CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021164Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

New Drug Application
Complete Response to Not Approvable Letter – OCP Review

NDA:	21-164
Serial Number:	AZ
Type of Submission:	Major Amendment – Multiple Disciplines (Complete Response to Not Approvable Letter of June 24th, 2004)
Generic Name:	Gepirone HCl MR Tablets
Brand Name:	To-be-determined
Formulation(s); **Strength(s);** **Route(s):**	Modified Release (Extended Release) Tablets 20 mg, 40 mg, 60 mg, 80 mg PO
Sponsor:	Fabre-Kramer Pharmaceuticals, Inc. Houston, Tx
Letter Date(s):	May 1, 2007 July 13, 2007 (BM)
Reviewer:	Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D.
Team Leader:	Raman Baweja, Ph.D.
OCP Division:	Division of Clinical Pharmacology -1 (DCP-1) HFD-860
ORM Division:	Division of Psychiatry Products (DPP) HFD-130

1 TABLE OF CONTENTS

1 TABLE OF CONTENTS 1

2 EXECUTIVE SUMMARY 2

2.1 BACKGROUND 2
2.2 RECOMMENDATIONS 2
2.3 SUMMARY OF IMPORTANT FINDINGS 3

3 COMMENTS 3

3.1 COMMENTS TO THE SPONSOR 3
3.2 PHASE IV COMMITMENT TO BE COMMUNICATED TO THE SPONSOR 4
3.3 LABELING COMMENTS 5

4 SIGNATURES 58

5 DETAILED REVIEW 59

5.1 REGULATORY HISTORY 59
5.2 COMPARATIVE DISSOLUTION 62
5.2.1 Product Description Update 62
5.2.2 Current Proposed Dissolution Specifications 64
5.2.3 Dissolution Method 65
5.2.4 Product Batch Descriptions 65
5.2.5 Comparative Dissoluton Profiles 66
5.2.5.1 Organon Biconvex Tablets and Fabre-Kramer Flat in 0.01 M HCl 66
5.2.5.2 Organon Biconvex Tablets and Organon Flat Tablets in 0.01 M HCl 67
5.2.5.3 Organon Biconvex Tablets and Organon Flat Tablets in 0.01 M HCl 68
5.2.5.4 Organon Biconvex Tablets and Fabre-Kramer Flat Tablets F2 Similarity Factors in Multiple Media 69
5.3 RE-EVALUATION OF REGULATORY DISSOLUTION SPECIFICATIONS 70
5.4 EFFECT OF FOOD AND MEAL COMPOSITION 72
5.5 COMMITMENTS TO PERFORM PREVIOUSLY PROPOSED PHASE IV STUDIES 77
5.5.1 Re-evaluation of 12 hour dissolution specification 77
5.5.2 Measurement of the effect of intermediate inducers such as rifabutin 77
5.6 NEW ADDITIONAL PROPOSED PHASE IV STUDIES 77

2 EXECUTIVE SUMMARY

2.1 BACKGROUND

On June 24th, 2004 a not approvable letter was issued due to a lack of evidence of effectiveness in the short or long term treatment of major depressive disorder.

This not approvable letter also requested the following:

- Comparative dissolution data in multiple media in order to request a biowaiver for a change in tablet shape (biconvex to modified flat) for the 40 mg and 60 mg strengths.

and agreement to perform three phase IV commitments:

a) *In vivo* effect of an intermediate inducer such as rifabutin
b) Effects of different meal compositions
c) Re-evaluation of the 12 hour dissolution specification after production of 20 batches of each strength

A type C Guidance Meeting was subsequently held on May 31, 2006. In this meeting the sponsor indicated that the embossment on the original modified flat tablet was being changed. It was agreed that comparative dissolution information in multiple media linking the modified flat tablet with the to-be-marketed embossment to the modified flat tablet with the original embossment, and to the original biconvex tablet would be provided in the complete response.

2.2 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology - 1 (OCP/DCP-1) has reviewed the Complete Response to the Not Approvable letter dated June for NDA #21-164 AZ submitted May 1, 2007.

OCP finds this application acceptable providing agreement can be reached on labeling and so long as the sponsor provides written agreement to a phase IV commitment to perform a drug-drug interaction study of the effect of an intermediate CYP 3A4 inducer such as rifabutin within 1 year of approval.

OCP also grants a waiver to the requirement for a bioequivalence study for the proposed 40 mg and 60 mg tablet strengths.

OCP recommends that the regulatory dissolution method and specifications be set if the product is approved. The previous recommendation that an interim specification be set and that there be a phase IV commitment to re-evaluate the specification for the 12 hour sampling time after the production of 20 batches of each strength should be disregarded.

Comments should be communicated to the sponsor as appropriate:
(See section 3.1 on page 3).

Phase IV commitments should be communicated to the sponsor as appropriate:
(See section 3.2 on page 4).

Labeling comments should also be communicated to the sponsor as appropriate:
(See section 3.3 on page 5).

2.3 SUMMARY OF IMPORTANT FINDINGS

1) **Phase IV commitment to study the *in vivo* effect of an intermediate inducer such as rifabutin.**

The sponsor has not made this commitment and will be requested again.

2) **Phase IV committment to study the effects of different meal compositions.**

This study has been completed and the results are acceptable.

The magnitude of the food effect was clearly dependent on the fat content of the breakfast. The peak concentration of gepirone after intake of low-fat breakfast was 27% higher, after medium-fat breakfast 55% higher and after a high-fat breakfast 62% higher as compared to the fasted state.

The total exposure to gepirone also increased with the fat content of the breakfast with the $AUC_{0\text{-}tlast}$ after intake of low-fat breakfast was 14% higher, after a medium-fat breakfast 22% higher and after a high-fat breakfast 37% higher as compared to the fasted state. For the AUC_{∞} similar results were found, i.e., 14%, 18% and 32% respectively.

The median Tmax was significantly shortened after intake of the medium-fat (3 hrs) and high-fat (3 hrs) meals compared to the fasted state (5 hrs), and was also shorter for the low-fat meal, (4 hrs).

The effect of varying amounts of fat on Cmax and AUC of the metabolites 3'-OH-gepirone and 1-PP has basically the same pattern as was found for gepirone itself although the magnitude of the effect is attenuated, resulting in sometimes a statistically significant effect and sometimes a statistically non-significant effect.

3) **Comparative dissolution data in multiple media in order to request a biowaiver for a change in tablet shape (biconvex to modified flat) for the 40 mg and 60 mg strengths, and a change in embossment for all strengths.**

Dissolution of all strengths of the final proposed Fabre-Kramer embossed flat tablet are acceptable and biowaivers should be granted.

4) **Phase IV committment to re-evaluate of the 12 hour dissolution specification after production of 20 batches of each strength.**

The dissolution method and specifications can be set now based upon the two pivotal clinical batches and a phase IV commitment is not appropriate or necessary.

3 COMMENTS

3.1 COMMENTS TO THE SPONSOR

1) All strengths of the modified flat tablet with the Fabre-Kramer embossment are acceptable based upon the submitted comparative dissolution data, a biowaiver is granted, and a bioequivalence study is not needed.

2) The sponsor is requested to adopt the following as the regulatory dissolution method and specifications, (see Table 1). A phase IV commitment to re-evaluate the 12 hour dissolution specification is not necessary or appropriate as specifications are being set based upon dissolution at release for pivotal clinical batches. (This is the typical practice.)

Table 1 Dissolution Method for Gepirone HCl Extended Release 20 mg, 40 mg, 60 mg, and 80 mg Tablets

Parameter	Dissolution Method
Apparatus:	USP Type II Paddle
Media:	0.01 M HCl
Volume:	900 ml
Temperature:	37 ± 0.5 ^{o}C
Rotation Speed:	50 RPM
Sampling Times:	1 hour 5 hours 12 hours 20 hours
Specifications:	1 hour 15% - 25% 5 hours (b) (4) 12 hours 65% - 85% 20 hours NLT 86%
Acceptance Criteria:	As per USP XXX – NF 25 Suppl. 1 Dissolution <711> Extended-Release Dosage Forms Acceptance Table 2

3.2 PHASE IV COMMITMENTS TO BE COMMUNICATED TO THE SPONSOR

1) The sponsor needs to provide written agreement to a phase IV commitment to perform a drug-drug interaction study of the effect of an intermediate CYP 3A4 inducer such as rifabutin within 1 year of approval.

2) The sponsor should conduct studies to investigate the potential for dose-dumping in the presence of alcohol for all strengths of extended release gepirone tablets. The dissolution conditions shown in the following table should be used.

Table 2 Dissolution Method for Gepirone HCl Extended Release 20 mg, 40 mg, 60 mg, and 80 mg Tablets

Parameter	Dissolution Method
Apparatus:	USP Type II Paddle
Media:	Medium 1: 0.01 M HCl Medium 2: 0.01 M HCl with 5% (v/v) EtOH Medium 3: 0.01 M HCl with 10% (v/v) EtOH Medium 4: 0.01 M HCl with 20% (v/v) EtOH
Volume:	900 ml
Temperature:	37 ± 0.5 ^{o}C
Rotation Speed:	50 RPM
Sampling Times:	Sufficient to adequately characterize the release profile, and should include the time points as per the regulatory dissolution method or until a plateau is reached.

3.3 LABELING COMMENTS

The sponsor's proposed labeling with OCP edits and comments may be found on the following pages.

Review of labeling was based on previous OCP reviews whenever possible.

Reviewer's edits to sponsor's proposed labeling are shown in red:

Deletions are shown by a ~~red strike-through.~~

Additions are shown by red underlined text.

Several sections of labeling have been moved within the labeling.

Blue text is used to denote removal of sections.

Green text is used to denote insertion of sections.

52 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 SIGNATURES

Ronald E. Kavanagh, B.S. Pharm., Pharm.D., Ph.D., OCP/DCP-1	**Date**
Raman Baweja, Ph.D., Team Leader, OCP/DCP-1	**Date**

CC:

NDA 21-164	(DFS)
HFD-130	(HearstE, KhinN, MathisM, LaughrenT, GrewalR, HardemannS, DavidP)
HFD-	(OliverT)
HFD-860	(KavanaghR, BawejaR, UppoorR, MehtaM)

5 DETAILED REVIEW

5.1 REGULATORY HISTORY

The cover letter for the present submission was quite confusing and goes in great length into the regulatory history. The following is a summary of this history gleened from the cover letter. After near completion of the review the pertinent facts for the present submission became much clearer and are included in §2.1 Executive Summary Background Information.

Table 3 Regulatory History of Gepirone HCl ER Tablets

Date	IND / NDA SN	Description	Comments
Sept 30, 1999	21-164	Original NDA	
May 18, 2001		NDA Resubmission	
Mar 15, 2002		Action Letter	Non-approval
April 17, 2003		Package outlining proposed response to March 15, 2002 non-approvable letter	We agreed only that we would probably be willing to file such an application, without reaching any agreement that this combination of studies would represent sufficient support of the effectiveness of gepirone. We noted that part of the difficulty was a preponderance of negative studies for gepirone in the application, making the overall program very weak indeed.
July 14, 2003		teleconference	Agreement that FDA would probably be willing to file an application with one positive short term study each for an IR and MR formulation along with a positive study for long term treatment.
Dec 23, 2003		NDA Amendment – Complete Response	CR to March 15, 2002 Action Letter
June 23, 2004		FDA Action Letter to Dec 23rd, 2003 Complete Response to March 15th, 2002 Action Letter	There is still not substantial evidence of the effectiveness of gepirone ER in the short-term or longer-term for treatment of MDD. Therefore, the application is not approvable OCP Comments 1. You have now changed the tablet shape with a change in commercial tooling from the original biconvex tablet to the modified flat tablets. Dissolution has only been evaluated for the 20 mg and 80 mg strength tablets. Therefore, the 20 and 80 mg strength tablets (with the modified flat tablet shape) are acceptable, but the 40 and 60 mg strength tablets (with the modified flat tablet shape) are not acceptable. Please submit results of dissolution comparisons (of the original vs.

Date	IND / NDA SN	Description	Comments
			modified shape) in multiple media with f2 comparisons to request a biowaiver for the 40 and 60 mg strength tablets. 2. Your proposed dissolution specifications are acceptable on an interim basis. The dissolution specifications are as follows: 15-25% at 1 h 40-85% at 5 h 65-86% at 12 h >86% at 20 h These specifications are acceptable provided that you adhere to your stated commitment to reevaluate the specification at 12 hours after the manufacture of 20 batches of each strength. 3. We ask that you agree to conduct the following studies as a Phase 4 commitment: a) Measurement of the effect of intermediate inducers such as rifabutin. *(Also gepirone's effect as inducer)* **b)** You previously agreed to conduct an *in vivo* study the effects of different meal compositions on gepirone ER pharmacokinetics as a Phase 4 commitment, and you have stated that the study has been initiated. c) We note your commitment to re-evaluate the dissolution specification at 12 hours after the manufacture of 20 batches of each strength.
Oct 12, 2005		Type B meeting (Attachment 2)	Discussion of new efficacy studies, safety information and sexual dysfunction claims, and submission format.
May 31, 2006		Type C meeting (Attachment 3)	Discussion of: Agreements reached re: information to support marketing approval, (i.e. Pooling IR and ER Data). Re: Pediatric Written Request – request for extension Analysis by Weight - ? For comments submit Ped PK study design to DPP All pediatric PK may be submitted with PWR response A change in the FMI is planned. • results of dissolution comparisons (of the original biconvex versus.

Date	IND / NDA SN	Description	Comments
			modified flat shape tablets with Organon trade dress) in multiple media • For new FMI to be submitted as a post-Approval Supplement. • f2 comparisons for all four strengths (20, 40, 60 and 80 mg). • Also CoAs • Info on all manufacturing changes • Complete information on all manufacturing changes from the original biconvex tablet to the modified flat tablets to the Fabre-Kramer market image. • Raw data and statistics for comparative dissolution profiles along with f1 and f2 comparisons in multiple media for the Fabre-Kramer market image relative to both the original biconvex tablet and to the modified flat tablets. • Complete descriptions of the dissolution methodologies employed. Discussion at Meeting: Fabre-Kramer clarified that their complete response would be intended to support the modified flat tablets with the Fabre-Kramer trade dress. As a result, the information requested in the preliminary comments will be included in the original complete response, and not in a chemistry supplement as discussed above and not during the review cycle. Sponsor told to submit in CR
?			Fabre-Kramer's responses to the CMC deficiencies listed in the June 23rd Action Letter.
Nov 13, 2006	IND 33,626, SN 173		Request for Tradename TRAVIVO
Dec 8, 2006	IND 33,626, SN 174		Regarding tradename of TRAVIVO
Dec 19, 2006	IND 33,626, SN 175		RE: Pediatric Written Request
Apr 2, 2007	IND 33,626, SN 176		RE: Pediatric Written Request
May 1, 2007 Present Submission		CR to June 23, 2004 Action Letter	CR and information intended to support the marketing approval based on the agreements reached at the May 30, 2006 Type C meeting
			Division's Written Request for Pediatric Information. Fabre-Kramer is currently waiting for a revised Written Request from the Division.

5.2 COMPARATIVE DISSOLUTION

5.2.1 PRODUCT DESCRIPTION UPDATE

The product descriptions for the original biconvex and final to-be-marketed Fabre-Kramer image, modified flat tablets as revised follow:

Table 4 Comparison of Original and To-Be-Marketed Product Descriptions

Strength	**20 mg**		**40 mg**		**60 mg**		**80 mg**	
Old / New	Original	TBM[1]	Original	TBM[1]	Original	TBM[1]	Original	TBM[1]
Color	Pink	Pink	Off-white	Off-white	Yellow	Yellow	Red-brown	Red-brown
Formulation	tablet	tablet	tablet	tablet	tablet	tablet	tablet	tablet
Shape	***Biconvex*** rectangular shaped	***Flat*** rectangular shaped	***Biconvex*** rectangular shaped	***Flat*** rectangular shaped	***Biconvex*** rectangular shaped	***Flat*** rectangular shaped	***Biconvex*** rectangular shaped	***Flat*** rectangular shaped
Method of Marking	Debossed	Debossed	Debossed	Debossed	Debossed	Debossed	Debossed	Debossed
Debossment Markings	(b) (4)	"FK" on one side and "1" on the other side	(b) (4)	"FK" on one side and "7" on the other side	(b) (4)	"FK" on one side and "11" on the other side	(b) (4)	"FK" on one side and "17" on the other side

1 TBM – To-be-marketed.

A visual comparison of the original biconvex and modified flat tablet shapes with the Organon embossment is shown in Figure 1. Note that this only demonstrates the change in tablet shape and does not show the final to-be-marketed Fabre-Kramer embossment.

Figure 1 Visual Comparison of Original and Previous Proposed To-Be-Marketed Tablet Images

***Change 2: Tablet Shape Change* (cont.)**

Original Tablet Shape

(b) (4)

Proposed Tablet Shape

(b) (4)

5.2.2 CURRENT PROPOSED DISSOLUTION SPECIFICATIONS

The following is from the OCPB review dated May 25, 2004 of the December 23, 2003 Complete Response to the March 15, 2002 Action Letter:

The Sponsor's original proposed dissolution specifications were:

15-25% at 1 h
40-85% at 5 h [1]
65-86% at 12 h
> (b)(4) % at 20 h

The original data on which the specifications were proposed is shown below (from the 2/19/02) OCPB review of the original NDA.

Table E. Drug Release Profiles of the Validation Batches vs. the Reference Product.

% Dissolved						
Control #	Strength, mg	1st Hr	5th Hr	12th Hr	20th Hr	Recovery
98 –013T	20	19	49	77	93	102
0300422	40	21	51	79	94	101
0300423	40	21	51	78	93	100
0300424	60	22	53	81	95	101
0300425	60	22	53	81	95	102
0300468	80	22	53	81	96	101
0300469	80	21	52	81	97	102

The Sponsor was requested to agree to change the dissolution specifications at 12 h and 20 h to 65-85% and > 85% respectively.

In the present submission, the Sponsor proposes to not change the upper limit of the 12-hour specification at this time from 86% to 85%, but to commit to re-evaluate the specification after the manufacture of 20 batches of each strength.

For the 20-hour time point, The Sponsor proposes to change the specification from NLT (b)(4) % to NLT 86%, in order to (b)(4) with the 12-hour specification.

OCPB finds these changes and commitments acceptable.

[1] The sponsor indicates in the present submission that this appears to be a typographical error and should have been (b)(4)

5.2.3 DISSOLUTION METHOD

The reported proposed regulatory dissolution method and for all tablet strengths is shown in Table 5.

Table 5 Proposed Regulatory Dissolution Method for Gepirone Extended Release Tablets 20 mg, 40 mg, 60 mg, and 80 mg

Parameter	Dissolution Method
Apparatus type:	USP Type II Paddle
Media:	0.01 M HCl
Volume:	900 ml
Temperature:	37 ± 0.5 °C
Rotation Speed:	50 RPM

5.2.4 PRODUCT BATCH DESCRIPTIONS

Descriptions of the product batches used in the various comparative dissolution experiments are shown in Table 6.

The batch numbers in red underlined text indicate the batches used in the comparative dissolution experiments.

The batch number in *green italicized text* is a pivotal clinical batch from study 134001. The other pivotal clinical batch from study FKGBE007, (see Table 10), was not used in the comparative dissolution experiments and so is not included inTable 6.

Table 6 Comparison of Batches Used in Comparative Dissolution Experiments[1]

Description	Organon Biconvex				Organon Modified Flat Tablets				Fabre-Kramer Modified Flat			
Nominal Description	Validation Batches				Scale-Up Batch				Technical Services Batch			
Strength	20 mg	40 mg	60 mg	80 mg	20 mg	40 mg	60 mg	80 mg	20 mg	40 mg	60 mg	80 mg
Batch No.	0581392 *0581393* 0581394	0300422 0300423	0300424 0300425	0300468 0300469	03-063T	03-064T	03-065T	03-066T	06-040T	06-033T	06-034T	06-035T
Formula Code	(b) (4)											
Batch Size												
Manufacture Date	May-June 1998	Mar-Apr 98	Mar-May 98	Mar-May 98	Dec 2003	Jan 2004	Feb 04	Dec 03 - Jan 04	Nov 2006	Nov 06	Nov 06	Nov 06

1 Location: Product 2007.pdf page 28/29 Manufacturing Comparison Table Section 2.4?

The primary difference in the method of manufacture between the various formulations is (b) (4) and this in theory could give rise to differences in dissolution.

5.2.5 COMPARATIVE DISSOLUTON PROFILES

Dissolution profiles of the proposed to-be-marketed Fabre-Kramer Flat Tablets to the original Organon Biconvex Tablets in the regulatory dissolution media are sufficiently similar that a biowaiver can be granted. This direct comparison is shown in the following subsection. In addition, the two step linkage of the Organon Biconvex Tablets to the Organon Flat Tablets, and the Organon Flat Tablets to the Fabre-Kramer Flat Tablets in the regulatory media was also acceptable and are shown in the following sections.

5.2.5.1 Organon Biconvex Tablets and Fabre-Kramer Flat in 0.01 M HCl

Direct comparison of dissolution profiles of the proposed to-be-marketed Fabre-Kramer Flat Tablets to the original Organon Biconvex Tablets are shown in the regulatory dissolution media for all strengths in

Table 7 Direct Comparison of Dissolution Profiles of Organon Biconvex Tablets and Fabre-Kramer Flat Tablets in 0.01 M HCl

Strength	R/T	Image	Batch #	Time	1	2	4	5	8	10	12	14	16	18	20	f2	f1
				Proposed Spec	15-25			(b) (4)			65-85				NLT 86		
20 mg	Ref	Organon Biconvex	581394	Mean	20	30	45		65	72	78	83	87	91	93	84.9	2.1
				Range	(b) (4)												
	Test	FK Flat	06-040T	Mean	21	31	46	52	65	72	77	81	84	88	91		
				Range	(b) (4)												
40 mg	Ref	Organon Biconvex	300423	Mean	21	31	46		66	73	79	84	88	92	94	83.9	2.3
				Range	(b) (4)												
	Test	FK Flat	06-033T	Mean	22	33	49	55	68	75	80	83	85	91	94		
				Range	(b) (4)												
60 mg	Ref	Organon Biconvex	300424	Mean	22	33	48		69	76	82	87	91	95	97	88.1	1.7
				Range	(b) (4)												
	Test	FK Flat	06-034T	Mean	23	33	49	58	68	76	80	85	90	93	95		
				Range	(b) (4)												
80 mg	Ref	Organon Biconvex	300468	Mean	22	33	48		69	76	82	87	91	95	97	90.5	1.4
				Range	(b) (4)												
	Test	FK Flat	06-035T	Mean	23	35	50	58	69	77	82	86	90	94	96		
				Range	(b) (4)												

5.2.5.2 Organon Biconvex Tablets and Organon Flat Tablets in 0.01 M HCl

Table 8 Comparison of Dissolution Profiles of Organon Biconvex Tablets and Organon Flat Tablets in 0.01 M HCl

Strength	R/T	Image	Batch #	Time	1	2	4	5	8	10	12	14	16	18	20	f2	f1
				Proposed Spec	15-25			(b) (4)			65-85				NLT 86		
20 mg	Ref	Organon Biconvex	581394	0.0	20.2	30.4	45.1		64.7	71.8	77.8	82.8	86.9	90.5	93.4	94.4	0.9
	Test	Organon Flat	03-063T	0.0	21.5	32.0	46.4		65.4	72.2	77.9	82.8	86.9	90.5	93.4		
40 mg	Ref	Organon Biconvex	300423	0.0	21.0	31.3	46.1		65.9	73.1	79.0	84.0	88.1	91.6	94.4	63.9	7.3
	Test	Organon Flat	03-064T	0.0	22.8	34.0	49.9		70.7	78.3	84.5	89.8	94.3	98.1	101.3		
60 mg	Ref	Organon Biconvex	300424	0.0	22.0	32.8	48.2		68.6	76.0	82.0	87.1	91.2	94.5	97.3	74.4	4.2
	Test	Organon Flat	03-065T	0.0	23.2	34.4	50.3		71.4	79.0	85.3	90.5	94.9	98.6	101.6		
80 mg	Ref	Organon Biconvex	300468	0.0	22.2	32.9	48.3		68.7	76.1	82.1	87.1	91.1	94.5	97.2	76.6	3.7
	Test	Organon Flat	03-066T	0.0	23.0	34.2	50.2		71.2	78.8	85.0	90.2	94.5	98.1	101.0		

5.2.5.3 Organon Biconvex Tablets and Organon Flat Tablets in 0.01 M HCl

Table 9 Comparison of Dissolution Profiles of Organon Flat Tablets and Fabre-Kramer Flat Tablets in 0.01 M HCl

Strength	R/T	Image	Batch #	Time	1	2	4	5	8	10	12	14	16	18	20	f2	f1
				Proposed Spec	15-25			(b) (4)			65-85				NLT 86		
20 mg	Ref	Organon Flat	03-063T	0.0	21.5	32.0	46.4		65.4	72.2	77.9	82.8	86.9	90.5	93.4	86.1	2.0
	Test	FK Flat	06-040T	0.0	21	31	46	52.0	65	72	77	81	84	88	91		
40 mg	Ref	Organon Flat	03-064T	0.0	22.8	34.0	49.9		70.7	78.3	84.5	89.8	94.3	98.1	101.3	63.5	6.0
	Test	FK Flat	06-033T	0.0	22	33	49	55.0	68	75	80	83	85	91	94		
60 mg	Ref	Organon Flat	03-065T	0.0	23.2	34.4	50.3		71.4	79.0	85.3	90.5	94.9	98.6	101.6	68.0	5.1
	Test	FK Flat	06-034T	0.0	23.0	33.0	49.0	58.0	68.0	76.0	80.0	85.0	90.0	93.0	95.0		
80 mg	Ref	Organon Flat	03-066T	0.0	23.0	34.2	50.2		71.2	78.8	85.0	90.2	94.5	98.1	101.0	74.3	3.5
	Test	FK Flat	06-035T	0.0	23	35	50	58.0	69	77	82	86	90	94	96		

5.2.5.4 Organon Biconvex Tablets and Fabre-Kramer Flat Tablets F2 Similarity Factors in Multiple Media

Acceptable comparative dissolution and similarity factors have also been demonstrated for all other media, see Figure 2.

Figure 2 Organon Biconvex Tablets and Fabre-Kramer Flat Tablets F2 Similarity Factors in Multiple Media

The following table summarizes the results of (f1) and (f2) testing of Gepirone ER Tablets 20 mg Technical Batch 06-040Tcompared to batch 0581394 in the listed dissolution media:

Dissolution media	(f1) values	(f2) values
0.01 M Hydrochloric Acid	2	86
0.1M Hydrochloric Acid	5	74
Purified Water, USP	2	89
USP buffer solution at pH 4.5	6	71
USP buffer solution at pH 6.8	5	75
Criteria	0 -15	50 -100

The following table summarizes the results of (f1) and (f2) testing of Gepirone ER Tablets 40 mg Technical Batch 06-033Tcompared to batch 0300423 in the listed dissolution media:

Dissolution media	(f1) values	(f2) values
0.01 M Hydrochloric Acid	2	84
0.1M Hydrochloric Acid	3	75
Purified Water, USP	2	88
USP buffer solution at pH 4.5	2	89
USP buffer solution at pH 6.8	5	73
Criteria	0 -15	50 -100

The following table summarizes the results of (f1) and (f2) testing of Gepirone ER Tablets 60 mg Technical Batch 06-034Tcompared to batch 0300424 in the listed dissolution media:

Dissolution media	(f1) values	(f2) values
0.01 M Hydrochloric Acid	2	88
0.1M Hydrochloric Acid	3	78
Purified Water, USP	2	85
USP buffer solution at pH 4.5	4	77
USP buffer solution at pH 6.8	7	67
Criteria	0 -15	50 -100

The following table summarizes the results of (f1) and (f2) testing of Gepirone ER Tablets 80 mg Technical Batch 06-035Tcompared to batch 0300468 in the listed dissolution media:

Dissolution media	(f1) values	(f2) values
0.01 M Hydrochloric Acid	1	91
0.1M Hydrochloric Acid	3	81
Purified Water, USP	3	82
USP buffer solution at pH 4.5	4	76
USP buffer solution at pH 6.8	3	82
Criteria	0 -15	50 -100

5.3 RE-EVALUATION OF REGULATORY DISSOLUTION SPECIFICATIONS

In the present submission the sponsor indicates that the proposed regulatory dissolution specifications were based on an analysis of all drug batches and stability data. This is inappropriate as stability data is intended to verify that the drug product will behave the same as the pivotal clinical batches over the entire product shelf-life.

Consequently, if approval is granted the regulatory dissolution specifications will be based upon the two pivotal efficacy studies.

The two pivotal efficacy studies and the gepirone ER tablets used in these studies are shown in Table 10, and more detailed information about the batches used in these studies is shown in Table 11.

The dissolution data for these two batches are shown in Table 12. Although the method is not mentioned, it is assumed that the currently proposed method in 0.01 M HCl was used as the mean dissolution values are similar to what has been reported previously with this methodology and since a different method was unlikely to have been employed, expecially for study FKGBE007.

Based upon the mean dissolution values for these two batches final dissolution specifications can be set as follows:

Sampling Time	Specification Range (% LC)
1 hour	(b) (4) [1]
5 hours	%
12 hours	65% - 85%
20 hours	NLT 86%

[1] It should be noted that the range of (b) (4) however, since a (b) (4) range of 15% - 25% was previously agreed to by the sponsor this (b) (4) range of (b) (4) % will be used for the actual regulatory specification.

Table 10 Pivotal Efficacy Studies and Gepirone MR Tablet Batches Used

Study No.	Study Title	Strength (mg)	Batch No.
134001	A double-blind, multicenter, randomized, placebo-controlled, efficacy and safety study of Org 33062 ER in subjects with major depressive disorder	20 mg	0581393
FKGBE007	A Double-Blind Multicenter, Randomized, Placebo-Controlled Efficacy and Safety Study of Org 33062 ER in Subjects with Major Depressive	20 mg	02-062T

Table 11 Information Regarding Gepirone MR Tablet Batches Used in Phase III Pivotal Efficacy Studies

Clinical Protocol	Clinical Phase	Dosage Formulation	Tablet Shape	Debossment	Site of Manufacture	Date of Manufacture	Batch No.	Drug Substance Batch	Batch Size (kg)	Batch Size (tablet #)	Formulation No.
134-001	III	20 mg ER tablet	Biconvex	FK on one side, plain on reverse	(b) (4)	May 1998	0581393	0198002	(b) (4)		
FKGBE007	IIIa	20 mg ER tablet	Flat	FK on one side, plain on reverse		Sep 2002	02-062T	010488			

Table 12 Dissolution Data for Gepirone MR Tablet Batches Used in Phase III Pivotal Efficacy Studies

[redacted]		% LC								
Time		1 hr		5 hr		12 hr		20 hr		Content Uniformity
Batch	Sample #	HPLC	UV	HPLC	UV	HPLC	UV	HPLC	UV	
0581393	1	(b) (4)								
	2									
	3									
	4									
	5									
	6									
	Average		18.8		47.8		74.0		89.3	98.7
02-062T	Average		20		51		78		92	

5.4 EFFECT OF FOOD AND MEAL COMPOSITION

I concur with the sponsor's conclusions regarding the effect of various meal compositions on the pharmacokinetics of Gepirone HCl MR tablets which is shown in the following italicized text with supporting data in Table 13 - Table 15 on the following pages:

> *"An effect of food was found for the peak concentration (Cmax) of gepirone and the total exposure (AUC0-tlast, AUC0∞) to gepirone. The magnitude of the food effect was clearly dependent of the fat content of the breakfast. The peak concentration of gepirone after intake of low-fat breakfast was 27% higher, after medium-fat breakfast 55% higher and after high-fat breakfast 62% higher as compared to the fasted state.*
>
> *The total exposure to gepirone increased with the fat content of the breakfast: the AUC0-tlast after intake of low-fat breakfast was 14% higher, after medium-fat breakfast 22% higher and after high-fat breakfast 37% higher as compared to the fasted state. For the AUC0-∞ similar results were found, i.e., 14%, 18% and 32% respectively.*
>
> *The time of occurrence of the peak concentration (tmax) was significantly decreased after intake of medium-fat (3 h) and high-fat (3 h) meals compared to the fasted state (5 h).*
>
> *The effect of varying amounts of fat on Cmax and AUC of the metabolites 3'-OH-gepirone and 1-PP has basically the same pattern as was found for gepirone itself although the magnitude of the effect is attenuated, resulting in sometimes a statistically significant effect and sometimes a statistically non-significant effect."*

This was single-dose, randomized, four-way cross-over study of the effect of various fed conditions, (fasted, low fat, medium fat, and high fat), on the pharmacokinetics of gepirone HCl from ER tablets and the pharmacokinetics of the 3'OH and 1-PP [1-(2-Pyrimidinyl) piperazine] metabolites in 32 healthy male Caucasian volunteers 18 – 45 years of age who are phenotypically CYP2D6 extensive metabolizers by a dextromethorphan test.

Subjects were hospitalized from the afternoon/evening of Day -1 until the morning of Day 3 in each treatment period.

The following treatments were given in randomized order with an interperiod washout of at least 1 week.

- Treatment A - 20 mg Gepirone HCl extended release (ER) tablets under fasting conditions.
- Treatment B - 20 mg Gepirone HCl ER tablets after consumption of a high-fat breakfast.
- Treatment C - 20 mg Gepirone HCl ER tablets after consumption of a medium-fat breakfast.
- Treatment D - 20 mg Gepirone HCl ER tablets after consumption of a low-fat breakfast.

There were no serious AEs in this trial, and none of the subjects discontinued from the trial due to AEs. Eleven subjects (34.4%) had one or more AEs during the trial. Headache (eight reports by five subjects) and dizziness (seven reports by three subjects) were the most commonly reported AEs. The incidence, intensity and time pattern (i.e., onset time and duration) for both events was similar for the various treatments.

As the single dose study of the lowest dose the effects this does not represent the clinical effects with clinical dosing, however this was addressed in a prior OCP review and was found acceptable.

This was the second study that the sponsor performed, in the first study (28725) it was found upon analysis that the fat content of the meals was incorrect. Thus the study was repeated. Prior to conducting the repeat study the meals were analyzed and the high-fat, high-caloric meal was found to be deficient in calories and fat content. Thus the meal was modified and the protocol amended. Because of all of the

problems with the meal contents this reviewer attempted to verify caloric contents. The analysis of the meal composition were not in English and insufficient data was provided to completely verify the final high fat content meal, however by assuming that the final high fat content meal only differed in the amount of fat as mentioned by the sponsor it was found that the final caloric content as calculated by the reviewer roughly matches that reported by the sponsor. The final compositions of the meals used are shown in Table 16 and are acceptable.

In spite of all the difficulties with meal content the results of this study are almost identical to the previous study (82725) where the meal composition was found to be deficient..

