitter receptor sites														
Serotonin-5HT2	3H-ketanserin	rat frontal cortex	0.12	0.02	4	0.22	0.04	4	0.19	0.02	3	0.24	0.04	3
Serotonin-5HT1A	3H-8OHDPAT	rat hippocampus	271	37	3	397	37	4	316	36	3	960	62	3
Serotonin-5HT1B	3H-serotonin	rat striatum	3728	1673	3	2530	329	2	3690	300	2			
Serotonin-5HT1D	3H-serotonin	calf substantia nigra	52	16	4	123	20	2	123	14	3	183	80	3
Serotonin-5HT1C	3H-mesulergine	pig choroid plexus	47	6	3	11	48	4	34	2	3	43	6	3
Serotonin-5HT3	3H-GR65630	NG 108CC15 cells	na			na			na			na		
alpha1-Adrenergic	3H-WB4101	rat forebrain	0.81	0.14	4	1.3	0.2	4	1.2	0.1	3	1.4	0.2	3
alpha2-Adrenergic	3H-clonidine	rat cortex	7.3	1.2	4	15	3	3	31	10	3	12	1	3
beta1-Adrenergic	125I-cyanopindolol	E coli Hu-beta1	na			na			na			na		
beta2-Adrenergic	125I-cyanopindolol	E coli Hu-beta2	na			na			na			na		
Dopamine-D2	3H-haloperidol	rat striatum	3.0	0.9	4	4.1	0.7	3	2.6	0.5	3	2.8	0.9	3
Dopamine-D1	3H-SCH23390	rat striatum	620	106	3	660	194	4	530	67	3	460	105	3
Histamine-H1	3H-pyrilamine	guinea pig cerebellum	2.1	0.0	3	7.9	0.5	3	15	3	4	10	1	3
Histamine-H2	3H-tiotidine	guinea pig striatum	890	290	3	4630	300	3	1840	0	2			
Cholinergic-muscarinic	3H-dexetimide	rat striatum	na			na			na			na		
Drug receptor binding sites														
mu-opiate	3H-sufentanil	rat forebrain	na			na			na			na		
Haloperidol sensitive sigma	3H-haloperidol	guinea pig medulla oblongata	805	216	3	1327	0	3	1500	170	3	945	108	3
Benzodiazepine	3H-flunitrazepam	rat forebrain	na			na			na			na		
PCP-NMDA sites	3H-TCP	rat hippocampus	na			na			na			na		
Ion channel ligand binding site														
Ca++-channel	3H-nitrendipine	rat cortex	na			na			na			na		
Na+-channel	3H-Batrachotoxin-B	rat cortex	3850	650	3	8040	1840	3	9470	2680	3	11700	2100	3
Peptide receptor binding sites														
Substance-P	3H-substance P	rat striatum	na			na			na			na		
Neurotensin	3H-neurotensin	rat forebrain	na			na			na			na		
CCK-A	3H-CCK	rat pancreas	na			na			na			na		
CCK-B	3H-CCK	guinea pig cortex	na			na			na			na		
Tetrabenazine sensitive release site														
	3H-ketanserin	rat striatum	132	28	3	394	116	4	568	97	3	554	156	3
Various														
Thromboxane A2	3H-SQ29548	human platelets	na			na			na			na		
PAF	3H-PAF	rabbit platelets	na			na			na			na		
Leukotriene D4	3H-leukotriene D4	guinea pig lung	na			na			na			na		

			R 64766 risperidone			R 76477 (±)9OH-risperidone			R 78543 (+)9OH-risperidone			R 78544 (-)9OH-risperidone		
Neurotransmitter uptake			IC50 nM	SD	n	IC50 nM	SD	n	IC50 nM	SD	n	IC50 nM	SD	n
Serotonin	3H-serotonin	rat cortex	544	75	4	2030	460	4	1870	336	3	2170	298	3
Norepinephrine	3H-noradrenaline	rat cortex	2544	475	4	1600	340	3	4140	280	3	834	150	3
Dopamine	3H-dopamine	rat striatum	4740	385	3	8910	400	3	10690	3150	3	9810	3690	3
GABA	3H-GABA	rat cortex	na			na			na			na		

3.7 Metabolism

3.7.1 *In Vivo* Metabolism

Study P01-103 was a single dose mass balance study of 1 mg of orally administered ^{14}C labeled paliperidone to 5 healthy male volunteers. Subjects included 3 phenotypic CYP2D6 extensive metabolizers and 2 poor metabolizers. Plasma, urine and feces samples were collected for up to 1 week post-dosing. Analysis of the urine and feces were reported in *in vitro* study report FK4612.

Figure 12 and Figure 13 show an over and under comparison of Total ^{14}C Radioactivity and unchanged paliperidone concentration-time profiles after administration of 1 mg ^{14}C-Paliperidone Oral Solution and Table 24 shows a comparison of their pharmacokinetic metrics.

The plasma concentration profiles of total radioactivity and unchanged paliperidone are very similar. Although terminal elimination of unchanged paliperidone appears to be paradoxically slower than for ^{14}C moieties this is probably due to a lack of assay sensitivity. Overall these figures and Table 24 indicate formation rate limited metabolite kinetics and little exposure to metabolites. Based upon this, the low molar exposures to metabolites, the metabolites probably don't contribute much to efficacy or to toxicities due to binding at serotonergic, dopaminergic, adrenergic, or histaminergic receptors, however without receptor binding and transporter data we can't be certain.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 9

Table 24 Comparison of Pharmacokinetic Metrics of Total 14C-Labeled Moieties and Unchanged Paliperidone after ^{14}C-Paliperidone 1 mg Solution PO – Study P01-103

Metric	Total ^{14}C-Labeled Moieties	Unchanged Paliperidone	Ratios ^{14}C-equivalents: Paliperidone
n	5	5	5
Cmax[a] (ng/ml)	9.54 ± 1.35 (14.2) 7.90 - 11.3 [9.00]	8.85 ± 1.31 (14.8) 7.18 - 10.6 [9.23]	1.081 ± 0.066 (6.1) 0.974 – 1.138 [1.100]
Tmax (hr)	1.40 ± 0.224 (16.0) 1.00 - 1.50 [1.50]	1.30 ± 0.274 (21.1) 1.00 - 1.50 [1.50]	—
AUC24[a] (ng/ml x hr^{-1})	114 ± 19.9 (17.5) 90.7 - 145 [113]	111 ± 22.0 (19.8) 85.3 - 145 [108]	0.970 ± 0.0250 (2.6) 0.940 - 1.00 [0.962]
AUClast[a] (ng/ml x hr^{-1})	120 ± 31.7 (26.4) 90.7 - 174 [113]	183 ± 29.3 (16.0) 143 - 218 [191]	0.653 ± 0.086 (13.1) 0.574 - 0.798 [0.634]
AUC∞[a] (ng/ml x hr^{-1})	175 ± 30.7 (17.5) 134 - 217 [175]	187 ± 29.3 (15.7) 147 - 221 [196]	0.935 ± 0.083 (8.8) 0.821 - 1.042 [0.921]
CL/F (ml/min)	97.9 ± 17.6 (18.0) 76.8 - 124 [95.2]	91.0 ± 15.0 (16.5) 75.4 - 113 [85.0]	—

a For ^{14}C-labeled metrics, units are ng-equivalent instead of ng.

The metabolic scheme for paliperidone as best as can be determined by this reviewer from the reports of studies P01-103 and FK4612 is shown in Figure 14.

The reported data for the breakdown of paliperidone recovery in urine and feces is show in Table 25. Unfortunately, recovery in feces of individual moieties from individual subjects was not reported. However, recoveries from some pooled feces samples were reported and are shown in Table 25. No unchanged paliperidone was recovered from feces.

In summary, the metabolism and excretion of paliperidone is as follows:

Just under 60% of an oral dose of paliperidone solution is eliminated unchanged in the urine, with about slightly more than 30% eliminated as metabolites in urine and feces and less than 10% of the dose was not recovered. This indicates that paliperidone is well absorbed and that both renal elimination and hepatic metabolism contribute significantly to elimination. Of the 30% of the dose that is metabolized approximately 1/3 is eliminated in the feces (range 25% - 50%), and the 2/3's is eliminated renally.

There are four primary metabolic pathways for paliperidone metabolism in humans:

- Dehydrogenation of a hydroxyl group to form paliperidone ketone
- Oxidation to form 1 or possibly 2 hydroxy-paliperidone products possibly mediated by CYP2D6
- Oxidative metabolism to form a benzisoxazole scission product possibly mediated by both CYP2D6 and CYP3A4
- N-dealkylation to form an acid and amine cleavage products.

Each of these primary pathways appears to mediate 12% or less of total elimination.

Secondary metabolism appears to include benzisoxazole scission of hydroxy-paliperidone and/or hydroxylation of the benzisoxazole scission product to yield a hydroxyl-benzisoxazole scission product, and glucuronidation of the benzisoxazole scission product.

Although 60% of the dose on average is eliminated unchanged in urine in CYP2D6 extensive metabolizers the average is 55% and in poor metabolizers it's 65%.

No single metabolic pathway can be singled out as being particularly significant, but both renal and total hepatic elimination are important.

Figure . . Paliperidone Metabolic Scheme as Determined from Studies P0 . .03 & FK4612

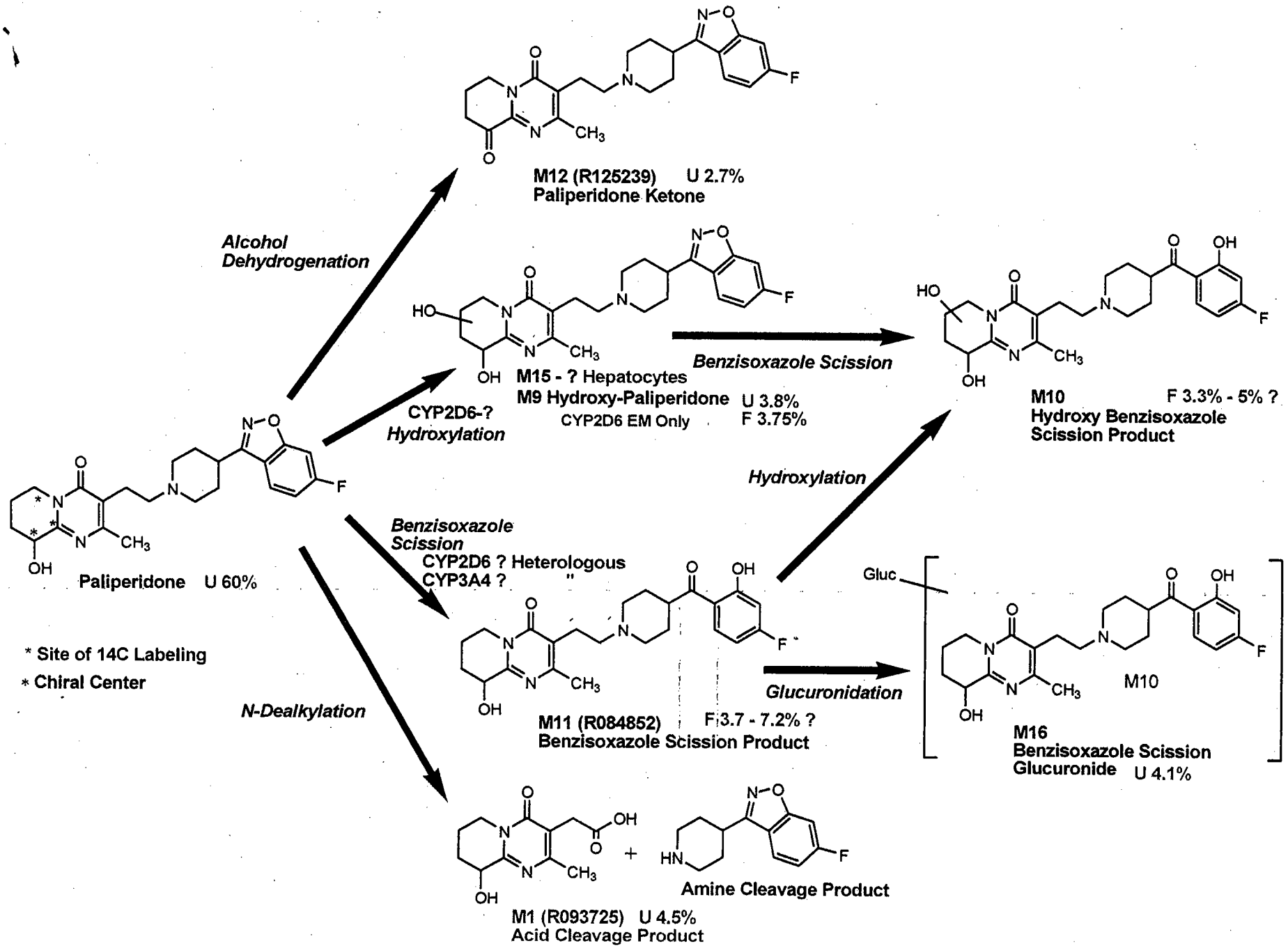


Table 25 Mass Balance Data from Study P01-103 as Reported in Study Report FK4612

Subj	CYP2D6	% of Dose Recovered in Urine as Paliperidone	% of Dose Recovered in Urine as M1	% of Dose Recovered in Urine as M16	% of Dose Recovered in Urine as M9	% of Dose Recovered in Urine as M12	Subtotal of Identified Moieties (% of Dose)	% of Dose Unidentified in Urine[a]	% of Dose Recovered in Urine (Total radioactivity)	% of Dose Recovered in Feces (total radioactivity)	% of Dose Total Recovered in Urine & Feces (total radioactivity	% of dose Recovered as Identified and unidentified metabolites in urine %& feces	% of Dose Not Recovered
103	PM												
105	PM												
101	EM												
104	EM												
106	EM												
Population	**N**	**Summary Statistics**											
All Subjs	5	59.4 ± 7.1 (12.0) 51.4 - 67.5 [62.3]	4.6 ± 1.4 (31.3) 2.5 - 6.5 [4.5]	4.1 ± 1.0 (25.4) 2.5 - 5.1 [4.4]	3.8 ± 1.4 (37.9) 2.7 - 5.4 [3.2]	2.7 ± 1.7 (60.4) 0.6 - 4.3 [3.1]	72.4 ± 5.8 (8.0) 66.9 - 79.6 [69.2]	7.2 ± 4.4 (61.7) -0.5 - 10.2 [9.1]	79.6 ± 4.2 (5.3) 77.1 - 87.1 [78.4]	11.4 ± 3.1 (26.9) 6.8 - 14.4 [12.3]	91.1 ± 2.1 (2.4) 88.4 - 93.8 [91.5]	31.7 ± 7.5 (23.8) 26.1 - 40.8 [26.4]	8.9 ± 2.1 (24.1) 6.2 - 11.6 [8.5]
PM	2	64.9 ± 3.7 (5.7) 62.3 - 67.5 [64.9]	4.6 ± 0.3 (5.9) 4.4 - 4.8 [4.6]	3.0 ± 0.7 (24.7) 2.5 - 3.6 [3.0]		3.7 ± 0 (0.0) 3.7 - 3.7 [3.7]	74.4 ± 7.3 (9.8) 69.2 - 79.6 [74.4]	8.3 ± 1.2 (14.1) 7.5 - 9.1 [8.3]	82.7 ± 6.2 (7.4) 78.4 - 87.1 [82.7]	8.4 ± 2.3 (27.6) 6.8 - 10.1 [8.4]	91.1 ± 3.8 (4.2) 88.4 - 93.8 [91.1]	26.2 ± 0.1 (0.5) 26.2 - 26.4 [26.3]	8.9 ± 3.8 (43.2) 6.2 - 11.6 [8.9]
EM	3	55.7 ± 6.6 (11.9) 51.4 - 63.4 [52.4]	4.5 ± 2.0 (44.5) 2.5 - 6.5 [4.5]	4.7 ± 0.3 (7.0) 4.4 - 5.1 [4.8]	3.8 ± 1.4 (37.9) 2.7 - 5.4 [3.2]	2.4 ± 1.9 (77.3) 0.6 - 4.3 [2.4]	71.1 ± 5.8 (8.1) 66.9 - 77.7 [68.8]	6.5 ± 6.1 (93.8) -0.5 - 10.2 [9.7]	77.6 ± 0.8 (1.0) 77.1 - 78.5 [77.2]	13.5 ± 1.0 (7.8) 12.3 - 14.4 [13.7]	91.0 ± 1.4 (1.5) 89.5 - 92.2 [91.5]	35.3 ± 8.0 (22.7) 26.1 - 40.8 [39.0]	9.0 ± 1.4 (15.3) 7.8 - 10.5 [8.5]

a Difference between % of dose recovered in urine as total radioactivity minus % of Dose recovered in urine and identified

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 10

Table 26 shows the metabolism rate of unchanged paliperidone and the formation rate of the benzisoxazole scission product, (R084852 aka M11) by CYP2D6 and CYP 3A4 in microsomes from E. Coli heterologous expression systems.

Table 26 Paliperidone Metabolism Rate and Formation Rate of R084852 by CYP2D6 and CYP3A4 from Heterologously Expressed Microsomes

CYP form	Metabolism Rate (pmol/min nmol P-450)	
	Overall Metabolism Rate	Formation Rate of R084852 (M11) (benzisoxazole scission product)
CYP2D6	0.107	0.069
CYP3A4	0.084	0.060

3.7.2.2 Pooled Human Hepatocytes

The metabolism of ^{14}C labeled racemic paliperidone (10 µM) and the (+) and (–) enantiomers (5 µM) were each examined in pooled human hepatocytes cultures in study FK2995. From (+)-paliperidone M1, the acid cleavage product, and M9, one of the alicyclic hydroxyl-paliperidones was formed, whereas only M1, the acid cleavage product, was detected after incubation of (-)-paliperidone.

3.7.2.3 Pooled Human 12,000 x g Subcellular Fractions

Study FK2995 examined the metabolism of ^{14}C labeled racemic paliperidone (10 µM) and the (+) and (–) enantiomers (5 µM) in pooled human 12,000 x *g* subcellular fractions and microsomes. M1, the acid cleavage product, and M9, an alicyclic monohydroxy-paliperidone were formed in 12,000 x *g* subcellular fractions as well as M15, a second alicyclic monohydroxy-paliperidone.

3.7.2.4 Pooled Human Microsomes

Study FK2995 also examined the metabolism of ^{14}C labeled racemic paliperidone (10 µM) and the (+) and (–) enantiomers (5 µM) in pooled human microsomes. Formation of M9, an alicyclic monohydroxy-paliperidone, M12, paliperidone ketone as well as M15, a second alicyclic monohydroxy-paliperidone, was detected.

3.7.2.5 Induction By Paliperidone

Induction experiments in human hepatocyte cultures do not appear to have been performed.

3.7.2.6 *Inhibition by Paliperidone*

Little to no inhibition of P450 isozymes examined *in vitro* was detected when incubated with a 50:50 mixture of racemic paliperidone at claimed clinically relevant concentrations, (Cmax < 150 ng/ml). However, concentrations *in vivo* are not at a 1:1 molar ratio of the (+) and (–) enantiomers so the *in vitro* data must be interpreted cautiously. In addition all inhibition experiments included a pre-incubation period of only 5 minutes, and no experiments were conducted without pre-incubation. Due to the lack of experiments without pre-incubation, the limited duration of the pre-incubations used, and the low absolute quantities of the incubation experiments thereby limiting the ability to detect metabolism, we need to conclude that the potential for mechanism based inhibition by paliperidone metabolites or suicide substrate inhibition was not adequately tested for *in vitro*.

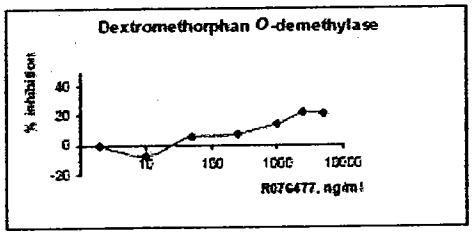
The interaction of paliperidone with the metabolism of a number of specific cytochrome P-450 substrates was investigated *in vitro* in a batch of human liver microsomes, (H-INT-1). The inhibitory effect on the overall metabolism of the specific substrates and/or on the formation of their major metabolites is shown in Table 27. When less than 50 % inhibition was observed at the highest concentration tested, the % inhibition at this concentration is given.

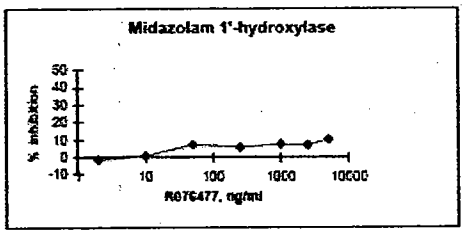
Examination of the inhibition by paliperidone of CYP2D6 and CYP3A4 using various substrates of CYP3A4 that may represent different binding sites also failed to show any significant inhibition *in vitro* at clinically relevant concentrations, (see Figure 16 and Table 28).