Table 13 Effect of Meal Composition on Gepirone Pharmacokinetics – Study 28727

Treatment / Metric	Summary Statistics				Geometric Means (%CV)				Geometric Mean Ratios (90% CI)		
	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Low fat : Fasted (D : A)	Medium fat: Fasted (C : A)	High fat: Fasted (B : A)
N	32	32	32	32	32	32	32	32	—	—	—
Tmax (h)	4.97 ± 1.91 (38.4) 1.00 - 10.0 [5.00]	3.91 ± 1.47 (37.6) 0.98 - 6.02 [4.00]	3.47 ± 1.27 (36.7) 1.00 - 6.00 [3.00]	3.62 ± 1.48 (40.7) 1.98 - 6.00 [3.00]	4.54 (49.9)	3.59 (47.3)	3.22 (42.7)	3.33 (43.9)			
Cmax (ng/mL)	5.27 ± 2.32 (44.0) 1.62 - 11.2 [4.68]	6.60 ± 2.89 (43.8) 2.94 - 14.9 [5.87]	8.27 ± 4.04 (48.8) 2.61 - 18.9 [7.61]	8.32 ± 3.28 (39.4) 4.51 - 14.1 [7.35	4.77 (49.5)	6.08 (42.4)	7.40 (51.1)	7.73 (39.9)	1.27 (1.17, 1.39)	1.55 (1.42, 1.69)	1.62 (1.49, 1.77)
AUC0−tlast (ng*h/mL)	72.3 ± 40.8 (56.4) 17.3 - 216 [60.2]	81.0 ± 40.3 (49.7) 18.8 - 198 [77.0]	84.6 ± 40.7 (48.1) 38.8 - 213 [73.3]	94.7 ± 44.0 (46.5) 41.9 - 228 [79.0]	63.0 (57.6)	72.0 (54.0)	76.8 (45.6)	86.0 (46.4)			
AUC0−inf (ng*h/mL)	75.6 ± 41.9 (55.5) 22.8 - 217 [61.2]	85.0 ± 41.8 (49.2) 19.5 - 204 [79.1]	85.9 ± 40.8 (47.5) 39.8 - 214 [76.6]	96.7 ± 44.8 (46.3) 42.6 - 228 [80.4]	66.4 (54.7)	75.8 (53.1)	78.2 (45.1)	87.8 (46.5)	1.14 (1.02, 1.27)	1.18 (1.06, 1.31)	1.32 (1.19, 1.48)
t1/2 (h)	6.39 ± 3.34 (52.2) 3.20 - 18.8 [5.49]	6.96 ± 4.14 (59.5) 3.25 - 22.6 [5.08]	4.99 ± 1.69 (33.9) 2.87 - 10.1 [4.53]	5.36 ± 2.32 (43.3) 3.16 - 13.3 [4.71]	5.77 (46.2)	6.14 (50.4)	4.74 (32.0)	5.01 (36.3)			

Table 14 Effect of Meal Composition on 3'-Hydroxy-Gepirone Pharmacokinetics – Study 28727

Treatment / Metric	Summary Statistics				Geometric Means (%CV)				Geometric Mean Ratios (90% CI)		
	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Low fat : Fasted (D : A)	Medium fat: Fasted (C : A)	High fat: Fasted (B : A)
N	32	32	32	32	32	32	32	32	—	—	—
Tmax (h)	6.34 ± 2.59 (40.8) 4.00 - 18.0 [5.02]	6.25 ± 1.90 (30.4) 4.00 - 12.0 [5.99]	7.13 ± 2.81 (39.5) 3.98 - 12.0 [6.00]	8.06 ± 3.41 (42.3) 2.00 - 18.0 [8.00]	6.01 (31.2)	6.03 (26.4)	6.62 (40.3)	7.32 (49.6)			
Cmax (ng/mL)	10.6 ± 2.80 (26.3) 2.79 - 16.2 [10.3]	12.5 ± 2.76 (22.1) 7.20 - 18.3 [12.2]	12.5 ± 3.17 (25.4) 6.88 - 19.2 [12.4]	12.5 ± 3.35 (26.9) 7.49 - 22.7 [12.0]	10.2 (32.7)	12.2 (23.0)	12.1 (26.0)	12.1 (26.2)	1.20 (1.12,1.28)	1.13 (1.11, 1.27)	1.14 (1.11, 1.26)
AUC_{tlast} (ng*h/mL)	214 ± 76.9 (36.0) 49.2 - 406 [201]	238 ± 79.1 (33.2) 89.6 - 418 [216]	235 ± 76.0 (32.3) 101 - 462 [231]	250 ± 84.5 (33.7) 124 - 444 [242]	200 (41.4)	226 (35.7)	223 (34.4)	237 (34.4)			
AUC0−inf (ng*h/mL)	225 ± 82.0 (36.4) 52.5 - 432 [211]	256 ± 93.0 (36.4) 93.0 - 485 [229]	246 ± 81.8 (33.3) 108 - 498 [242]	262 ± 90.6 (34.6) 127 - 474 [248]	210 (41.7)	240 (38.3)	233 (34.9)	247 (35.4)	1.18 (1.05, 1.24)	1.19 (1.02, 1.21)	1.18 (1.08, 1.28)
t1/2 (h)	9.77 ± 2.45 (25.1) 6.36 - 17.5 [9.00]	10.4 ± 3.28 (31.6) 5.84 - 20.2 [9.33]	8.93 ± 1.84 (20.6) 5.34 - 12.9 [8.56]	9.08 ± 1.86 (20.4) 6.04 - 14.6 [9.12]	9.51 (23.6)	9.95 (29.5)	8.74 (21.0)	8.91 (19.7)			

Table 15 Effect of Meal Composition on 1-(2-Pyrimidinyl) piperazine (1-PP) Pharmacokinetics – Study 28727

Treatment / Metric	Summary Statistics				Geometric Means (%CV)				Geometric Mean Ratios (90% CI)		
	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Fasted (A)	Low fat (D)	Medium fat (C)	High fat (B)	Low fat : Fasted (D : A)	Medium fat: Fasted (C : A)	High fat: Fasted (B : A)
N									—	—	—
Tmax (h)	4.97 ± 1.99 (40.1) 2.00 - 12.0 [5.00]	5.06 ± 0.914 (18.0) 3.00 - 8.00 [5.00]	5.78 ± 2.08 (35.9) 2.98 - 10.0 [5.01]	5.78 ± 2.20 (38.0) 1.98 - 12.0 [5.00]	4.64 (38.2)	4.99 (18.2)	5.45 (36.3)	5.38 (41.6)			
Cmax (ng/mL)	2.07 ± 0.731 (35.3) 1.00 - 3.64 [1.93]	2.46 ± 0.838 (34.0) 1.38 - 4.83 [2.28]	2.48 ± 0.988 (39.9) 1.13 - 5.04 [2.33]	2.66 ± 0.904 (34.0) 1.14 - 5.24 [2.65]	1.95 (35.7)	2.34 (32.5)	2.29 (41.7)	2.51 (35.6)	1.21 (1.13, 1.30)	1.19 (1.11, 1.27)	1.30 (1.22, 1.39)
AUCtlast (ng*h/mL)	31.0 ± 17.5 (56.4) 7.45 - 83.6 [28.4]	34.6 ± 19.2 (55.5) 9.36 - 107 [31.9]	33.9 ± 18.0 (53.2) 10.3 - 81.5 [33.4]	37.8 ± 18.5 (49.0) 8.01 - 84.2 [37.8]	26.4 (64.6)	30.2 (58.4)	29.5 (59.1)	33.3 (57.6)			
AUC0−inf (ng*h/mL)	36.5 ± 18.4 (50.3) 10.1 - 85.8 [33.2]	39.9 ± 20.2 (50.5) 12.2 - 110 [37.6]	38.3 ± 18.7 (48.7) 13.7 - 87.6 [36.4]	42.9 ± 20.4 (47.7) 16.1 - 99.7 [41.8]	32.1 (56.5)	35.3 (55.9)	34.0 (53.6)	38.5 (50.7)	1.15 (1.04, 1.27)	1.06 (0.96, 1.17)	1.20 (1.09, 1.33)
t1/2 (h)	8.99 ± 4.43 (49.3) 4.37 - 22.2 [7.57]	10.4 ± 8.30 (79.7) 2.10 - 39.6 [8.15]	8.13 ± 5.23 (64.3) 3.85 - 32.6 [7.23]	7.65 ± 2.98 (39.0) 3.45 - 16.8 [7.44]	8.11 (47.2)	8.47 (69.2)	7.19 (48.9)	7.12 (40.4)			

Table 16 Caloric Composition of Meals Actually Used in Study 82727 as Calculated by the Reviewer

	Low Fat Meal				Medium Fat Meal				High Fat Meal				FDA Meal Recommendations	
	Treatment D				Treatment C				Treatment B					
	% w/w	Weight (gms)	Calories	% of Calories	% w/w	Weight (gms)	Calories	% of Calories	% w/w	Weight (gms)	Calories	% of Calories	Calories	Percent of Total Calories
Protein	3.79	15.3	61.2	31.5	5.03	21.3	85.3	15.5	6.94	37.5	149.9	18.2	150	15
Fat	1.01	4.1	36.7	**18.9**	4.82	20.4	183.9	**33.5**	9.08	49.0	441.0	**53.6**	500-600	60
Carbohydrate	5.96	24.1	96.3	49.6	16.5	70.0	279.8	51.0	10.7	57.8	231.1	18.1	250	25
Total Weight		404.0				424.0								
Total Calories			194.3	100.0			549.1	100.0			822.0	100.0	800-1000	

5.5 COMMITMENTS TO PERFORM PREVIOUSLY PROPOSED PHASE IV STUDIES

5.5.1 RE-EVALUATION OF 12 HOUR DISSOLUTION SPECIFICATION

Fabre-Kramer agreed in their cover memo, however there is no need for the sponsor to perform this commitment as specifications need to be based on release data of pivotal clinical batches and not on production batches or stability data.

5.5.2 MEASUREMENT OF THE EFFECT OF INTERMEDIATE INDUCERS SUCH AS RIFABUTIN

There was no mention of this in the cover memo where the sponsor addresses other requested phase IV commitments and there is no obvious place to find such a commitment elsewhere in the submission. Consequently, it is assumed that the sponsor has not commited to perform this proposed phase IV study. This is a clinically appropriate request and if the product is to be approved the sponsor should be asked to commit to this study prior to approval.

5.6 NEW ADDITIONAL PROPOSED PHASE IV STUDIES

OCP has recommended that the potental of alcohol to induce dose-dumping be examined as a phase IV commitment, and this reviewer concurs.

OCP has requested that the conditions to be used are the tentative conditions that have been proposed by the FDA working group. This reviewer acquieses to this request, otherwise this reviewer would normally suggest alcohol concentrations in 4% increments with investigation of additional intermediate alcohol concentrations.

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
10/1/2007 03:59:48 PM
BIOPHARMACEUTICS

Raman Baweja
10/1/2007 04:34:48 PM
BIOPHARMACEUTICS

Mehul Mehta
10/1/2007 04:50:31 PM
BIOPHARMACEUTICS

NDA 21-164
Org 33062

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-164
Brand Name:	To Be Determined
Generic Name:	Gepirone HCl (Org 33062)
Type of Dosage Form:	Extended Release Tablets
Strengths:	20, 40, 60, 80 mg
Indications:	Major Depressive Disorder
Type of Submission:	NDA Resubmission (Response to Not Approvable)
Sponsor:	Organon
Submission Date:	December 23, 2003, March 19, 2004, May 19, 2004
OCPB Division:	DPE-I
OND Division:	Division of Neuropharmacological Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

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

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

- The pivotal bioequivalence study did not show that the 40 and 80 mg strengths were bioequivalent to the 20 mg strength tablet that was used in the clinical trials. No adequate data were provided comparing the 60 mg strength to the 20 mg strength. The 40, 60, and 80 mg strengths were not approvable.
- The food effect study showed a significant effect on gepirone bioavailability (increase in Cmax approximately 62%). The Sponsor should conduct an in vivo study evaluating the effects of different meal composition on gepirone ER pharmacokinetics.
- A strong pharmacokinetic interaction was observed between gepirone and ketoconazole (5-fold increase in gepirone concentrations). The Sponsor should conduct an in vivo drug interaction study to evaluate the effects of gepirone co-administration with an intermediate inhibitor of CYP3A4, such as verapamil.
- The Sponsor should conduct an in vitro assessment of (a) potential drug-drug interactions between gepirone and potent CYP3A4 inducers and (b) the drug's ability to induce CYP3A4 enzymes.

- The Sponsor should conduct an in vivo drug-drug interaction study with a potent CYP2D6 inhibitor to assess its effects on the pharmacokinetics of gepirone and its metabolites.
- The dissolution specification at 12 h and 20 h should be changed to 65-85% and > 85%, respectively.
- The Sponsor should clarify whether or not plasma gepirone (and any metabolites) concentrations were measured in any of the pivotal efficacy trials following administration of the IR and/or ER formulations of gepirone.

In the present review, OCPB has evaluated the following responses to OCPB comments that were submitted by the Sponsor in this resubmission:

- Evaluation of Safety data to consider whether there is likely to be a clinically relevant difference in safety due to the difference in exposure due to the 4x20 mg tablets compared to exposure after administration of the 80 mg strength tablets.
- Dissolution studies to support request for biowaiver of 60 mg strength
- Verapamil Interaction Study (28724)
- In Vivo CYP3A4 induction study (28705)
    - Includes assessment of gepirone's ability to induce or inhibit CYP3A4 enzymes
- In Vivo study with paroxetine as a potent inhibitor of CYP2D6 (28703)
- The dissolution specification has been addressed
- Trough plasma concentrations measured in the pivotal efficacy studies

In addition the Sponsor has submitted the following drug interaction studies that have been reviewed:

- Study 28704 – Warfarin Interaction Study
- Study 28706 – Lithium Interaction study
- Study 28707 – Glibenclamide interaction study

The Sponsor has initiated a food effect study, and as agreed by the Agency, it would be part of a Phase IV commitment.

The Sponsor has submitted the results of study 28721 to assess steady state pharmacokinetics in children. However, this study is part of a response to a pediatric written request for which additional studies are ongoing. Study 28721 will not be reviewed at this time.

The Sponsor has also submitted information regarding changes to the drug product since the original submission, some of which have resulting requirements for in vitro bioequivalence testing.

1.1 Recommendations

The Sponsor has provided studies or justification to address the recommendations of the Office of Clinical Pharmacology and Biopharmaceutics that were identified in the not approvable letter. Although the Sponsor's responses were generally acceptable, there are several recently identified issues regarding the pharmacokinetics as well as recent changes in the drug product that are of some concern.

- The 20 and 80 mg strength tablets (with the modified flat tablet shape) are acceptable, but the 40 and 80 mg strength tablets (with the modified flat tablet shape) are not acceptable.

  The nonequivalence of the 40 and 80 mg strength tablets compared to the approved 20 mg strength of gepirone would most likely have little impact on the adverse event profile. A biowaiver for the 60 mg strength as originally manufactured could be granted. However, the Sponsor has now changed the tablet shape with a change in commercial tooling from the original biconvex tablet to the modified flat tablets. Dissolution has only been evaluated for the 20 mg and 80 mg strength tablets. Therefore the 40 and 60 mg strength tablets (with the modified flat tablet shape) are not considered approvable at this time.

    - The Sponsor should submit results of dissolution comparisons (of the original vs. modified shape) in multiple media with f2 comparisons to request a biowaiver for the 40 and 60 mg strength tablets.

- The Sponsor's proposed dissolution specifications are acceptable on an interim basis. The dissolution specifications are as follows:

  15-25% at 1 h
  40-85% at 5 h
  65-86% at 12 h
  > 86% at 20 h

  These specifications are acceptable provided that the Sponsor adheres to the stated commitment to re-evaluate the specification at 12 hours after the manufacture of 20 batches of each strength.

1.2 Recommended Phase 4 Study Commitments

- The effect of intermediate inducers such as rifabutin should be evaluated as a Phase IV commitment.
- The Sponsor has previously agreed to conduct an *in vivo* study evaluating the effects of different meal compositions on gepirone ER pharmacokinetics as a Phase IV commitment and states that the study has been initiated.

- The Sponsor has stated a commitment to re-evaluate the specification at 12 hours after the manufacture of 20 batches of each strength.

The proposed labeling is acceptable from the OCPB perspective provided that the Sponsor make the recommended changes. Labeling comments can be found in section 4.

Please forward these comments as well as the labeling comments in Section 4 to the Sponsor.

Comments to Medical Officer (do not send to Sponsor)

- In the original submission, a significant pharmacokinetic interaction was observed between ketoconazole, a potent inhibitor of CYP3A4, and gepirone (a 5-fold increase in gepirone AUC). To minimize the risk of toxicity, we recommend that coadministration with ketoconazole or other potent inhibitors of CYP3A4 be considered as a warning.

- A significant pharmacokinetic interaction was observed between gepirone and rifampin, a potent inducer of CYP3A4 (a 20-fold decrease in Cmax and a 29-fold decrease in AUC for gepirone). Because of the risk of reduced efficacy, we recommend that coadministration with rifampin and other potent inducers should be contraindicated.

- A significant pharmacokinetic interaction was observed between gepirone and verapamil, an intermediate inhibitor of CYP3A4 (a 2.6 fold increase in Cmax and AUC was observed). To minimize the risk of toxicity, when verapamil and gepirone are co-administered, gepirone should be used cautiously. A low dose of gepirone is recommended with subsequent dosage adjustment based on clinical assessment. We recommend that the dose of gepirone in these patients not exceed 40 mg/day.

- As noted in the original submission, gepirone concentrations are increased 50-80% in the elderly. However, exposure depends on other factors as well (such as race for which there is a 1.5-2-fold decrease in AUC in Blacks and Asians compared to Caucasians). To minimize the risk of toxicity in the elderly we recommend that dosing in each patient should be individualized. Dosing of gepirone in the elderly should be started at the lowest strength and (b) (4) .

- In the original submission it was noted that plasma concentrations of gepirone and its metabolites were elevated by approximately 70% in patients with moderate and severe renal impairment. To minimize the risk of toxicity in patients with moderate or severe renal impairment we recommend that dosing in each patient

should be individualized. Dosing of gepirone in patients with moderate or severe renal impairment should be started at the lowest strength and (b) (4).

- In the original submission it was noted that gepirone exposure is augmented 2-fold in patients with moderately impaired hepatic function. To minimize the risk of toxicity, gepirone should be used cautiously in patients with moderately impaired hepatic function. A low dose of gepirone is recommended with subsequent dosage adjustment based on clinical assessment. We recommend that the dose of gepirone in these patients not exceed 40 mg/day.

- The pharmacokinetics of gepirone have not been adequately studied in patients with severe hepatic impairment. Therefore we recommend that the drug not be administered in this population and that there should be a warning or a contraindication regarding use of gepirone in this population.

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

Concurrence: NAM Atiqur Rahman, PhD
Acting Deputy Director, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc:	HFD-120	NDA 21-164, T. Laughren
		CSO/P. David
		/Biopharm/S. Yasuda
		/TL Biopharm/R. Uppoor
	HFD-860	//DD DPE1/M. Mehta, A. Rahman

Table of Contents

1 Executive Summary 1
1.1 Recommendations 3
1.2 Recommended Phase 4 Study Commitments 3
2 Table of Contents 6
3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 7
3.1 Background 7
3.2 Current Submission 9
3.3 Recommendations 24
4 Detailed Labeling Recommendations 27
5 Appendices 50
5.1 Package Insert (Annotated) 50
5.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review 101
5.2.1 Sponsor's Approach to Justification for Approval of the 40 and 80 mg Strength Tablets 101
5.2.2 Request for biowaiver for 60 mg strength tablets 106
5.2.3 Verapamil Interaction Study (Study 28724) 111
5.2.4 Rifampin Interaction Study 117
5.2.5 Paroxetine Interaction Study 124
5.2.7 Lithium Interaction Study 143
5.2.8 Warfarin Interaction Study 151
5.2.8 Organon Bioanalytical Method for Gepirone, Org 25907, and 1-PP in Plasma 159

2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

NDA 21-346 for Gepirone HCl (Org 33062) extended release (ER) tablets for use in the treatment of major depressive disorder was submitted May 18, 2001. Gepirone is a relatively selective partial agonist at serotonergic 5-HT1A receptors with lower affinity for 5-HT1B and other CNS receptors. In addition, 3'-OH gepirone, a metabolite of gepirone, has antidepressant activity as well. The recommended starting dose was to be 20 mg/day. The minimum efficacious dose was thought to be 40 mg. The dose could be increased to a maximum dose of 80 mg/day.

According to the OCPB review of February 19, 2002 the pharmacokinetic characteristics of gepirone are as follows:

- Poor oral absorption; F=14-17%
- Linear PK for ER tablets at 20-80 mg doses (high intra- and inter-subject variability)
- Steady state PK: approaches nonlinearity at higher doses
- Terminal half life: 4.5-12 h following ER administration
- Metabolism: 1-PP and 3'OH-geprione are both present at higher plasma levels than parent drug
    - Mediated via CYP3A4 and to a lesser extent 2D6
    - Other hydroxylated metabolites present in urine; mainly 3;5-dihydroxy-gepirone
- Elimination: 81% of administered dose in urine and 13% in feces

NDA 21-346 received a not approvable Action Letter (issued March 14, 2002). The non-approval deficiencies were related to inadequate efficacy data and inadequate safety data.

OCPB review of that submission resulted in the following comments and requests to the Sponsor:

- The pivotal bioequivalence study did not show that the 40 and 80 mg strengths were bioequivalent to the 20 mg strength tablet that was used in the clinical trials. No adequate data were provided comparing the 60 mg strength to the 20 mg strength. The 40, 60, and 80 mg strengths were not approvable.
- The food effect study showed a significant effect on gepirone bioavailability (increase in Cmax approximately 62%). The Sponsor should conduct an in vivo study evaluating the effects of different meal composition on gepirone ER pharmacokinetics.
- A strong pharmacokinetic interaction was observed between gepirone and ketoconazole (5-fold increase in gepirone concentrations). The Sponsor should conduct an in vivo drug interaction study to evaluate the effects of gepirone co-administration with an intermediate inhibitor of CYP3A4, such as verapamil.

- The Sponsor should conduct an in vitro assessment of (a) potential drug-drug interactions between gepirone and potent CYP3A4 inducers and (b) the drug's ability to induce CYP3A4 enzymes.
- The Sponsor should conduct an in vivo drug-drug interaction study with a potent CYP2D6 inhibitor to assess its effects on the pharmacokinetics of gepirone and its metabolites.
- The dissolution specification at 12 h and 20 h should be changed to 65-85% and > 85%, respectively.
- The Sponsor should clarify whether or not plasma gepirone (and any metabolites) concentrations were measured in any of the pivotal efficacy trials following administration of the IR and/or ER formulations of gepirone.

In the present review, OCPB has evaluated the following responses to OCPB comments that were submitted by the Sponsor in this resubmission:

- Evaluation of Safety data to consider whether there is likely to be a clinically relevant difference in safety due to the difference in exposure due to the 4x20 mg tablets compared to exposure after administration of the 80 mg strength tablets.
- Dissolution studies to support request for biowaiver of 60 mg strength
- Verapamil Interaction Study (28724)
- In Vivo CYP3A4 induction study (28705)
    - Includes assessment of gepirone's ability to induce or inhibit CYP3A4 enzymes
- In Vivo study with paroxetine as a potent inhibitor of CYP2D6 (28703)
- The dissolution specification has been addressed
- Trough plasma concentrations measured in the pivotal efficacy studies

In addition the Sponsor has submitted the following drug interaction studies that have been reviewed:

- Study 28704 – Warfarin Interaction Study
- Study 28706 – Lithium Interaction study
- Study 28707 – Glibenclamide interaction study

The Sponsor has initiated a food effect study, and as previously agreed by the Agency, it would be part of a Phase IV commitment.

The Sponsor has submitted the results of study 28721 to assess steady state pharmacokinetics in children. However, this study is part of a response to a pediatric written request for which additional studies are ongoing. Study 28721 will not be reviewed at this time.

The Sponsor has submitted addition information regarding changes that have been made in the manufacturing of the drug product since the original submission.

3.2 Current Submission

3.2.1 Justification for approval of the 40 and 80 mg tablet strengths

Are the 40 and 80 mg strengths approvable?

The pivotal bioequivalence study compared the bioavailability of 2x 40 mg with 2x20 mg and 1x 80 with 4x20 mg tablets. The results of that study indicated that the bioequivalence criterion was not met on Cmax and AUC for the comparison between 1x 40 mg vs 2x20 mg (90% C.I. for Cmax: 1.02-1.35, 90% CI for AUC: 0.99-1.33). In addition the Cmax of the 1x80 mg strength was significantly higher than the 4x20 mg tablets (90% CI for Cmax: 0.96-1.26).

The Sponsor's approach to justify the approval of the 40 and 80 mg strength tablets was to evaluating the relationship between dose or plasma concentrations and safety measures, bracketing the plasma concentrations from these strengths with higher exposures due to drug interactions or doses greater than 80 mg. The Sponsor has provided the following two considerations:

- **Plasma concentration-adverse event (AE) relationship in healthy subjects**
  The Sponsor determined the relationship between exposure (Cmax and AUC) and intensity of AE in healthy male subjects using data from Study 28717 (ketoconazole interaction study) and Study 28718 (pivotal BE Study). (Both studies were reviewed in the original submission of the NDA). Of note, due to the ketoconazole interaction with gepirone, Cmax and AUC were approximately 40% higher in study 28717 than in Study 28718 for a given 2x20 mg dose. The mean results are shown in the Tables below. A positive relationship between exposure parameters and AE intensity for dizziness and nausea is observed. In comparing the two studies, Study 28718 showed lower Cmax and AUC values compared with values observed in study 28717 at comparable AE intensities.

Table 1 Mean (SD) values for Cmax and AUC by AE intensity for dizziness (Study 28717) after a single dose of gepirone*

PARAMETER	NO AE (N = 14)	AE INTENSITY		
		Mild (N = 12)	Moderate (N = 8)	Severe (N = 14)
Cmax, ng/mL	8.29 (4.92)	9.30 (6.83)	21.1 (11.5)	26.4 (9.4)
AUC, ng.h/mL	143 (111)	184 (179)	387 (248)	425 (119)

*** Note: these data are independent of dose or presence or absence of ketoconazole**

Table 2 Mean (SD) values for C_{max} and AUC by AE intensity for dizziness (study 28718)

PARAMETER	NO AE (N=75)	AE INTENSITY		
		Mild (N =42)	Moderate (N = 6)	Severe (N = 0)
Cmax, ng/mL	6.37 (5.36)	9.71 (5.94)	6.0 (3.41)	na
AUC, ng.h/mL	96.1 (67.1)	142 (87.1)	81.7 (55.9)	na

The Sponsor has concluded that a 30% increase in Cmax and AUC for subjects not experiencing AEs will not lead to a moderate or severe AE intensity.

- **Dose-AE relationship in patients with depression**

The sponsor conducted an analysis to investigate the relationship between dose and adverse events. A logistic regression model was fit to AE data collected in 8 clinical trials in patients with depression. The six adverse events included in the model were dizziness, headache, insomnia, nausea, nervousness, and somnolence. The doses of gepirone ranged from 20 to 80 mg across studies.

The final model was used to predict the increased risk for a given AE due to a 17% increase in exposure when switching from 4 x 20 mg to 1 x 80 mg ER tablets. This was accomplished by evaluating the risk of a particular AE for a 93.6 mg dose, which was calculated as the "exposure equivalent" dose to the 1 x 80 mg dosage strength. The logistic regression model predicted a 7% increase in dizziness and less than 3% increase for insomnia and nausea.

OCPB review of the concentration-AE relationship attempts to bracket the exposure after the 1x80 mg tablets and 4x20 mg tablet with exposures known to result in AEs. Based on plasma concentrations observed in phase I studies, the highest exposure to drug occurred in Study 28717 during concomitant administration of a single dose of 40 mg (2x20 mg) ER tablets with 200 mg ketoconazole. In that treatment group 100% of the subjects experienced dizziness, 92% experienced nausea, and 67% vomited. The Cmax values for this treatment group ranged from 17.3-42.8 ng/ml. In comparison, co-administration of 20 mg gepirone with 200 mg ketoconazole resulted in greater than 50% of subjects experiencing dizziness and nausea; 8% of subjects vomited.

A plot of the mean (±sd) concentration-time profiles for 1 x 80 mg and 4 x 20 mg ER tablets administered as a single dose to 32 healthy males (study 28718) shows that both profiles fall within the range of concentrations known to cause AEs (Figure 1). Furthermore, the plot shows that the variability for both formulations is comparable, even at peak concentrations.

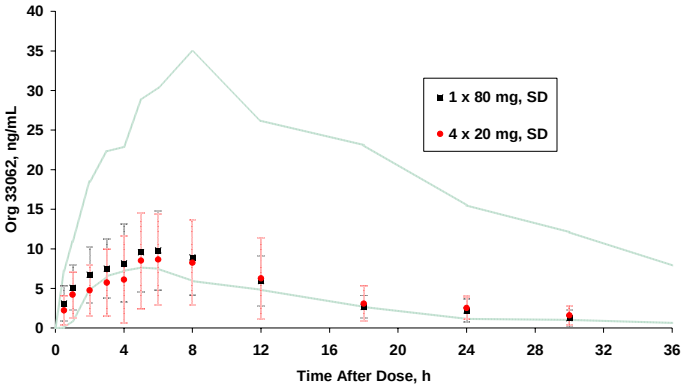


Figure 1 Mean (SD) concentration-time data (symbols) from a single dose of 1 x 80 mg vs. 4 x 20 mg gepirone compared to the range of observed concentrations (broken lines) from a single dose of 20 mg gepirone co-administered with 200 mg ketoconazole.

Since gepirone will be used to treat a chronic condition, the difference between the two formulations at steady-state is more clinically relevant than the differences following a single dose. Nonparametric superposition was used to simulate the mean steady-state concentrations for the 1 x 80 mg and 4 x 20 mg ER tablets (Figure 2). Predicted steady state concentrations for each formulation are very similar, with mean peak concentrations of 11.1 ng/ml for the 1 x 80 mg tablets and 10.4 ng/ml for the 2 x 40 mg tablets. Total predicted exposures, as measured by AUC over the dosing interval, for each formulation are 153 ng.h/ml and 155 ng.h/ml, respectively.

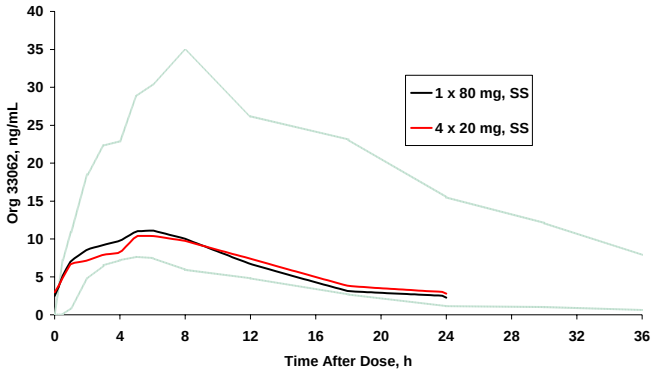


Figure 2. Simulated mean concentration-time data from multiple doses of 1 x 80 mg vs. 4 x 20 mg gepirone (solid lines) compared to the range of observed concentrations (broken lines) from a single dose of 20 mg gepirone co-administered with 200 mg ketoconazole.

<u>Are the 40 and 80 mg strengths approvable?</u> OCPB concurs with the Sponsor that the nonequivalence of the to-be-marketed strengths compared to the approved 20 mg strength of gepirone will most likely have little impact on the adverse event profile. Thus 80 mg strength can be considered approvable. In addition, since the 40 mg strength is bracketed by the 20 and 80 mg strengths, it can also be considered approvable.

3.2.2 Justification for Approval of the 60 mg tablet strength

Is there data to support the approval of the 60 mg tablet strength?

The Sponsor has requested a biowaiver for the 60 mg strength Org 33062 ER tablets. For a full review please refer to Appendix 5, Section 5.2.2.

The composition of the 60 mg tablet compared to the 20 mg tablet difference in the (b) (4). The difference is (b) (4)% relative to the total weight of the 20 mg tablet. Since this falls within the SUPAC MR level (b) (4) changes for (b) (4), *in vitro* documentation requires dissolution profile comparison in multiple media.

The Sponsor has carried out dissolution testing for all tablet strengths in multiple media (0.01 M HCl, pH 4.5 buffer, pH 6.8 buffer, water, and 0.1 M HCl). The 0.01 N HCl is the medium used in the method that was found acceptable in the OCPB review of the original NDA.

The results of the dissolution profile comparisons of the 20 mg and 60 mg tablet strengths showed f2 values between 50 -100 in each of the media tested. In addition the f1 values were between 0-15 in all cases. For the 40 and 80 mg tablets, the f1 and f2 test results were also in acceptable ranges, in comparison to the 20 mg strength tablets, in all media.

A biowaiver can be granted for the 60 mg strength tablets based on similarity of the *in vitro* dissolution profiles in multiple media in comparison to the 20 mg strength tablet. In addition, the 40 and 80 mg strength tablets showed similarity in all *in vitro* dissolution conditions to the 20 mg strength tablets.

The studies for the biowaiver were performed with the original biconvex tablet shape. Subsequently, the Sponsor change the shape of the tablets from biconvex to flat. In order to be acceptable for commercial use, a comparative dissolution study should be performed. Such a study was performed for the 20 and 80 mg strengths, but not for the proposed 40 and 60 mg strengths. Please see section 3.2.8 for a review of these and other changes in the drug product, and resulting recommendations.

3.2.3 Verapamil Interaction Study (Study 28724)

What effect does an intermediate inhibitor of CYP3A4 have on Org 33062 pharmacokinetics?

The Sponsor has submitted the results of Study 28724 that evaluated the effect of verapamil, an intermediate inhibitor of CCYP3A4, on the pharmacokinetics of Org 33062 in healthy male subjects ages 21-44 years old. This study was an open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study design with multiple doses of verapamil and single doses of Org 33062, as shown in Table 1, below.

Treatment Sequence and Dosing Schedule in Study 28724

Sequence Number	***Treatment Period 1***	**Treatment Period 2**
1	20 mg Org 33062 (Day 1)	Verapamil 80 mg tid x 9 days (Days 8-16) plus 20 mg Org 33062 on Day 15
2	Verapamil 80 mg tid x 9 days (Day-7 to Day 2) plus 20 mg Org 33062 on Day 1	20 mg Org 33062 (Day 15)

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3’-OH-gepirone, and 1-PP are shown in the Tables below.

Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28724)

	Test (Gepirone + Verapamil) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Gepirone		
tmax (hr)a	2.50 (1.0-8.0)	6.00 (2.0-24.0)
Cmax (ng/mL)	7.9 (35)	3.0 (43)
AUC 0-24 (ng*h/mL)	105.4 (37)	40.4 (43)
AUC 0-∞ (ng*hr/mL)	142.1 (38)	50.0 (43)
Cl apparent oral (L/hr)	165.5 (46)	485.3 (48)
t ½ (hr)	8.3 (53)	6.7 (60)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	8.00 (4.0-24.0)	7.0 (4.0-18.0)
Cmax (ng/mL)	8.3 (32)	8.6 (27)
AUC 0-24 (ng*h/mL)	148.3 (29)	142.5 (24)
AUC 0-∞ (ng*hr/mL)	263.5 (30)	207.4 (31)
Cl apparent oral (L/hr)	86.3 (50)	107.1 (36)
t ½ (hr)	14.0 (76)	10.6 (34)
1-PP		
tmax (hr)a	5.5 (4.0-24.0)	5.0 (3.0-12.0)
Cmax (ng/mL)	2.3 (49)	2.4 (39)
AUC 0-24 (ng*h/mL)	32.9 (45)	35.3 (49)
AUC 0-∞ (ng*hr/mL)	53.8(49)	49.6 (59)
Cl apparent oral (L/hr)	472.9 (52)	524.9 (50)
t ½ (hr)	15.5 (114)	10.1 (49)

a median (range)

These results show a greater than two-fold increase in systemic exposure to gepirone (approximately 163% increase in Cmax and in AUC), with an approximate 65% decrease in apparent oral clearance following co-administration of gepirone with verapamil. The 90% confidence intervals (2.237-3.149 for Cmax, 2.193 to 3.199 for AUC) indicate a significant interaction. A shortening of the tmax was also observed. There was little change in exposure to either of the metabolites.

This study demonstrated a significant pharmacokinetic interaction between gepirone and verapamil, resulting in significantly increased exposure to gepirone.

3.2.4 In Vivo CYP3A4 Induction Study (Study 28705)

Can the metabolism of gepirone via CYP3A4 be induced?

The Sponsor evaluated whether gepirone CYP3A4-mediated metabolism could be induced by assessing the effect of multiple oral dosing of rifampicin (a known CYP3A4 inducer) on the steady state pharmacokinetics of Org 33062 and its metabolites. This study was an open-label, randomized, multiple dose, 2-period, 2-treatment, 2-sequence crossover study design with multiple doses of rifampicin and multiple doses of Org 33062, as shown in the Table below. There was a washout of at least 4 weeks between

the 2 treatment periods. The Study was performed in 27 healthy male and female subjects ages 22-45 years old.

Treatment Sequence and Dosing Schedule in Study 28724

Sequence Number	Treatment Period 1	**Treatment Period 2**
1	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) **(Reference, Treatment A)**	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) 600 mg rifampicin daily (Days 1-8) **(Test, Treatment B)**
2	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) 600 mg rifampicin daily (Days 1-8) **(Test, Treatment B)**	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) **(Reference, Treatment A)**

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3'-OH-gepirone, and 1-PP are shown in the Tables below.

Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28705)

	Test (Gepirone + Rifampicin) (% CV) n=24	**Reference (Gepirone)** (% CV) n=24
Gepirone		
tmax (hr)a	4.00 (0.50-24.0)	4.00 (1.00-10.00)
Cmax (ng/mL)	0.7 (110)	10.6 (46)
AUC 0-24 (ng*h/mL)	6.7 (105)	137.6 (48)
Cl apparent oral (L/hr)	13618.7 (103)	332.2 (52)
Cminav(ng/mL)	0.2 (134)	2.8 (71)
Cav(ng/mL)	0.3 (105)	5.7 (48)
Degree of Fluctuation (%)	232.2 (69)	145.6 (31)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	3.5 (3.0-10.0)	6.0 (3.0-10.0)
Cmax (ng/mL)	10.0 (38)	24.2 (36)
AUC 0-24 (ng*h/mL)	134.5 (41)	388.3 (32)
Cl apparent oral (L/hr)	307.0 (35)	102.6 (32)
Cminav(ng/mL)	2.8 (51)	9.6 (46)
Cav(ng/mL)	5.6 (41)	16.2 (32)
Degree of Fluctuation (%)	134.2 (23)	94.1 (38)
1-PP		
tmax (hr)a	3.0 (1.0-10.0)	4.0 (3.0-10.0)
Cmax (ng/mL)	6.7 (44)	6.8 (36)
AUC 0-24 (ng*h/mL)	93.3 (54)	102.0 (46)
Cl apparent oral (L/hr)	514.2 (53)	431.6 (44)
Cminav(ng/mL)	1.8 (58)	2.0 (60)
Cav(ng/mL)	3.9 (54)	4.2 (46)
Degree of Fluctuation (%)	136.2 (26)	120.8 (26)

a median (range)

These results show a decrease in exposure to gepirone of approximately 20-fold and 29-fold as determined by Cmax and AUC, respectively, after exposure to rifampin, with an approximate 29-fold increase in apparent oral clearance. There were also decreases in exposure observed for the 3'-OH gepirone metabolite (an approximate 2.5-fold decrease in Cmax, a 2.9-fold decrease in AUC, and a 2.9-fold increase in apparent oral clearance), but much smaller changes were observed for the 1-PP metabolite. The 90% confidence intervals (0.037 to 0.07 for Cmax, 0.024 to 0.048 for AUC, and 19.6 to 43.9 for Cl) indicate a significant interaction.

Co-administration of gepirone with rifampin resulted in significantly reduced exposure to gepirone that could result in therapeutic failure. Similar reduction in gepirone exposure is expected with other potent CYP3A4 inducers.

Does gepirone inhibit or induce CYP3A4?

The ratio of 6β-hydroxycoritsol to free cortisol in urine was used as a marker for CYP3A4 activity, in which a higher ratio would indicate higher CYP3A4 activity. For this evaluation there were 20 evaluable subjects with complete data. For Gepirone alone,

the point estimate for the ratio of post/pre-treatment (Day 7/8: Day -1/1) is 1.03 (90% confidence interval 0.85-1.26). For gepirone + rifampin the point estimate for the ratio of post/pre-treatment is 4.62 (90% confidence interval 3.83-5.57). These results confirm that induction occurred in the presence of rifampin, and suggest that gepirone alone did not induce CYP3A4. However, the dose of gepirone used was not the maximal planned dose of gepirone, and therefore an effect at a higher dose cannot be ruled out.

3.2.5 In Vivo Paroxetine-Mediated CYP2D6 inhibition Study (Study 28703)

Can a potent CYP2D6 inhibitor (paroxetine) result in significantly increased exposure when co-administered with Org 33062?

Study 28703 evaluated the effects of multiple oral dosing of paroxetine on the steady state pharmacokinetics of Org 33062 and vice versa. This study was double-blind, multiple oral dose, randomized, three-period cross-over pharmacokinetic interaction trial of Org 33062 and paroxetine. The study was performed in 30 healthy male and female subjects from 20-45 years old who were extensive metabolizers of CYP2D6. The treatments were as follows:

Treatment A: oral administration of 20 mg Org 33062 once daily on Days 1 and 2, 40 mg Org 33062 once daily on Days 3 to 8 and paroxetine placebo Days 1-9

Treatment B: oral administration of 20 mg paroxetine once daily on Days 1-9 Org 33062 placebo on Days 1-8

Treatment C: oral administration of 20 mg Org 33062 once daily on Days 1 and 2, 40 mg Org 33062 once daily on Days 3-8 and 20 mg paroxetine once daily on Days 1-9.

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3'-OH-gepirone, and 1-PP are shown in the Table below.

Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28703)

	Test (Gepirone + Paroxetine) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Gepirone		
tmax (hr)a	4.5 (1.0-5.0)	3.0 (0.5-8.0)
Cmax (ng/mL)	10.1 (53)	9.7 (57)
AUC 0-24 (ng*h/mL)	121.6 (52)	124.4 (56)
Cl apparent oral (L/hr)	398.7 (58)	410.7 (83)
Cminav(ng/mL)	2.9 (59)	2.8 (76)
Cssav(ng/mL)	5.1 (52)	5.2 (56)
Degree of Fluctuation (%)	148.5 (30)	155.1 (42)
t ½ (hr)	11.3 (61)	8.3 (84)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	5.0 (2.0-8.0)	5.0 (2.0-12.0)
Cmax (ng/mL)	34.3 (28)	28.2 (23)
AUC 0-24 (ng*h/mL)	551.1 (31)	460.4 (26)
Cl apparent oral (L/hr)	73.0 (35)	85.7 (34)
Cminav(ng/mL)	15.1 (40)	11.9 (34)
Cssav (ng/mL)	23.0 (31)	19.2 (26)
Degree of Fluctuation (%)	90.0 (24)	92.9 (25)
t ½ (hr)	18.4 (64)	12.3 (49)
1-PP		
tmax (hr)a	5.0 (2.0-8.0)	4.0 (2.0-8.0)
Cmax (ng/mL)	23.2 (32)	9.3 (45)
AUC 0-24 (ng*h/mL)	137.1 (35)	75.9 (57)
Cl apparent oral (L/hr)	107.3 (48)	348.2 (51)
Cminav(ng/mL)	10.8 (43)	2.9 (67)
Cssav (ng/mL)	16.5 (35)	5.6 (57)
Degree of Fluctuation (%)	82.3 (23)	130.3 (28)
t ½ (hr)	16.1 (56)	8.1 (38)

a median (range)

The inhibitory effect of paroxetine on CYP2D6 was confirmed by the change in CYP2D6 phenotype (assessed by dextromethorphan/dextrorphan urinary ratio). These results show no significant impact of paroxetine on exposure to gepirone or 3'OH-gepirone. However, an approximate 2.6-fold (155%) increase in Cmax and an approximate 3.12-fold (195%) increase in the AUC for the 1-PP metabolite is observed (90% confidence intervals 2.31 to 2.89 and 2.74 to 3.55, respectively), with an approximate 3-fold (69%) decrease in apparent oral clearance and an approximate 4-fold (270%) increase in $Cmin_{avg}$ for that metabolite. It is also noted that the mean t1/2 for gepirone, 1-PP, and Org 25907 were prolonged 1.6, 1.9, and 1.4 times, respectively after exposure to paroxetine. The clinical relevance of this interaction is unknown.

Does Org 33062 inhibit CYP2D6?

The pharmacokinetics of paroxetine after co-administration with Org 33062 in Study 28703 are shown below.

Pharmacokinetic parameters (arithmetic mean) for paroxetine (Study 28703)

	Test (Gepirone + Paroxetine) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Paroxetine		
tmax (hr)a	4.5 (3.0-8.0)	4.0 (3.0-8.0)
Cmax (ng/mL)	54.1 (49)	56.0 (51)
AUC 0-24 (ng*h/mL)	874.2 (58)	913.0 (59)
Cl apparent oral (L/hr)	42.6 (120)	39.0 (106)
Cminav(ng/mL)	27.9 (66)	29.4 (63)
Cssav (ng/mL)	29.4 (58)	38.0 (59)
Degree of Fluctuation (%)	101.1 (65)	93.7 (71)

a median (range)

This study indicates that gepirone at a 40 mg dose does not inhibit the metabolism of paroxetine, a CYP2D6 substrate. The results (no inhibition) are consistent with *in vitro* studies showing no inhibition of CYP2D6 by gepirone, and suggest that gepirone will not alter the metabolism of drugs metabolized by CYP2D6 when used at this dose. However, the dose of Org 33062 selected was not optimal for showing an inhibitory effect on CYP2D6 as this is not the maximum planned dose.

3.2.6 Other In Vivo Drug-Interaction Studies

Are there any other in vivo drug-drug interaction studies that indicate the exposure to Org 33062 when given alone is different when drugs are co-administered?

The Sponsor has conducted drug-drug interaction study to investigate the effect of Org 33062 on glibenclamide pharmacodynamics and pharmacokinetics (and on glycemic control), to investigate the effect of multiple doses of Org 33062 on steady state pharmacokinetics of lithium, and to study the effect of multiple oral doses of Org 33062 on steady state pharmacodynamics of warfarin.

Glibenclamide (glyburide) – The Sponsor has evaluated the effect of Org 33062 on insulin sensitivity in eighteen Type II diabetic patients before and after administration of multiple doses of Org 33062 (40 mg daily). Insulin sensitivity index (mean glucose infusion rate/((steady state insulin concentration)*(mean blood glucose)) was the outcome measured in a test using the hyperinsulinemic, euglycemic clamp technique. No statistically significant difference between Org 33062 and placebo were demonstrated. In addition, in sixteen subjects with Type II diabetes taking individually adjusted glibenclamide at an unchanged dose for at least 3 months, there was little change in glucose tolerance (as measured by an oral glucose tolerance test) following 60day administration of 40 mg daily Org 33062.

Glibenclamide pharmacokinetics were evaluated before and after administration of Org 33062 in the 16 patients who had the oral glucose tolerance test. There was an approximate 20% decrease in Cmax and AUC for glibenclamide after exposure to Org

33062. In some cases the reduction was up to 50%, whereas some subjects had little change. This resulted in a 90% confidence interval for the ratio of geometric means of 0.668-0.954. Since the 40 mg dose used in this study is considered to be a minimally effective dose, and the dose could be titrated to 80 mg, the 40 mg dose used in this study may not be clinically relevant, and the results cannot rule out an effect at the higher doses that may be used clinically.

Lithium - The sponsor has evaluated the effect of multiple oral doses of Org 33062 (40 mg daily) on the steady state pharmacokinetics of lithium in twelve healthy male subjects. In addition, the effect o multiple doses of lithium on steady state pharmacokinetics was evaluated. Lithium was titrated over a 3-day period to a dose of 600 mg bid, and was maintained at that dose for 9 days. Org 40 mg was given on Days 7-10. There was a slight decrease in lithium Cmax (approximately 11%) in the presence of Org 33062. After co-administration of lithium and Org- 33063, there was a slight (<6%) decrease in Cmax and decrease in AUC for gepirone and a slight (<6%) increase in AUC for 1-PP and for 3'-OH-geprione. This suggests no significant pharmacokinetic interaction at a dose of Org 33062 40 mg daily co-administered with lithium. However, as above, since the 40 mg dose of Org 33062 used in this study is considered to be a minimally effective dose, and the dose could be titrated to 80 mg, the 40 mg dose used in this study may not be clinically relevant, and the results cannot rule out a greater effect on lithium pharmacokinetics at the higher doses that may be used clinically.

Warfarin - The Sponsor evaluated the effect of multiple oral doses of Org 33062 (40 mg daily) on steady state pharmacodynamics of orally administered warfarin in sixteen healthy male subjects. The outcome measure was the prothrombin time (PT), standardized and expressed as the International Normalized Ratio (INR). The no effect level (90% confidence interval) was considered by the Sponsor to be in the range of 0.9-1.11. The study showed that gepirone given at a dose of 40 mg daily had no effect on anticoagulation in the presence of warfarin given 5 mg daily. Co-administration of warfarin with Org 33062 caused a < 17% increase in exposure to gepirone and its metabolites. The results do not support dose adjustment for either warfarin or Org 33062 during concomitant therapy. However, the dose of gepirone used was not the maximal planned dose, and an effect at the 80 mg dose cannot be ruled out.

3.2.7 Plasma Concentrations in Pivotal Efficacy Trials

Were plasma concentrations of gepirone or any metabolites measured in the pivotal efficacy trials?

The Sponsor has responded to the question above posed by OCPB in the nonapproval letter. The Sponsor has replied that in two efficacy trials (134-001 and 134-002) trough concentrations were measured during all dosages of 20, 40, 60, and 80 mg in a total of 192 subjects. The findings were as follows:

- The dose normalized concentrations of each analyte were similar across the dose levels (40-60 mg).

- The Sponsor states that dose-normalized trough concentrations did not show any increasing or decreasing trend with time and/or dose.
- No correlation between plasma concentrations of gepirone and 3'-OH gepirone with a subset of efficacy outcomes was found, although a weak but significant inverse correlation was found between plasma concentrations of 1-PP with efficacy outcomes.

3.2.7 Dissolution Justification

Did the Sponsor accept the Agency's recommended dissolution specification?

The Sponsor's original proposed dissolution specifications were:

15-25% at 1 h
40-85% at 5 h
65-86% at 12 h
> (b)(4)% at 20 h

The original data on which the specifications were proposed is shown below (from the 2/19/02) OCPB review of the original NDA.

Table E. Drug Release Profiles of the Validation Batches *vs.* the Reference Product.

% Dissolved						
Control #	Strength, mg	1st Hr	5th Hr	12th Hr	20th Hr	Recovery
98 –013T	20	19	49	77	93	102
0300422	40	21	51	79	94	101
0300423	40	21	51	78	93	100
0300424	60	22	53	81	95	101
0300425	60	22	53	81	95	102
0300468	80	22	53	81	96	101
0300469	80	21	52	81	97	102

The Sponsor was requested to agree to change the dissolution specifications at 12 h and 20 h to 65-85% and > 85% respectively.

In the present submission, the Sponsor proposes to not change the upper limit of the 12-hour specification at this time from 86% to 85%, but to commit to re-evaluate the specification after the manufacture of 20 batches of each strength.

For the 20-hour time point, The Sponsor proposes to change the specification from NLT (b)(4)% to NLT 86%, in order to (b) (4) with the 12-hour specification.

OCPB finds these changes and commitments acceptable.

3.2.8 Changes in the Drug Product Since Original Submission

Are there any changes in the drug product since the original submission that would require additional in vitro or in vitro bioequivalence testing?

The Sponsor has submitted information regarding changes to the drug product. The changes reported by the Sponsor, and resulting requirements for in vitro or in vivo bioequivalence testing are listed below:

- A change to the colorants from red (b) (4) oxide (b) (4), Red (b) (4) Oxide (b) (4), Yellow (b) (4) Oxide (b) (4), or Yellow (b) (4) Oxide (b) (4) to Red (b) (4) Oxide (b) (4) or Yellow (b) (4) Oxide (b) (4)
    - No additional testing needed
- Manufacturer – There are no changes in the manufacturing site for the drug product. There are several changes for test and release facilities that do not require additional in vitro dissolution studies or in vivo BE testing.
- Method of Manufacture – The Sponsor has made a change in the in the building and equipment for the (b) (4) vs new building on (b) (4) for the 20 mg strength tablets.
  This change requires dissolution profile comparison in 3 media in addition to the media in the approved method. The Sponsor has provided the results of dissolution testing as shown in the following table. Dissolution media were 0.01 M HCl (approved media), pH 4.5 buffer solution, pH 6.8 buffer solution, USP Water for Injection, and 0.1 M HCl. Twelve tablets were used for each study and there were multiple sampling times. The results of dissolution profile comparisons are shown in the Table below.

Table 2: Dissolution Results Comparison, Building (b) (4) vs Building (b) (4)

20 mg tablets	Dissolution Media	f_1	f_2
		Criteria 0-15	Criteria 50-100
Lot 0581394 (original) versus Lot 02-014T (proposed)	0.1 M HCl	0.7	97.5
	0.01 M HCl	2.0	88.6
	USP pH 4.5 buffer	0.1	99.9
	USP pH 6.8 buffer	1.2	94.6
	Water for Injection	1.3	94.4

These results suggest that there are no differences between dissolution profiles of Org 33062 ER tablets 20 mg manufactured in the old building on a (b) (4) compared to the new building on a (b) (4).

- Tablet Shape – The proposed commercial tooling results in a change in tablet shape [redacted] (b) (4). The Sponsor conducted a dissolution study to compare the change in the commercial tooling changing from the original biconvex tablet to the modified flat tablets. This change results in a change in [redacted] (b) (4). Dissolution profiles were performed in multiple media. Dissolution profiles were evaluated for only the 20mg and 80 mg tablets. The results (as provided by Sponsor) are shown in the Table below.

Table 3: Dissolution Results Comparing Biconvex and Modified Rectangular (Flat) Tablets

	Dissolution Media	f_1 Criteria 0-15	f_2 Criteria 50-100
20 mg tablets: Lot 02-014T biconvex versus Lot 02-001T/V Flat	0.1 M HCl	1.2	93.0
	0.01 M HCl	3.0	81.4
	USP pH 4.5 buffer	1.0	94.8
	USP pH 6.8 buffer	2.5	86.8
	Water for Injection	2.2	85.4
80 mg tablets: Lot 02-001T/I biconvex versus Lot 02-001T/IV Flat	0.1 M HCl	1.9	87.6
	0.01 M HCl	1.0	93.8
	USP pH 4.5 buffer	3.0	81.8
	USP pH 6.8 buffer	1.9	90.0
	Water for Injection	2.3	85.2

The results suggest that there is no difference between dissolution profiles when the two tablet shapes are compared for the 20mg and 80 mg strengths. However, the Sponsor claims that due to similarity of the formulations and manufacturing processes for all tablet strengths, these data are representative of all strengths and should be considered to bracket 40 mg and 60 mg tablets.

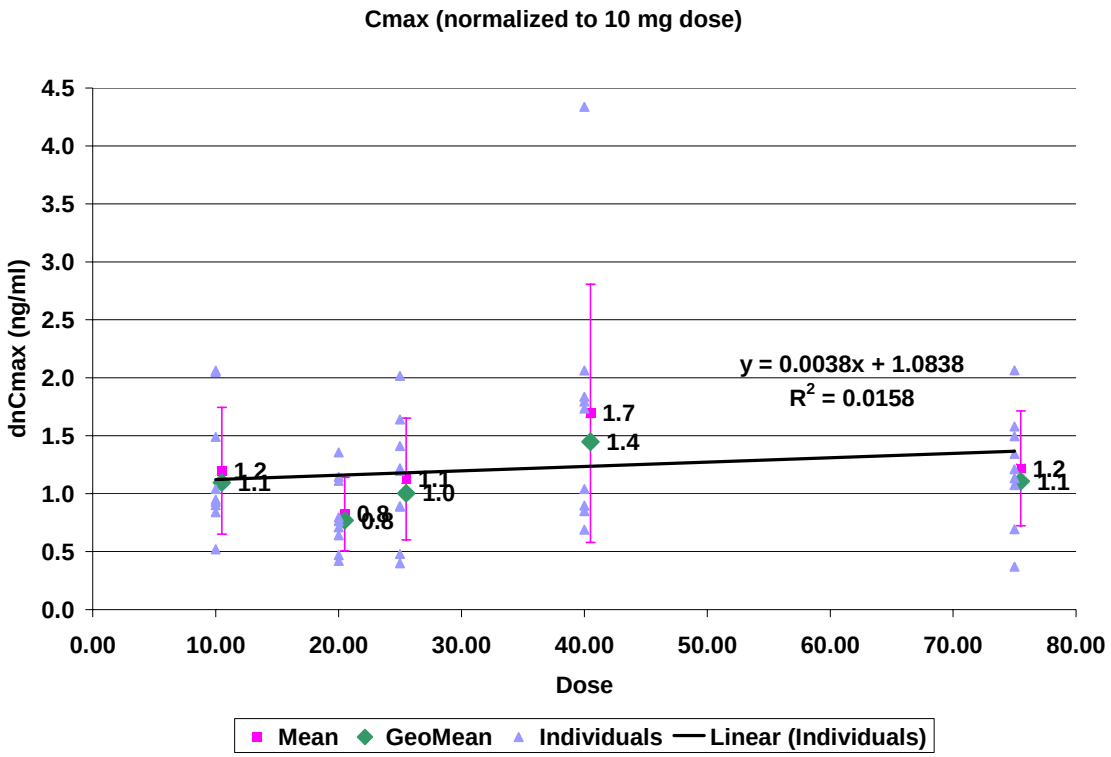
Because the *in vitro* testing provides support for product performance in lieu of an in vivo study, the requirement for dissolution studies with the 40 mg and 60 mg tablet strengths cannot be waived. Therefore, only the 20 and 80 mg strengths can be considered approvable until the Sponsor provides data for the 40 and 60 mg strengths.

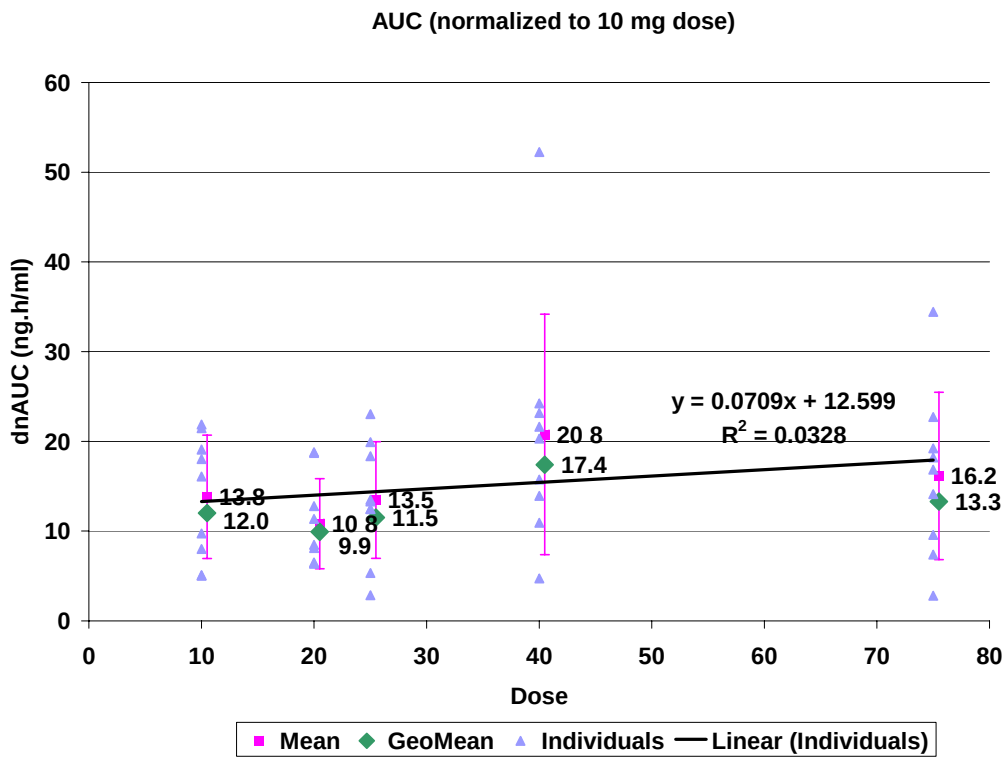
- Scale-Up Process Related Changes – Change of batch size is a factor of 3.
  - There is no additional *in vitro* or *in vivo* requirement.

3.2.8 *Dose linearity*

Has linear PK been demonstrated for Org 33062 ER tablets?

Re-analysis of data submitted in the original NDA submission (Protocol CN105-049) suggests a linear relationship for Cmax and AUC over the dosage range of 20-80 mg following a single dose. This analysis is shown below.


Cmax (normalized to 10 mg dose)
dnCmax (ng/ml)
Dose
y = 0.0038x + 1.0838
R2 = 0.0158
1.2
1.1
0.8
0.8
1.1
1.0
1.7
1.4
1.2
1.1
Mean
GeoMean
Individuals
Linear (Individuals)


AUC (normalized to 10 mg dose)
dnAUC (ng.h/ml)
Dose
y = 0.0709x + 12.599
R2 = 0.0328
13.8
12.0
10 8
9.9
13.5
11.5
20 8
17.4
16.2
13.3
Mean
GeoMean
Individuals
Linear (Individuals)

3.3 Recommendations

The Sponsor has provided studies or justification to address the recommendations of the Office of Clinical Pharmacology and Biopharmaceutics that were identified in the not approvable letter. Although the Sponsor's responses were generally acceptable, there are several recently identified issues regarding the pharmacokinetics as well as recent changes in the drug product that are of some concern.

- The 20 and 80 mg strength tablets (with the modified flat tablet shape) are acceptable, but the 40 and 80 mg strength tablets (with the modified flat tablet shape) are not acceptable.

  The nonequivalence of the 40 and 80 mg strength tablets compared to the approved 20 mg strength of gepirone would most likely have little impact on the adverse event profile. A biowaiver for the 60 mg strength as originally manufactured could be granted. However, the Sponsor has now changed the tablet shape with a change in commercial tooling from the original biconvex tablet to the modified flat tablets. Dissolution has only been evaluated for the 20 mg and 80 mg strength tablets. Therefore the 40 and 60 mg strength tablets (with the modified flat tablet shape) are not considered approvable at this time.

    - The Sponsor should submit results of dissolution comparisons (of the original vs. modified shape) in multiple media with f2 comparisons to request a biowaiver for the 40 and 60 mg strength tablets.

- The Sponsor's proposed dissolution specifications are acceptable on an interim basis. The dissolution specifications are as follows:

  15-25% at 1 h
  40-85% at 5 h
  65-86% at 12 h
  > 86% at 20 h

  These specifications are acceptable provided that the Sponsor adheres to the stated commitment to re-evaluate the specification at 12 hours after the manufacture of 20 batches of each strength.

1.2 Recommended Phase 4 Study Commitments

- The effect of intermediate inducers such as rifabutin should be evaluated as a Phase IV commitment.
- The Sponsor has previously agreed to conduct an *in vivo* study evaluating the effects of different meal compositions on gepirone ER pharmacokinetics as a Phase IV commitment and states that the study has been initiated.

- The Sponsor has stated a commitment to re-evaluate the specification at 12 hours after the manufacture of 20 batches of each strength.

The proposed labeling is acceptable from the OCPB perspective provided that the Sponsor make the recommended changes. Labeling comments can be found in section 4.

Comments to Medical Officer (do not send to Sponsor)

- In the original submission, a significant pharmacokinetic interaction was observed between ketoconazole, a potent inhibitor of CYP3A4, and gepirone (a 5-fold increase in gepirone AUC). To minimize the risk of toxicity, we recommend that coadministration with ketoconazole or other potent inhibitors of CYP3A4 be considered as a warning.

- A significant pharmacokinetic interaction was observed between gepirone and rifampin, a potent inducer of CYP3A4 (a 20-fold decrease in Cmax and a 29-fold decrease in AUC for gepirone). Because of the risk of reduced efficacy, we recommend that coadministration with rifampin and other potent inducers should be contraindicated.

- A significant pharmacokinetic interaction was observed between gepirone and verapamil, an intermediate inhibitor of CYP3A4 (a 2.6 fold increase in Cmax and AUC was observed). To minimize the risk of toxicity, when verapamil and gepirone are co-administered, gepirone should be used cautiously. A low dose of gepirone is recommended with subsequent dosage adjustment based on clinical assessment. We recommend that the dose of gepirone in these patients not exceed 40 mg/day.

- As noted in the original submission, gepirone concentrations are increased 50-80% in the elderly. However, exposure depends on other factors as well (such as race for which there is a 1.5-2-fold decrease in AUC in Blacks and Asians compared to Caucasians). To minimize the risk of toxicity in the elderly we recommend that dosing in each patient should be individualized. Dosing of gepirone in the elderly should be started at the lowest strength and (b) (4) .

- In the original submission it was noted that plasma concentrations of gepirone and its metabolites were elevated by approximately 70% in patients with moderate and severe renal impairment. To minimize the risk of toxicity in patients with moderate or severe renal impairment we recommend that dosing in each patient should be individualized. Dosing of gepirone in patients with moderate or severe renal impairment should be started at the lowest strength and (b) (4).

- In the original submission it was noted that gepirone exposure is augmented 2-fold in patients with moderately impaired hepatic function. To minimize the risk

of toxicity, gepirone should be used cautiously in patients with moderately impaired hepatic function. A low dose of gepirone is recommended with subsequent dosage adjustment based on clinical assessment. We recommend that the dose of gepirone in these patients not exceed 40 mg/day.

- The pharmacokinetics of gepirone have not been adequately studied in patients with severe hepatic impairment. Therefore we recommend that the drug not be administered in this population and that there should be a warning or a contraindication regarding use of gepirone in this population.

4 Detailed Labeling Recommendations

(***Note***: only the Clinical Pharmacology sections have been reviewed. Changes are in track changes. See also notes to medical officer from OCPB in bold italics).

(b) (4)

73 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

5.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review

5.2.1 Sponsor's Approach to Justification for Approval of the 40 and 80 mg Strength Tablets

Background

The sponsor requested approval of the 40, 60, and 80 mg Org 33062 ER tablets even though the 40 mg and 80 mg tablets failed to meet bioequivalence to the 2 x 20 mg and 4 x 20 mg ER tablets. The sponsor claims that the increased plasma concentrations observed from the 1 x 80 mg ER tablets are not clinically relevant. The sponsor's claim was based on the following evidence:

1. Plasma concentration-AE relationship in healthy subjects
2. Dose-AE relationship in patients with depression

Plasma concentration-AE relationship in healthy subjects

The sponsor conducted an analysis to determine the relationship between the exposure parameters (Cmax, AUC) and the intensity of AE in healthy male subjects. Data for this analysis came from studies 28717 and 28718.

> Study 28717 was an open-label, randomized, single and multiple dose, three treatment, two period crossover study in 25 healthy male subjects. Each subject received a single 40 mg dose on day 1 followed by repeat dosing every 24 hours until steady state concentrations were achieved (Treatment A). Each subject also received multiple doses of 200 mg ketoconazole every 12 hours for 3 days followed by a single dose of either 20 mg (treatment B) or 40 mg (treatment C) gepirone.
>
> Study 28718 was an open-label, randomized, single dose, four-way crossover study in 32 healthy male subjects. Each subject received 1) 1 x 80 mg, 2) 4 x 20 mg, 3) 1 x 40 mg, and 4) 2 x 20 mg ER tablets in 4-way crossover design separated by 7-day washout period.

To investigate the relationship between exposure parameters and AE intensity from these studies, the sponsor compared the descriptive statistics of parameter values for subjects who experienced dizziness, nausea, and vomiting to those subjects who did not have an AE. Data was pooled by study day, i.e., single dose vs. steady state.

The results showed that for study 28717 there was a positive relationship between exposure parameters and AE intensity for dizziness and nausea. A descriptive summary for parameter values and AE intensity for dizziness is shown in Table 1.

Table 3 Mean (SD) values for Cmax and AUC by AE intensity for dizziness (Study 28717)

PARAMETER	NO AE (N = 14)	AE INTENSITY		
		Mild (N = 12)	Moderate (N = 8)	Severe (N = 14)
Cmax, ng/mL	8.29 (4.92)	9.30 (6.83)	21.1 (11.5)	26.4 (9.4)
AUC, ng.h/mL	143 (111)	184 (179)	387 (248)	425 (119)

Plasma concentrations were lower in study 28718 since subjects received single doses of either 40 mg or 80 mg gepirone and there were a lower number of AEs. Consequently, a clear relationship between exposure parameters and AE intensity could not be made (* Note: these data are independent of dose or presence or absence of ketoconazole

APPEARS THIS WAY ON ORIGINAL

Table 2).

Table 2 Mean (SD) values for C_{max} and AUC by AE intensity for dizziness (study 28718)

PARAMETER	NO AE (N=75)	AE INTENSITY		
		Mild (N =42)	Moderate (N = 6)	Severe (N = 0)
Cmax, ng/mL	6.37 (5.36)	9.71 (5.94)	6.0 (3.41)	na
AUC, ng.h/mL	96.1 (67.1)	142 (87.1)	81.7 (55.9)	na

The sponsor made the following conclusions:

1. The results of study 28718 showed lower Cmax and AUC values compared with values observed in study 28717 at comparable AE intensities.
2. .For the same given dose, 2 x 20 mg ER tablets, exposure parameters were approximately 40% lower in study 28718 (Table 3).