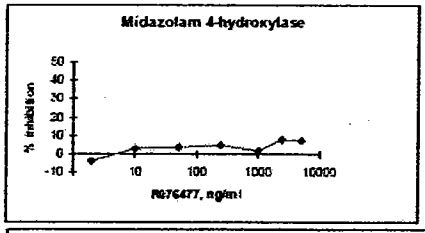
Table 27 Inhibition of Metabolism of CYP Isozyme Probes by Paliperidone – Study FK3103

CYP Involved	Substrate	Monitored Product	IC_{50} or Highest Concentration Tested (µg/ml)	% Inhibition at Highest Concentration Tested
CYP1A2	Caffeine	N3-desmethyl caffeine formation	>60	-28.0
CYP2A6	Coumarin	7-OH-coumarin formation	>30	7.34
CYP2C8,9,10	Tolbutamide	4-OH-tolbutamide formation	>30	-38.15
	Phenytoin	4-OH-phenytoin formation	>60	17.93
CYP2D6	Dextromethorphan	overall metabolism	>100	-1.37
		dextrorphan formation	61.9	50.0
CYP2D6	Debrisoquine	overall metabolism	30	67.9
		4-OH-hydroxylation	>30	37.9
CYP2E1	Chlorzoxazone	6-OH-chlorzoxazone formation	>30	-9.28
CYP3A4	Cyclosporine A	overall metabolism	>30	11.66
CYP3A4	Testosterone	overall metabolism	>60	16.6
		6-β-OH testosterone formation	>60	9.90
CYP4A	Lauric acid	ω- and (ω-1)-hydroxylated acids	>30	6.85

Figure 16 Percentage of Dextromethorphan *O*-demethylase, Midazolam 1'- and 4-hydroxylase and Testosterone 6-ß hydroxylase Inhibition in the Presence of Various Concentrations of Paliperidone (2-5000 ng/ml)







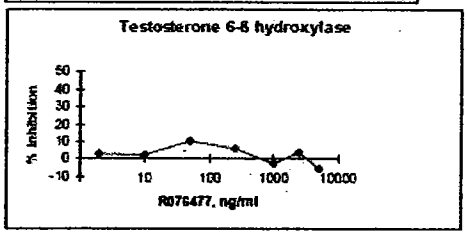


Table 28 Dextromethorphan *O*-demethylase, Midazolam 1'- and 4- hydroxylase and Testosterone 6-ß hydroxylase activities in the Absence and Presence of Various Concentrations of Paliperidone (0-5000 ng/ml) – Study FK5304

Paliperidone (ng/ml)	Enzyme activity (nmol/min per mg protein)[1,2]			
	Dextromethorphan-O-demethylase (CYP2D6- mediated)	Midazolam 1'-hydroxylase (CYP3A4/3A5- mediated)	Midazolam 4-hydroxylase (CYP3A4/3A5- mediated)	Testosterone 6-ß-hydroxylase (CYP3A4-mediated)
0	0.039 ± 0.001 1) (100) 2)	0.76 ± 0.01 (100)	0.32 ± 0.02 (100)	3.54 ± 0.16 (100)
2	0.039 ± 0.003 (100.7)	0.78 ± 0.03 (101.8)	0.33 ± 0.01 (103.6)	3.44 ± 0.10 (97.1)
10	0.042 ± 0.002 (107.6)	0.76 ± 0.03 (99.6)	0.31 ± 0.03 (96.8)	3.47 ± 0.11 (97.9)
50	0.037 ± 0.001 (94.7)	0.71 ± 0.01 (93.1)	0.31 ± 0.01 (96.2)	3.17 ± 0.09 (89.5)
250	0.036 ± 0.001 (93.1)	0.72 ± 0.01 (94.5)	0.31 ± 0.01 (95.0)	3.33 ± 0.28 (94.0)
1000	0.033 ± 0.001 (86.1)	0.71 ± 0.01 (92.9)	0.32 ± 0.01 (98.4)	3.65 ± 0.09 (103.0)
2500	0.030 ± 0.002 (78.3)	0.71 ± 0.03 (93.2)	0.30 ± 0.00 (92.3)	3.42 ± 0.31 (96.6)
5000	0.031 ± 0.003 (78.9)	0.69 ± 0.02 (90.1)	0.30 ± 0.02 (92.4)	3.73 ± 0.31 (105.3)

1) Results are presented as mean ± S.D. for 3 determinations.
2) Figures in parentheses are percentages of enzyme activity versus control in the absence of paliperidone.

3.8 Protein Binding

Experiments of human plasma protein binding of paliperidone and its enantiomers were conducted using ^{14}C-labeled drug equilibrium dialysis.

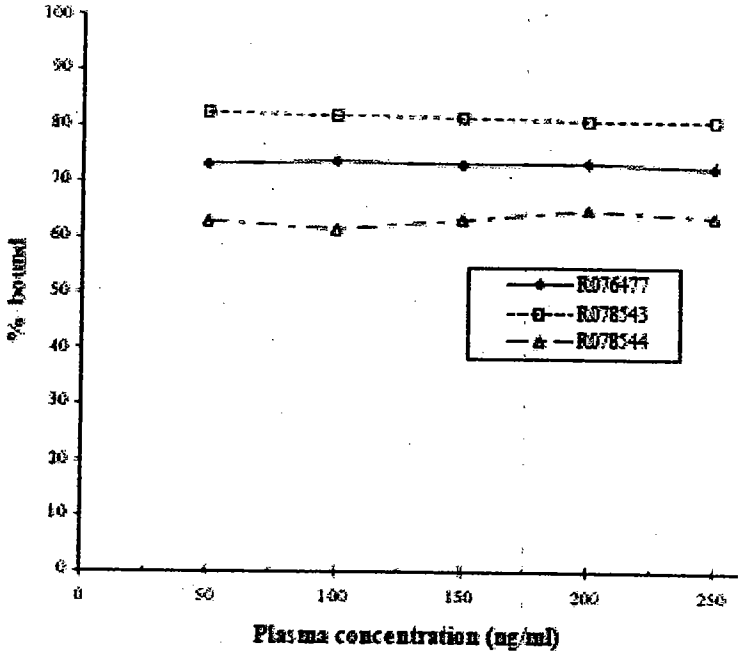
At concentrations achieved with clinical usage, (<250 ng/ml), the overall plasma protein binding of paliperidone and its enantiomers were concentration independent under the conditions studied, (see Table 29 and Figure 17).

Table 29 Concentration Dependency of Protein Binding of Paliperidone and its Enantiomers in Pooled Human Plasma - Study FK5209[a,b]

Concentration (ng/ml)	% Bound			Ratio % free (+)-paliperidone / (-)-paliperidone
	Racemic Paliperidone (R076477)	(+)-Paliperidone (R078543)	(-)-Paliperidone (R078544)	
50	73.2	82.4	62.8	2.11
100	73.8	81.8	61.5	2.12
150	73.2	81.6	63.1	2.01
200	73.4	81.1	64.8	1.86
250	72.4	80.9	63.8	1.90
Mean % Bound	73.2	81.6	63.2	2.00
Mean % Free	26.8	18.4	36.8	

a Pooled plasma from five male healthy subjects.
b Each value represents the mean of two determinations.

Figure 17 Plots of Concentration Dependency of Plasma Protein Binding of Paliperidone and its Enantiomers in Pooled Human Plasma - Study FK5209[a,b]



However, when protein binding to purified protein solutions of human serum albumin and α1-acid glycoprotein was examined at paliperidone concentrations of 50 ng/ml; there was a clear relationship of protein concentration to the amount of drug bound that was different for each enantiomer. Consequently, there may be some clinical consequences to this differential binding in situations where plasma protein concentrations are altered.

Table 30 Concentration Dependence of Binding of Paliperidone and its Enantiomers to Purified Human Serum Albumin at concentrations of 50 ng/ml - Study FK5209[a]

Human serum albumin Concentration (gm/100 ml)	% bound			Ratio % free (+)-paliperidone / (-)-paliperidone
	Racemic Paliperidone (R076477)	(+)-Paliperidone (R078543)	(-)-Paliperidone (R078544)	
0.1	2.9	8.0	7.3	0.992
0.25	6.9	21.2	14.4	0.921
0.50	11.4	22.4	20.7	0.979
1.0	16.5	21.2	21.2	1.000
2.0	26.7	37.1	33.3	0.943
4.3	43.8	38.5	46.5	1.150
6.0	50.1	45.7	52.1	1.134
% Free				
4.3	56.2	61.5	53.5	1.150

a Each value represents the mean of two determinations

Table 31 Concentration Dependence of Binding of Paliperidone and its Enantiomers to Purified α1-Acid Glycoprotein - Study FK5209[a]

α1-acid Glycoprotein Concentration (gm/100 ml)	% bound			Ratio % free (+)-paliperidone / (-)-paliperidone
	Racemic Paliperidone (R076477)	(+)-Paliperidone (R078543)	(-)-Paliperidone (R078544)	
0.02	38.9	45.1	29.1	0.77
0.05	66.5	74.1	58.6	0.63
0.10	81.0	85.1	75.4	0.61
0.15	84.6	89.9	79.3	0.49
0.20	87.9	91.9	84.0	0.51
% Free				
0.10	19.0	14.9	24.6	0.61

a Each value represents the mean of two determinations

3.9 Cell Transport

The presence and characteristics of trans-epithelial transport of paliperidone was investigated in CaCO-2 monolayers. The integrity of cell monolayers was evaluated by measuring transepithelial electrical resistance (TEER) before the transport experiment, and by determining the leakage of ^{14}C- or ^{3}H-mannitol during the experiment. In addition, each Caco-2 cell batch was validated by measuring transport of ^{14}C-alniditan and ^{3}H-levocabastine and ^{3}H-theophylline which are marker compounds for low, medium and high transepithelial permeation rates, respectively.

3.9.1 Facilitated Trans-Epithelial Transport of Paliperidone

The highest Cmax observed *in vivo* with multiple dosing of paliperidone OROS 12 mg was 166 ng/ml or 390 nM/L.

At a paliperidone concentration of 1 µM/L at physiologic pH, the efflux ratio (ER) is 1.8 indicating facilitated efflux of paliperidone at this concentration. In addition, as concentration increases well above clinically achieved concentrations passive absorption becomes more prominent as indicated by a decreasing ER ratio, (see Table 32).

Paliperidone has a pKa of 8.24. When the effect of pH is examined, facilitated absorption increases as pH decreases as is shown by an increasing ER ratio indicated increased paliperidone transport with ionization.

Table 32 Effect of Paliperidone Concentration and Apical pH on Transepithelial Transport of Paliperidone across Caco-2 Monolayers – Study FK4856

Treatment		Papp Mean ± SD (10^{-6} cm / sec)[a]		ER (Efflux : Influx)
Compound	Condition	Basolateral to Apical (Efflux)	Apical to Basolateral (Influx)	
paliperidone	3 µM	34.0 ± 1.3	21.3 ± 2.3	1.6
	10 µM	32.2 ± 1.4	22.4 ± 4.5	1.4
	30 µM	30.1 ± 0.9	26.5 ± 4.0	1.1
	100 µM	28.8 ± 1.2	30.4 ± 5.2	0.9
	1 µM (pH 6.0)	58.3 ± 8.5	4.1 ± 0.7	14.0
	1 µM (pH 6.5)	30.1 ± 4.6	8.9 ± 0.8	3.4
	1 µM (pH 7.0)	30.9 ± 3.2	16.2 ± 3.5	1.9
	1 µM (pH 7.4)	34.7 ± 2.4	18.9 ± 1.3	1.8
	1 µM (pH 8.0)	26.2 ± 1.8	28.1 ± 2.4	0.9
alniditan[a]	20 µM	0.7 ± 0.2	1.7 ± 0.9	0.4
levocabastine[b]	20 µM	21.3 ± 1.4	13.0 ± 1.3	1.8
theophylline[c]	20 µM	34.2 ± 2.2	36.5 ± 7.0	1.0

a low permeability control – High Facilitated Excretion
b medium permeability control – High Facilitated Absorption
c high permeability control – Passive Transport

These effects of concentration and pH on paliperidone bidirectional transport are shown graphically in Figure 18, Figure 19 and Figure 20.