Table 3 Mean (SD) values for C_{max} and AUC for studies 28717 and 28718 following single dose administration of 2 x 20 mg ER tablets

Parameter	Study 28717 (N = 24)	Study 28718 (N = 32)	% Difference
Cmax, ng/mL	7.18 (3.74)	4.15 (1.95)	42%
AUC, ng.h/mL	109 (53.2)	64.1 (29.1)	41%

3. Based on these results, it can be concluded that a 30% increase in Cmax and AUC for subjects not experiencing AEs will not lead to a moderate or severe AE intensity. Therefore, a bioequivalence acceptance range of (b) (4) to (b) (4) might be appropriate for BE studies with gepirone.

Dose-AE relationship in patients with depression

The sponsor conducted an analysis to investigate the relationship between dose and adverse events. A logistic regression model was fit to AE data collected in 8 clinical trials in patients with depression. The six adverse events included in the model were dizziness, headache, insomnia, nausea, nervousness, and somnolence. The doses of gepirone ranged from 20 to 80 mg across studies.

The final model was used to predict the increased risk for a given AE due to a 17% increase in exposure when switching from 4 x 20 mg to 1 x 80 mg ER tablets. This was accomplished by evaluating the risk of a particular AE for a 93.6 mg dose, which was calculated as the "exposure equivalent" dose to the 1 x 80 mg dosage strength. The logistic regression model predicted a 7% increase in dizziness and less than 3% increase for insomnia and nausea.

Reviewer's Comments

The reviewer concurs with the sponsor that the nonequivalence of the to-be-marketed dosage strengths compared to the approved 20 mg dosage strength of gepirone will most likely have little impact on the adverse event profile. Based on plasma concentration observed in the phase 1 studies, the highest exposure to drug occurred in study 28717 during the concomitant administration of a single dose of 40 mg (2 x 20 mg) ER tablets with 200 mg ketoconazole (Table 4). In that treatment group, 100 % of the subjects experienced dizziness, 92% experienced nausea and 67% vomited. The Cmax values for this treatment group ranged from 17.3–42.8 ng/ml. In comparison, co-administration of 20 mg gepirone with 200 mg ketoconazole resulted in greater than 50% of subjects experiencing dizziness and nausea and 8% of subjects vomited.

Table 4 Descriptive summary of Cmax values stratified by incidence of AE and dose in healthy subjects in study 28717

AE	Treatment	Experienced AE?	% Subjects (N=12)	Cmax Range
Dizziness	20 mg + Keto	Yes	83%	8.98-34.9
	20 mg + Keto	No	17%	7.49-22.9
	40 mg + Keto	Yes	100%	17.3-42.8
	40 mg + Keto	No	0	--
Nausea	20 mg + Keto	Yes	58%	8.98-34.9
	20 mg + Keto	No	42%	7.49-30.4
	40 mg + Keto	Yes	92%	17.3-42.8
	40 mg + Keto	No	8%	32.4
Vomiting	20 mg + Keto	Yes	8%	25.2
	20 mg + Keto	No	92%	8.89-34.9
	40 mg + Keto	Yes	67%	17.3-41.3
	40 mg + Keto	No	33%	24.8-42.8

A plot of the mean (±sd) concentration-time profiles for 1 x 80 mg and 4 x 20 mg ER tablets administered as a single dose to 32 healthy males (study 28718) shows that both

profiles fall within the range of concentrations known to cause AEs (Figure 1). Furthermore, the plot shows that the variability for both formulations is comparable, even at peak concentrations.

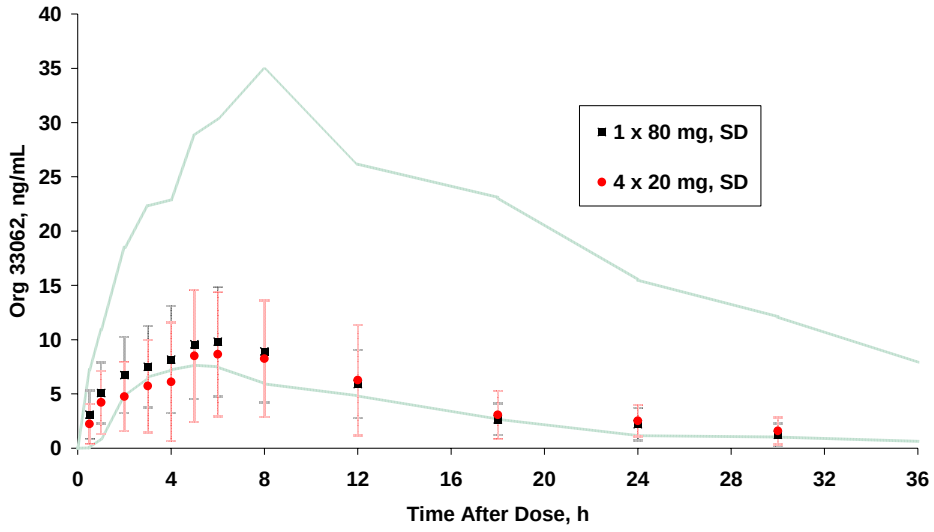


Figure 2 Mean (SD) concentration-time data from a single dose of 1 x 80 mg vs. 4 x 20 mg gepirone compared to the range of observed concentrations from a single dose of 20 mg gepirone co-administered with 200 mg ketoconazole.

Since gepirone will be used to treat a chronic condition, the difference between the two formulations at steady-state is more clinically relevant than the differences following a single dose. Nonparametric superposition was used to simulate the mean steady-state concentrations for the 1 x 80 mg and 4 x 20 mg ER tablets (Figure 2). Predicted steady state concentrations for each formulation are very similar, with mean peak concentrations of 11.1 ng/ml for the 1 x 80 mg tablets and 10.4 ng/ml for the 2 x 40 mg tablets. Total exposures, as measured by AUC over the dosing interval, for each formulation are 153 ng.h/ml and 155 ng.h/ml, respectively.

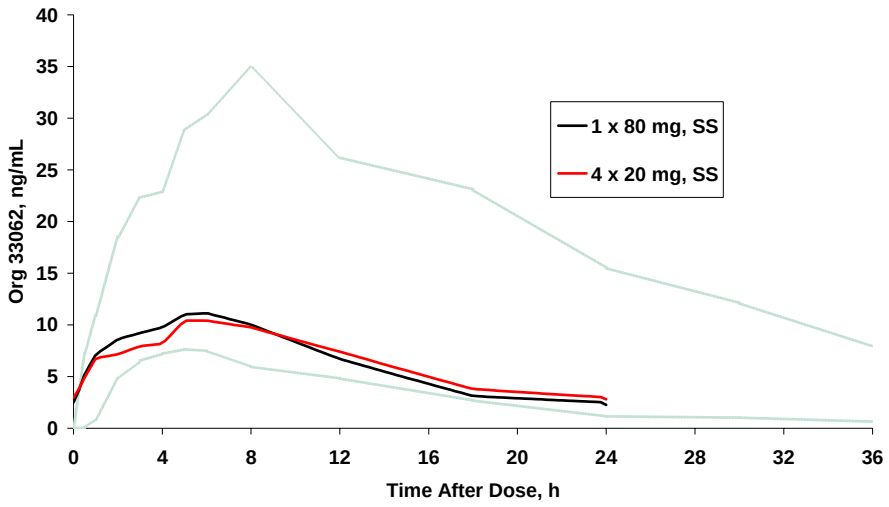


Figure 2. Simulated mean concentration-time data from multiple doses of 1 x 80 mg vs. 4 x 20 mg gepirone compared to the range of observed concentrations from a single dose of 20 mg gepirone co-administered with 200 mg ketoconazole.

Conclusions:

OCPB concurs with the Sponsor that the nonequivalence of the to-be-marketed strengths compared to the approved 20 mg strength of gepirone will most likely have little impact on the adverse event profile. Thus 80 mg strength can be considered approvable. In addition, since the 40 mg strength is bracketed by the 20 and 80 mg strengths, it can also be considered approvable.

5.2.2 Request for biowaiver for 60 mg strength tablets

The Sponsor has requested a biowaiver for the 60 mg strength Org 33062 ER Tablets.

The composition of all strengths of Org 33062 ER Tablets is shown in the table below. The tablets are the same dosage form, with the same release mechanism.

		Tablet Strength			
Ingredient (mg/tablet)	Function	20 mg	40 mg	60 mg	80 mg
Org 33062, gepirone HCl		20	40	60	80
Microcrystalline cellulose	(b) (4)				
Hypromellose					
Iron oxide (b) (4), red	Colorant	(b) (4)			
Iron oxide (b) (4), yellow	Colorant				
Colloidal silicon dioxide	(b) (4)				
Magnesium stearate					
Total					

It can be seen that active and inactive ingredients are not in exactly the same proportion. For the 60 mg tablet compared to the 20 mg tablet, the difference in (b) (4) is (b) (4)% relative to the total weight of the 20 mg tablet. This falls within the SUPAC MR Level (b) (4) changes for (b) (4). *In vitro* documentation requires dissolution profile comparison in multiple media.

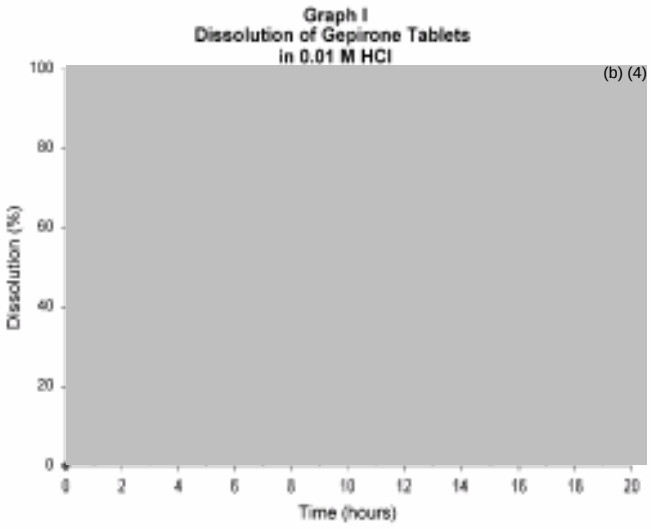
The Sponsor has provided dissolution profile comparison of all strengths of Org 33062 ER tablets in multiple media as shown below. Dissolution testing, using 12 tablets for each study, was carried out using USP Apparatus II (paddle) 50 rpm in 900 ml using the following media: 0.01 M HCl, pH 4.5 buffer, pH 6.8 buffer, water, and 0.1 M HCl. (The apparatus, volume, and rotation speed conform to the approved method). Gepirone was detected by UV spectrophotometry.

The lot numbers used in these studies are shown below:

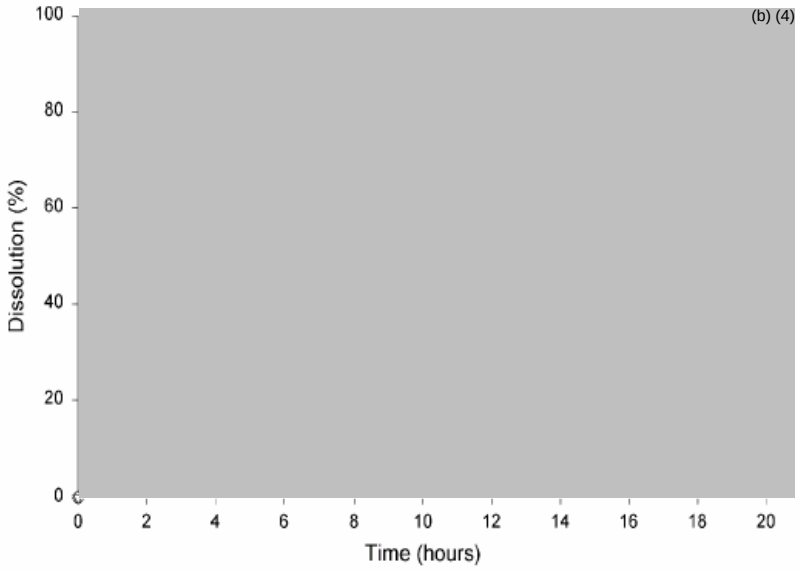
Lot #	Strength	Batch Size	Clinical Study
051394	20 mg	(b) (4)	28718 (BE), 28708 (PK)
0300423	40 mg		28718 (BE)
0300424	60 mg		none
0300468	80 mg		28718 (BE)

The dissolution profiles in each media are shown below. A review of the graphic representation of the mean dissolution profiles for the test (20 mg tablet) and reference (60 mg tablet) products as well as the 40 and 80 mg strength tablets in the five media suggest similarity of the profiles in multiple media. In 0.01 M HCl, in pH 4.5 buffer, and in water the curves for the 60 mg and 80 mg strengths are practically super-imposable and cannot be distinguished from each other.

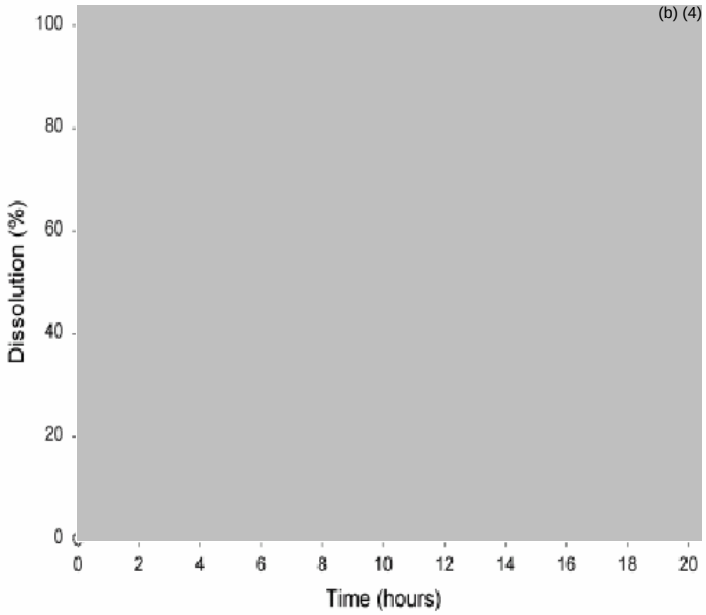
Figure I : Dissolution profile data for the Org 33062 20mg, 40mg, 60mg and 80mg ER Tablets in 0.01 M HCl.

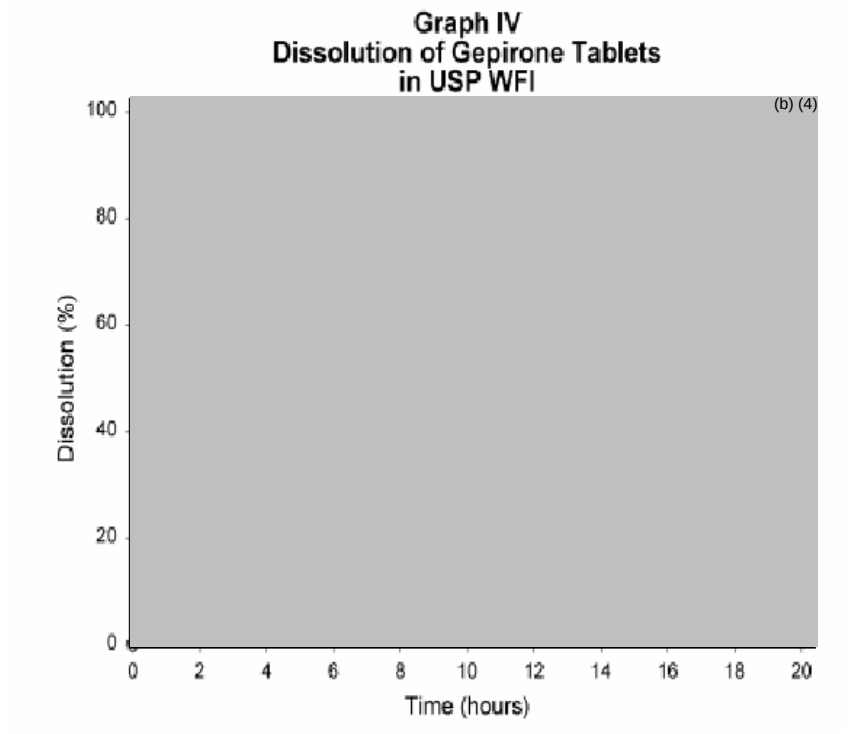


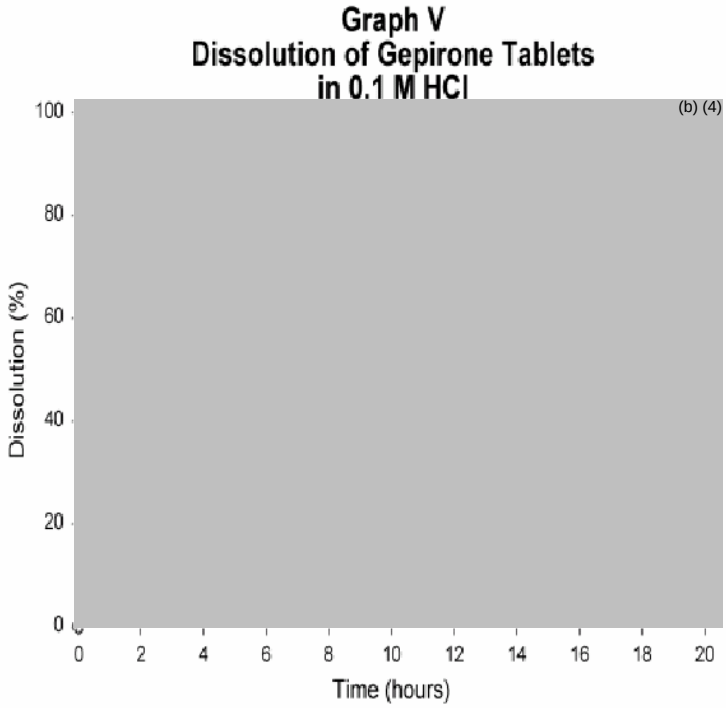
Graph II
Dissolution of Gepirone Tablets
in USP Buffer @ pH 4.5



Graph III
Dissolution of Gepirone Tablets
in USP Buffer @ pH 6.8




Graph IV
Dissolution of Gepirone Tablets
in USP WFI
(b) (4)
Dissolution (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
Time (hours)


Graph V
Dissolution of Gepirone Tablets
in 0.1 M HCl
(b) (4)
Dissolution (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
Time (hours)

Dissolution profiles for test (60 mg) and reference (20 mg) tablets were compared using the similarity factor (f2). Dissolution profiles for the 40 and 80 mg tablets were similarly compared to the 20 mg tablet. For each profile, the coefficient of variation was less than 10%, allowing for use of mean data.

The results of the dissolution profile comparisons of the 20 mg and 60 mg tablet strengths showed f2 values between 50 -100 in each of the media tested. In addition the f1 values were between 0-15 in all cases. For the 40 and 80 mg tablets, the f1 and f2 test results were also in acceptable ranges, in comparison to the 20 mg strength tablets, in all media.

Conclusions:

A biowaiver can be granted for the 60 mg strength tablets based on similarity of the *in vitro* dissolution profiles in multiple media in comparison to the 20 mg strength tablet. In addition, the 40 and 80 mg strength tablets showed similarity in all *in vitro* dissolution conditions to the 20 mg strength tablets.

5.2.3 Verapamil Interaction Study (Study 28724)

A RANDOMIZED TWO-WAY CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF VERAPAMIL CO-ADMINISTRATION ON ORG33062 PHARMACOKINETICS

Study Investigators and Site:

A. Schrödter, Dr. med.
FOCUS Clinical Drug Development, GmbH

Neuss, Germany

Protocol Number: 28724

OBJECTIVES:

To study the effect of verapamil co-administration on the pharmacokinetics of Org 33062.

FORMULATIONS:

Table 1. Products used in 28724

	Package Lot Number	Batch Lot Number	Expiration Date (Dates of Study)
Org 33062 20 mg extended release tablets (N.V. Organon, OSS, The Netherlands))	PW110	CW 033	01/2005 (August 26, 2002 – October 23, 2002)
ISOPTIN 80 mg tablets (Abbott, Wiesbaden, Germany)	-	47556	12/2006 (August 26, 2002 – October 23, 2002)

STUDY DESIGN:

This study was an open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study design with multiple doses of verapamil and single doses of Org 33062, as shown in Table 2, below. For Sequence 1, subjects received a single oral dose of 20 mg Org 33062 ER on Day 1 (with blood samples drawn for 48 hours after dosing on Days 1-2). Days 3-7 were a wash out period. Verapamil 80 mg tid was then dosed for 9 days (Day 8-16) and Org 33062 20 mg ER was co-administered on Day 15. For Sequence 2, subjects received verapamil 80 mg tid for 9 days (starting at Day -7) and Org 33062 ER was co-administered on Day 1 (with blood samples drawn from 48 hours after dosing on

Days 1-2). After a 12-day washout period (Days 3-14), Org 33062 20 mg ER was administered on Day 15.

Table 2. Treatment Sequence and Dosing Schedule in 28724

Sequence Number	Treatment Period 1	Treatment Period 2
1	20 mg Org 33062 (Day 1)	Verapamil 80 mg tid x 9 days (Days 8-16) plus 20 mg Org 33062 on Day 15
2	Verapamil 80 mg tid x 9 days (Day-7 to Day 2) plus 20 mg Org 33062 on Day 1	20 mg Org 33062 (Day 15)

Inclusion criteria included healthy male Caucasian subjects 18-45 y.o. Subjects were to smoke < 10 cigarettes/day and be able to refrain from smoking during the in-house period. Subjects were to refrain from use of methylxanthines from 48 hours prior to the first dose to after the last pharmacokinetic sample, and refrain from grapefruit-containing products from 7 days before the 1st dose to after the last pharmacokinetic sample. Exclusion criteria included the use of any drug or substance known to induce drug metabolizing enzymes within 1 month prior to the 1st dose, and any substance known to inhibit drug metabolizing enzymes or any drug within 1 week prior to the 1st dose (except for acetaminophen).

Subjects were fasted from 10 hours prior to the dose of Org 33062 until 4 hours after dosing. Blood samples were collected at fixed times and plasma stored at –20° C. In each sequence blood samples were collected for determination of gepirone, 3′-OH-gepirone, and 1-PP pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36, and 48 hours after dosing of Org 33062. Twenty-four hour urine collection was performed on Days 1 and 15 of each Sequence for determination of 6β-hydroxycortisol and free cortisol.

ASSAY:

The assay was performed at Organon according to the established bioanalytical methods.

Table 3. Performance of Analytical Method for 28724

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Gepirone	LC/MS/MS	0.1-50 ng/ml	r > 0.995	0.1 ng/ml	0.3 ng/ml 5.0 ng/ml 40 ng/ml	7.4 10.8 3.9	8.7 5.4 -8.8
Org 25907	LC/MS/MS	0.2-50 ng/ml	r > 0.996	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/m	8.8 10.0 5.7	8.0 -5.8 -2.8
1-PP	LC/MS/MS	0.2-50 ng/ml	r > 0.995	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/ml	9.3 8.9 8.3	-7.2 -3.6 0.7

The selectivity of the assay with respect to verapamil demonstrated no significant interference with the assay, according to the Sponsor.

The assay deviated from the method in that the samples were for gepirone and Org 25907 were dissolved in 20:80 acetonitrile/0.05 M ammonium acetate solution pH 4.2 instead of 50:50 acetonitrile 0/05 M ammonium acetate solution pH 4.2 as described in the protocol. Two calibration curves and triplicate QC samples were analyzed with each batch of study samples. Linearity was demonstrated in the calibration curves as shown in the table above. For gepirone and Org 25907 at least 75% of the standards from each run fell within 15% of the nominal value. For one run for 1-PP, duplicate samples for 2 of the standards (0.5 and 1.0 ng/ml) were rejected, as were single samples from the 2.0 and 5.0 ng/ml samples, such that < 75% of the samples fell within 15% of the nominal concentration. However, the accuracy and precision were acceptable for the remaining samples.

Samples were analyzed within the period for which the samples are stable. The performance of the assays for all analytes is considered acceptable.

RESULTS:

Demographics

Thirty-one subjects (healthy male Caucasians) were enrolled in the study. The mean age of the subjects was 31.3 years of age, and the range was 21 to 44 years old. Twenty-eight subjects completed the entire study and were eligible for pharmacokinetic analysis. Two subjects were withdrawn due to noncompliance and 1 subject discontinued prematurely because of a tooth infection requiring co-medication. Demographics of the subjects completing the study are shown below.

Table 4. Demographics of Subjects Completing the Study

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
32 (21-44)	Male	75.14 ± 9.8 kg (n=28)	Caucasian

Pharmacokinetics

The plasma concentration time course profiles for gepirone, 3/-OH-gepirone, and 1-PP are shown in the figures below. Each figure shows the pertinent analyte in the presence or absence of verapamil (mean values).

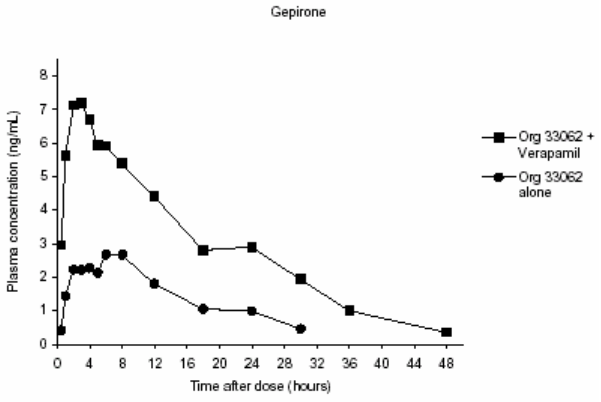


Figure 1 Mean concentration-versus-time profiles for gepirone

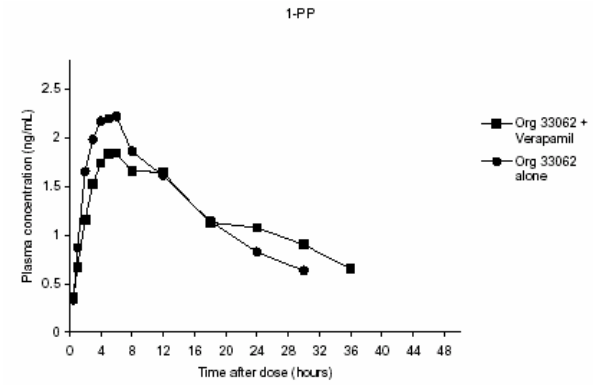


Figure 2 Mean concentration-versus-time profiles for 1-PP

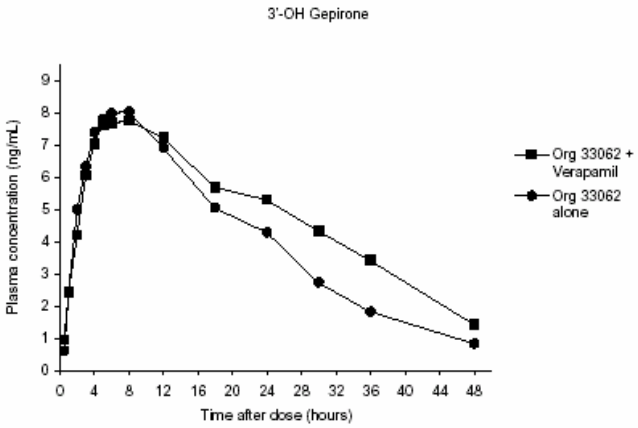


Figure 3 Mean concentration-versus-time profiles for 3'-OH-gepirone

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3'-OH-gepirone, and 1-PP are shown in the Tables 5 and 6, below.

Table 5. Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28724)

	Test (Gepirone + Verapamil) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Gepirone		
tmax (hr)a	2.50 (1.0-8.0)	6.00 (2.0-24.0)
Cmax (ng/mL)	7.9 (35)	3.0 (43)
AUC 0-24 (ng*h/mL)	105.4 (37)	40.4 (43)
AUC 0-∞ (ng*hr/mL)	142.1 (38)	50.0 (43)
Cl apparent oral (L/hr)	165.5 (46)	485.3 (48)
t ½ (hr)	8.3 (53)	6.7 (60)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	8.00 (4.0-24.0)	7.0 (4.0-18.0)
Cmax (ng/mL)	8.3 (32)	8.6 (27)
AUC 0-24 (ng*h/mL)	148.3 (29)	142.5 (24)
AUC 0-∞ (ng*hr/mL)	263.5 (30)	207.4 (31)
Cl apparent oral (L/hr)	86.3 (50)	107.1 (36)
t ½ (hr)	14.0 (76)	10.6 (34)
1-PP		
tmax (hr)a	5.5 (4.0-24.0)	5.0 (3.0-12.0)
Cmax (ng/mL)	2.3 (49)	2.4 (39)
AUC 0-24 (ng*h/mL)	32.9 (45)	35.3 (49)
AUC 0-∞ (ng*hr/mL)	53.8(49)	49.6 (59)
Cl apparent oral (L/hr)	472.9 (52)	524.9 (50)
t ½ (hr)	15.5 (114)	10.1 (49)

[a] median (range)

Table 6. Interaction Assessment for Study 28724

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Meansa
	Reference	Test		
Gepirone				
Cmax (ng/mL)	2.80	7.42	2.654	(2.237, 3.149)
AUC 0-24 (ng*h/mL)	37.0	98.0	2.649	(2.193, 3.199)
AUC 0-∞ (ng*hr/mL)	45.6	131.7	2.891	(2.382, 3.508)
Cl apparent oral (L/hr)	439.0	151.8	0.346	(0.285, 0.420)
t ½ (hr)	5.8	7.5	1.290	(1.037, 1.605)
Org 25907 (3'-OH gepirone)				
Cmax (ng/mL)	8.3	7.9	0.955	(0.83, 1.09)
AUC 0-24 (ng*h/mL)	138.3	141.3	1.022	(0.89, 1.17)
AUC 0-∞ (ng*hr/mL)	197.3	249.8	1.266	(1.09, 1.47)
Cl apparent oral (L/hr)	101.4	80.1	0.790	(0.67, 0.92)
t ½ (hr)	10.1	12.2	1.199	(1.01, 1.43)
1-PP				
Cmax (ng/mL)	2.23	2.05	0.92	(0.77, 1.10)
AUC 0-24 (ng*h/mL)	32.0	29.8	0.93	(0.76, 1.14)
AUC 0-∞ (ng*hr/mL)	43.1	47.8	1.11	(0.88, 1.40)
Cl apparent oral (L/hr)	463.6	418.7	0.90	(0.71, 1.14)
t ½ (hr)	9.1	12.4	1.36	(1.08, 1.70)

[a] as calculated by reviewer

These results show a greater than two-fold increase in systemic exposure to gepirone (approximately 163% increase in Cmax and in AUC), with an approximate 65% decrease in apparent oral clearance following co-administration of gepirone with verapamil. A shortening of the tmax was also observed. There was little change in exposure to either of the metabolites.

Safety

Fourteen of 31 subjects eligible for the safety analysis reported adverse events. The most prominent adverse events were dizziness and headache. The majority of adverse events were reported during the verapamil dosing phase with headache and dizziness most frequently observed. Headache and dizziness were also reported after Org 33062 alone, and these were the only adverse effects reported with Org 33062 alone. Incidence of headache increased when Org 33062 was given with verapamil, compared to when Org 33062 was given alone. Adverse events of toothache, upper respiratory tract infection, and increased sweating were not considered to be drug-related. The Sponsor states that there were no clinically significant abnormal laboratory values, vital signs, or changes in ECG. The Sponsor states that gepirone given alone or with verapamil was well tolerated in this study.

CONCLUSIONS:

This study demonstrated a significant pharmacokinetic interaction between gepirone and verapamil, resulting in significantly increased exposure (163%) to gepirone.

5.2.4 Rifampin Interaction Study

AN OPEN LABEL, MULTIPLE ORAL DOSE STUDY TO ASSESS THE EFFECT OF THE CYP3A4 ENZYME INDUCER RIFAMPICINE ON THE PHARMACOKINETICS OF ORG 33062 ER IN HEALTHY VOLUNTEERS

Study Investigators and Site:
A. Port
FOCUS Clinical Drug Development, GmbH
Neuss, Germany

Protocol Number: 28705

OBJECTIVES:

The primary objective was to assess the effect of multiple oral dosing of rifampicin (rifampicin) (CYP3A4 induction) on the steady state pharmacokinetics of Org 33062 and its main metabolites 1-PP and 3'-OH-gepirone. The secondary objective was to assess the safety and tolerability of multiple oral doses of Org 33062, given alone and in combination with rifampicin.

FORMULATIONS:

Table 1. Products used in 28705

	Package Lot Number	Batch Lot Number	Expiration Date (Dates of Study)
Org 33062 20 mg extended release tablets (b) (4)	PV114	01-007T	03/04 (August 2001 – December 2001)
Rifampicin 600 mg dragees (RIFADIN, Hoechst Marion Roussel B.V.; Hoevelaken, The Netherlands)	PV136	A0008	07/04 (August 2001 – December 2001)

STUDY DESIGN:
This study was an open-label, randomized, multiple dose, 2-period, 2-treatment, 2-sequence crossover study design with multiple doses of rifampicin and multiple doses of Org 33062, as shown in Table 1, below. There was a washout of at least 4 weeks between the 2 treatment periods.

Table 2. Treatment Sequence and Dosing Schedule in 28724

Sequence Number	Treatment Period 1	Treatment Period 2
1	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) (Reference, Treatment A)	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) 600 mg rifampicin daily (Days 1-8) (Test, Treatment B)
2	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) 600 mg rifampicin daily (Days 1-8) (Test, Treatment B)	20 mg Org 33062 (Days 1 and 2) 40 mg Org 33062 daily (Days 3-7) (Reference, Treatment A)

Inclusion criteria included healthy male or female subjects 18-45 y.o. Subjects were to be nonsmokers for at least 3 months. Subjects were to be extensive metabolizers of CYP2D6 (as determined phenotyping with sparteine at least one week prior to the first dose). Exclusion criteria included medication or drug use of any kind within 2 weeks of the first dosing (except for acetaminophen and sparteine (that was used for phenotyping)) or within 1 month prior to the first dosing with any agent known to induce or inhibit drug metabolizing enzymes (e.g. rifampicin, cimetidine, ketoconazole, phenytoin, macrolides, and compounds in the barbiturate and phenothiazine classes). Consumption of alcohol, caffeine, and other methylxanthines was not allowed from 48 hours prior to the first dosing on day 1 until the last pharmacokinetic blood sampling during each study period. Consumption of St. John's wort and grapefruit containing products was not allowed from 10 days prior to the first dosing on Day 1 until the last pharmacokinetic blood sampling during each study period.

Subjects were dosed between 8AM and 10AM each morning, without having had breakfast. On Day 7, the dose was administered after a 10 hour overnight fast, with fasting continued until at least 4 hours after dosing (except for a light snack of toast with butter/marmalade and orange juice) at 2 hours post dose). Blood samples were collected at fixed times and plasma stored at –20° C. Blood samples were collected for determination of gepirone, 3′-OH-gepirone, and 1-PP pre-dose on days 1, 5, 6, and 7 and at 0.5, 1, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, 36, and 48 hours after dosing on day 7. Twenty-four hour urine collection was performed on Days -1 and 7 of each trial period and stored at -20° C for determination of 6β-hydroxycortisol and free cortisol.