Figure 18 Mean (±sd, n=4) Amount of AP-BL and BL-AP Paliperidone Transport vs. Time across Caco-2 Monolayers for Initial Paliperidone Concentrations of 3-100 µM.

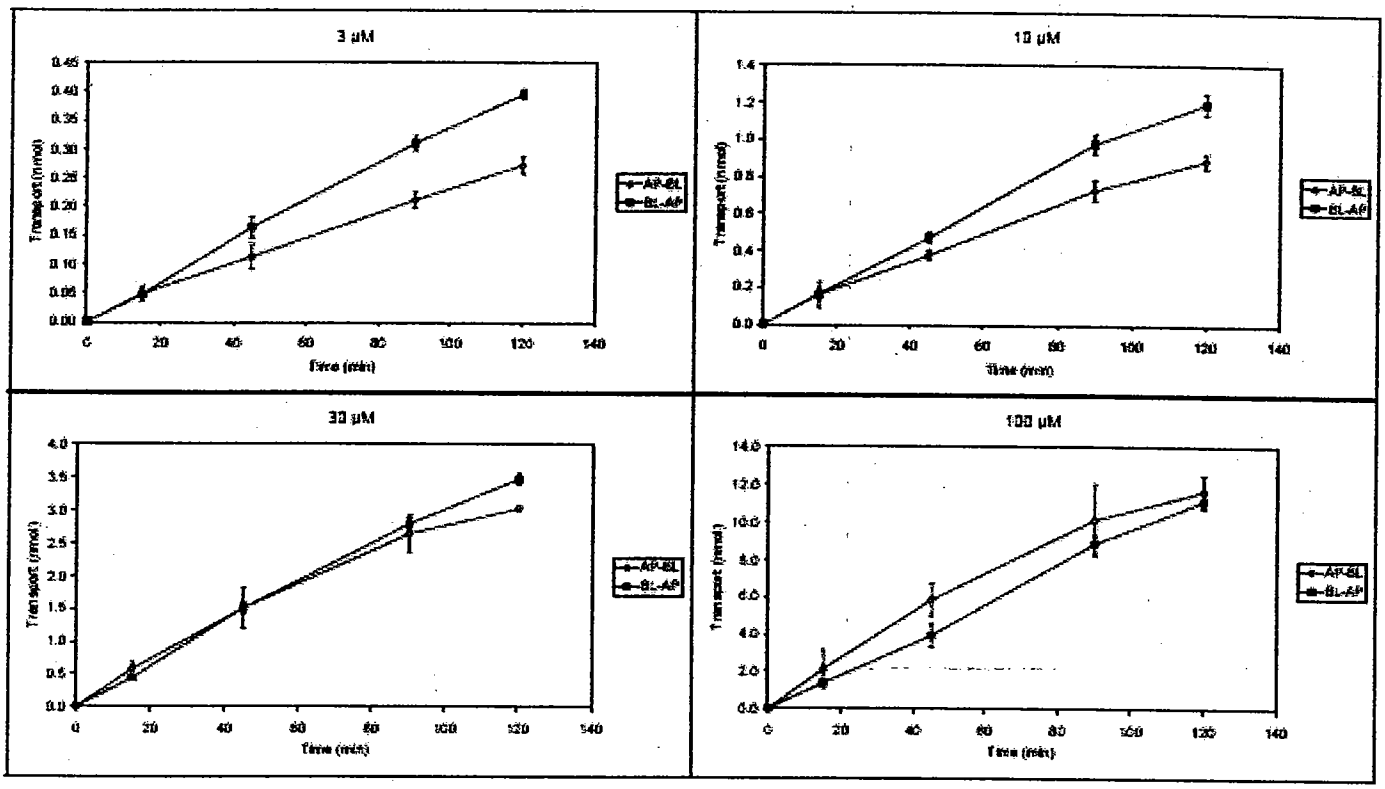


Figure 19 Effect of Apical pH on absorptive (AP-BL) and secretory (BL-AP) Transport of paliperidone (1 µM) across Caco-2 monolayers. Bars represent average (± sd, n=4) Papp values as determined from the 15-45-90 min (steady-state) slopes of the transport-time profiles. The basolateral pH was always adjusted to 7.4.

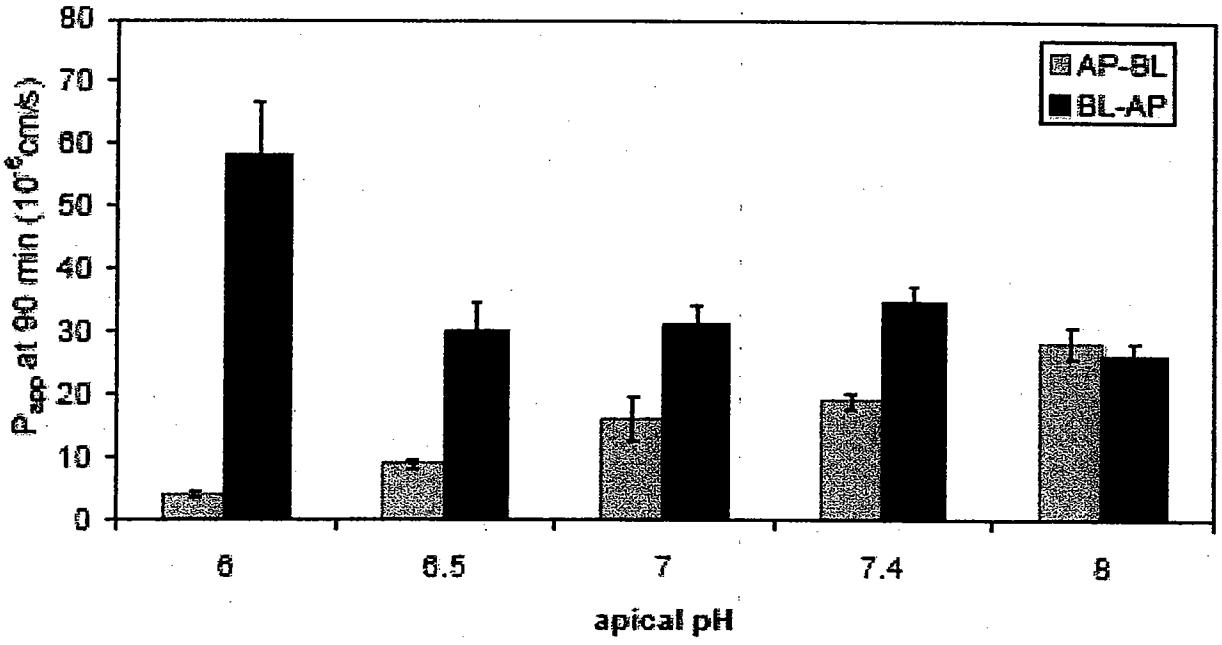
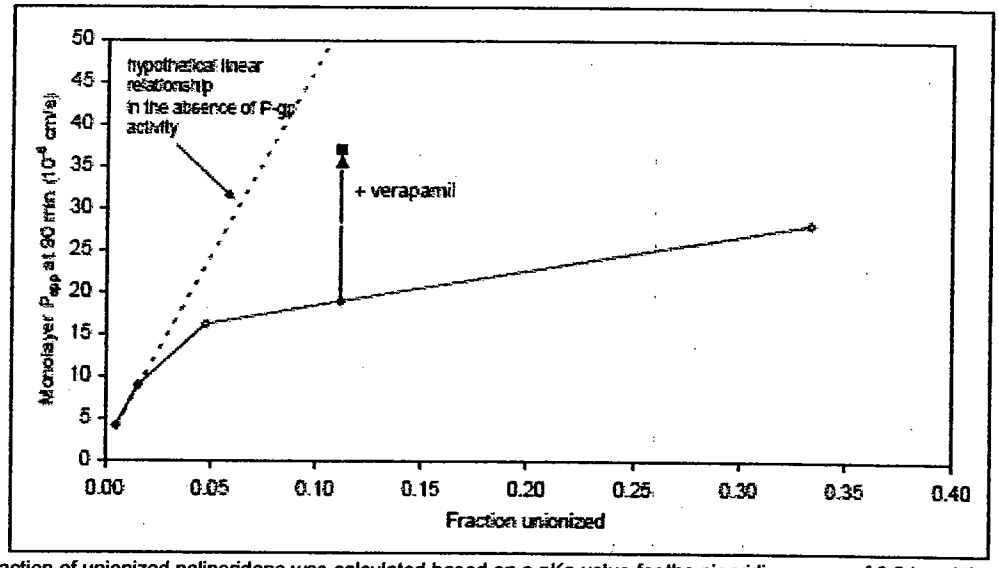


Figure 20 Relationship between fraction of paliperidone in the apical compartment in unionized form and the Papp value for paliperidone obtained for absorptive transport across Caco-2 monolayers[a]



a The fraction of unionized paliperidone was calculated based on a pKa value for the piperidine group of 8.24 and the apical pH during the transport experiments.

3.9.2 Paliperidone Inhibition of pGP Trans-Epithelial Transport

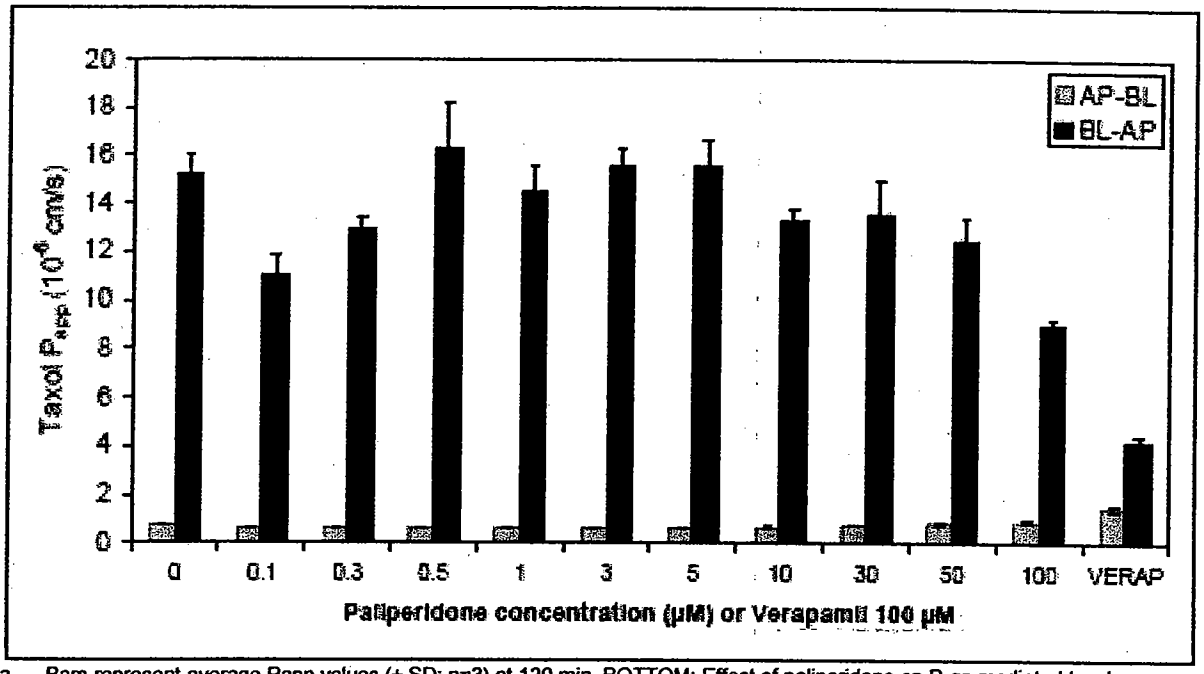
At clinically achieved concentrations paliperidone has little ability to inhibit pGP transport. However, if paliperidone is concentrated the GI track, bile track, renal tubules, or other tissues, concentrations might be sufficiently high to inhibit pGP transport, (see Table 33, Figure 21, and Figure 22).