ASSAY:

The assay for gepirone, 1-PP, and 3'-OH in plasma was performed at Organon according to the established bioanalytical methods (Organon R&D RR NL0031235 and Organon R&D RR NL0030691).

Table 3. Performance of Analytical Method for 28705

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Gepirone	LC/MS/MS	0.1-50 ng/ml	r > 0.991	0.1 ng/ml	0.3 ng/ml 5.0 ng/ml 40 ng/ml	7.0 7.7 8.7	13.3 4.2 -7.8
Org 25907	LC/MS/MS	0.2-50 ng/ml	r > 0.994	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/m	13.2 8.8 6.6	3.8 -5.0 -9.5
1-PP	LC/MS/MS	0.2-50 ng/ml	r > 0.997	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/ml	7.8 4.5 5.2	4.7 -1.2 1.3

The selectivity of the assay with respect to rifampicin demonstrated no significant interference with the assay, according to the Sponsor.

Two calibration curves and triplicate QC samples (at a minimum) were analyzed with each batch of study samples. Linearity was demonstrated in the calibration curves as shown in the table above. For gepirone in 1 run, both calibration standards for the highest concentration fell below 15% of the nominal concentration and in that run at least 6 standards (but less than 75% of the standards) fell within 15% of the nominal value. In a second run, both calibration standards for the highest concentration fell below 15% of the nominal concentration (although in that case 75% of the standards fell within 15% of the nominal value. The maximum concentration detected in any sample did not exceed 23.1; the calibration standard just below 50 ng/ml was 20 ng/ml. (It should be noted that the Sponsor's acceptance criteria for the calibration curves included accuracy of between (b) (4) % of nominal concentrations, and the curves were acceptable to the Sponsor based on these criteria). For Org 25907 and 1-PP at least 75% of the standards from each run fell within 15% of the nominal value. The values for the samples for gepirone and its metabolites fell within the values of the respective standard curve.

Samples were analyzed within the 13-month period in which the samples are stable.

The performance of the assays for all analytes is acceptable.

The assay for 6B-hydroxycortisol and free cortisol in urine was performed at (b) (4) .

Table 4. Performance of Analytical Method for 28705 for 6β-hydroxycoritsol and free cortisol in urine

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
6β-hydroxycortisol	HPLC	17.3-1041 ng/ml	r > 0.999	15 ng/ml	40.8 204 815	1.1 4.4 7.1	-3.4 -5.4 0.7
Free cortisol	HPLC	17.6-527 ng/ml	r > 0.999	10.4 ng/ml	52.2 208.86 522	5.3 1.3 17.8	0 -2.3 -8.8

One calibration curve and duplicate QC samples were analyzed with each batch of study samples. For 6-β-hydroxycortisol the calibration standards fell within 15% of the nominal concentration (except for 1 standard in 1 run that was within 16%). For free cortisol the calibration standards all fell within 15% of the nominal values. The QC samples for 6-β-hydroxycortisol were acceptable. In one run for free cortisol both the high QC samples fell outside of 15% of the nominal value. However, since the actual values for the experimental samples fell within the low and medium QC samples, the Sponsor considered this run to be acceptable.

There was no information provided on the stability of the samples. The samples were analyzed within 6 months of beginning the clinical study.

RESULTS:

Demographics

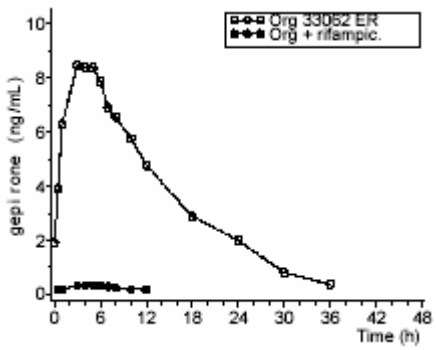
Twenty-seven subjects (22 male and 5 female) were enrolled in the study. Three male subjects discontinued and were replaced. Twenty-four subjects completed the study and were eligible for pharmacokinetic analysis. Of the three subjects who withdrew from the study, 1 subject discontinued due to adverse effects (dizziness, headache, and disorientation) on day 4 of study period 1 (treatment A), 1 subject was withdrawn due to a protocol violation, and 1 subject discontinued after completion of trial period 1 (treatment B) due to abnormal high laboratory values (AST and ALT) that subsequently returned to normal ranges. The mean age of subjects enrolled in the study was 33 years of age, and the range was 22 to 45 years old. Demographics of the subjects completing the study are shown below.

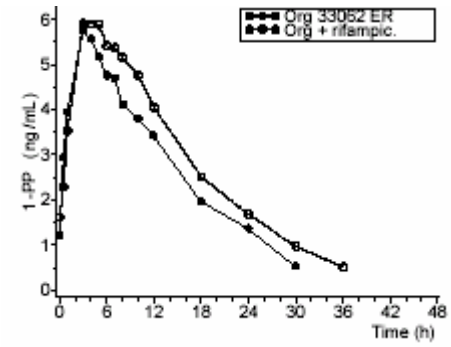
Table 4. Demographics of Subjects Completing the Study

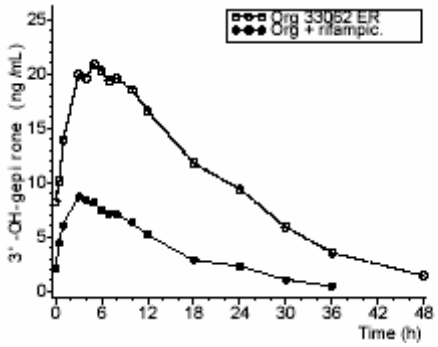
Mean Age (Range)	Gender	Weight (mean ± SD)	Race
33 (25-45)	19 Males 5 Females	76.7 ± 11.5 kg (n=24) 80.2 ± 9.8 kg (male) 63 ± 5.7 kg (female)	Caucasian

Pharmacokinetics

Attainment of steady state was demonstrated for Org 33062. The plasma concentration time course profiles for gepirone, 3'-OH-gepirone, and 1-PP after the dose on Day 7 are shown in the figures below, as provided by the Sponsor. Each figure shows the pertinent analyte in the presence or absence of rifampicin (geometric mean values).







Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3'-OH-gepirone, and 1-PP are shown in the Tables 5 and 6, below.

Table 5. Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28705)

	Test (Gepirone + Rifampicin) (% CV) n=24	**Reference (Gepirone)** (% CV) n=24
Gepirone		
tmax (hr)a	4.00 (0.50-24.0)	4.00 (1.00-10.00)
Cmax (ng/mL)	0.7 (110)	10.6 (46)
AUC 0-24 (ng*h/mL)	6.7 (105)	137.6 (48)
Cl apparent oral (L/hr)	13618.7 (103)	332.2 (52)
Cminav(ng/mL)	0.2 (134)	2.8 (71)
Cav(ng/mL)	0.3 (105)	5.7 (48)
Degree of Fluctuation (%)	232.2 (69)	145.6 (31)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	3.5 (3.0-10.0)	6.0 (3.0-10.0)
Cmax (ng/mL)	10.0 (38)	24.2 (36)
AUC 0-24 (ng*h/mL)	134.5 (41)	388.3 (32)
Cl apparent oral (L/hr)	307.0 (35)	102.6 (32)
Cminav(ng/mL)	2.8 (51)	9.6 (46)
Cav(ng/mL)	5.6 (41)	16.2 (32)
Degree of Fluctuation (%)	134.2 (23)	94.1 (38)
1-PP		
tmax (hr)a	3.0 (1.0-10.0)	4.0 (3.0-10.0)
Cmax (ng/mL)	6.7 (44)	6.8 (36)
AUC 0-24 (ng*h/mL)	93.3 (54)	102.0 (46)
Cl apparent oral (L/hr)	514.2 (53)	431.6 (44)
Cminav(ng/mL)	1.8 (58)	2.0 (60)
Cav(ng/mL)	3.9 (54)	4.2 (46)
Degree of Fluctuation (%)	136.2 (26)	120.8 (26)

[a] median (range)

Table 6. Interaction Assessment for Study 28705

	Geometric Mean		**Ratio of Geometric Means**	**90% CI for the Ratio of Geometric Means[a]**
	Reference	**Test**		
Gepirone				
Cmax (ng/mL)	9.63	0.49	0.051	(0.037-0.07)
AUC 0-24 (ng*h/mL)	123	4.19	0.034	(0.024-0.048)
Cl apparent oral (L/hr)	295	8663	29.4	(19.6-43.9)
Org 25907 (3'-OH gepirone)				
Cmax (ng/mL)	23.0	9.3	0.40	(0.37-0.45)
AUC 0-24 (ng*h/mL)	370.8	125.7	0.34	(0.30-0.38)
Cl apparent oral (L/hr)	97.9	289.0	2.95	(2.59-3.36)
1-PP				
Cmax (ng/mL)	6.4	6.0	0.94	(0.86-1.04)
AUC 0-24 (ng*h/mL)	92.5	81.1	0.88	(0.77-1.00)
Cl apparent oral (L/hr)	392.6	447.6	1.14	(0.98-1.33)

[a] as calculated by reviewer

These results show a decrease in exposure to gepirone of approximately 20-fold and 29-fold as determined by Cmax and AUC, respectively, after exposure to rifampin, with an approximate 29-fold increase in apparent oral clearance. There were also decreases in exposure observed for the 3'-OH gepirone metabolite (an approximate 2.5-fold decrease in Cmax, a 2.9-fold decrease in AUC, and a 2.9-fold increase in apparent oral clearance), but much smaller changes were observed for the 1-PP metabolite.

The ratio of 6β-hydroxycoritsol to free cortisol in urine was used as a marker for CYP3A4 activity, in which a higher ratio would indicate higher CYP3A4 activity. For this evaluation there were 20 evaluable subjects with complete data. The results in the evaluable subjects are shown below.

Table 7. Ratio of 6β-hydroxycoritsol to free cortisol in urine) (Study 28705)

	Arithmetic mean (% CV)		**Geometric Mean**	
	Day -1/1	**Day 7/8**	**Day -1/1**	**Day 7/8**
Test (Gepirone + Rifampicin)	4.6 (54)	20.6 (42)	4.1	18.8
Reference (Gepirone)	4.4 (48)	4.2 (35)	3.8	3.9

For Gepirone alone, the point estimate for the ratio of post/pre-treatment (Day 7/8: Day -1/1) is 1.03 (90% confidence interval 0.85-1.26). For gepirone + rifampin the point estimate for the ratio of post/pre-treatment is 4.62 (90% confidence interval 3.83-5.57). These results confirm that induction occurred in the presence of rifampin, and suggest that gepirone alone did not induce CYP3A4.

Safety

All but one subject eligible for safety evaluation (26 subjects who received treatment A and 25 subjects who received treatment B) experienced at least one adverse event after administration of Org 33062 alone or concomitant with rifampicin. This included 88.5% of subjects who received treatment A and 76% of subjects who received treatment B. One subject experienced severe dizziness on Day 4 of period 1 (Treatment A). This subject discontinued due to severe dizziness, mild headache, and mild disorientation. The most prominent adverse events were headache, dizziness, fatigue, diarrhea, and nausea in both reference and test groups. Headache and dizziness were more often reported during treatment with Org 33062 alone, while diarrhea was reported more often with concomitant rifampicin. The dizziness reported with Org 33062 alone was of greater intensity than that with Org 30062 given with rifampicin. One subject had significantly high values of AST and ALT on day 8 of treatment B that returned to the normal range after discontinuation.

CONCLUSIONS:

This study demonstrated a significant pharmacokinetic interaction between gepirone and rifampicin, resulting in significantly reduced exposure to gepirone (more than 20-fold) and its 3'-OH metabolite (more than 2-fold).

5.2.5 Paroxetine Interaction Study

A DOUBLE-BLIND, RANDOMIZED MULTIPLE ORAL DOSE, THREE-WAY CROSS-OVER STUDY TO ASSESS THE PHARMACOKINETIC INTERACTION OF ORG 33062 AND PAROXETINE IN HEALTHY VOLUNTEERS

Study Investigators and Site:
L. Tritsmans, MD
C&T Paradigm NV
Antwerp, Belgium

Protocol Number: 28703

OBJECTIVES:

The primary objective was to assess the effect of multiple oral dosing of paroxetine on the steady state pharmacokinetics of Org 33062 and vice versa. Secondary objectives were to assess the effect of multiple oral dosing of paroxetine on the pharmacodynamics of Org 33062 and vice versa, and to assess the safety and tolerability of multiple oral doses of paroxetine and Org 33062, given separately and in combination.

FORMULATIONS:

Table 1. Products used in 28703

	Batch Lot Number	Expiration Date (Dates of Study)
Org 33062 20 mg extended release tablets ((b) (4))	CV053	03/2004 (June 11, 2001-September 5, 2001)
Paroxetine 20 mg tablet (SmithKline Beecham Laboratoires Pharmaceutiques, France)	CV074	02/2004 (June 11, 2001-September 5, 2001)

STUDY DESIGN:

This study was double-blind, multiple oral dose, randomized, three-period cross-over pharmacokinetic interaction trial of Org 33062 and paroxetine. The treatments were as follows:

Treatment A: oral administration of 20 mg Org 33062 once daily on Days 1 and 2, 40 mg Org 33062 once daily on Days 3 to 8 and paroxetine placebo Days 1-9

Treatment B: oral administration of 20 mg paroxetine once daily on Days 1-9
Org 33062 placebo on Days 1-8

Treatment C: oral administration of 20 mg Org 33062 once daily on Days 1 and 2, 40 mg Org 33062 once daily on Days 3-8 and 20 mg paroxetine once daily on Days 1-9.

The design is shown in Table 1 below (as provided by Sponsor). There was a washout of at least 2 weeks between successive treatment periods.

Sequence	Number of subjects	Treatment		
		Period 1	Period 2	Period 3
1	5	A	B	C
2	5	A	C	B
3	5	B	A	C
4	5	B	C	A
5	5	C	A	B
6	5	C	B	A

Inclusion criteria included healthy male or female subjects 18-45 y.o. Subjects were to be nonsmokers for at least 3 months. Subjects were to be extensive metabolizers of CYP2D6 (as determined by phenotyping with dextromethorphan at least one week prior to the first dose). Exclusion criteria included medication or drug use of any kind within 2 weeks of the first dosing (except for acetaminophen and dextromethorphan (for phenotyping)) or within 1 month prior to the first dosing with any agent known to induce or inhibit drug metabolizing enzymes (e.g. rifampicin, cimetidine, ketoconazole, phenytoin, macrolides, and compounds in the barbiturate and phenothiazine classes). Consumption of alcohol, grapefruit-containing products, and caffeine or other methylxanthines was not allowed from 48 hours prior to the first dosing on Day 1 until the last pharmacokinetic blood sampling in each trial period.

Subjects were dosed between 8AM and 10AM each morning. Breakfast was eaten between 0.5 and 1 hour after dosing, except on Day 8 of each period in which the dose was administered after a 10-hour overnight fast and fasting continued until at least 4 hours after dosing (except for a snack at 2 hours after dosing). Blood samples were collected at fixed times and plasma stored at –20° C. Blood samples were collected for determination of gepirone, 3′-OH-gepirone, and 1-PP as well as paroxetine at pre-dose on days 1, 6, and 7, as well as at pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30, 36, and 48 hours after dosing on Day 8 in each period. Psychopharmacologic effects were to be studied using a visual analogue rating scale that included the following items: alert/drowsy, calm/excited, strong/feeble, muzzy/clear headed, well-coordinated/clumsy, lethargic/energetic, contented/discontented, trouble/tranquil, mentally slow/quick witted, tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/amicable, interested/bored, withdrawn/gregarious. The Visual Analogue Scales were to be completed in each period on Days 1 and 8 at 0, 1, 3, 5, and 8 hours after dosing.

Phenotyping for CYP2D6 was performed at screening more than 1 week prior to the first dose of trial medication in Period 1 and was repeated in the mornings of Day 7 of each period. Subjects were given 30 mg dextromethorphan hydrobromide (Touxium) with 200 ml of water after emptying their bladder for phenotyping for CYP2D6. Urine samples were collected from 0-8 hours post-dose. Urine aliquots were frozen and stored at -86° C until assayed.

ASSAY:

The assay for gepirone, 1-PP, and 3'-OH in plasma was performed at Organon according to the established bioanalytical methods (Organon R&D RR NL0031235 and Organon R&D RR NL0030691).

Table 3. Performance of Analytical Method for 28703

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Gepirone	LC/MS/MS	0.1-50 ng/ml	r > 0.990	0.1 ng/ml	0.3 ng/ml 5.0 ng/ml 40 ng/ml	15.3 8.0 8.0	2.3 5.2 -9.0
Org 25907	LC/MS/MS	0.2-50 ng/ml	r > 0.993	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/m	9.8 11.6 9.4	3.8 2.0 -1.8
1-PP	LC/MS/MS	0.2-50 ng/ml	r > 0.994	0.2 ng/ml	0.6 ng/ml 5.0 ng/ml 40 ng/ml	11.0 7.6 6.0	4.2 -2.4 5.0

The selectivity of the assay with respect to paroxetine demonstrated no significant interference with the assay, according to the Sponsor.

Two calibration curves and triplicate QC samples (at a minimum) were analyzed with each batch of study samples. Linearity was demonstrated in the calibration curves as shown in the table above. For gepirone in 1 run, less than 75% of the standards were acceptable, although linearity was still demonstrated in that curve with r > 0.992. In the 10 remaining runs all standards were acceptable. (It should be noted that the Sponsor's acceptance criteria for the calibration curves included accuracy of between (b) (4) % of nominal, and that the reported runs were considered to be acceptable). For Org 25907 and 1-PP at least 75% of the standards from each run fell within 15% of the nominal value.

For the QC samples for Org 33062 (gepirone) the QC samples were acceptable except in 1 run in which all 3 low QC samples were outside of the 15% acceptance range (although 2of the 3 were within the Sponsor's acceptance range). For that run, the calibration curve was acceptable. For Org 25907 (3'-OH metabolite) 1 run had 4/9 samples that were outside of the acceptance range (although 1 of these was within the Sponsor's acceptance

range). The outlying samples were not all at the same QC concentration, and for that run the calibration curve was acceptable. The QC samples for 1-PP were acceptable.

Samples were analyzed within the 13-month period in which the samples are stable.

The assay for paroxetine was performed at (b) (4) . Only samples up to 24 hour post-dose were analyzed for paroxetine.

Table 4. Performance of Analytical Method for 28703 for Paroxetine in Plasma

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Paroxetine	HPLC	4.87-97.3 ng/ml	r > 0.996	6 ng/ml	20.3 50.8 91.5	12.70 7.62 6.68	-5.4 0.1 3.0

The selectivity of the paroxetine assay with respect to Org 33062 and its two metabolites demonstrated no significant interference with the assay, according to the Sponsor.

One calibration curve and duplicate QC samples were analyzed with each batch of study samples. Linearity (as calculated by reviewer) was demonstrated in the calibration curves as shown in the table above. A minimum of 75% of the calibration standards for paroxetine fell within 15% of the nominal concentration (or 20% for the LLOQ). The QC samples for paroxetine were acceptable, with 4 out of 6 falling within 20% of the nominal value, except in 1 run where both low QC samples fell outside of this range. However, the calibration curve for that run was acceptable. An addition set of QC samples were run as a "1-day validation". In that series, the QC samples ranged from 6.1-91.5 ng/ml. The samples were performed in 6 replicates of each of 4 concentrations had had precision of 3.2-9.7 and accuracy of -7.4 to 1.5%.

The study started in June 2001 and ended in September 2001 and the samples were analyzed from September 20 October 2001. Stability of the samples was not reported.

The assay for dextromethorphan and dextrorphan was performed at (b) (4) . Dextromethorphan and dextrorphan were determined by HPLC with fluorescence detection. When the metabolic ratio is calculated, an antimode of 0.35 separates extensive metabolizers from poor metabolizers.

Table 5. Performance of Analytical Method for 28703 for Dextromethorphan and Dextrorphan in Urine

Analyte	Method	Range (µg/ml)	Linearity	LOQ (µg/ml)	QC (µg/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Dextromethorphan	HPLC	0.01-10 µg/ml	r > 0.9974	0.01 µg/ml	0.025 0.25 5.00	10.5 2.4 2.0	-7.2 -2.5 3.6
Dextrorphan	HPLC	0.025-10 µg/ml	r > 0.9972	0.025 µg/ml	0.05 0.25 5.00	5.8 2.2 2.8	7.9 0.2 4.5

RESULTS:

Demographics

Thirty subjects (10 males and 20 females) were enrolled in the study. These subjects ranged in age from 20-45 years, with an average of 33 years. Two subjects temporarily interrupted treatment due to occurrence of adverse events in Period 1, but they both continued in the next period. However, their treatment was interrupted in Period 1, they were excluded from the pharmacokinetic analysis. Twenty-eight subjects completed the study and were eligible for pharmacokinetic analysis. Demographics of the subjects completing the study are shown below.

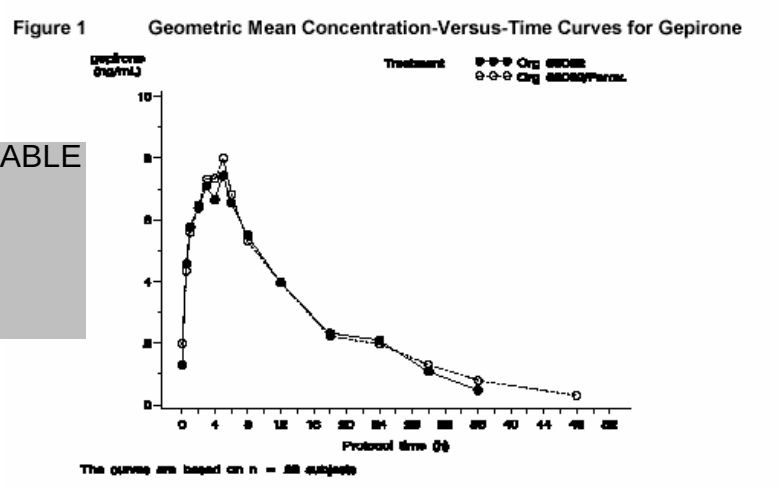
Table 6. Demographics of Subjects Completing the Study

Mean Age (Range)	Gender	Weight (mean ± SD)	Race
33 (20-45)	9 Males 19 Females	70 ± 13 kg (n=28) 82 ± 10 kg (male) 64 ± 11 kg (female)	Caucasian 27 Black 1

Pharmacokinetics

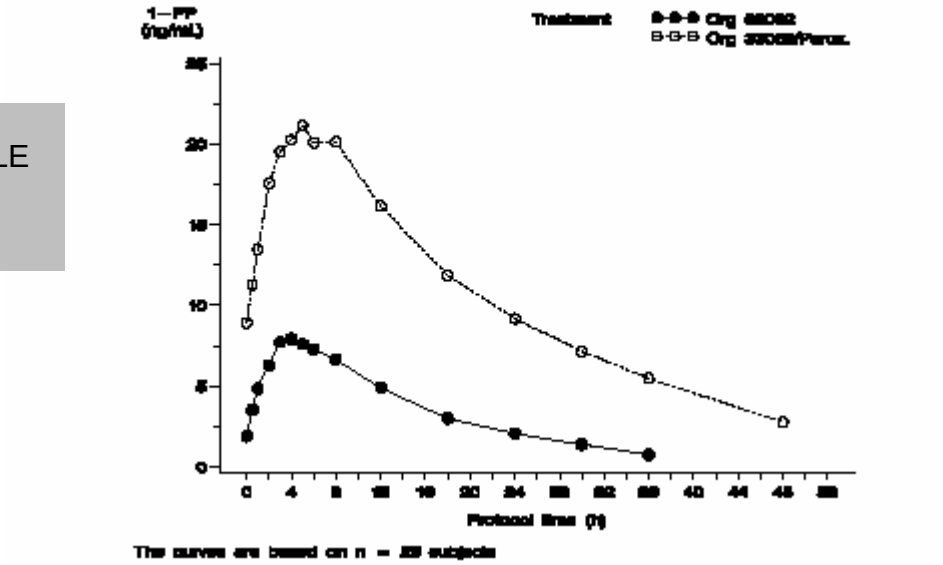
The Sponsor's analysis demonstrated that steady state had been attained by Day 6 for gepirone and its metabolites and by Day 8 for paroxetine. The plasma concentration time course profiles for gepirone, 3'-OH-gepirone, and 1-PP after the dose on Day 8 are shown in the figures below, as provided by the Sponsor. Each figure shows the pertinent analyte in the presence (open circles) or absence (closed circles) of paroxetine (geometric mean values).

Figure 1 Geometric Mean Concentration-Versus-Time Curves for Gepirone



BEST AVAILABLE COPY

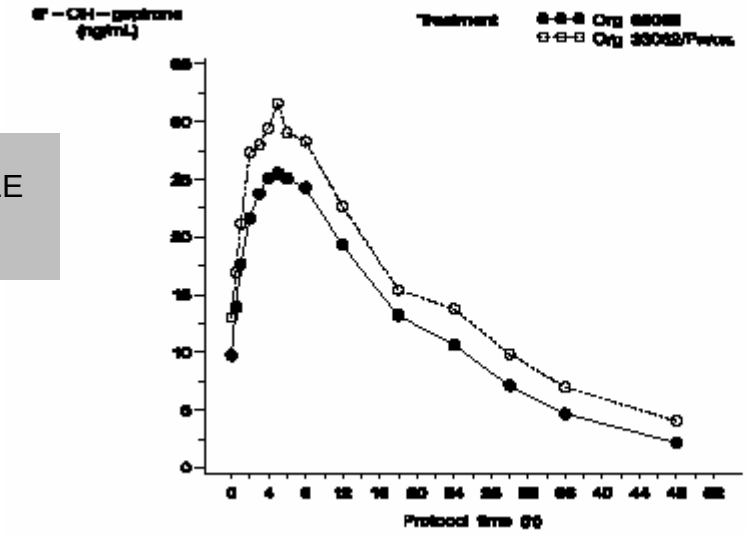
Figure 2 Geometric Mean Concentration-Versus-Time Curves for 1-PP



BEST AVAILABLE COPY

BEST AVAILABLE COPY

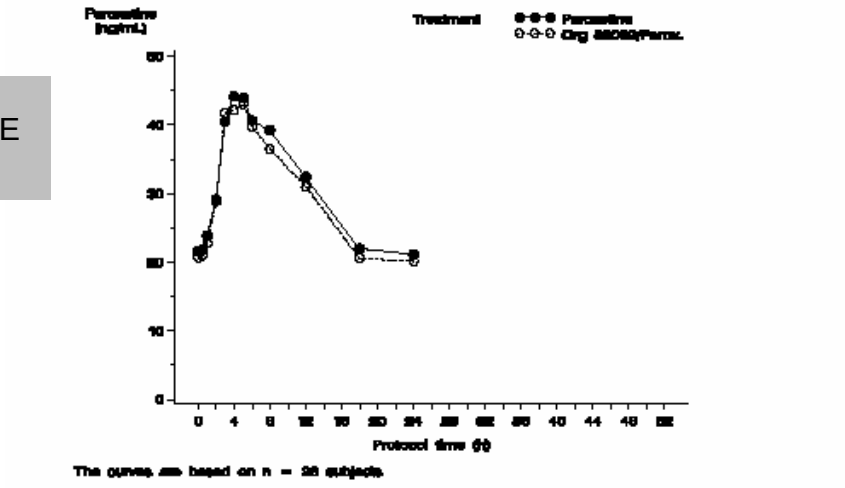
Figure 3 Geometric Mean Concentration-Versus-Time Curves for 3'-OH-gepirone



The curves are based on n = [illegible] subjects

The plasma concentration time course profiles for paroxetine in the presence (open circles) or absence (closed circles) of gepirone (geometric mean values) are shown below.

Figure 4 Geometric Mean Concentration-Versus-Time Curves for Paroxetine



BEST AVAILABLE COPY

Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for gepirone, 3'-OH-gepirone, and 1-PP are shown in the Tables 7 and 8, below.

Table 7. Pharmacokinetic parameters (arithmetic mean) for gepirone and metabolites (Study 28703)

	Test (Gepirone + Paroxetine) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Gepirone		
tmax (hr)a	4.5 (1.0-5.0)	3.0 (0.5-8.0)
Cmax (ng/mL)	10.1 (53)	9.7 (57)
AUC 0-24 (ng*h/mL)	121.6 (52)	124.4 (56)
Cl apparent oral (L/hr)	398.7 (58)	410.7 (83)
Cminav(ng/mL)	2.9 (59)	2.8 (76)
Cssav(ng/mL)	5.1 (52)	5.2 (56)
Degree of Fluctuation (%)	148.5 (30)	155.1 (42)
t ½ (hr)	11.3 (61)	8.3 (84)
Org 25907 (3'-OH gepirone)		
tmax (hr)a	5.0 (2.0-8.0)	5.0 (2.0-12.0)
Cmax (ng/mL)	34.3 (28)	28.2 (23)
AUC 0-24 (ng*h/mL)	551.1 (31)	460.4 (26)
Cl apparent oral (L/hr)	73.0 (35)	85.7 (34)
Cminav(ng/mL)	15.1 (40)	11.9 (34)
Cssav (ng/mL)	23.0 (31)	19.2 (26)
Degree of Fluctuation (%)	90.0 (24)	92.9 (25)
t ½ (hr)	18.4 (64)	12.3 (49)
1-PP		
tmax (hr)a	5.0 (2.0-8.0)	4.0 (2.0-8.0)
Cmax (ng/mL)	23.2 (32)	9.3 (45)
AUC 0-24 (ng*h/mL)	137.1 (35)	75.9 (57)
Cl apparent oral (L/hr)	107.3 (48)	348.2 (51)
Cminav(ng/mL)	10.8 (43)	2.9 (67)
Cssav (ng/mL)	16.5 (35)	5.6 (57)
Degree of Fluctuation (%)	82.3 (23)	130.3 (28)
t ½ (hr)	16.1 (56)	8.1 (38)

[a] median (range)

Table 8. Pharmacokinetic parameters (arithmetic mean) for paroxetine (Study 28703)

	Test (Gepirone + Paroxetine) (% CV) n=28	**Reference (Gepirone)** (% CV) n=28
Paroxetine		
tmax (hr)a	4.5 (3.0-8.0)	4.0 (3.0-8.0)
Cmax (ng/mL)	54.1 (49)	56.0 (51)
AUC 0-24 (ng*h/mL)	874.2 (58)	913.0 (59)
Cl apparent oral (L/hr)	42.6 (120)	39.0 (106)
Cminav(ng/mL)	27.9 (66)	29.4 (63)
Cssav (ng/mL)	29.4 (58)	38.0 (59)
Degree of Fluctuation (%)	101.1 (65)	93.7 (71)

[a] median (range)

Table 9. Interaction Assessment for Study 28703a

	Geometric Mean		Ratio of Geometric Means	90% CI for the Ratio of Geometric Means
	Reference	Test		
Gepirone				
Cmax (ng/mL)	8.6	8.8	1.03	(0.85-1.14)
AUC 0-24 (ng*h/mL)	106.9	105.7	0.99	(0.94-1.14)
Org 25907 (3'-OH gepirone)				
Cmax (ng/mL)	27.4	33.0	1.20	(1.13-1.27)
AUC 0-24 (ng*h/mL)	443.4	524.8	1.18	(1.08-1.28)
1-PP				
Cmax (ng/mL)	8.4	21.9	2.59	(2.31-2.89)
AUC 0-24 (ng*h/mL)	117.8	369.3	3.12	(2.74-3.55)
Paroxetine				
Cmax (ng/mL)	48.5	47.2	0.97	(0.91-1.04)
AUC 0-24 (ng*h/mL)	724.9	691.6	0.95	(0.90-1.01)

[a] as calculated by reviewer

These results show no significant impact of paroxetine on exposure to gepirone or 3'OH-gepirone. However, an approximate 2.6-fold (155%) increase in Cmax and an approximate 3.12-fold (195%) increase in the 1-PP metabolite is observed, with an approximate 3-fold (69%) decrease in apparent oral clearance and an approximate 4-fold (270%) increase in $Cmin_{avg}$ for that metabolite. It is also noted that the mean t1/2 for gepirone, 1-PP, and Org 25907 were prolonged 1.6, 1.9, and 1.4 times, respectively after exposure to paroxetine.

No significant impact of gepirone on exposure to paroxetine is observed.

Effect of Treatment on CYP2D6 Phenotype

The Sponsor evaluated the effect of each treatment on CYP2D6 phenotype (assessed by dextromethorphan/dextrorphan urinary ratio). The results are shown in the table below, as provided by the Sponsor.

Treatment			
Pre-treatment (screening)	Org 33062 ER	Paroxetine	Org 33062 ER + Paroxetine
0.00434 (230)	0.0116 (314)	0.371 (126)	0.533 (157)

Presented are geometric mean (geometric CV %).
Data were taken from Table 8-2 of Appendix BI: Pharmacokinetics.

The ratios were higher (2.7, 86, and 123 times) for Org 33062 alone, paroxetine alone, and combination, respectively, compared to pre-treatment screening, and the effect was statistically significant. However, it should be noted that exposure to the 40 mg Org 33062 was not sufficient to convert extensive metabolizers to phenotypic poor

metabolizers. There was no statistically significant difference in the ratios following paroxetine alone treatment and the combination treatment. This data supports the inhibitory effect of paroxetine on CYP2D6.

Pharmacodynamics

There were no statistically significant effects and no consistent effects between treatments on the Visual Analogue Scales.

Safety

There were no deaths or serious adverse events in this trial, and none of the subjects discontinued the trial due to adverse events. Two subjects temporarily interrupted treatment due to adverse events in period one that included nausea and dizziness. One or more adverse events occurred in a total of 29 subjects. There were 321 adverse events reported, and 46.4% were reported during the first treatment period, mostly during the first 3 treatment days. The most frequently reported adverse events were dizziness, headache, nausea, somnolence, and fatigue. Dizziness was mostly reported in the Org 33062 treatment period. Systolic and diastolic blood pressures were lower during treatment with Org 33062 than during paroxetine or combination treatment. Seven subjects had abnormally low vital signs values during treatment with Org 33062 and/or combination treatment. One subject had syncope during treatment with Org 33062 and one subject had syncope during combination treatment. One other subject had orthostatic dizziness during treatment with Org 33062.

CONCLUSIONS:

Data from this study suggest that paroxetine alters the disposition of gepirone by increasing exposure to the 1-PP metabolite, but not to the parent compound or to the 3'-OH metabolite. The clinical relevance of this is unknown.

This study indicates that gepirone at a 40 mg dose does not inhibit the metabolism of paroxetine, a CYP2D6 substrate. The results (no inhibition) are consistent with *in vitro* studies showing no inhibition of CYP2D6 by gepirone, and suggest that gepirone will not alter the metabolism of drugs metabolized by CYP2D6 when used at this dose. However, the dose of Org 33062 selected was not optimal for showing an inhibitory effect on CYP2D6 as this is not the maximum planned dose.