Table 33 Effect of Paliperidone on Polarized Transport of the P-glycoprotein Substrate ^{3}H-taxol across Caco-2 Monolayers – Study FK4856

Test Substance	Inhibitor	Concentration	Papp (10^{-6} cm / sec) Mean ± SD[a]		Efflux Ratio (B to A / A to B)
			Basolateral to Apical	Apical to Basolateral	
^{3}H-taxol (control)	—	—	15.3 ± 0.8	0.74 ± 0.02	21 ± 1.2
^{3}H-taxol	Paliperidone	0.1 µM	11.0 ± 0.8	0.61 ± 0.03	18 ± 1.6
		0.3 µM	12.9 ± 0.4	0.61 ± 0.03	21 ± 1.1
		0.5 µM	16.3 ± 1.9	0.64 ± 0.03	25 ± 3.2
		1 µM	14.5 ± 1.2	0.60 ± 0.01	24 ± 2.0
		3 µM	15.5 ± 0.8	0.61 ± 0.02	25 ± 1.5
		5 µM	15.5 ± 1.1	0.65 ± 0.02	24 ± 1.8
		10 µM	13.3 ± 0.5	0.66 ± 0.04	20 ± 1.3
		30 µM	13.6 ± 1.4	0.74 ± 0.03	18 ± 1.9
		50 µM	12.5 ± 0.9	0.81 ± 0.03	16 ± 1.2 *
		100 µM	9.0 ± 0.2	0.91 ± 0.03	10 ± 0.4 *
^{3}H-taxol	verapamil (+ control)	100 µM	4.2 ± 0.2	1.50 ± 0.14	3 ± 0.3 *

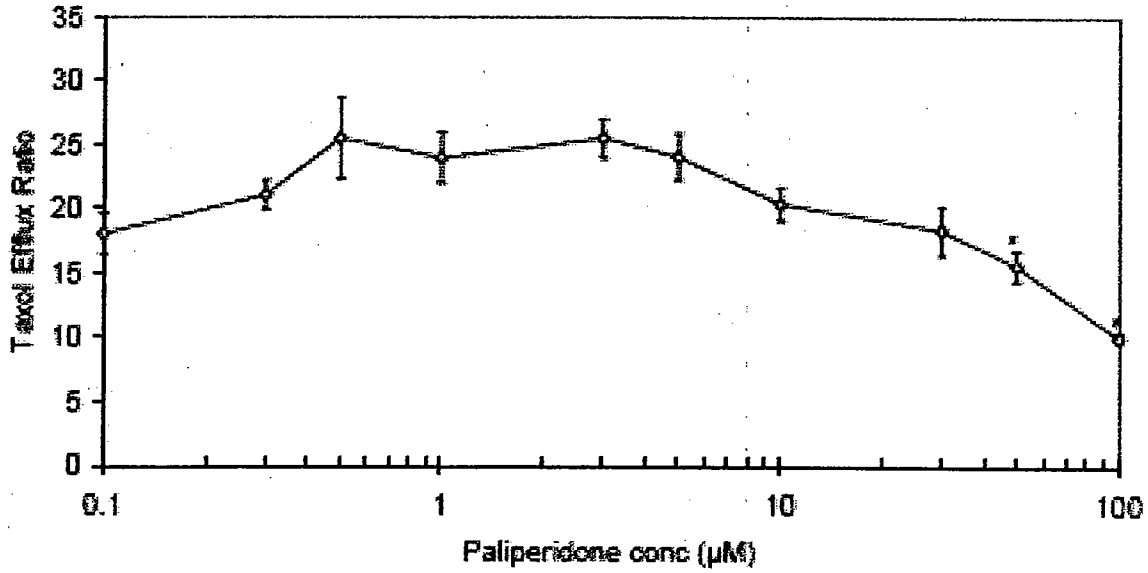
a Caco-2 cell monolayers were maintained for 22 days on cell culture inserts. 3H-taxol (75 nM) was added to the apical or to the basolateral compartment. All Taxol Papp values were calculated based on 120 min transport data (0-120 min slope). Values shown in this table result from incubations conducted in the presence of Hank's Balanced Salt Solution, adjusted to pH 7.4 in both compartments. The average mannitol permeability value across all incubation conditions included in this table was 0.4 × 10^{-6} cm/s and the highest average mannitol permeability value measured was 0.6 × 10^{-6} cm/s. This indicates that tight junctional and cell monolayer integrity were maintained for all incubations. (*) denotes statistically significantly different from control based on one-way ANOVA followed by post-hoc Dunnett's test for pair-wise comparison of each condition with control (α=0.01)

Figure 21 Effect of Increasing Concentrations of paliperidone (0.1- 100 µM) or of 100 µM of the P-gp inhibitor verapamil (positive control) on absorptive (AP-BL) and secretory (BL-AP) transport of the P-gp substrate taxol (75 nM) across Caco-2 monolayers[a]



a Bars represent average Papp values (± SD; n=3) at 120 min. BOTTOM: Effect of paliperidone on P-gp mediated taxol transport, represented by: *i)* taxol efflux ratio (=secretory/absorptive transport), and *ii)* taxol efflux transport (= secretory - absorptive transport, as % of control). Points are average (± sd, n=3).

Figure 22 Effect of paliperidone on P-gp mediated taxol transport, represented by taxol efflux ratio (=secretory/absorptive transport). Points are average (± sd, n=3). ANOVA followed by Dunnett's post-hoc test (for pair-wise comparison of each treatment with control) was used to evaluate statistical significance of the ER values. * denotes statistically significantly different from control at the 0.01 level.



3.9.3 Inhibition of Paliperidone pGP Facilitated Trans-Epithelial Transport

Consistent with the data that paliperidone is a moderately potent competitive inhibitor of pGP transepithelial transporters, some potent pGP transport inhibitors inhibit paliperidone transport whereas others don't. The pGP substrates that don't inhibit paliperidone are instead potentially inhibited by paliperidone, (see Table 34 and Figure 23).

Table 34 Effect of Transport Inhibitors on Transepithelial Transport of Paliperidone across Caco-2 Monolayers– Study FK4856

Condition	Inhibitor	Papp[a] Mean ± SD (10^{-6} cm / sec)[a]		ER
		Apical to Basolateral	Basolateral to Apical	
paliperidone 1 µM (control)	—	18.9 ± 1.3	34.7 ± 2.4	1.8
paliperidone 1 µM	cimetidine	21.4 ± 2.0	35.6 ± 1.9	1.7
	quinidine	36.2 ± 2.6	27.2 ± 1.2	0.8 [b]
	metformin	18.0 ± 4.4	37.2 ± 1.7	2.1
	levofloxacin	18.1 ± 4.0	35.0 ± 2.6	1.9
	verapamil	36.9 ± 4.6	29.8 ± 1.3	0.8 [b]
	procainamide	18.7 ± 1.7	36.7 ± 2.6	2.0
	imipramine	36.8 ± 3.1	28.6 ± 0.8	0.8 [b]
	probenecid	19.7 ± 1.7	36.3 ± 1.8	1.8
	trimethoprim	19.9 ± 3.9	34.9 ± 2.1	1.8

a All Papp values were calculated from the slopes of 15-45-90 min transport-time profiles. Unless specified otherwise, figures shown in this table result from incubations conducted in the presence of Hank's Balanced Salt Solution, adjusted to pH 7.4 in the apical compartment. Inhibitor concentrations were 200 µM. The pH in the basolateral compartment was always adjusted to 7.4. The average absorptive mannitol permeability (determined over the 15-45-90 min incubation period) value across for incubation conditions included in this table was 1.2 × 10-6 cm/s and the highest average absorptive mannitol permeability value measured was 1.9 × 10-6 cm/s. This indicates that tight junctional and cell monolayer integrity were maintained for all incubations

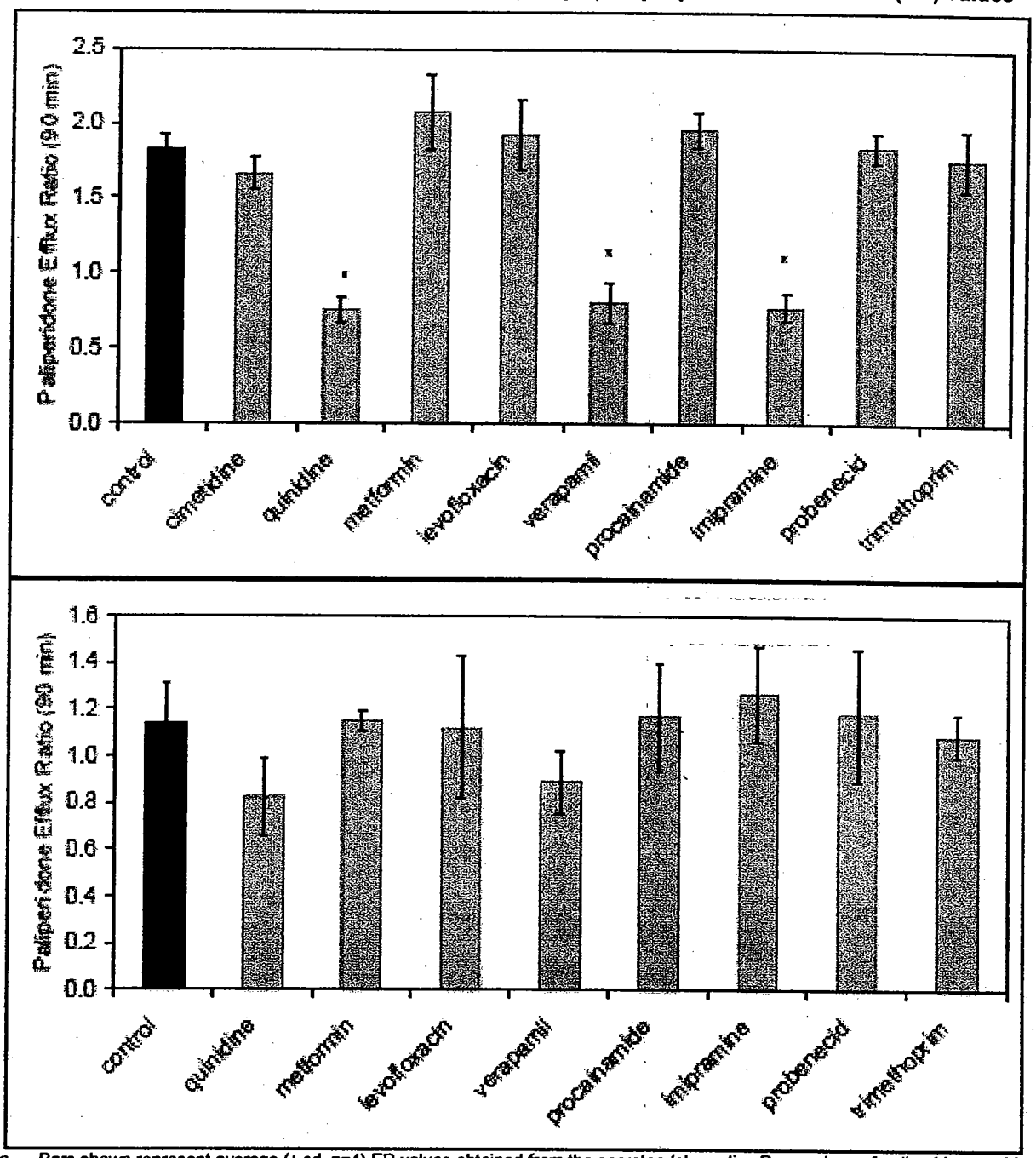
b Statistically significantly different from control based on one-way ANOVA followed by post-hoc Dunnett's test for pair-wise comparison of each inhibitor-treated condition with control (α=0.005).

As shown in Table 34 quinidine, verapamil, and imipramine inhibit paliperidone efflux at a paliperidone concentration of 1 µM. A concentration of 1 µM is about 10 fold higher than the average peak concentration with maintenance dosing of paliperidone OROS 12 mg, and 20 fold higher than with a maintenance dose of 6 mg. Consequently this raises a concern of decreased paliperidone efflux and increased bioavailability in the presence of these pGP inhibitors. Since, both inhibitors and paliperidone were used at excessive concentrations, (i.e. 200 µM and 1 µM respectively), the potential for *in vivo* inhibitor becomes more difficult to assess. However, the ratio of inhibitor to paliperidone was 200:1. In addition inhibition appears to be 100% and since the ratio of inhibitor to substrate concentration/Ki ratios needs to be 10 fold for complete competitive inhibition. Based on the *in vivo* concentration ratios as shown in Table 35 both quinidine and verapamil are predicted to increase paliperidone bioavailability *in vivo*.

Table 35 Prediction of pGP Inhibitor to Paliperidone Concentration Ratios *In Vivo*

Inhibitor	~Max Peak Concentrations		Concentrations Used in Efflux Experiment	Possible Inhibitor to Paliperidone Concentration Ratio *In Vivo*
	(mcg/ml)	(µM/L)	(µM/L)	
Quinidine	8	16.2	200	311.5
Verapamil	0.5	1	200	19.2
Imipramine	0.5	0.002	200	0.038
Substrate				
Paliperidone 6 mg	0.022	0.052	1	—

Figure 23 Effect of various transport inhibitors (200 µM) on paliperidone efflux ratio (ER) values[a]



a Bars shown represent average (± sd, n=4) ER values obtained from the secretory/absorptive Papp values of paliperidone at 90 min. The initial paliperidone concentration in the donor compartment was 1 µM (TOP panel) or 30 µM (BOTTOM panel). ANOVA followed by Dunnett's post-hoc test was applied to compare treatments with control condition. * denotes significantly different from control at the 0.005 level.

3.10 Pharmacokinetics

3.10.1 Review of Amendments to Original Submission

The sponsor submitted a number of amendments to the NDA that are listed on the first page of this review in the review header table.

Each submission has been checked to determine if there was any information that is pertinent to the OCP review. Three submissions were found to have information of interest to OCP, one included changes to a phase I study, (0008). None of the three submissions were found to have any bearing on the conclusions of this review.

One of the submissions (0006) included revised labeling and that version of labeling was used as the basis for OCP labeling comments.

In addition, the sponsor sent an e-mail dated Aug-23-2006 to this reviewer that was intended to alleviate this reviewer's concerns regarding the lack of a dissolution assay method that is adequate to cover the upper range needed for the assay. This e-mail failed to address the issue and instead addressed a different unasked question. A followup T-con resolved the issue and is addressed in the dissolution section. The sponsor was requested to submit a minor amendment to the NDA for documentation, however as of September 12, 2006 the amendment was not recorded in the electronic document room submission.

3.10.2 Initial Investigations of Paliperidone Pharmacokinetics

3.10.2.1 Comparison of Immediate Release Paliperidone and Risperidone GI Absorption and Exposure

Study BEL-28 was a crossover study that compared the absorption characteristics and relative exposures of equal mass doses of 1 mg of risperidone and paliperidone administered orally as solutions to young males. Both drugs were absorbed rapidly with lag times of only 15 minutes. Exposure after administration of paliperidone was slightly higher than exposures to all active moieties combined from Risperidone. Although not corrected for on a molar basis, as paliperidone has a slightly higher molecular weight, exposures on a molar basis should be slightly higher for paliperidone compared to risperidone. Overall the data suggests that dosages of paliperidone should be similar to dosages of Risperidone, (see Table 36).

Table 36 Comparative Single Dose Pharmacokinetic Metrics of Equal Mass Doses (1 mg) of Risperidone and Paliperidone Oral Solutions - Study CR-EL-28

Rx	Analyte	Pop	N	Tlag (hr)	Tmax (hr)	Cmax (ng/ml)	AUCt (ng/ml x hr^{-1})	AUCinf (ng/ml x hr^{-1})	t1/2 (hrs)	AUC Fraction	AUC Ratio	Frel
Ris 1 mg	Ris	All	8	0.25 ± 0 (0) 0.25 - 0.25 [0.25]	0.9 ± 0.5 (52.9) 0.5 - 2.0 [1.0]	8.6 ± 3.9 (45.2) 3.9 - 14.4 [9.3]	94.7 ± 90.5 (95.6) 11.3 - 226.0 [55.5]	95.7 ± 93.8 (98.0) 10.2 - 236.0 [55.4]	8.2 ± 7.6 (92.4) 1.7 - 20.5 [4.3]	0.39 ± 0.30 (76.1) 0.08 - 0.76 [0.31]		
		EM	5	0.25 ± 0 (0) 0.25 - 0.25 [0.25]	0.7 ± 0.3 (39.1) 0.5 - 1.0 [0.5]	6.4 ± 2.7 (42.2) 3.9 - 9.6 [5.3]	32.0 ± 21.7 (67.9) 11.3 - 58.4 [19.5]	30.9 ± 22.6 (73.0) 10.2 - 57.8 [17.4]	2.9 ± 1.3 (45.2) 1.7 - 4.7 [2.2]	0.18 ± 0.12 (62.8) 0.08 - 0.32 [0.13]		
		PM	3	0.25 ± 0 (0) 0.25 - 0.25 [0.25]	1.3 ± 0.6 (43.3) 1.0 - 2.0 [1.0]	12.3 ± 2.3 (19.1) 9.8 - 14.4 [12.7]	199.1 ± 39.4 (19.8) 153.9 - 226.0 [217.5]	203.7 ± 42.1 (20.7) 156.0 - 236.0 [219.0]	17.1 ± 3.0 (17.6) 14.9 - 20.5 [15.8]	0.73 ± 0.04 (5.5) 0.68 - 0.76 [0.74]		
	Pal	All	8	0.38 ± 0.27 (71.3) 0.25 - 1.00 [0.25]	2.3 ± 1.2 (51.8) 1.0 - 4.0 [2.0]	5.6 ± 1.2 (21.9) 3.7 - 7.1 [5.8]	103.0 ± 32.1 (31.2) 47.3 - 145.5 [108.1]	108.1 ± 32.7 (30.3) 53.0 - 154.0 [112.0]	19.7 ± 4.3 (22.0) 14.4 - 26.7 [17.7]	0.61 ± 0.29 (47.7) 0.24 - 0.90 [0.69]	4.11 ± 4.38 (106.5) 0.33 - 11.18 [2.24]	
		EM	5	0.25 ± 0.00 (0.0) 0.25 - 0.25 [0.25]	2.2 ± 1.1 (49.8) 1.0 - 4.0 [2.0]	6.1 ± 0.8 (12.7) 5.1 - 7.1 [5.9]	121.3 ± 17.9 (14.7) 107.9 - 145.5 [109.4]	126.4 ± 19.2 [15.2] 110.0 - 154.0 [115.0]	20.5 ± 4.5 [21.7] 16.7 - 26.7 [17.7]	0.81 ± 0.11 [13.3] 0.67 - 0.90 [0.85]	6.36 ± 4.10 [64.5] 2.08 - 11.18 [6.61]	
		PM	3	0.58 ± 0.38 (65.5) 0.25 - 1.00 [0.50]	2.3 ± 1.5 (65.5) 1.0 - 4.0 [2.0]	4.6 ± 1.3 (29.0) 3.7 - 6.1 [3.9]	72.6 ± 27.4 (37.8) 47.3 - 101.8 [68.9]	77.6 ± 27.9 (36.0) 53.0 - 108.0 [71.9]	17.8 ± 4.7 (26.7) 14.4 - 21.1 [17.8]	0.27 ± 0.04 (13.2) 0.24 - 0.31 [0.26]	0.38 ± 0.07 (19.1) 0.33 - 0.46 [0.34]	
	Active Moiety	All	8	0.25 ± 0.00 (0.0) 0.25 - 0.25 [0.25]	1.2 ± 0.5 (44.7) 0.5 - 2.0 [1.0]	12.7 ± 3.7 (28.8) 8.4 - 20.2 [11.9]	198.1 ± 75.2 (38.0) 118.1 - 330.6 [178.5]	205.0 ± 77.3 (37.7) 126.0 - 346.0 185.0]	19.3 ± 4.0 (21.0) 15.6 - 26.6 [17.3			
		EM	5	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	1.1 ± 0.5 (49.8) 0.5 - 2.0 [1.0]	10.9 ± 1.8 (16.8) 8.4 - 12.9 [11.6]	152.7 ± 29.3 (19.2) 118.1 - 190.4 [159.8]	158.8 ± 28.8 (18.1) 126.0 - 197.0 [163.0]	20.4 ± 4.5 (22.0) 17.1 - 26.6 [17.4]			
		PM	3	0.25 ± 0.0 (0.0) 0.25 - 0.25 [0.25]	1.3 ± 0.6 (43.3) 1.0 - 2.0 [1.0]	15.8 ± 4.3 (27.0) 11.7 - 20.2 [15.4]	273.7 ± 66.2 (24.2) 201.1 - 330.6 [289.3]	282.0 ± 70.8 (25.1) 206.0 - 346.0 [294.0]	17.5 ± 3.1 (17.5) 15.6 - 21.0 [15.8]			
Pal 1 mg	Pal	All	9	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	1.8 ± 0.4 (24.8) 1.0 - 2.0 [2.0]	10.0 ± 2.9 (29.3) 6.9 - 15.9 [9.2]	198.8 ± 48.7 (24.5) 139.0 - 277.7 [181.0]	210.7 ± 54.8 (26.0) 148.0 - 284.0 [186.0]	20.4 ± 3.7 (18.3) 15.7 - 24.9 [19.2]			113.9 ± 27.6 (24.2) 85.5 - 169.0 [109.0]
		EM	6	0.25 ± 0.00 (0.0) 0.25 - 0.25 [0.25]	1.8 ± 0.4 (22.3) 1.0 - 2.0 [2.0]	8.8 ± 1.8 (20.4) 6.9 - 11.1 [8.8]	169.3 ± 23.4 (13.8) 139.0 - 204.6 [171.2]	176.3 ± 23.2 (13.2) 148.0 - 213.0 [178.0]	20.9 ± 3.5 (16.9) 15.7 - 24.1 [21.5]			114.8 ± 33.2 (28.9) 85.5 - 169.0 [114.0]
		PM	3	0.25 ± 0.00 (0.00) 0.25 - 0.25 [0.25]	1.7 ± 0.6 (34.6) 1.0 - 2.0 [2.0]	12.4 ± 3.7 (29.7) 8.6 - 15.9 [12.6]	257.7 ± 17.6 (6.8) 244.7 - 277.7 [250.8]	279.3 ± 7.2 (2.6) 271.0 - 284.0 [283.0]	19.4 ± 4.8 (24.5) 16.2 - 24.9 [17.2]			112.5 ± 21.5 (19.1) 96.6 - 137.0 [104.0]