5.2.6. Glyburide Interaction Study (Study 28707)

THE EFFECT OF ORG 33062 ON INSULIN SENSITIVITY AND GLIBENCLAMIDE PHARMACOKIENTICS AND PHARMACODYNAMICS

Study Investigators and Site:
A. Schrödter, MD, PhD
FOCUS Clinical Drug Development, GmbH
Neuss, Germany

Protocol Number: 28707

OBJECTIVES:

The objective of Trial block I was to investigate the effect of Org 33062 on insulin sensitivity in type II diabetic patients.

The objectives of Trial block II were 1) to investigate the effect of Org 33062 on glibenclamide pharmacokinetics in type II diabetic patients and 2) to investigate the effect of Org 33062 on glibenclamide pharmacodynamics in type II diabetic patients. (***Note:*** glibenclamide is the same drug as glyburide, the name used in the United States).

FORMULATIONS:

Table 1. Products used in 28707

	Batch Lot Number	**Expiration Date (Dates of Study)**
Org 33062 20 mg extended release tablets ([redacted] (b) (4) [redacted])	CP CV053	03/2004 (August, 2001 – June 2002)

STUDY DESIGN:

Block I was a randomized, double-blind, placebo controlled multiple dose trial in obese Type II diabetic patients. Each subject received only 1 treatment (9 subjects received Org 33062 and 9 subjects received placebo). Following a washout period of 3 weeks during which subjects were to discontinue their current drug therapy, subjects received placebo or Org 33062 for 3 weeks. The dose regimen for Org 33062 was 20 mg once daily for 2 days and then 40 mg (2x20 mg) taken once daily 1 hour before breakfast.

In Block 1, insulin-mediated glucose disposal was to be measured using a two-step hyperinsulinemic, euglycemic clamp technique as follows. Blood glucose concentrations were clamped at 110 mg/dl (6.1 mmol/L). The blood glucose concentration had to be established for at least 32 hours before the insulin infusion rate was changed. At time 0, the insulin infusion rate was 0.5 mU/kg/min for 2 hours after which it was changed to 1.5

mU/kg/min for 2 hours. The last 30 minutes of the 2 insulin infusion rate phases were to be regarded as steady state phases. After an initial baseline clamp, subjects began the treatment period. Subjects reported to the clinic on days 7 and 14 for assessment of fasted blood glucose. A second clamp was performed on day 21. Compliance of treatment and diet were ascertained by interview, measurement of body weight, pill count, and trough concentrations of Org 33062.

Block II was an open, one sequence crossover, non-controlled study in Type II diabetic subjects with an individually adjusted anti-diabetic treatment with glibenclamide unchanged for at least 3 months. Org 33062 (2x20 mg) was to be co-administered once daily 1 hour before breakfast for 6 days. Pharmacokinetic and pharmacodynamic assessments (oral glucose tolerance test) were to be performed before Org 33062 dosing and at the sixth day of Org 33062 co-administration.

Inclusion criteria for both study blocks included male or female subjects between 18 and 70 years of age. All physical examination parameters were to be without signs of clinically relevant pathology and all values for hematology and clinical chemistry within the normal range or showing no clinically relevant deviations (except for triglycerides and cholesterol). Women must have been post-menopausal, surgically sterile, or practice an acceptable method of contraception. In addition, for Block I, subjects were to be obese Type II diabetes mellitus patients for at least 3 months duration, controlled with diet alone and/or on oral hypoglycemics, with fasting blood sugar greater than 7.0 mmol/L. Subjects for Block II must have been Type II diabetic patients treated with glibenclamide for at least 3 months before the study and have a fasting blood sugar greater than 7.0 mmol/L and HbA1c up to 8%. Exclusion criteria included history of liver disease or abnormal renal function. Subjects were not allowed to use concomitant medication within 21 days prior to the first administration of trial medication until follow-up except for sporadic use3 of acetaminophen. However, subjects were allowed to maintain their usual antihypertensive or contraceptive medication or hormone replace therapy, and for block II glibenclamide was permitted.

In Block 1, blood samples were collected for determination of Org 33062 trough concentrations on days -1, 7, 14, and 21 prior to the daily dose. In Block 2, pre-dose blood samples for determination of Org 33062 trough concentrations were collected on days 1-6. Blood samples for determination of glibenclamide plasma concentrations were collected on day -1 and on day 6. On both days samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing. Plasma was stored at -18º C until analysis.

ASSAY:

Table 2. Performance of Analytical Methods for 28707

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Gepirone	LC/MS/MS	0.1-50 ng/ml	r > 0.995	0.1 ng/ml	0.3 ng/ml	10.2	4.3
					5.0 ng/ml	5.1	9.8
					40 ng/ml	1.9	-6.8
Glibenclamide	LC/MS/MS	1-500 ng/ml	r > 0.991	1 ng/ml	3.66 ng/ml	7.2	0.8
					227 ng/ml	6.8	-8.6
					390 ng/ml	4.7	-3.8

The assay for Org 33062 was performed at Organon according to the established bioanalytical methods using a liquid chromatographic-mass spectrometric assay (LC-MS) using electrospray ionization. The selectivity with respect to glibenclamide demonstrated no significant interference with the assay, according to the Sponsor. For Org 33062, the assay deviated from the method in that the samples were dissolved in 20:80 acetonitrile/0.05 M ammonium acetate solution pH 4.2 instead of 50:50 acetonitrile 0/05 M ammonium acetate solution pH 4.2 as described in the protocol. Two calibration curves and triplicate QC samples were analyzed with each batch of study samples. Linearity was demonstrated in the calibration curves as shown in the table above. Accuracy and precision were acceptable. Samples were analyzed within the period for which the samples are stable. Concentrations were within the range of the standard curves. The performance of the assays is considered acceptable.

Glibenclamide was assayed at (b) (4) using a method developed in that laboratory and partially validated. The time period for stability of the samples was not shown. The samples were analyzed within 11 months of collection. According to the Sponsor, the selectivity of the assay with respect to Org 33062 and bupropion showed no significant interference. A single calibration curve and duplicate QC samples were analyzed with each batch of study samples.

RESULTS:

Demographics

Eighteen subjects (15 males, 3 females) were enrolled in Block 1 and completed the study. Sixteen subjects were enrolled and completed Block II. Demographics are shown in the table below. Of note: Eight subjects in Block II were on stable therapy with an antihypertensive agent, and 2 of these subjects were taking calcium channel blockers, but none were taking verapamil or diltiazem.

Table 4. Demographics of Subjects Completing the Study

Study Block	Mean Age (Range)	Gender	Weight (mean ± SD)	Race
I	Org 33062: 61.9 (51-70)	3 Female 6 Male	100.78 ± 25.28 kg (n=9) 101.3 ± 15.8 (male) 99.7 ± 17.6 (female)	Caucasian
	Placebo: 57.1 (42-60)	9 Male	98.00 ± 7.20 kg	
II	63.5 (55-70)	2 Male 14 Female	83.5 ± 13.1 (n=16) 85.4 ± 11.8 (male) 70.0 (range 56.9-83.0, female)	Caucasian

Pharmacokinetics

In Blocks I and II, the Sponsor obtained trough concentrations of Org 33062 on Day 7, 14, and 21 to determine compliance with Org 33062 administration. In addition, the reviewer has reviewed the slopes of the trough concentrations for individual subjects that suggest steady state had been reached (with the exception of 1 individual in block 2 for whom plasma concentrations continued to increase on each day).

Glibenclamide Pharmacokinetics in Block II

Individual plasma concentration-time profiles for glibenclamide before and after administration of Org 33062 were shown by the Sponsor. However, since each patient had an individually adjusted dosage regimen, the mean curves were not presented by the Sponsor.

Pharmacokinetic parameters for glibenclamide were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters are shown in the Tables 5 and 6, below. Two subjects had unusually high pre-dose glibenclamide values on Day -1 compared to pre-dose values on Day 6 , suggesting that they had taken a dose on the evening prior to dosing on Day -1. A separate analysis excluded these patients, with pharmacokinetic results similar to that of the whole group. The results of the whole

group are shown below. In addition, since some patients were taking glibenclamide twice daily rather than once daily, both AUC0-12 and AUC0-24 have been determined.

Table 5. Pharmacokinetic parameters (arithmetic mean) for glibenclamide (Study 28707)

	Test (Gepirone + Glibenclamide) (% CV) n=16	**Reference (Glibenclamide)** (% CV) n=16
Glibenclamide		
tmax (hr)a	2.50 (1.0-24.0)	2.00 (0.5-8.0)
Cmax (ng/mL)	128.5 (93.7)	158.9 (89.5)
AUC 0-24 (ng*h/mL)	979.1 (113.4)	869.4 (79.4)
AUC 0-12 (ng*hr/mL)	617.5 (80.3)	730.1 (78.1)

[a] median (range)

Table 6. Interaction Assessment for Study 28707

	Geometric Mean		**Ratio of Geometric Means**	**90% CI for the Ratio of Geometric Means**
	Reference	**Test**		
Glibenclamide				
Cmax (ng/mL)	121.0	96.6	0.798	(0.668, 0.954)
AUC 0-24 (ng*h/mL)	677.3	621.6	0.918	(0.776, 1.085)
AUC 0-12 (ng*hr/mL)	574.8	483.0	0.840	(0.759, 0.930)

These results show an approximate 20%decrease in Cmax and AUC for glibenclamide after exposure to Org 33062. In some cases the reduction was up to 50% whereas some subjects had little change. This decrease resulted in confidence intervals outside of the 0.80 - 1.25 range.

Pharmacodynamics

In Block I, the main objective was to show that the change of insulin sensitivity index to the baseline value is higher for treatment with Org 33062 than for treatment with placebo (using an unpaired t-test or non-parametric Wilcoxon test if the distribution was not normal. Insulin sensitivity index was defined as follows where GIR is mean glucose infusion rate, Ins is steady state insulin concentration and BG is mean blood glucose:

$$SI = \frac{\Delta GIR}{\Delta Ins \bullet BG}$$

The Table below (as provided by Sponsor) shows mean values for changes from baseline for SI as well as for GIR and other parameters as indicated. No statistically significant differences between Org 33062 and placebo were demonstrated (either by t-test or Wilcoxon).

Table 18 Mean Values and SD for Changes from Baseline

Parameter (unit)	Steady State	Org 33062		Placebo	
		Mean (SD)	Median (range)	Mean (SD)	Median (range)
SI (mL/min /µU/ml)		0.02 (0.84)	-0.10 (-0.9 – 1.6)	-0.76 (1.28)	-1.00 (-2.8 – 0.9)
GIR (mg/min)	1	7.69 (133.98)	-27.80 (-145.4 – 263.7)	31.69 (101.66)	-16.6 (-83.8 – 152.9)
	2	-5.16 (182.29)	13.40 (-295.6 – 251.8)	-42.33 (282.30)	-37.50 (-529.8 – 442.9)
M-Value (mg/kg/min)	1	0.07 (1.37)	-0.20 (-1.6 – 2.8)	0.33 (0.99)	-0.10 (-0.7 – 1.5)
	2	-0.06 (1.83)	0.20 (-2.9 – 2.6)	-0.26 (2.82)	-0.15 (-4.8 – 4.8)
MCR (mg/kg/min per mmol/l)	1	0.00 (0.21)	-0.10 (-0.2 – 0.4)	0.04 (0.18)	0.00 (-0.2 – 0.3)
	2	-0.03 (0.30)	0.00 (-0.5 – 0.4)	-0.09 0.46)	-0.05 (-0.8 – 0.7)
M/I-Value (mg/kg/min per µU/ml)	1	0.0041 (0.0412)	-0.0040 (-0.042 – 0.010)	0.0052 (0.0231)	-0.0030 (-0.023 – 0.043)
	2	0.0016 (0.0122)	0.0040 (-0.019 –0.019)	-0.0113 (0.0220)	-0.0100 (-0.045 – 0.019)

Source: Appendix F (Block I): Tables 1.4.1-1.4.5

SI = insulin sensivity index

GIR = mean glucose infusion rate

M-value = GIR corrected for body weight

MCR = mean clearance rate

M/I-value = amount of glucose infused/mean insulin infusion rate in each steady state phase

In Block II an oral glucose tolerance test (OGTT) was performed on Day -1, immediately after glibenclamide administration and on Day 6, immediately after administration of Org 33062. Food intake was standardized and patients were not allowed to exert unusual physical activity on the 2 days preceding the test and during the days of the measurements. On the days of the OGTT, following overnight fast, patients drank a solution of 75 g glucose in 300 ml over not more than 5 minutes. The test was performed at the same time of day for each subject. Blood samples were collected after glucose administration for measurement of glucose and insulin. Summary statistics for AUC0-4, Cmax and Tmax for glucose and insulin, as well as a comparison between Day 6 (Gepirone + Glibenclamide) and Day -1 (Glibenclamide), are shown in the Tables below, as provided by the Sponsor. (The AUC0-6 has not been considered by the reviewer since this data was missing in 5/16 subjects).

Table 7. Pharmacodynamic parameters (arithmetic mean) for glucose and insulin (Study 28707)

	Test (Gepirone + Glibenclamide) (% CV) n=16	**Reference (Glibenclamide)** (% CV) n=16
Glucose		
tmax (hr)a	1.50 (1.00-2.00)	1.25 (0.5 – 2.00)
Cmax (mmol/L)	(16.6 (21.7)	17.5 (20.3)
AUC 0-4 (mmol*h/L)	50.9 (25.7)	51.3 (29.8)
Insulin		
tmax (hr)a	1.50 (1.0-2.0)	1.75 (1.0-2.0)
Cmax (MCU/ml)	75.19 (67)	65.2 (65.1)
AUC 0-4 (MCU*h/ml)	176.4 (71.8)	159.9 (68.0)

[a] median (range)

Table 8. Interaction Assessment for Study 28707

	Geometric Mean		**Ratio of Geometric Means**	**90% CI for the Ratio of Geometric Means**
	Reference	**Test**		
Glucose				
Cmax (mmol/L)	17.19	16.23	0.944	(0.668, 0.954)
AUC 0-4 (mmol*h/L)	49.46	49.34	0.840	(0.776, 1.085)
Insulin				
Cmax (MCU/ml)	55.83	63.12	1.131	(0.995, 1.285)
AUC 0-4 (MCU*h/ml)	135.42	147.67	1.091	(0.975, 1.219)

In addition, the reviewer has evaluated the results at 2 hours, the standard time for evaluation of the OGTT. The ratio of the geometric means (Test Day 6/Ref Day-1) was 1.01 for glucose and 1.03 for insulin, with 90% confidence intervals of 0.78-1.30 and 0.66-1.59, respectively. Thus following a 6-day administration of 40 mg daily Org 33062, there was little change in glucose tolerance.

Safety

In trial Block I there were 4 subjects dosed with Org 33062 and 4 subjects dosed with placebo that reported possible drug-related adverse events. These included dizziness, headache, paresthesia, abdominal pain, diarrhea, nervousness, and sleep disorder for Org 33062 and headache, diarrhea, impotence, insomnia, and somnolence for placebo. Most adverse events were judged as mild in severity. Two subjects on Org 33062 and two on placebo reported moderate adverse events. In one subject the maximum intensity (of dizziness) was severe).

In trial Block II there were 11 reports of baseline adverse events in 8 subjects, including 3 subjects with mild to moderate hypoglycemia during the oral glucose tolerance test on day -1, and 1 subject with hypoglycemic shock. All of those subjects recovered after intake of dextrose. There were 32 adverse events in trial block 2, of which 24 were

assessed as possibly drug related. These included dizziness, fatigue, and insomnia, as well as headache, tremor, asthenia, cold clammy skin, and sweating. There were no abnormalities in laboratory values, ECG or vital signs that were considered by the investigator or Sponsor to be clinically relevant.

CONCLUSIONS:

This study did not result in overall significant changes in insulin sensitivity in Type II diabetes mellitus patients or in glibenclamide pharmacodynamics (as determined by OGTT) in Type II diabetes mellitus patients. There were statistically significant changes in glibenclamide Cmax and AUC (mean approximately 20%) with up to a 50% reduction in some cases. However, since the 40 mg dose used in this study is considered to be a minimally effective dose, and the dose could be titrated clinically to 80 mg, the 40 mg dose used in this study may not be clinically relevant. Therefore, the results of this study cannot rule out a greater effect at the higher doses that may be used clinically.

5.2.7 Lithium Interaction Study

A double-blind, randomized, two way crossover study to investigate the steady state pharmacokinetics and tolerability of Org 33062 and lithium, given alone and co-administered, in healthy, young male subjects

Study Investigators and Site:

J-P Decourt, MD
Parexel-Cemef
6, Avenue Mozart
86000 Poitiers, France

Protocol Number: 28706

OBJECTIVES:

The primary objective was to study the effect of multiple oral doses of Org 33602 on steady state pharmacokinetics of lithium.

Secondary objectives were to investigate the effect of multiple doses of Lithium on steady state pharmacokinetics of Org 33062, to investigate safety and tolerability of multiple doses of Org 33062 and lithium, to explore the effects of Org 33062 on Lithium pharmacodynamics, and to explore the effect of Lithium on Org 33062 pharmacodynamics.

FORMULATIONS:

Table 1. Products used in 28706

FORMULATIONS	BATCH LOT NUMBER	EXPIRATION DATE (DATES OF STUDY)
Org 3302 20 mg extended release tablets ([redacted] (b) (4))	00-011T	03/2003 (27 June 2001 to 10 September 2001)
Placebo tablets ([redacted] (b) (4), NV Organon Oss, The Netherlands)	CP099211	07/2002 (27 June 2001 to 10 September 2001)
Lithium carbonate 150 mg capsules ([redacted] (b) (4), NV Organon Oss, The Netherlands)	CU275	07/2002 (27 June 2001 to 10 September 2001)

STUDY DESIGN:

The study was a double-blind (for lithium), randomized, two-period, crossover design in 12 healthy male subjects. Each subject was randomized to a two-period, treatment sequence with a one-week washout period between periods (Table 2).

Table 2. Treatment Sequence and Dosing Schedule in 28706

SEQUENCE NUMBER	TREATMENT PERIOD 1	TREATMENT PERIOD 2
1	300-600 mg lithium bid x 12 days (Days 1 to Day 12) plus 40 mg Org 33062 qd x 3 days (Day 7 to Day 10)	Placebo bid x 12 days (Days 1 to Day 12) plus 40 mg Org 33062 qd x 3 days (Day 7 to Day 10)
2	Placebo bid x 12 days (Days 1 to Day 12) plus 40 mg Org 33062 qd x 3 days (Day 7 to Day 10)	300-600 mg lithium bid x 12 days (Days 1 to Day 12) plus 40 mg Org 33062 qd x 3 days (Day 7 to Day 10)

Subjects were included if they were healthy, Caucasian males between the ages of 18 and 45 years, and having a body mass index within 18 to 28 kg/m^2. Exclusion criteria included the use of any drug or substance known to induce of inhibit drug metabolizing enzymes within one month prior to the first dose; and any drug within two weeks of dosing (except for acetaminophen and dextromethorphan). Furthermore, subjects were excluded if they had sub-clinical hypothyroidism, low serum-sodium concentrations, and smoked more than 5 cigarettes per day.

Lithium was titrated over a three day period; each subject received 300 mg bid on Day 1, 450 mg bid on Day 2, and 600 mg bid on Day 3. The investigator was able to adjust the lithium dose in individuals who had serum concentrations outside the safety range of 0.5–0.8 mmol/L. Subjects were maintained on 600 mg bid for 9 more days. Blood samples were collected prior to the morning dose (trough concentration) on Days 2 to Day 12 to assess safety. In addition, blood samples were collected on Day 6 and Day 10 at 1, 2, 3, 4, 6, 8, 10, and 12 hours after the morning dose to assess lithium pharmacokinetics in the absence and presence, respectively, of steady state concentrations of gepirone and its metabolites.

Subjects received a 40 mg dose of Org 33062 once daily on Day 7 to Day 10. Blood samples for determination of Org 33062, 1-PP, and 3'-OH plasma concentrations were taken pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36, 48, 60 and 72 hours after administration of Org 3308 on Day 10. An additional blood sample was taken pre-dose on Day 9 for determination of the attainment of steady state. Urine collection was not performed.

Pharmacodynamic effects were evaluated using visual analogue scales for mood and sleep on Days 6, 7, and 10.

BIOANALYTICAL ASSAY:

The bioassay for gepirone and its metabolites was performed at Organon according to validated methodologies. The bioassay for lithium was developed, validated, and performed at (b) (4). The samples were analyzed during the period in which they are stable. The performances of the assays are shown in Table 3.

Table 3. Performance of Analytical Methodology for 28706

Analyte	Method	Range (ng/ml)	Linearity	LOQ (ng/ml)	QC (ng/ml)	Inter-Assay Precision (%CV)	Inter-Assay Accuracy (%)
gepirone (Org 33062)	(ESP)-HPLC/MS	0.1 to 50	r > 0.993	0.1	0.3 5.0 40.0	6.3 4.1 5.3	2.3 3.0 -13.5
1-PP	(ESP)-HPLC/MS	0.2 to 50	r > 0.998	0.2	0.6 5.0 40.0	14.8 11.7 12.6	13.3 12.4 5.2
3'-OH-gepirone (Org 25907)	(ESP)-HPLC/MS	0.2 to 50	r > 0.993	0.2	0.6 5.0 40.0	10.2 6.5 7.3	3.7 11.8 1.8
lithium	ICP/MS	25 to 10000	r > 0.999	25	75 750 7500	5.3 3.5 2.9	1.1 -0.6 -0.3

RESULTS:

Demographics

Twelve healthy Caucasian male volunteers were enrolled and completed the study. All subjects were included in the pharmacokinetic evaluations. Table 4 shows a summary of the demographic information.

Table 4. Demographic Data for 28706

Mean Age (Range)	Weight (mean ± SD)	BMI (mean ± SD)
27.9 (18-39)	66.6 ± 7.9 kg	22.7 ± 1.9 kg/m^2

Lithium Pharmacokinetics

The mean steady state time course of lithium in the absence or presence of Org 33062 is shown in Figure 1.

Figure 1. Geometric mean concentration-time course for lithium when administered alone and with Org 33062

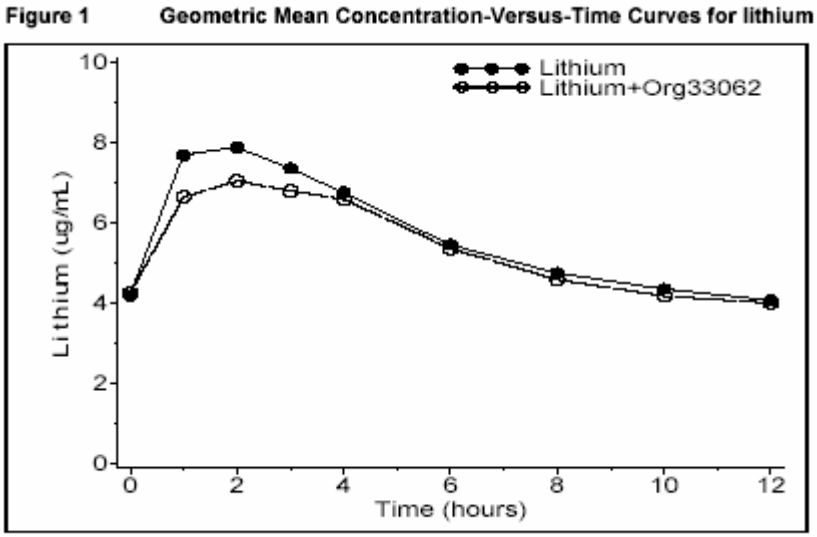


Table 5 shows a summary of derived pharmacokinetic parameters. Analysis of pre-dose concentrations in the lithium alone period showed no significant difference between day 5 and days 6 and 7, and for the combined administration pre-dose concentrations did not differ from Day 9 onward, suggesting steady state had been reached. There was a slight decrease in lithium Cmax (approximately 11%) in the presence of Org 33062.

Table 5. Summary of lithium pharmacokinetic parameters (arithmetic mean)

	Lithium (% CV) n=12	
	Lithium	**Lithium + Org 33062**
Tmax (h)[a]	1.50 (1.00-3.00)	2.50 (1.00-4.00)
Cmax (µg/ml)	8.49 (10.9)	7.57 (21.1)
AUC0-12 (µg*h/ml)	68.8 (9.81)	65.4 (14.5)
Cl_{app} (l/h)	1.65 (9.34)	1.76 (14.4)
wn-Cl_{app} (L/h/kg)	0.0243 (12.5)	0.0258 (16.7)
C_{av} (µg/ml)	5.73 (9.81)	5.45 (14.5)
DF (%)[b]	73.6 (23.5)	59.5 (32)
Swing (%)[b]	102 (29.5)	77.3 (38)
$Cmin,_{av}$ (µg/ml)[b]	5.73 (9.81)	4.31 (13.3)

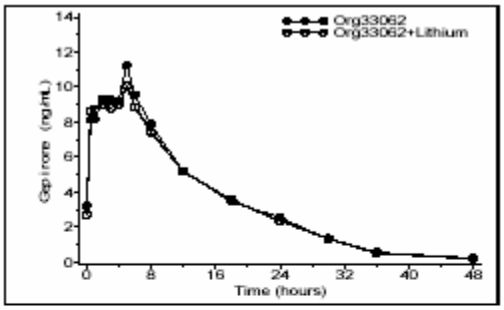
[a] median (range)
[b] n=11 for lithium treatment without Org 33062

ORG 33062 Pharmacokinetics

Mean concentration-time profiles for gepirone, 1-PP, and 3'-OH gepirone are shown in Figure . analysis of pre-dose concentrations suggested that steady state had been reached. A summary of pharmacokinetic parameters obtained by noncompartmental analysis is shown in Table 6.

Figure 2. Mean time course of plasma concentrations of gepirone and its metabolites

Figure 2 Geometric Mean Concentration-Versus-Time Curves for gepirone



The curves are based on n=12 subjects
Data were taken from Table 3-5 of Appendix 8I: Pharmacokinetics.

Figure 3 Geometric Mean Concentration-Versus-Time Curves for 1-PP

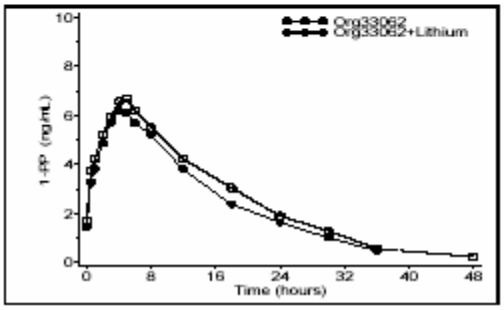
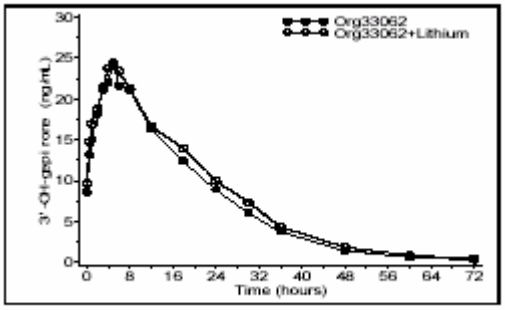


Figure 4 Geometric Mean Concentration-Versus-Time Curves for 3'-OH-gepirone



The curves are based on n=12 subjects
Data were taken from Table 3-7 of Appendix 8I: Pharmacokinetics.

Table 6. Summary of pharmacokinetic parameters (arithmetic mean)

	Gepirone (% CV) n=12		**1-PP (%CV) n=12**		**3′-OH-geprione (% CV) n=12**	
	A	**B**	**A**	**B**	**A**	**B**
Tmax (h)[a]	5.00 (0.50-6.00)	5.00 (0.500-6.00)	4.02 (3.00-6.00)	4.50 (4.00-6.00)	5.00 (3.00-5.00)	5.00 (3.00-8.00)
Cmax (ng/ml)	12.7 (36.7)	12.0 (41.0)	6.94 (37.4)	7.15 (28.4)	25.4 (18.9)	25.7 (17.3)
AUC_{0-24} (ng*h/ml)	173 (46.4)	168 (50.2)	102 (47.6)	108 (31.8)	402 (27.4)	421 (22.5)
$t_{1/2}$ (h)	7.27 (46.8)	8.17 (73.6)	7.59 (29.2)	6.86 (27)	12.1 (39.3)	12.8 (40.6)
Cl_{app} (l/h)	291 (79)	289 (69.5)	435 (44.8)	381 (41.7)	96.4 (26.7)	90.3 (22.5)
wn-Cl_{app} (l/h/kg)	4.39 (87.7)	4.42(82.3)	6.37 (45.1)	5.55 (37.3)	1.43 (31.2)	1.34 (29.6)
Vz_{app} (l)	2617 (50.9)	2923 (70.1)	4831 (62.1)	3769 (47.9)	1644 (37.6)	1740(59.9)
wn-Vz_{app} (l/kg)	38.1 (48.4)	42.3 (64.8)	70.4 (64.7)	54.9 (30)	24 (36.5)	25.8 (62.9)
C_{av} (ng/ml)	7.21 (46.4)	6.99 (50.2)	4.26 (47.6)	4.49 (31.8)	16.8 (27.4)	17.5 (22.5)
DF(%)	142 (50.0)	141 (62)	132 (25.4)	120 (19.4)	101 (26.2)	89.7 (25.1)
Swing (%)	322 (103)	462 (82.3)	390 (57.7)	3346 (70.7)	201 (42.9)	90.3 (22.5)
$Cmin_{av}$ (ng/ml)	4.04 (52.4)	3.47 (55.5)	2.00 (60.9)	2.12 (37.1)	9.94 (38.2)	10.6 (2.92)

[a] median (range)
A= Org 33062 alone
B=lithium + Org 33062

The results show a slight (< 6%) decrease in Cmax and decrease in AUC for gepirone and a slight (<6%) increase in AUC for 1-PP and for 3′-OH-gepirone.

Statistical Testing for Drug Interaction

The results of statistical testing for drug interaction testing for lithium, as well as for gepirone and its metabolites are shown in Table 7. The sponsor concluded the absence of a drug interaction if the 90% confidence interval for geometric mean ratio of (test/reference) was contained within the no effect range of 0.80–1.25. The test treatment was concomitant administration of Org 33062 with lithium and the reference treatment was administration of either Org 33062 or lithium alone.

Table 7. Statistical testing for drug interaction with lithium

Table 3: Results of Drug Effect Testing

Parameter (units)	Geometric mean		p-value	Point estimate	90% CI
	Test (n=12)	Reference (n=12)			
gepirone					
C_{max} (ng/mL)	11.2	11.8	0.652	0.95	0.79-1.15
AUC_{0-24} (ng*h/mL)	148	152	0.883	0.97	0.71-1.33
1-PP					
C_{max} (ng/mL)	6.84	6.49	0.449	1.06	0.93-1.19
AUC_{0-24} (ng*h/mL)	102	92.2	0.347	1.11	0.92-1.33
3'-OH-gepirone					
C_{max} (ng/mL)	25.4	25.0	0.832	1.02	0.88-1.17
AUC_{0-24} (ng*h/mL)	412	389	0.647	1.06	0.85-1.31
lithium					
C_{max} (µg/mL)	7.42	8.44	0.0741	0.88	0.78-0.99
AUC_{0-12} (µg*h/mL)	64.8	68.5	0.324	0.95	0.86-1.04

Point estimate: Point estimate for ratio (test to reference) of geometric means.
90% CI: 90% confidence interval for true ratio.
Drug interaction absent: 90% CI inside acceptance range 0.80-1.25.
Drug interaction indeterminant: p-value >0.05 and 90% CI not fully contained wit range 0.80-1.25.
Data were taken from Listing 6.2-1, 6.3-1, 6.4-1 and 6.5-1 of Appendix BI: Pharmaco

Pharmacodynamics

No effect on mood or sleep scale parameters was noted.

Safety

Nine of 12 subjects reported a total of 36 adverse events (21 were mild and 15 were moderate in intensity). The most common AE was nausea (reported in 6/12 subjects) followed by dizziness (reported in 5/12 subjects) and diarrhea (reported in 4/12 subjects).

Subjects presented normal laboratory values (hematology, biochemistry, and urinalysis) during the study. Values outside the normal range were judged by the investigator to be not clinically significant. One subject, however, experienced a transient increase in ALAT concentration that resolved without further incidence.

There was no influence of study treatment on vital sign parameters, ECG, and physical examination.

Conclusions

This study showed there is no significant pharmacokinetic interaction between lithium and Org 33062 at a gepirone dose of 40 mg daily coadministered for 3 days with lithium. Since the 40 mg dose used in this study is not the maximally planned dose, an effect of the 80 mg dose cannot be ruled out.

5.2.8 Warfarin Interaction Study

A trial to study the effect of multiple oral doses Org 33062 on steady state pharmacodynamics of orally administered warfarin in healthy male volunteers

Study Investigators and Site:

KM. Eckl, MD
Pharm PlanNet Contract Research GmbH
Hindenburgstr. 306
D-41061 Monchengladbach, Germany

Protocol Number: 28704

OBJECTIVES:

The primary objective was to study the effect of multiple oral doses of Org 33602 on steady state pharmacodynamics of orally administered warfarin in healthy volunteers.

Secondary objectives were 1) to study the effect of multiple oral doses of warfarin on single dose pharmacokinetics of Org 33062 and 2) to study the safety and tolerability of the combined use of warfarin and Org 33062.

FORMULATIONS:

Table 1. Products used in 28704

FORMULATIONS	PACKAGE LOT NUMBER	BATCH LOT NUMBER	EXPIRATION DATE (DATES OF STUDY)
Org 3302 20 mg extended release tablets ([redacted] (b) (4))	CP 099114	0581394	05/2001 (06 November 2000 to 01 February 2001)
Placebo tablets ([redacted] (b) (4) [redacted])	CP 099113	99-009T	01/2002 (06 November 2000 to 01 February 2001)
Warfarin 5 mg tablets (DuPont Pharma, Bad Homburg, Germany)	--	950 9C	12/2004 (06 November 2000 to 01 February 2001)

STUDY DESIGN:

The study was a multiple dose, double-blind (for gepirone), placebo controlled, randomized, two-sequence, two-period, crossover study to evaluate the effects of Org 33062 on steady state warfarin pharmacodynamics. Sixteen healthy male volunteers were randomized to a treatment sequence (Table 2).

Table 2. Treatment Sequence and Dosing Schedule in 28704

SEQUENCE NUMBER	TREATMENT PERIOD 1	TREATMENT PERIOD 2
1	40 mg Org 33062 (Day 1) followed by warfarin 20 mg (Day 2), 15 mg (Day 3) 5 mg (Days 4-12) plus 40 mg Org 33062qd x 6 days (Days 7 to 12)	Warfarin 5 mg qd (Days 13 to 22) plus placebo qd x 6 days (Days 18 to 23)
2	40 mg Org 33062 (Day 1) followed by warfarin 20 mg (Day 2), 15 mg (Day 3) 5 mg (Days 4-12) plus placebo qd x 6 days (Days 7 to 12)	Warfarin 5 mg qd (Days 13 to 22) plus 40 mg Org 33062 qd x 6 days (Days 18 to 23)

Subjects were included if they were healthy, nonsmoking, Caucasian males between the ages of 18 and 45 years, and having a body mass index within 19 to 29 kg/m^2. Exclusion criteria included the use of any drug or substance known to induce of inhibit drug metabolizing enzymes within one month prior to the first dose; any drug or vitamin within one week of dosing (except for acetaminophen); and vitamin K containing preparations.