3.10.2.2 *Relative Bioavailability of Paliperidone IR Tablets and Effect of Food*

Next the relative bioavailability of a 0.5 mg immediate release tablet under both fasted and fed conditions was compared to an oral solution in a 3-way crossover study, BEL-1, in 12 young males and females.

This study revealed that absorption from a tablet was only slightly slower than from a solution, as shown by both a delay in Tlag and an even greater lag in Tmax, with no effect on the extent of absorption.

Table 37 Single Dose Pharmacokinetic Metrics of Paliperidone when Administered as 0.5 mg Tablet in the Fed and Fasted State Compared to Administration as a Solution – Study BEL-1

Treatment	N	Tlag (hrs)	Cmax (ng/ml)	Tmax (hrs)	AUClast (ng/ml x hr^{-1})	AUC∞ (ng/ml x hr^{-1})	% extrap	t½ (hrs)
Solution Fasted	12	0.5 ± 0 (0.0) 0.5 - 0.5 [0.5]	4.4 ± 1.6 (0.4) 3.1 - 9.0 [4.0]	2.4 ± 0.7 (0.3) 2 - 4 [2]	107 ± 35 (0.3) 67.4 - 173 [100]	113 ± 38 (0.3) 73.9 - 185 [103]	8.3 ± 1.2 (0.1) 6.5 - 9.9 [8.5]	24.2 ± 2.6 (0.1) 20.1 - 27.9 [23.6]
Tablet Fasted	12	0.54 ± 0.14 (26.6) 0.5 - 1 [0.5]	4.5 ± 1.1 (23.7) 3.2 - 6.7 [4.5]	2.2 ± 0.6 (27.3) 1 - 3 [2]	104 ± 28 (26.9) 62 - 140 [106]	116 ± 29 (25) 70 - 153 [116]	10.5 ± 3.7 (35.2) 4.8 - 20.3 [10.1]	27.4 ± 4.5 (16.4) 16.6 - 32.5 [27.8]
Tablet Fed	12	0.8 ± 0.4 (53.3) 0.5 - 2 [0.75]	4.3 ± 1.2 (28.2) 2.6 - 6.1 [4.4]	3.1 ± 1 (32.3) 1 - 4 [3]	102 ± 30 (29.4) 102 - 58.1 [154]	113 ± 31 (27.4) 112 - 66.1 [163]	10 ± 3.5 (35) 9.2 - 5.5 [17.5]	26.1 ± 5.1 (19.5) 24.4 - 18.4 [36.5]
Ratio Tab Fasted : Solution	12	—	111 ± 40 (36) 62.8 - 217 [99.3]	—	100 ± 26 (26) 78.6 - 175 [92]	103 ± 25 (24.3) 80.5 - 165 [98.2]	—	—
Tablets Fasted : Fed	12	—	95.6 ± 20.1 (21) 97 - 47.1 [134]	—	99.9 ± 21.2 (21.2) 98.9 - 53.8 [143]	98.6 ± 17.8 (18.1) 96.8 - 55.6 [124]	—	—

3.10.2.3 Dose Proportionality and Time Invariance of Paliperidone IR Tablets

A single rising dose pharmacokinetic study of dose proportionality was not performed, presumably due to issues of tolerability. However a multiple dose study (INT-1) of IR doses of 1 mg, 4 mg, and 8 mg titrated over a period of a week was performed in young male and female patients. Although the most rigorous design and analysis methods were not used, based on the results of this study paliperidone appears to be exhibit dose proportional and time invariant kinetics from 1 mg to 8 mg over a period of 1 – 2 weeks, (see Table 38, Figure 24, Figure 25, Figure 26, Figure 27, and Table 39). (N.B. the sponsor's AUC values in Table 38 don't match those in Table 39).

Table 38 Multiple Dose Pharmacokinetics of Paliperidone IR Tablets – Study INT -1

Rx	Day	N	Tlag (hrs)	Tmax (hrs)	Cmax (ng/ml)	Tmin (hrs)	Cmin (ng/ml)	AUC0-24 (ng/ml/hr^{-1})	Cl/F (ml/min)	R Cmax	R AUC
Pal 1 mg	1	11	1 ± 0 (0) 1 - 1 [1]	2.8 ± 1.2 (41.4) 1 - 4 [2]	11.7 ± 2.7 (23.2) 9.31 - 17.1 [10.7]	21.9 ± 6.9 (31.7) 1 - 24 [24]	4.0 ± 1.5 (38.4) 2.84 - 8.4 [3.88]	162.6 ± 42.2 (25.9) 127.1 - 269.2 [148.52]			
	14	11	1 ± 0 (0) 1 - 1 [1]	2.0 ± 1.1 (51.8) 1.0 - 4.0 [2.0]	19.6 ± 6.7 (34.3) 13.4 - 33.8 [17.7]	13.1 ± 12.5 (95.7) 0.0 - 24.0 [24.0]	7.5 ± 3.8 (51.0) 4.4 - 17.2 [6.4]	296.1 ± 108.7 (36.7) 184.8 - 528.8 [256.1]	62.4 ± 19.0 (30.5) 31.5 - 90.2 [65.1]	1.69 ± 0.48 (28.5) 1.07 - 2.83 [1.70]	1.82 ± 0.46 (25.4) 1.34 - 2.83 [1.78]
Pal 4 mg[a]	1	11	0.9 ± 0.3 (33.2) 0 - 1 [1]	3.2 ± 3.1 (96.2) 1 - 12 [2]	21.0 ± 10.1 (48.0) 10.9 - 41.6 [19.2]	21.9 ± 6.9 (31.7) 1 - 24 [24]	7.3 ± 4.6 (62.1) 2.62 - 17.5 [5.65]	306.7 ± 179.9 (58.7) 164.38 - 694.9 [248.6]			
	14	10	1 ± 0 (0) 1 - 1 [1]	3.2 ± 3.3 (101.8) 1.0 - 12.0 [2.0]	63.0 ± 22.2 (35.3) 39.8 - 102.0 [54.2]	9.6 ± 12.4 (129.1) 0.0 - 24.0 [0.0]	25.7 ± 12.5 (48.7) 11.0 - 47.9 [23.6]	1022.1 ± 451.1 (44.1) 518.9 - 1845.9 [829.3]	76.5 ± 30.0 (39.3) 36.1 - 128.5 [81.0]	3.2 ± 0.9 (27.6) 2.1 - 4.6 [3.4]	3.4 ± 0.8 (24.7) 2.1 - 4.4 [3.6]
Pal 8 mg[a]	1	12	0.8 ± 0.4 (46.7) 0.0 - 1.0 [1.0]	2.7 ± 1.2 (46.2) 1.0 - 4.0 [2.0]	18.3 ± 4.5 (24.4) 11.5 - 25.2 [18.6]	22.1 ± 6.6 (30.1) 1.0 - 24.0 [24.0]	5.2 ± 2.7 (52.2) 0.8 - 9.1 [5.3]	250.7 ± 60.3 (24.1) 163.4 - 322.7 [249.6]			
	14	10	1.1 ± 0.3 (28.7) 1.0 - 2.0 [1.0]	1.4 ± 0.5 (36.9) 1.0 - 2.0 [1.0]	139.9 ± 46.9 (33.5) 69.1 - 223.0 [131.0]	12.0 ± 12.6 (105.4) 0.0 - 24.0 [12.0]	46.3 ± 21.0 (45.3) 22.7 - 83.5 [48.1]	1889.0 ± 655.1 (34.7) 1052.9 - 2966.7 [1899.4]	79.4 ± 29.6 (37.2) 44.9 - 126.6 [70.3]	8.27 ± 3.05 (36.8) 5.64 - 15.49 [7.19]	7.99 ± 2.27 (28.3) 5.30 - 11.99 [7.94]

a Dose increased by 2 mg qod during first week, Starting Dose 2 mg.

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 11

Table 39 Day 14 Renal Elimination of Paliperidone from IR Tablets – Study INT-1

Dose	N	Ae24h (µg)	% of the dose	AUCτ (ng/ml x hr^{-1})	Clren (ml/min)
1 mg	7	379 ± 212 110 - 592 [504]	38 ± 21 11 - 59 [50]	271 ± 117 192 - 530 [238]	27.4 ± 17.6 3.5 – 51.4 [35.6]
4 mg	4 or 5	1448 ± 867 1.93 - 2280 [1622]	36 ± 22 0.048 - 57 [41]	1125 ± 411 720 - 1659 [1061]	30.4 ± 15.7 16.3 – 52.8 [26.3]
8 mg	3	2640 ± 498 2250 - 3201 [2468]	33 ± 6 28 - 40 [31]	1968 ± 497 1476 - 2470 [1957]	23.4 ± 7.2 15.2 – 27.9 [27.3]

3.10.2.4 Paliperidone Modified Release GI Absorption Characteristics

After the examination of paliperidone IR pharmacokinetics three studies were conducted to examine the feasibility of a slower releasing modified release formulation.

These 3 studies included:

- ALZA-C-2001-032 — A pilot study comparing the absorption of both paliperidone and risperidone from both oral solutions and osmotic modules in young males and female adults
- ALZA-C-2001-039 — An exploratory PK/PD study comparing the incidence and severity of hypotension from paliperidone after drug delivery and absorption by 3 different delivery rates in male and female adults
- ALZA-C-2002-019 — An exploratory PK/PD study comparing the incidence and severity of hypotension from both paliperidone and Risperidone after drug delivery and absorption by 2 different delivery rates in male and female adults

3.10.2.4.1 Exploratory Study Alza-C-2001-032

Study Alza-032 showed that the total exposure to active moieties after administration of solutions of risperidone and paliperidone were similar, although the Cmax of total active moieties was slightly higher after administration of risperidone. When administered as osmotic modules Tmax was delayed and Cmax was decreased as expected for both risperidone and paliperidone as expected, although to a greater extent with risperidone. Total exposure to active moieties was also decreased for both drugs by about 1/3 to 40%, (i.e. Frel ~ 0.6 – 0.67), suggesting either incomplete release or differences in regional absorption, (see Table 40).