Warfarin was initiated with a loading dose (20/15/5 mg/day) for 3 days to obtain steady state prothrombin time by Day 4. This dosing regimen aimed to have subjects within a sub-therapeutic anticoagulation range of 1.4 – 2.0 International Normalized Ratio (INR). Subjects were maintained on 5 mg/d until Day 23. Blood samples were collected on Days 5–6, 11–12, and 22–23 for determination of prothrombin time.

Subjects received a single 40 mg dose of Org 33062 on Day 1, followed by multiple daily doses of 40 mg on Days 7-12 in Period 1 (Sequence 1) and Days 18-23 in Period 2 (Sequence 2). Blood samples for determination of Org 33062, 1-PP, and 3'-OH were taken pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, and 24 hours after administration of Org 3308 on Days 1, 7 (period 1), and 18 (period 2). Furthermore, blood samples were taken at pre-dose on Days 8–11 (period 1) and Days 19–22 (period 2) for determination of the attainment of steady state. Urine collection was not performed.

Bioanalytical Assay

The bioassays for gepirone and its metabolites were performed at (b) (4) according to validated methodologies. Calibration curves were run in duplicate with a minimum of duplicate QC samples for each run. Concentrations exceeding the upper limit of quantitation (10 ng/mL) were diluted with free drug matrix and reassayed. The performance of the assays is shown in Table 3.

Table 3. Performance of Analytical Methodology for 28704

Analyte	Method	Range (ng/ml)	Linearity (correlation coefficient)	LOQ (ng/ml)	QC (ng/ml)	Inter-assay precision (%)	Inter-assay accuracy (%)
gepirone	(ESP)-HPLC/MS	0.1 to 10	0.9957	0.1	0.3 4.0 8.0	13.2 13.1 14.8	-2.0 -3.5 3.75
1-PP	(ESP)-HPLC/MS	0.2 to 10	0.9964	0.2	0.6 4.0 8.0	14.8 11.7 12.6	7.2 8.0 6.6
3'-OH-gepirone	(ESP)-HPLC/MS	0.25 to 10	0.9951	0.25	0.3 4.0 8.0	11.5 8.94 8.87	-2.7 -3.3 1.8

RESULTS:

Demographics

Sixteen healthy male Caucasian volunteers were enrolled and completed the study. All subjects were included in the pharmacodynamic and pharmacokinetic evaluations. Table 4 shows a summary of the demographic information. There were no statistical differences between subjects randomized to sequence 1 vs. sequence 2.

Table 4. Demographic Data for 28704

VARIABLE	N= 16
Age (y) mean (range)	34.4 (22-44)
Weight (kg)	82.1 (8.1)
BMI (kg/m^2) (mean ± SD)	25.5 (1.79)
Baseline INR (mean ± SD)	1.04 (0.07)

Warfarin Pharmacodynamics

The mean time course of prothombin time (PT), standardized and expressed as the INR is shown in Figure 1. Table 5 shows a summary of PT derived parameters.

Figure 1. Mean time course of PT (INR)

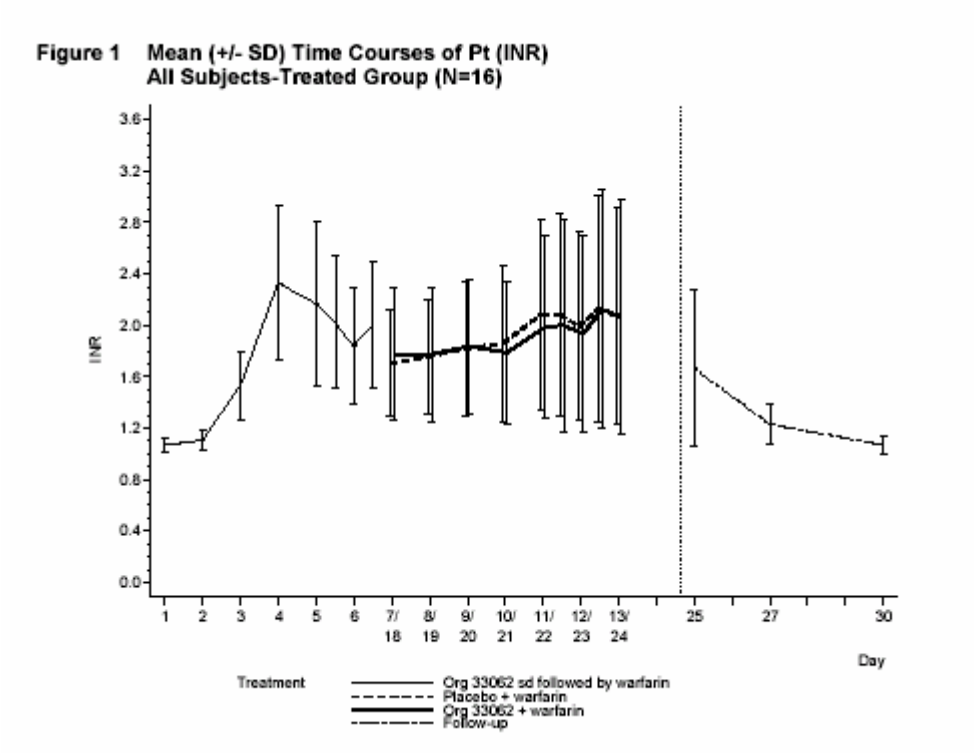


Table 5. Summary of derived PT (INR) parameters

Table 6 Summary of Derived Pt Parameters All Subjects-Treated Group (N=16)

Parameter	Mono warfarin (days 5/6) *		Org 33062 + warfarin		Placebo + warfarin	
	mean (sd)	range	mean (sd)	range	mean (sd)	range
AUCPt (0-48h) (INR*h)	94.3 (23.4)	61.8 - 141	97.0 (39.8)	58.8 – 181	99.4 (38.2)	56.6 - 168
Average Pt (INR)	1.98 (0.49)	1.3 – 2.9	2.02 (0.82)	1.2 – 3.7	2.07 (0.80)	1.1 – 3.5
Maximum Pt (0-48h) (INR)	2.21 (0.66)	1.4 – 3.4	2.17 (0.94)	1.3 – 4.1	2.18 (0.87)	1.2 – 3.9
Maximum Pt increase (INR)	-0.09 (0.26)	-0.7 – 0.2	0.17 (0.29)	-0.1 – 0.9	0.07 (0.18)	-0.1 – 0.5
Average daily warfarin dose in mg on days 7-12 or days 18-23			4.89 (0.42)	3.33 – 5.00	5.16 (0.45)	5.00 – 6.67

* Org 33062 single dose was given on day 1

For comparison of pharmacodynamic effects the comparison groups were placebo + warfarin and Org 33062 + warfarin (the warfarin alone period was used as a run-in). Results of statistical comparisons are shown below. The no effect level was considered by the Sponsor to be in the range of 0.9-1.11.

Table 8 Summary of Analyses of Variance of Derived Pt Parameters All Subjects-Treated Group (N=16)

Parameter	Estimate	Org 33062 + warfarin LSmean	Placebo + warfarin LSmean	90% confidence interval	
	Org 33082 / placebo			lower	upper
AUC Pt (0-48h) (INR*h)	0.98	97.0	99.4	0.91	1.04
Average Pt (INR)	0.98	2.02	2.07	0.91	1.04
Maximum Pt (0-48h) (INR)	1.00	2.17	2.18	0.94	1.05

ORG 33062 Pharmacokinetics

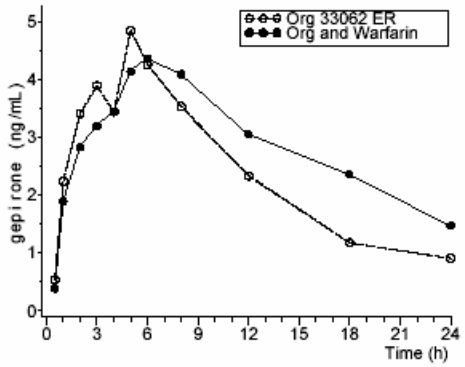
Mean concentration-time profiles for gepirone, 1-PP, and 3'-OH gepirone are shown in Figure 2. A summary of pharmacokinetic parameters obtained by noncompartmental analysis is shown in Table 6. The results of the statistical testing for the presence of a drug-interaction with warfarin are shown in Table 7. The results show a slight (< 6%) decrease in Cmax and decrease in AUC for gepirone and a slight (<6%) increase in AUC for 1-PP and for 3'-OH-gepirone.

Statistical Testing for Drug Interaction

The results of statistical testing for drug interaction testing for lithium, as well as for gepirone and its metabolites are shown in table 7. The sponsor concluded the absence of a drug interaction if the 90% confidence interval for geometric mean ratio of (test/reference) was contained within the no effect range 0.80-1.25. The test treatment was concomitant administration of Org 33062 with lithium and the reference treatment was administration of either Org 33062 or lithium alone.

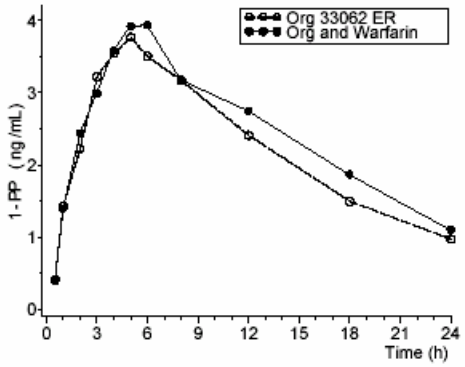
Figure 2. Mean time course of plasma concentrations of gepirone and its metabolites following a single dose of Org 33062 in the absence and presence of warfarin

Figure 2 Geometric Mean Concentration-Versus-Time Curves for gepirone



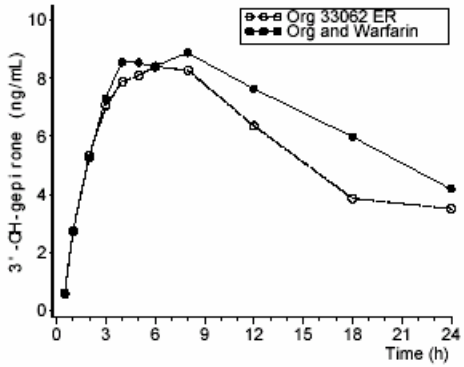
Data were taken from Table 3-2 of Appendix BI: Pharmacokinetics.

Figure 3 Geometric Mean Concentration-Versus-Time Curves for 1-PP



Data were taken from Table 3-2 of Appendix BI: Pharmacokinetics.

Figure 4 Geometric Mean Concentration-Versus-Time Curves for 3'-OH-gepirone



Data were taken from Table 3-2 of Appendix BI: Pharmacokinetics.

Table 6. Summary of single dose pharmacokinetic parameters (arithmetic mean ± SD)

	Gepirone		1-PP		3'-OH-gepirone	
	Org 33062	**Org 33062 + warfarin**	**Org 33062**	**Org 33062 + warfarin**	**Org 33062**	**Org 33062 + warfarin**
C_{max} (ng/ml)	5.92 (46.4)	5.44 (37.6)	4.55 (47.3)	5.13 (48.5)	9.25 (17.3)	9.73 (17.3)
T_{max} (hr)[a]	5.00 (1.00-8.00)	7.00 (4.00-24.00)	5.00 (3.00-12.00)	5.50 (3.00-18.0)	6.00 (3.00-18.0)	5.00 (3.00-12.0)
AUC_{0-24} (ng*h/ml)	68.0 (42.5)	76.3 (39.5)	63.8 (49.0)	72.1 (62.7)	146 (24.3)	166 (22.0)

[a] median (range)

Table 7. Statistical testing for drug interaction with warfarin

Table 10 Results of Testing on PK Drug Interaction

Parameter	p-value	Point Estimate of true Ratio*)	90% Confidence Interval
Gepirone			
$C_{sd,max}$	0.710	0.96	0.81-1.15
$AUC_{sd,0-24}$	0.239	1.16	0.94-1.43
1-PP			
$C_{sd,max}$	0.232	1.12	0.95-1.33
$AUC_{sd,0-24}$	0.211	1.10	0.97-1.26
3'-OH-gepirone			
$C_{sd,max}$	0.205	1.05	0.98-1.12
$AUC_{sd,0-24}$	0.060	1.14	1.02-1.29

Data were taken from Analysis 6-1 of Appendix BI: Pharmacokinetics, BI.6.

*) parameter ratio of Org 33062 alone and Org 33062 + warfarin

These results show that the 90% confidence interval for the geometric mean ratio of Cmax for gepirone and 3'-OH gepirone fall within the no effect range of 0.8 to 1.25. For the metabolite 1-PP, the geometric mean for Cmax was approximately 12% higher in the presence of warfarin. The 90% confidence interval for the geometric mean ratio fell outside the no effect range, indicating that the absence of a drug interaction could not be shown.

For AUC for gepirone and both metabolites, absence of a drug interaction could not be shown as the 90% confidence interval for gepirone and its metabolites was outside the no effect interval of 0.80 to 1.25.

Safety:

Eleven of 16 subjects reported adverse events. Dizziness was the most common AE reported following administration of Org 33062. Five subjects reported mild dizziness following single dose administration of Org 33062 on Day 1. Eight subjects reported

dizziness (7 were mild and 1 moderate) following the co-administration of Org 33062 with warfarin.

Compared to baseline, laboratory values for prothrombin time and factors II, VII, and IX were decreased and the parameters for aPTT and PT (INR) were increased during warfarin treatment.

There was no influence of Org 33062 on vital sign parameters, ECG, and physical examination.

Conclusions:

This study showed that gepirone given at a dose of 40 mg daily had no effect on anticoagulation in the presence of warfarin given 5 mg daily. Co-administration of warfarin with Org 33062 caused < 17% increase in exposure to gepirone and its metabolites. The treatment regimens were safe and well-tolerated.

In the opinion of the reviewer, the results of this study do not support dose adjustment for either warfarin or Org 33062 during concomitant therapy of Org 33062 and warfarin. However, the dose of gepirone used was not the maximal planned dose and an effect at the 80 mg dose cannot be ruled out.

5.2.8 Organon Bioanalytical Method for Gepirone, Org 25907, and 1-PP in Plasma

The following method was performed for samples from Study 28724, 28707, and 28705.

Analyses of plasma concentrations of gepirone and Org 25907 (3'-OH-gepirone) and its metabolite 1-PP were performed using and electrospray (ESP)-HPLC/MS (LC/MS) procedure in multi reaction monitoring mode. The methods were developed and performed at Organon Development GmbH, Waltrop, Germany. (Organon R&D RR report NL0031235 for Org 33062 and Org 25907 and report NL0030691 for 1-PP).

For gepirone and Org 25907, aliquots of plasma are spiked with (b) (4) as internal standard. Saturated sodium borate solution is added to the samples, and the samples are then extracted with (2:1) n-hexane:chloroform. The organic layer is evaporated to dryness and the residue is reconstituted in 100 µl of 50:50 acetonitrile/0.05 M ammonium acetate solution, pH 4.2. An aliquot is injected into the LC, and the analysis is performed using LC-MS/MS.

For 1-PP, aliquots of plasma are spiked with (b) (4) as internal standard. Saturated sodium borate solution is added to the samples, and the samples are then extracted with (2:1) n-hexane:chloroform. The organic layer is extracted with 1: formic acid solution. The organic layer is discarded and the analysis is performed on the 1% formic acid layer. An aliquot is injected into the LC, and the analysis is performed using LC-MS/MS.

Standard operating procedures (SOPs) were in place for sample preparation, the analytical procedure, acceptance of the bioanalytical run (system suitability and acceptance of calibration standards and quality control (QC) samples).

<u>Selectivity, Accuracy, Precision, and Recovery</u>

Selectivity was determined by analysis of blank samples from 10 different individuals with respect to gepirone, Org 25907, 1-PP, and internal standard. Ranges of the calibration curves, LOQ for each analyte, and nominal values for the QC samples are shown in Table 1 below.

Table 1. Summary of standard curves and QC samples for method validation for gepirone, Org 25907, and 1-PP.

Analyte	Range of Calibration Curve	LOQ	QC samples
Gepirone	0.100 ng/ml 0.200 ng/ml 0.500 ng/ml 1.0 ng/ml 2.0 ng/ml 10.0 ng/ml 20.0 ng/ml 50.0 ng/ml	0.1 ng/ml	0.1 ng/ml 0.3 ng/ml 5.0 ng/ml 40 ng/ml 400 ng/ml
3′-OH-gepirone	0.200 ng/ml 0.500 ng/ml 1.0 ng/ml 2.0 ng/ml 5.0 ng/ml 10.0 ng/ml 20.0 ng/ml 50.0 ng/ml	0.2 ng/ml	0.2 ng/ml 0.6 ng/ml 5.0 ng/ml 40 ng/ml 400 ng/ml
1-PP	0.200 ng/ml 0.500 ng/ml 1.0 ng/ml 2.0 ng/ml 5.0 ng/ml 10.0 ng/ml 20.0 ng/ml 50.0 ng/ml	0.20 ng/ml	0.2 ng/ml 0.6 ng/ml 5.0 ng/ml 40.0 ng/ml 400 ng/ml

A calibration curve consisted of 8 non-zero standards run in duplicate. Also included are a blank and a zero sample (plasma with internal standard) for each analytical run. Seven sets of calibration curves were performed for gepirone and Org 25907, and six series were performed for 1-PP. Linearity was established (mean r > .994), using linear weighted ($1/conc^2$) regression. The accuracy (calculated by the reviewer) and precision for each nonzero standard ranged from -12.0-10.2% and 3.7-7.4%, respectively, for gepirone and from -3.6-4.0% and from 2.9-6.2%, respectively, for Org 25907, and are therefore acceptable. For 1-PP the accuracy ranged from -4.0-3.5% and the precision ranged from 3.4-6.2%. These values are acceptable.

For gepirone and for Org 25907, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 5 quality control (QC) samples listed above for each analyte. The 400 ng/ml sample was diluted 10-fold with blank human plasma prior to analysis. The intra-day accuracy and precision ranged from -15.0-2.7% and from 4.7-9.9%, respectively for gepirone and from -14.2-8.5% and from 4.6-8.6%, respectively for Org 25907. Seven sets of QC samples run in triplicate (in three series there were 6

replicates) were used to determine inter-day accuracy and precision. Accuracy and precision ranged from -12.3-6.3% and 2.8-6.7%, respectively for gepirone except at the LOQ where accuracy was 5% and precision was 20%. For Org 25907, accuracy and precision ranged from -9.0-4.5% and from 4.5-9.6%, respectively. These values are acceptable.

For 1-PP, accuracy and precision were analyzed on one assay day for 6 replicates of each of the 5 quality control (QC) samples listed above. The 400 ng/ml sample was diluted 10-fold with blank human plasma prior to analysis. The intra-day accuracy and precision ranged from -2.6-7.5% and from 2.7-5.3%, respectively. Six sets of QC samples run in triplicate (in three series there were 6 replicates) were used to determine inter-day accuracy and precision. Accuracy and precision ranged from 0.8-15% and 1.3-10.7%, respectively. These values are acceptable.

Stability

Stability of gepirone, Org 25907, and 1-PP was demonstrated for the QC samples as follows. Long-term stability for 13 months at -20º C has been demonstrated. Freeze-thaw stability in plasma was demonstrated after three freeze-thaw cycles. In-process stability was demonstrated in human plasma for 24 hours at room temperature for gepirone and for 6 hours for Org 25907. For 1-PP in-process stability is extrapolated from the freeze thaw experiments in which the samples were at room temperature for 18.5 hours between freezing cycles. The Sponsor infers autosampler stability of extracted samples by inclusion of QC samples that must meet acceptance criteria at the beginning and end of each run.

According to the Method, the stability of the stock solutions is 6 months at 4º C. The data are not shown.

In conclusion, the Organon bioanalytical method used for analysis of plasma samples (in Study 28724) for gepirone, Org 25907, and 1-PP is adequately documented and validated.

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

/s/

Sally Yasuda
5/24/04 05:02:57 PM
BIOPHARMACEUTICS

Atiqur Rahman
5/25/04 09:27:18 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS (OCPB) REVIEW

NDA: **21-164**

Submission Dates: **5/18/01,**
8/31/01
1/23/02
1/31/02

OCPB Receipt Dates: **5/25/01**
9/17/01
1/24/02
2/1/02

Brand Name:	**Ariza®**
Generic Name:	**Gepirone HCL; ORG 33062**
Dosage Strength(s):	**20, 40, 60, and 80 mg extended-release oral tablets**
Indication:	**Depression**
Sponsor:	**Organon Inc., West Orange, NJ**
Type:	**1S NDA (NME)**
Primary Reviewer:	**Gerald J. Fetterly, Ph.D.**
Team Leader:	**Ramana Uppoor, Ph.D.**
Acting Team Leader:	**Vanitha Sekar, Ph.D.**

I. Executive Summary.

Recommendations.

The pharmacokinetic studies provided an understanding of the systemic exposure of gepirone and its major metabolites and are considered acceptable for this NDA from the Clinical Pharmacology and Biopharmaceutics view provided the sponsor adequately addresses the general and labeling comments. The General Comments given below and the Labeling Comments should be conveyed to the sponsor.

General Comments.

1. In the pivotal bioequivalence study comparing different strengths of gepirone ER, the 40 and 80 mg strengths were not shown to be bioequivalent to the 20 mg tablets, which were used in the clinical trials. No data were provided comparing the 60 mg strength to the 20 mg strength of gepirone ER. Upon approval of gepirone ER, only the 20 mg strength can be marketed.
2. In the food effect study, the data showed that food has a significant effect on gepirone bioavailability (approximately increase in C_{max} of 62%). This pronounced effect of food on the bioavailability of gepirone suggests that food intake relative to administration is crucial in affecting an augmentation in the bioavailability of the drug. We recommend that the sponsor conduct an *in vivo* study evaluating the effects of different meal compositions on gepirone ER pharmacokinetics. This information would help provide appropriate labeling recommendations regarding gepirone administration with respect to food consumption.
3. Throughout all of the pharmacokinetic studies, multiple peaks of gepirone and its metabolites, along with high variability in the data, were observed following administration. These fluctuations in absorption may be attributed to a pronounced effect of food on the bioavailability of the drug and/or enterohepatic recycling of the parent drug and its metabolites. We recommend *in vitro* assessment of Phase 2 metabolism since this may explain the presence of multiple peaks observed in patients receiving gepirone.
4. A strong pharmacokinetic interaction was observed between gepirone and ketoconazole (5-fold increase in gepirone concentrations). The effect of other CYP3A4 inhibitors that can be potentially coadministered with gepirone ER has not been evaluated. We recommend that the sponsor conduct an *in vivo* drug interaction study to evaluate the effects of gepirone coadministration with an intermediate inhibitor of CYP3A4, such as verapamil.
5. We recommend that the sponsor perform an *in vitro* assessment of (a) potential drug-drug interactions between gepirone and potent CYP3A4 inducers and (b) the drug's ability to induce CYP3A4 enzymes.
6. We recommend that the sponsor conduct an in vivo drug-drug interaction study with a potent CYP2D6 inhibitor to assess its effects on the pharmacokinetics of gepirone and its metabolites.
7. The results of the hepatic impairment study showed that the gepirone exposure was augmented 2-fold, in conjunction with a 3- and 2-fold reduction in the C_{max} and AUC

of 1-PP. The maintenance dose for gepirone in moderate hepatic impairment should not exceed 40 mg/day. The pharmacokinetics of gepirone has not been adequately characterized in severe hepatic impairment, thus it is recommended that the drug be not administered to this patient population.

8. The results of the renal impairment study suggested that the plasma levels of gepirone and its major metabolites were elevated by approximately 70% in patients with moderate and severe renal impairment. The maintenance dose for gepirone in moderate and severe renal impairment should not exceed 40 mg/day.
9. Gepirone plasma concentrations are increased 50-80% in the elderly. We recommend that the maintenance dose in the elderly should not exceed 40 mg/day.
10. The dissolution specifications at 12 h and 20 h should be changed to 65-85% and >85%, respectively.
11. We request that the sponsor clarify as to whether plasma gepirone (and any metabolites) concentrations were measured in any of the pivotal efficacy trials following administration of the IR and/or ER formulations of gepirone.
12. In all of the additional studies to be conducted, the sponsor should include gepirone and its two major metabolites, 1-PP and 3'OH-gepirone in the analysis.

Labeling Comments.

See the proposed label for OCPB comments (p. 16)

Gerald J. Fetterly, Ph.D. _____

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

CC: NDA 21-164, HFD-120, HFD-850 (PLee, LLesko), HFD-860 (Mehta, Uppoor, Sekar, Fetterly), CDR (Clin. Pharm./Biopharm.)

II. Table of Contents.

Executive Summary **2**

General Recommendations and Comments 2-3

Table of Contents **4-5**

Summary of Clinical Pharmacology and Biopharmaceutics Findings **6-7**

Question-Based Review **8-15**

Appendices **16**

Proposed Labeling With OCPB Comments 16-52

Individual Study Reviews 53

1. Bioavailability and Bioequivalence Studies.

- Gepirone Formulations 53
- Study 28718: Bioequivalence of Gepirone 40 or 80 mg ER Tablets Versus Multiple 20 mg ER Tablets 54-62
- Study FK-GBE-001: Relative Bioavailability of Gepirone ER Tablets Manufactured by (b) (4) and Bristol-Myers Squibb 62-66
- Study FK-GBE-002: Effect of Food on Gepirone ER Bioavailability ((b) (4) Tablets) 66-72
- Study CN105-046: Effect of Food on Gepirone ER Bioavailability (BMS Tablets) 72-76
- Study 59B4B-001-2587: Effect of Food on Gepirone IR Bioavailability (BMS) 76-80
- Study CN105-026: Relative Bioavailability of Gepirone ER Tablets and IR Capsules (BMS) 81-86
- Study CN105-060: Relative Bioavailability of Gepirone ER Tablets and IR Solution (BMS) 87-93

2. *In Vitro/In Vivo* Correlation **93-94**

3. Development of Dissolution Method and Specifications **94-97**

4. *In Vitro* Metabolism Studies

- Greenblatt Study 97-99
- Von Moltke Study 99-100

5. Plasma Protein Binding Studies

- (b) (4)-21085 101-102
- (b) (4)-11887 102-103

6. Gepirone ER and Special Populations Pharmacokinetic Studies

- Study CN105-049: Pharmacokinetics and Linearity During Single and Multiple Dose Administration of Gepirone ER 104-108
- Study CN105-068: Effect of Age and Gender on Pharmacokinetics During Steady-State 109-114
- Study FK-GBE-005: Pharmacokinetics of Gepirone and Metabolites in Patients with Hepatic Impairment 114-118
- Study 28708: Effect of Renal Impairment on the Pharmacokinetics of Gepirone and its Metabolites 119-125
- Study 28717: Drug Interaction Study Between Gepirone and Ketoconazole 125-131
- Study FK-GBE-004: Pharmacokinetics of Single and Multiple Dose Administration of Gepirone in Caucasians, Blacks, and Asians 131-135
- Study CN105-085: Steady-State Pharmacokinetics of High-Dose Gepirone ER 136-139
- Study FK-GBE-003: Pilot Pharmacokinetics of Gepirone ER 140-141

7. Gepirone IR Pharmacokinetic Studies

- Study CN105-007: Excretion and Mass Balance after Oral and Intravenous Administration of ^{14}C-Gepirone 142-146
- Study CN105-025: Metabolism of Gepirone IR in Poor and Extensive Metabolizers of Dextromethorphan 146-150
- Study CN105-012: Site of Gepirone Absorption 150-155
- Study CN105-005: Gepirone IR Pharmacokinetics in Young and Elderly 155-162
- Study 030L1-0001-1700: Rising Single Dose Pharmacokinetics and Tolerance 162-165
- Study 030L1-0002-1869: Single and Multiple Dose Pharmacokinetics and Linearity 166-169
- Study 59B4A-001-2579: Single and Multiple Dose Pharmacokinetics and Linearity 169-176

OCPB Filing/Review Form 177-179

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings.

Organon Inc. is seeking approval of Ariza™ (Gepirone HCL) for the treatment of depression in adults. Gepirone is an azapirone derivative that has both antidepressant and anxiolytic properties. The parent drug is a relatively selective partial agonist at serotonergic 5-HT_{1A} receptors with lower affinity for 5-HT_{1B} and other CNS receptors. In addition, 3'OH-gepirone, a metabolite of gepirone, has illustrated antidepressant activity as well. Bristol-Myers Squibb developed Gepirone originally as an immediate release formulation. Following review of the safety data and to encourage compliance in patients, an extended release formulation was developed by Bristol-Myers Squibb and subsequently licensed to Organon. The results of the clinical trials suggest that a minimum dose of 40 mg is efficacious. Thus, the recommended starting dose for Ariza extended release (ER) tablets consists of 20 mg/day, administered as a single dose, preferably in the morning. After assessing response to Ariza, the dose may be increased up to a maximum dose of 80 mg/day in 20 mg increments.

The pharmacokinetic characteristics of gepirone are as follows:

- Poor absorption; F=14-17%
- Linear PK for ER tablets; 20-80 mg (high intra- and inter-subject variability)
- Steady-state PK; approaches nonlinearity at higher doses
- Plasma Protein binding; 72% for gepirone and 59% for 1-PP
- Terminal half-life; 2.5-3 h (4.5-12 h following ER administration)
- Metabolism; 1-PP and 3'OH-gepirone (active), which are both present at higher plasma levels than parent drug.
    - Mediated *via* CYP3A4 and to a lesser extent 2D6
    - Other hydroxylated metabolites present in urine; mainly 3'5-dihyroxy-gepirone
- Elimination; 81% of administered dose in urine and 13% in feces

Table A. Results of Clinical Pharmacology Studies.

Prognostic Factor	Results (for parent drug only)	Recommendation
Age	C_{max} ↑ by 30 and 60% AUC_{ss} ↑ by 50-80% (women) ↑ by 50% (men)	Maintenance dose should not exceed 40 mg/day in the elderly.
Race	AUC ↓ 1.5-2-fold in Blacks and Asians compared to Caucasians	Titrate for individual patient
Gender	C_{max} = similar AUC = similar	Clinically NS
DDI with ketoconazole	AUC ↑ 5-fold	Contraindicated
Hepatic Impairment	C_{max} and AUC ↑ 2-fold (moderate) --severe not studied	Dose should not exceed 40 mg/day in moderate impairment; contraindicated in severe impairment
Renal Impairment	C_{max} ↑ by 74% (severe) AUC ↑ by 65-71% (moderate and severe)	Dose should not exceed 40 mg/day in moderate and severe impairment
Poor and Extensive Metabolizers of Dextromethorphan	C_{max} and AUC = similar	Clinically NS
Food Effect ***(in presence of high fat meal)***	C_{max} ↑ by 62% AUC ↑ by 24%	Difficult to make dosing recommendation due to continuous absorption of drug from ER product

Table B. Results of Biopharmaceutics Studies.

Prognostic Factor	Results	Recommendation
Bioequivalence of 20 mg BMS and (b) (4) ER product	Satisfied the BE criteria for C_{max} and AUC for gepirone (C.I.; 80-125%)	BMS and (b) (4) 20 mg gepirone ER formulations are bioequivalent
Bioequivalence of 20, 40, and 80 mg (b) (4) ER tablets	Failed acceptance criteria; 40 mg vs. 20 mg (C.I. for C_{max}; 1.02-1.35, AUC; 0.99-1.33), 80 mg vs. 20 mg (C.I. for C_{max}; 0.96-1.26)	40 and 80 mg strengths are not bioequivalent to the 20 mg strength. Thus, 40 and 80 mg strengths cannot be marketed. Only the 20 mg strength can be approved at this time.
Approval of 60 mg strength	No data submitted	60 mg strength cannot be marketed
Dissolution Method and Specifications	Profiles were similar for 20, 40, 60, and 80 mg strengths. **Method:** Medium; 0.01 N HCL Apparatus; USP paddle 2 Speed; 50 rpm **Specification:** Q: 15-25% at 1 h (b) (4)% at 5 h 65-86% at 12th h >(b) (4)% at 20th h	Change specification at 12th h to 65-85% and at 20th h to >85%.

IV. Question-Based Review.

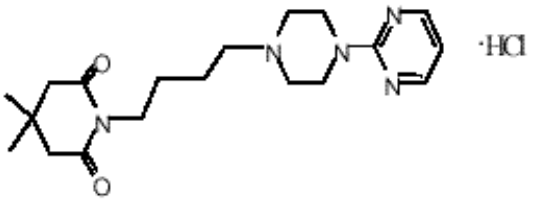
1. Introduction

What Are the Highlights of the Chemistry and Physicochemical Properties of the Drug?

Structure

The chemical name for gepirone is 3, 3 dimethyl-N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]glutarimide monohydrochloride. The molecular formula is $C_{19}H_{29}N_5O_2$•HCL and the molecular weight is 396 grams/mole. The chemical structure is shown in Figure A:

Figure A. Chemical Structure of Gepirone HCL.



Formulation and Manufacturing

Gepirone is a white to off-white, crystalline powder, which is lipophilic in character and highly soluble under acidic conditions. Gepirone ER tablets contain the active moiety, with colloidal silicon dioxide, red (b) (4) oxide, hydroxypropyl methylcellulose, microcrystalline cellulose, and magnesium stearate (Table C).

Table C. Composition of Gepirone ER Tablets (To-Be-Marketed).

Ingredient	Quantity per Tablet (mg)			
	20 mg	40 mg	60 mg	80 mg
Gepirone HCl	20.0	40.0	60.0	80.0
HPMC	(b) (4)			
Microcrystalline Cellulose, NF				
Colloidal Silicon Dioxide, NF				
Magnesium Stearate, NF				
Red (b) (4) Oxide ((b) (4)				
Yellow (b) (4) Oxide ((b) (4)				
(b) (4)				
HPMC = hydroxypropyl methylcellulose				

Initially, Bristol-Myers Squibb developed Gepirone originally as an immediate release formulation. Following review of the safety data and to encourage compliance in patients, an extended release formulation was developed by Bristol-Myers Squibb (BMS)

and subsequently licensed to Organon. The final ER formulations developed by BMS and (b) (4) were used in the pivotal clinical trials. (b) (4) is manufacturing the to-be-marketed formulation for Organon. The (b) (4) ER formulation of gepirone, which is to-be-marketed, is (b) (4) composition to the BMS product.

What Is the Proposed Mechanism of Action and Therapeutic Indication?

Gepirone is an azapirone derivative that has both antidepressant and anxiolytic properties. The parent drug is a relatively selective partial agonist at serotonergic 5-HT_{1A} receptors with lower affinity for 5-HT_{1B} and other CNS receptors. Gepirone is metabolized primarily to 1-PP and 3'OH-gepirone. 3'OH-gepirone has illustrated antidepressant activity as well. The proposed indication for gepirone is the treatment of depression in adults.