3.10.2.4.2 Exploratory Studies Alza-019 and Alza-039

When paliperidone oral solutions were administered in multiple small doses over the course of a day in studies ALZA-039 and ALZA-019, the total exposures and Cmaxs after adjustment for dose are similar to total exposures to active moieties after administration of paliperidone and risperidone as immediate release formulations, (see Table 41, Table 42 and Table 43). This suggests that the lower bioavailability seen in study ALZA-032 is either due to incomplete release, a drug by formulation interaction, a spurious finding, or due to regional differences in absorption, (see §3.5.2Dissolution Data

Table 40 Comparative Single Dose Pharmacokinetics of Equal Mass Doses (2 mg) of Risperidone and Paliperidone each Administered as both Osmotic Modules and Oral Solutions - Study Alza 032

Treatment	Analyte	Subjects	N	Cmax (ng/mL)	Tmax (h)	t1/2 (h)	AUCt (ng·h/mL)	AUC(0-96) (ng·h/mL)	AUCinf (ng·h/mL)	Cavg (ng/mL)	GeoMean Cmax	GeoMean AUCinf	GeoMean Ratio	Rel Bioavailability (%)
Oral solution (risperidone)	Ris	All	16	15.6 ± 6.2 (40.0) 4.0 - 25.0 [15.2]	1.0 ± 0.2 (23.3) 0.5 - 1.5 [1.0]	6.5 ± 6.4 (98.9) 4.3 - 1 [23]	128.2 ± 127.9 (99.8) 10 - 469 [82.7]	141.2 ± 164.8 (116.7) 10 - 659 [83.5]	136.1 ± 145.2 (106.7) 11 - 556 [84.0]	1.47 ± 1.71 (116.72) 0.1 - 6.8 [0.87]				
				14.0	1.0	4.7	84.5	87.8	87.8	0.91				
Oral solution (risperidone)	Pal	All	16	8.5 ± 3.6 (43.0) 8.3 - 1.8 [15.1]	6.6 ± 5.4 (82.1) 6.0 - 1.5 [24.0]	27.1 ± 9.4 (34.8) 16 - 50 [25.5]	260.9 ± 83.9 (32.1) 117 - 406 [266.6]	261.1 ± 83.6 (32.0) 117 - 406 [266.6]	283.7 ± 83.8 (29.5) 139 - 426 [291.8]	2.71 ± 0.87 (32.06) 1.2 - 4.2 [2.77]				
				7.5	5.2	25.8	246.6	246.9	270.7	2.56				
Oral solution (risperidone)	Act	All	16	21.8 ± 5.5 (25.0) 13.0 - 30.4 [21.1]	1.9 ± 2.1 (110.5) 1.0 - 9.0 [1.0]		389.1 ± 142.6 (36.7) 151 - 735 [362.4]	402.2 ± 176.9 (44.0) 154 - 926 [363.3]	419.8 ± 169.0 (40.3) 156 - 894 [385.1]	4.18 ± 1.84 (44.03) 1.6 - 9.6 [3.77]				
				21.1	1.42		364.9	371.7	390.8	3.86				
OSMOTIC MODULE (risperidone)	Ris	All	16	4.3 ± 2.5 (58.5) 0.7 - 10.7 [4.0]	6.6 ± 2.3 (35.2) 4.0 - 12.0 [6.0]	7.6 ± 5.9 (77.4) 5.4 - 1 [20]	77.3 ± 81.3 (105.2) 6 - 318 [51.4]	78.3 ± 80.9 (103.3) 6 - 318 [53.1]	79.6 ± 83.4 (104.8) 7 - 328 [53.2]	0.81 ± 0.84 (103.28) 0.1 - 3.3 [0.55]				59.6 ± 18.8 (31.6) 32 - 98 [60.3]
OSMOTIC MODULE (risperidone)	Pal	All	16	4.35 ± 1.4 (31.2) 4.14 - 1.58 [6.8]	15.2 ± 6.0 (39.6) 15.0 - 6.0 [24.1]	24.4 ± 6.3 (25.7) 15 - 38 [23.5]	166.5 ± 46.0 (27.7) 93 - 270 [160.9]	167.2 ± 45.8 (27.4) 93 - 270 [161.9]	182.4 ± 47.7 (26.2) 119 - 296 [179.3]	1.74 ± 0.48 (27.40) 1.0 - 2.8 1.68]				67.1 ± 15.6 (23.3) 43 - 97 [62.0]
				4.1	14.1	23.7	160.6	161.4	176.9	1.68				65.4
OSMOTIC MODULE (risperidone)	Act	All	16	*7.8 ± 1.8* *(23.0)* *4.7 - 11.5* *[8.1]*	8.1 ± 2.5 (30.8) 4.0 - 12.0 [9.0]		243.7 ± 79.7 (32.7) 137 - 411 [246.3]	245.6 ± 79.0 (32.2) 138 - 411 [248.6]	*262.0 ± 87.6* *(33.4)* *144 - 447* *[264.8]*	2.56 ± 0.82 (32.18) 1.4 - 4.3 [2.58]				65.6 ± 16.7 (25.4) 40 - 96 [63.2]
				7.6	7.8		231.6	233.7	248.3	2.43				63.5
Oral solution (Pal)	Pal	All	15	17.7 ± 4.5 (25.21) 11.8 - 26.9 [16.7]	1.3 ± 0.6 (44.8) 0.5 - 2.5 [1.0]	29.3 ± 9.9 (33.9) 23 - 61 [25.8]	399.6 ± 103.8 (26.0) 190 - 608 [399.0]	399.6 ± 103.8 (26.0) 190 - 608 [399.0]	439.4 ± 128.6 (29.3) 198 - 731 [433.3]	4.15 ± 1.08 (26.04) 2. - 6. [4.14]				
				17.2	1.2	28.2	386.2	386.2	421.6	4.01				
OSMOTIC MODULE (Pal)	Pal	All	15	*6.4 ± 1.9* *(29.9)* *3.5 - 10.4* *[5.8]*	11.3 ± 3.4 (30.1) 6.0 - 16.0 [12.0]	27.5 ± 4.3 (15.7) 19 - 33 [28.9]	246.0 ± 75.4 (30.7) 115 - 428 [244.1]	246.0 ± 75.4 (30.7) 115 - 428 [244.1]	*271.4 ± 81.8* *(30.2)* *123 - 465* *[257.2]*	2.56 ± 0.78 (30.67) 1.2 - 4.4 [2.54]				62.5 ± 11.3 (18.0) 44 - 80 [61.8]
				6.1	10.7	27.2	235.1	235.1	259.6	2.44				61.6

Oral solution (risperidone)	Pal	Exclude 103	15	8.2 ± 3.6 (44.1) 8.3 - 1.8 [15.1]	7.0 ± 5.4 (78.2) 6.0 - 1.5 [24.0]	27.1 ± 9.4 (34.8) 16 - 50 [25.5]	263.7 ± 86.0 (32.6) 117 - 406 [266.7]	263.9 ± 85.7 (32.5) 117 - 406 [266.7]	287.1 ± 85.5 (29.8) 139 - 426 [291.9]	2.74 ± 0.89 (32.48) 1.2 - 4.2 [2.77]				
				7.3	5.6	25.8	248.7	249.0	273.5	2.59				
Oral solution (risperidone)	Act	Exclude 103	15	22.2 ± 5.5 (24.69) 13.0 - 30.4 [21.8]	1.9 ± 2.1 (112.8) 1.0 - 9.0 [1.0]		399.4 ± 141.3 (35.4) 151 - 735 [366.1]	413.5 ± 177.2 (42.8) 154 - 926 [366.9]	431.2 ± 168.4 (39.0) 156 - 894 [395.8]	4.30 ± 1.84 (42.85) 1.6 - 9.6 [3.81]				
				21.5	1.4		375.9	383.3	402.9	3.98				
OSMOTIC MODULE (risperidone)	Pal	Exclude 103	15	4.4 ± 1.4 (32.2) 4.1 - 1.6 [6.8]	15.6 ± 6.0 (38.4) 15.0 - 6.0 [24.1]	24.6 ± 6.4 (26.0) 15 - 38 [23.8]	168.8 ± 46.6 (27.6) 93 - 270 [166.7]	169.7 ± 46.3 (27.3) 93 - 270 [166.7]	185.5 ± 47.8 (25.8) 119 - 298 [181.3]	1.76 ± 0.48 (27.32) 1.0 - 2.8 [1.73]				87.6 ± 16.0 (23.7) 43 - 97 [62.7]
				4.2	14.5	23.9	162.8	163.7	180.0	1.70				65.8
OSMOTIC MODULE (risperidone)	Act	Exclude #103	15	8.0 ± 1.7 (20.6) 5.9 - 11.5 [8.2]	8.1 ± 2.6 (31.9) 4.0 - 12.0 [9.0]		250.8 ± 77.1 (30.7 143 - 411 [263.0]	252.8 ± 76.2 (30.1) 144 - 411 [256.1]	269.9 ± 84.6 (31.3) 148 - 447 [272.4]	2.63 ± 0.79 (30.15) 1.5 - 4.3 [2.66]				66.1 ± 17.1 (25.9) 40 - 95 [65.0]
				7.9	*7.7*		*239.8*	*242.0*	*257.5*	*2.51*				*63.9*
Oral solution (Pal)	Pal	Exclude 103	15	17.7 ± 4.5 (25.2) 11.8 - 26.9 [16.7]	1.3 ± 0.6 (44.8) 0.5 - 2.5 [1.0]	29.3 ± 9.9 (33.9) 23 - 61 [25.8]	399.6 ± 103.8 (26.0) 190 - 608 [399.0]	399.6 ± 103.8 (26.0) 190 - 608 [399.0]	439.4 ± 128.6 (29.3) 198 - 731 [433.3]	4.15 ± 1.08 (26.04) 2. - 6. [4.14]				
				17.2	1.2	28.2	386.2	386.2	421.6	4.01				
OSMOTIC MODULE (Pal)	Pal	Exclude 103	15	6.4 ± 1.9 (29.90) 3.5 - 10.4 [5.8]	11.3 ± 3.4 (30.1) 6.0 - 16.0 [12.0]	27.5 ± 4.3 (15.7) 19 - 33 [28.9]	246.0 ± 75.4 (30.7) 116 - 428 [244.1]	246.0 ± 75.4 (30.7) 116 - 428 [244.1]	271.4 ± 81.8 (30.2) 123 - 465 [257.2]	2.56 ± 0.78 (30.67) 1.2 - 4.4 [2.54]				62.5 ± 11.3 (18.0) 44 - 80 [61.8]
				6.1	10.7	27.2	236.1	235.1	259.6	2.44				61.6