What Is the Proposed Dosage Regimen?

The recommended starting dose for Ariza extended release tablets consists of 20 mg/day, administered as a single dose, preferably in the morning. After assessing response to Ariza, the dose may be increased up to a maximum dose of 80 mg/day in 20 mg increments. The minimum effective dose observed is 40 mg/day.

2. Clinical Pharmacology

Was the bioanalytical method adequate for quantification of gepirone and any other moieties?

In all of the pharmacokinetic studies that BMS conducted, gepirone was administered orally and a validated GC/MS assay or a radioimmunoassay was used to quantitate the drug and its metabolites. In contrast, Organon developed a LC/MS assay that was utilized for the determination of gepirone and significant metabolite concentrations. Based on the assay performance in all pharmacokinetic studies, the assay is considered acceptable.

What Were the Clinical Endpoints Measured and Was An Exposure-Response Relationship Established for Efficacy and Safety?

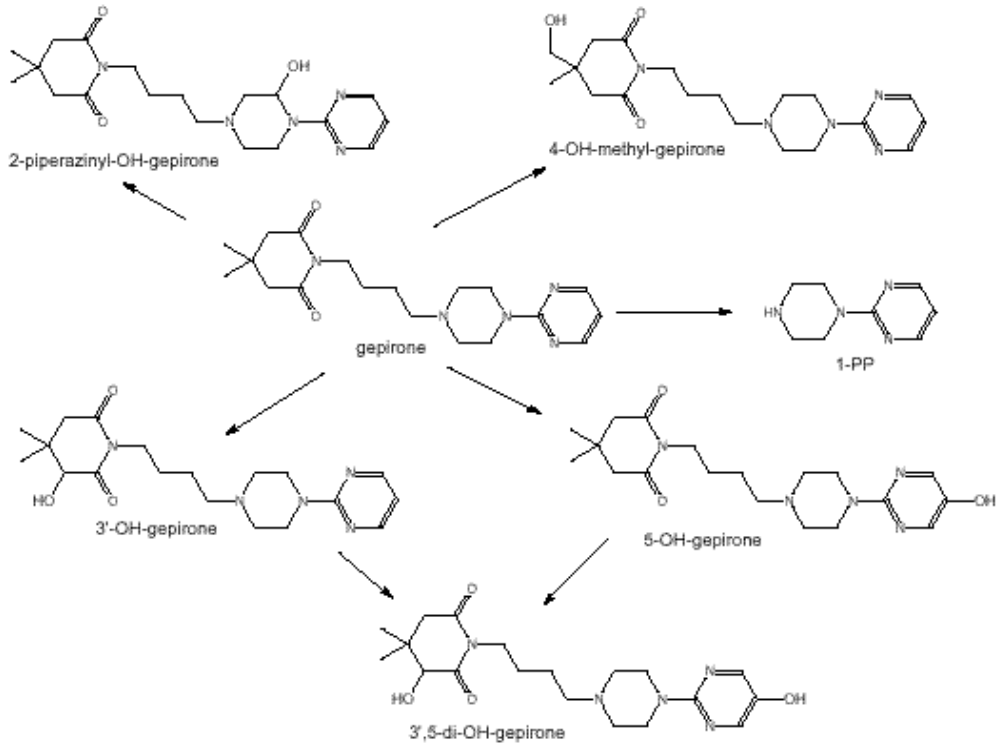
In order to evaluate the antidepressant activity of gepirone, the clinical endpoints measured included the CGI (Clinical Global Impression) improvement score and the Hamilton Depression scale. The clinical trial designs incorporated a flexible dose schedule where the patients were dose-titrated to effect and subsequently doses were decreased if any adverse events were observed. The sponsor analyzed the entire dose range (20-80 mg) by comparing it to placebo, and 40-80 mg was considered to be effective compared to placebo. The same analysis was performed for the observed adverse events. In addition, the majority of the patients in the clinical trials received less than 40 mg. Thus, a true dose-response relationship could not be determined for gepirone.

Absorption and Distribution

Several studies have shown that gepirone has a high first pass effect following oral absorption, resulting in poor bioavailability (F) of 14-17%. The absolute bioavailability ranged from 6-34%, which is indicative of the high within and between-subject variability. The parent drug is rapidly cleared from the plasma and has a large volume of distribution, which can be attributed to its lipophilic structure. Across all of the studies, various subjects exhibited multiple peaks of gepirone and its metabolites. The plasma protein binding of gepirone and 1-PP were 72% and 59%, respectively.

Metabolism

Figure 1. Metabolic Scheme of Gepirone in Humans.



Note: additional monohydroxy, dihydroxy, and trihydroxy metabolites appear to be present in human urine in small amounts (relative to the other hydroxylated metabolites).

Following oral administration of gepirone, less than 9% of the radioactivity in plasma was unchanged gepirone. In contrast, intravenous administration of the drug resulted in greater than 50% of unchanged drug in the plasma. Thus, gepirone is subjected to first pass metabolism by the liver and/or the gut wall. The biotransformation pathway for gepirone consists of conversion to two major metabolites, 1-PP and 3'OH-gepirone (Fig. 1). These two metabolites are present at higher concentrations in the plasma compared to gepirone, and 3'OH is considered to be also active in addition to the parent compound. 3', 5 dihyroxy-gepirone is the predominant metabolite in the urine. In addition, incubation of gepirone with ketoconazole, a potent CYP3A4 inhibitor, resulted in complete suppression of 1-PP formation and a reduction in the formation of 3'OH-

gepirone to 17%. Based on *in vitro* assessment of the metabolism, these routes are mediated by CYP3A4 and CYP2D6, with 3A4 being the predominant isozyme. Also, several other metabolites have been detected in the plasma and urine.

Elimination

Following oral administration, gepirone has a $t_{1/2}$ of approximately 3 h and is primarily cleared from the bloodstream as metabolites in urine. Following administration of the ER product, the terminal $t_{1/2}$ is approximately 6-12 h.

Are the pharmacokinetics of gepirone linear with respect to dose?

Table D: MEAN(SD) PHARMACOKINETIC PARAMETERS OF ARIZA™(gepirone HCl) EXTENDED-RELEASE TABLETS

(n=9)

	Day	Dose mg	C_{max} ng/mL	T_{max}[a] H	$t_{1/2}$ h	AUC ng/mL·hr
Single Dose	1	20	1.7(0.6)	5.0	10.0(5.8)	21.7(10.0)
	1	40	6.8(4.5)	5.0	8.4(5.5)	83.1(53.6)
	1[b]	40	5.08(3.37)	6.0	8.01(4.76)	69.3(46.5)
	1	75	9.14(3.7)	5.0	4.4(2.0)	121(69.9)
	1[b]	80	11.2(5.36)	5.5	7.93(8.26)	151(69.2)[c]
Steady State	8	20	3.2(1.3)	5.0	11.9(6.5)	41.4(20.2)
	8	40	8.8(3.2)	5.0	12.3(13.2)	121(45.6)
	8	75	16.4(7.8)	5.0	6.1(2.9)	210(119)

[a]Median

[b] Results from separate single dose pharmacokinetic study (n=32)

[c] $AUC_{0\text{-}tlast}$

C_{max}-measured peak plasma concentration

T_{max}-observed time of peak plasma concentration

$t_{1/2}$- plasma elimination half-life, calculated by $0.693/k_{elim}$

AUC-area under the curve, Single dose: $AUC_{0\text{-}24}$; Steady state: AUC_{ss}

Following single and multiple dose administration of the extended release formulation, a trend was observed that C_{max} and AUC showed a greater than proportional increase with respect to dose. But, due to high variability in the data, both C_{max} and AUC were found to be proportional in the dose range of 20-80 mg.

What is the effect of Food on the pharmacokinetics of Gepirone?

The effect of food on the bioavailability of gepirone ER was investigated following a single dose of 20 mg. The results showed that the C_{max} and AUC were increased by 62% and 24%, respectively in the presence of a high fat meal. Continuous absorption was observed, suggesting no indication of dose dumping when gepirone ER is administered with food. However, in order to make appropriate labeling recommendations regarding gepirone administration with respect to food intake, we recommend that the sponsor conduct a study that evaluates different meal compositions (See General Comments).

What is the inhibitory potential of Gepirone on various CYP450 isozymes?

Based on *in vitro* studies the inhibitory potential of gepirone and 1-PP on CYP450 isozymes was tested across a concentration range of 0-250 μM. As a result, the IC_{50} was determined to be greater than 250 μM (90 μg/ml) for both compounds. Clinically, plasma concentrations that were achieved following a dose of 80 mg (highest recommended dose) did not exceed 40 ng/ml. Thus, the possibility that gepirone and 1-PP can inhibit the activity of CYP450s is not plausible.

Do drug interactions exist between gepirone and ketoconazole, a potent inhibitor CYP3A4?

A potential pharmacokinetic interaction was investigated between gepirone and ketoconazole, a potent inhibitor of CYP3A4. Following a 20 mg dose of ER gepirone in combination with ketoconazole (200 mg b.i.d.), the results illustrated that plasma concentrations of the parent compound increased 5-fold while 1-PP decreased by approximately 2-3-fold, in line with the metabolic conversion of gepirone to 1-PP via the CYP3A4 route. In contrast, 3'OH metabolite concentrations increased 1.5-2-fold. As a result, concomitant administration of gepirone with ketoconazole is not recommended. Caution needs to be exercised when gepirone is coadministered with other drugs that are also inhibited by CYP3A4, such as erythromycin, itraconazole, ritonavir, and nefazadone. Dose reduction of gepirone may be warranted when gepirone is co-administered with these drugs (See Labeling Comments).

Is there an age or gender effect on the pharmacokinetics of Gepirone?

Following multiple dose administration of 20, 40, and 80 mg of gepirone ER, no significant gender differences were observed. In contrast, an age difference in pharmacokinetic parameters was observed, with the elderly exhibiting higher values of C_{max} by 30% and 60% in men and women, and AUC by 50-80% in men and women, compared with the young subjects. Thus, the maintenance dose of gepirone should not exceed 40 mg/day in the elderly.

What is the effect of hepatic impairment on the pharmacokinetics of Gepirone?

In the hepatic impairment study following administration of a 20 mg dose of the ER formulation, both gepirone and 1-PP pharmacokinetics were altered. The C_{max} and

AUC of gepirone were augmented approximately 2-fold, in conjunction with a 3- and 2-fold reduction in the C_{max} and AUC of 1-PP in hepatically impaired subjects. The gepirone maintenance dose should not exceed 40 mg/day in moderately impaired patients. Although, gepirone plasma concentrations in patients with mild hepatic impairment were increased, these differences were not statistically significant compared to normal subjects. Patients with severe hepatic impairment have not been adequately studied. Administration of gepirone to patients with severe hepatic impairment is not recommended.

What is the effect of renal impairment on the pharmacokinetics of Gepirone?

In the renal impairment study following a single dose of 40 mg of the ER formulation, plasma levels of gepirone, 1-PP, and 3'OH-gepirone increased in relation to the level of renal impairment. The C_{max} of gepirone increased by 74% in severely impaired patients, while the AUC was increased by 65-71% in moderately and severely impaired patients. In mildly impaired patients, the C_{max} and AUC of gepirone and its metabolites were elevated, but not statistically different from normal subjects. The gepirone maintenance dose should not exceed 40 mg/day in both moderate and severely impaired patients since the kidneys play a key role in the elimination of the metabolites of gepirone.

What is the effect of poor and extensive metabolizers of dextromethorphan on the pharmacokinetics of Gepirone?

Since gepirone is metabolized by CYP2D6 to a minor extent, a study was conducted to evaluate the bioavailability in poor and extensive metabolizers of dextromethorphan, using 15 mg b.i.d. of gepirone IR. No change was observed in C_{max} and AUC for gepirone in subjects with reduced activity of CYP2D6, but a 2.5 fold increase was shown in the AUC for 1-PP. Poor metabolizers of dextromethorphan compensated for the reduced metabolism of gepirone through the 2D6 pathway with an increase in the conversion of gepirone to 1-PP probably via the 3A4 route. The sponsor has not evaluated the effects of CYP2D6 inhibitors on the pharmacokinetics of gepirone. We recommend that the sponsor conduct such a study *in vivo* (See General Comments).

What is the effect of race on the pharmacokinetics of Gepirone?

The effect of race was investigated following single and multiple dose administration of 20 mg of gepirone ER. Gepirone plasma concentrations were 1.5-2-fold higher in Caucasians, compared to Blacks and Asians. The results showed that the difference in the extent of gepirone bioavailability was due to higher conversion of gepirone to 1-PP in Black and Asian subjects. No dose adjustment is warranted in Blacks and Asians since patients are dose-titrated to effect.

3. Biopharmaceutics.

Is the ER formulation manufactured by Bristol-Myers Squibb bioequivalent to the ER product manufactured by (b) (4) (to be marketed)?

C_{max} and AUC for gepirone and 1-PP for the test product were within 80-125% of the reference product. Thus, the BMS and (b) (4) ER products are bioequivalent.

Are the sponsor's proposed dissolution medium and specifications acceptable?

The following proposed dissolution method was set by Bristol-Myers Squibb and also utilized by (b) (4) in testing their ER formulation:

Apparatus:	**USP Apparatus 2 (rotating paddle)**
Speed:	**50 rpm**
Medium:	**0.01 N HCL (900 ml)**
Temperature:	**37 ˚C**

Table E. Drug Release Profiles of the Validation Batches *vs*. the Reference Product.

% Dissolved						
Control #	Strength, mg	1st Hr	5th Hr	12th Hr	20th Hr	Recovery
98 –013T	20	19	49	77	93	102
0300422	40	21	51	79	94	101
0300423	40	21	51	78	93	100
0300424	60	22	53	81	95	101
0300425	60	22	53	81	95	102
0300468	80	22	53	81	96	101
0300469	80	21	52	81	97	102

The dissolution profiles for the 20, 40, 60, and 80 mg strengths were similar and satisfied the specifications set by the sponsor.

The proposed specifications are reasonable and include:

Q: **15-25% at 1h**
(b) (4) **% at 5 h**
65-86% at 12h
> (b) (4) **% at 20 h**

We recommend that the specifications at 12 h and 20 h be changed to 65-85% and >85%, respectively.

Are the different strengths of Gepirone ER (20, 40, and 80 mg) bioequivalent?

A bioequivalence study was performed by the sponsor to compare the bioavailability of 1 x 40 mg with 2 x 20 mg and 1 x 80 mg with 4 x 20 mg tablets. The results of that study indicated that the bioequivalence criterion was not met on C_{max} and AUC for the comparison between 1 x 40 mg vs. 2 x 20 mg (90% C.I. for C_{max}; 1.02-1.35, AUC; 0.99-1.33). In addition, the C_{max} of the 1 x 80 mg was significantly higher than the 4 x 20 mg tablets (90% C.I. for C_{max}; 0.96-1.26). The 40 mg and 80 mg strengths of gepirone ER are not bioequivalent to the 20 mg ER strength. Thus, only the 20 mg strength of gepirone ER can be marketed upon approval at this time.

Can the sponsor be granted an approval for the 60 mg strength of gepirone ER?

The sponsor has not submitted any data to address this question. Thus, the 60 mg strength of gepirone ER is not recommended for approval.

Was the sponsor's development of an IVIVC adequate for gepirone ER?

The sponsor attempted to develop an *in vitro-in vivo* correlation with the ER formulation. (b) (4) The analysis performed was inadequate to establish an IVIVC for this product. (b) (4)

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

B. Clinical Pharmacology and Biopharmaceutics Individual Study Review

1. Gepirone Drug Formulations.

Table 1. Overview of the IR and ER formulations of Gepirone.

Formulation code / Batch properties		IR	ER-1	ER-2	ER-3	ER-4(BMS)	ER-4(b) (4))
Batch No.		E89C663	E89F089	E89F090	E89F091	E92B325	98-013T
Product No.		(b) (4)					commercial
Clinical studies in which the same formulation was used		CN105- 003 (E) CN105- 004 (E) CN105- 019 (E) CN105- 022 (E) CN105-025 (PK) CN105-026 (PK) CN105- 028 (E) CN105-029 (E) CN105-037 (E) CN105- 041 (E) CN105- 043 (E) CN105-045 (b) (4)) 03A7B- 004 (E) 03A7C- 001 (E)	CN105-026 (PK)	CN105-049 CN105-046 CN105-026 (all PK)	CN105-04 CN105-026 (both PK)	FK-GBE-001 (BE) CN105-060 CN105-068 CN105-085 (all PK) CN105-057* CN105-071* CN105-078* CN105-083* (all E)	FK-GBE-001 (BE) FK-GBE-002 (PK) FK-GBE-003 (PK) FK-GBE-004 (PK) FK-GBE-005 (PK)
Formulation		capsule	tablet	tablet	tablet	tablet	tablet
Org 33062	mg	5.0	10.0	10.0	25.0	20.0	20.0
	%	(b) (4)					
HPMC	mg						
	%						
(b) (4)	mg						
	%						
(b) (4)	mg						
	%						
Microcrystalline cellulose	mg						
	%						
Colloidal silicon dioxide	mg						
	%						
Magnesium stearate	mg						
	%						
Red iron oxide	mg						
	%						
Total mass	mg						

BE= bioequivalence; E = efficacy; PK = pharmacokinetic; (b) (4)
HPMC = hydroxypropyl methylcellulose.
* The 20 mg formulation used for these studies ((b) (4)) is very close to that for batch E92B325 ((b) (4)).
The only difference relative to batch E92B325 is (b) (4)
(b) (4)

In addition, two clinical studies (#134001 and 134002) utilized the (b) (4) 20 mg ER tablet.

2. Protocol 28718: Bioequivalence of Gepirone 20, 40, and 80 mg ER Tablets ([redacted] (b) (4)) in Healthy, Young, Extensive Metabolizers of Dextromethorphan, Male Subjects.

Investigator.

S. De Bruyn, M.D., Wavre, Belgium.

Objectives.

The objective of this study was to (1) determine the bioequivalence of one 40 mg gepirone ER tablet vs. 2 x 20 mg tablets and one 80 mg tablet vs. 4 x 20 mg tablets, investigate the dose proportionality over the dose range 40-80 mg, and (3) investigate the safety of the above mentioned dose regimens.

Study Design and Methods:

This study consisted of an open-label, randomized, four-way single dose, crossover design. Each period was separated by a one-week washout period between treatments. During each period, a single dose of one formulation strength of gepirone was administered in the morning following a 10-h overnight fast and no food was permitted until 4 h after administration. Serial blood samples were collected over a 72-h period following each dose and were assayed for gepirone, 1-PP, and 3'OH-gepirone concentration utilizing a validated LC/MS method.

Subjects:

Thirty-seven healthy male volunteers (age range: 18 - 50 yrs; all Caucasian) were enrolled and thirty-two completed the study. The completed subjects received the following treatments in a randomized order as a single dose:

(1) 1 x 40 mg ER tablet;

(2) 2 x 20 mg ER tablets;

(3) 1 x 80 mg ER tablet;

(4) 4 x 20 mg ER tablets.

Test Product, Dose, and Mode of Administration:

The test and reference formulations of gepirone were supplied to the investigator by (b) (4), which included:

- (b) (4) ER tablet formulation, product #(b) (4) (Lot # 0581394), containing 20 mg of gepirone HCl. This strength was used as the reference product.
- (b) (4) ER tablet formulation, product #(b) (4) (Lot # 0300423), containing 40 mg of gepirone HCl. This strength was a test formulation.
- (b) (4) ER tablet formulation, product #(b) (4) (Lot # 0300468), containing 80 mg of gepirone HCl. This strength was also a test formulation.

Assay Validation:

An LC/MS assay was used to quantitate gepirone, 1-PP, and 3'OH in this study. The calibration curves in plasma were linear for the concentration range from 0.1 – 10.0 ng/ml for gepirone, 0.20-10.0 ng/ml for 1-PP, and 0.25-10.0 ng/ml for 3'OH ($r \geq 0.993$ for all analytes). Low, medium, and high QC samples were prepared at concentrations of 0.3, 4.0, and 8.0 ng/ml for gepirone and 3'OH, and 0.6, 4.0, and 8.0 ng/ml for 1-PP. The deviations from the mean for gepirone were within 15.2% for the low QCs, 12.6% for the medium QCs, and 13.1% for the high QCs. The corresponding values for 1-PP were 14.8%, 11.5%, and 14.0%, respectively. The corresponding values for 3'OH were 14.5%, 12.0%, and 13.2%, respectively.

Criteria for Evaluation:

Various pharmacokinetic parameters were determined for gepirone, 1-PP, and 3'OH-gepirone, which included C_{max}, t_{max}, AUC, V_z, CL, and $t_{1/2}$. In addition, they were normalized to a 1-mg dose. Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Statistical analysis was performed using an ANOVA for C_{max} and AUC from which the point estimates with their 90% confidence intervals were derived for average bioequivalence testing. For t_{max}, the ANOVA was performed on ranks and the 95% non-parametric confidence interval of the true difference was calculated. Additionally, bioequivalence testing was performed post-hoc using the population approach. Also, dose proportionality was assessed using the same ANOVA using the data collected from the 40 and 80 mg doses.

Results.

Figure 2. Mean Gepirone Plasma Concentrations.

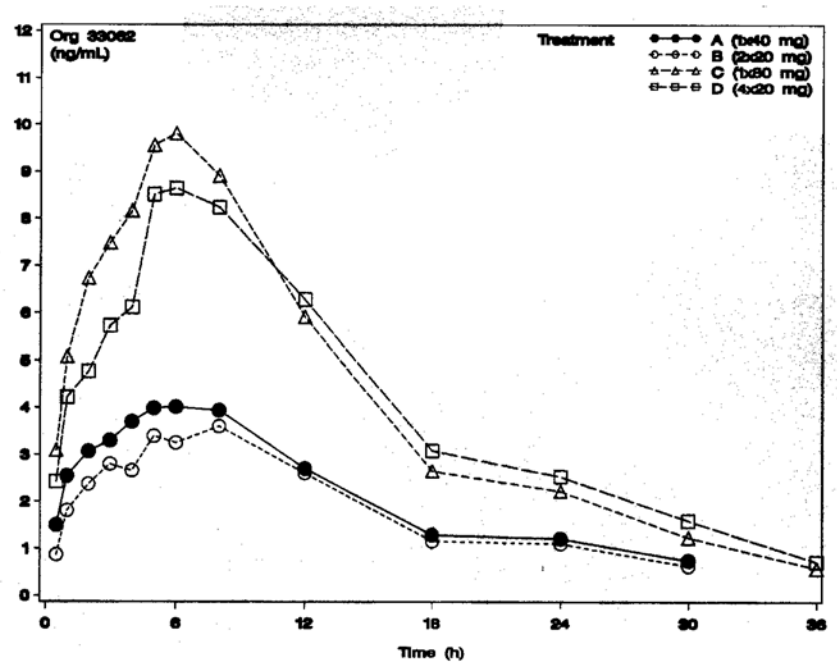


Figure 3. Mean 1-PP Plasma Concentrations.

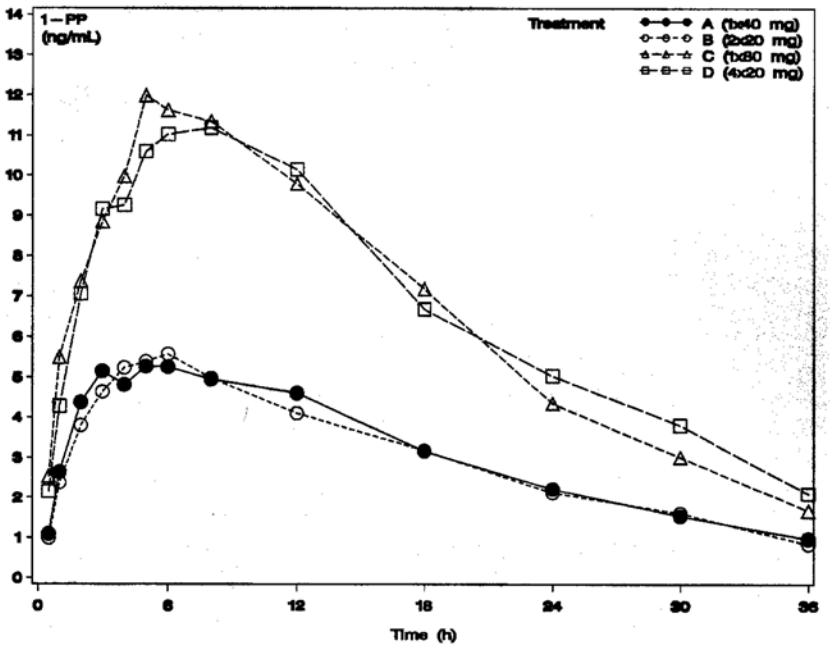


Figure 4. Mean 3'OH-gepirone Plasma Concentrations.

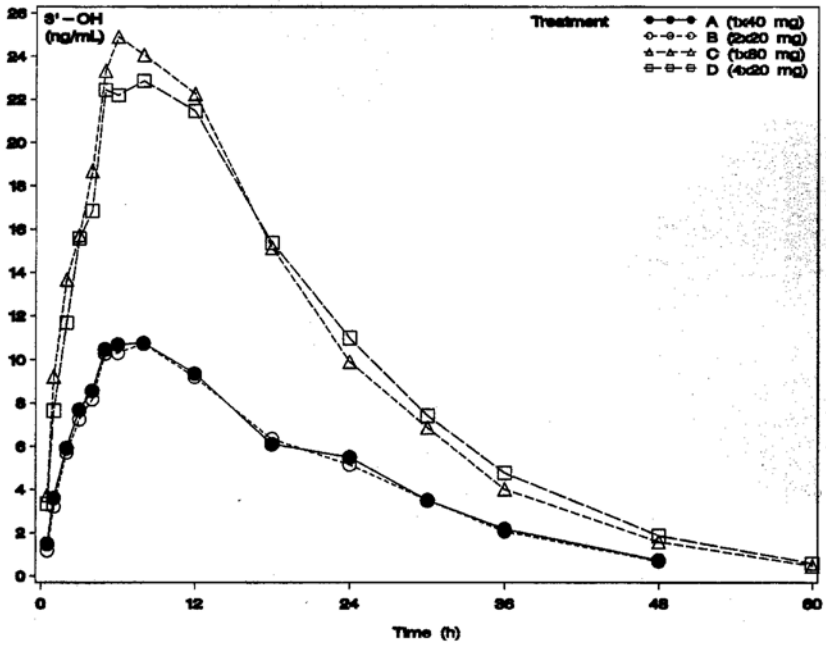


Table 2. Mean (SD) Pharmacokinetic Parameters.

Parameter		Treatment			
		A (1 x 40 mg)	B (2 x 20 mg)	C (1 x 80 mg)	D (4 x 20 mg)
Org 33062					
C_{max}	(ng/mL)	5.08 (3.37)	4.15 (1.95)	11.2 (5.36)	10.2 (7.05)
t_{max}[1]	(h)	6.0 (1.0 - 12.0)	6.0 (2.0 - 12.0)	5.5 (2.0 - 12.0)	6.0 (0.5 - 12.0)
$AUC_{0\text{-last}}$	(ng.h/mL)	69.3 (46.5)	59.7 (27.8)	151 (69.2)	149 (89.8)
$AUC_{0\text{-}\infty}$	(ng.h/mL)	74.4 (48.6)	64.1 (29.1)	158 (73.4)	155 (88.1)
$t_{½}$	(h)	8.01 (4.76)	7.71 (5.87)	7.93 (8.26)	8.22 (9.12)
1-PP					
C_{max}	(ng/mL)	6.78 (3.30)	6.46 (3.46)	14.2 (10.0)	13.1 (7.05)
t_{max}[1]	(h)	5.0 (2.0 - 12.0)	5.5 (2.0 – 12.0)	5.0 (3.0 – 18.0)	6.0 (2.0 – 12.0)
$AUC_{0\text{-last}}$	(ng.h/mL)	119 (87.2)	114 (91.8)	250 (214)	260 (200)
$AUC_{0\text{-}\infty}$	(ng.h/mL)	128 (88.0)	122 (91.4)	259 (213)	268 (202)
$t_{½}$	(h)	10.5 (8.93)	9.49 (6.14)	9.43 (6.06)	7.41 (3.34)
3'-OH					
C_{max}	(ng/mL)	12.0 (3.37)	11.7 (4.08)	26.9 (7.24)	25.1 (6.99)
t_{max}[1]	(h)	6.0 (4.0 - 24.0)	8.0 (3.0 – 12.0)	6.0 (4.0-12.0)	8.0 (4.0 – 12.0)
$AUC_{0\text{-last}}$	(ng.h/mL)	249 (87.4)	244 (97.7)	551 (170)	557 (181)
$AUC_{0\text{-}\infty}$	(ng.h/mL)	255 (89.0)	254 (98.4)	558 (170)	562 (183)
$t_{½}$	(h)	7.80 (2.91)	8.60 (3.06)	8.14 (3.30)	7.40 (2.13)

[1] median (range)

Table 3. Results of Average Bioequivalence Testing for Gepirone.

Comparison: 1 x 40 mg (test) versus 2 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.108	0.093	1.16	1.02 – 1.32	Indeterminant
dn-$AUC_{0-\infty}$	1.61	1.44	1.11	0.97 – 1.27	Indeterminant
dn-$AUC_{0-tlast}$	1.50	1.34	1.12	0.98 – 1.28	Indeterminant
Comparison: 1 x 80 mg (test) versus 4 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.123	0.105	1.17	1.02 – 1.33	Indeterminant
dn-$AUC_{0-\infty}$	1.71	1.68	1.02	0.89 – 1.16	Bioequivalent
dn-$AUC_{0-tlast}$	1.63	1.59	1.03	0.90 – 1.18	Bioequivalent

Table 4. Results of Average Bioequivalence Testing for 1-PP.

Comparison: 1 x 40 mg (test) versus 2 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.153	0.143	1.07	0.98 – 1.17	Bioequivalent
dn-$AUC_{0-\infty}$	2.72	2.53	1.07	0.98 – 1.18	Bioequivalent
dn-$AUC_{0-tlast}$	2.47	2.30	1.07	0.98 – 1.17	Bioequivalent
Comparison: 1 x 80 mg (test) versus 4 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.151	0.146	1.03	0.94 – 1.13	Bioequivalent
dn-$AUC_{0-\infty}$	2.60	2.74	0.95	0.87 – 1.04	Bioequivalent
dn-$AUC_{0-tlast}$	2.47	2.62	0.94	0.86 – 1.03	Bioequivalent

Table 5. Results of Average Bioequivalence Testing for 3'OH-gepirone.

Comparison: 1 x 40 mg (test) versus 2 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.290	0.278	1.04	0.95 – 1.15	Bioequivalent
dn-$AUC_{0-\infty}$	6.06	5.97	1.02	0.93 – 1.11	Bioequivalent
dn-$AUC_{0-tlast}$	5.91	5.72	1.03	0.94 – 1.14	Bioequivalent
Comparison: 1 x 80 mg (test) versus 4 x 20 mg (reference)					
Parameter	**Geom. mean test formulation**	**Geom. mean reference formulation**	**Point Estimate test/ref.**	**90% Confidence interval**	**Conclusion**
dn-C_{max}	0.325	0.303	1.07	0.98 – 1.18	Bioequivalent
dn-$AUC_{0-\infty}$	6.62	6.67	0.99	0.90 – 1.09	Bioequivalent
dn-$AUC_{0-tlast}$	6.54	6.61	0.99	0.90 – 1.09	Bioequivalent

Table 6. Inter- and Intra-subject Coefficients of Variation.

Compound	Parameter	Inter-subject CV (%)	Intra-subject CV (%)
Org 33062	dn-C_{max}	47.7	32.8
	dn-$AUC_{0-\infty}$	47.5	32.9
	dn-$AUC_{0-tlast}$	48.1	33.8
1-PP	dn-C_{max}	46.0	21.7
	dn-$AUC_{0-\infty}$	62.0	22.3
	dn-$AUC_{0-tlast}$	66.1	21.1
3'-OH	dn-C_{max}	17.1	23.1
	dn-$AUC_{0-\infty}$	25.2	22.7
	dn-$AUC_{0-tlast}$	25.6	23.1

Average BE Testing.

When the 1 x 40 mg gepirone ER tablet was compared with 2 x 20 mg tablets, the rate and extent of absorption was found to be equivalent for 1-PP and 3'OH-gepirone (Tables 4, 5). In contrast, the C_{max} and AUC for gepirone were significantly greater for the 1 x 40 mg tablet compared to the 2 x 20 mg tablets; thus bioequivalence could not be established between the 20 and 40 mg strengths (Table 3).

The sponsor also compared the 1 x 80 mg strength tablet to 4 x 20 mg tablets. For all three compounds (gepirone, 1-PP, and 3'OH), bioequivalence was proven for AUC between the test and reference (Tables 3-5). C_{max} was also equivalent for the two metabolites, but was not found to be equivalent for gepirone since a slightly higher C_{max} was observed for the 80 mg strength. Hence, BE could not be established between the 20 and 80 mg strengths either.

Table 7.

Table 14 Results of the population bioequivalence testing for Org 33062

Comparison: 1 x 40 mg (test) versus 2 x 20 mg (reference)						
Parameter	s_T^2	s_R^2	s_d^2	$\theta_1(0.50)$	$\theta_1(0.95)$	**Conclusion*)**
dn-C_{max}	0.3103	0.2099	0.1113	0.519	1.010	Bioequivalent
dn-$AUC_{0-\infty}$	0.2782	0.2282	0.1361	0.229	0.755	Bioequivalent
dn-$AUC_{0-tlast}$	0.2785	0.2270	0.1321	0.257	0.811	Bioequivalent
Comparison: 1 x 80 mg (test) versus 4 x 20 mg (reference)						
Parameter	s_T^2	s_R^2	s_d^2	$\theta_1(0.50)$	$\theta_1(0.95)$	**Conclusion*)**
dn-C_{max}	0.3318	0.3755	0.2699	-0.033	0.401	Bioequivalent
dn-$AUC_{0-\infty}$	0.4063	0.3114	0.2747	0.268	0.876	Bioequivalent
dn-$AUC_{0-tlast}$	0.4154	0.3449	0.3233	0.193	0.768	Bioequivalent

<u>BE Testing using the Population Approach (Sponsor's Analysis).</u>

When comparing the 1 x 40 mg tablet with the 2 x 20 mg tablets using a population BE approach, they were found to be bioequivalent with respect to C_{max} and AUC for all three compounds (Table 7).

Similarly, the 80 mg tablet was bioequivalent to the 4 x 20 mg tablets with respect to both C_{max} and AUC for all analytes.

Amendment.

Based on an audit by the Division of Scientific Investigation at the FDA, study 28718 was re-evaluated.

Study 28718: Re-Evaluation of Bioequivalence and Dose Proportionality Data Excluding Subjects Who Vomited After Dosing

Bioequivalence and dose proportionality testing in Study 28718 has been reevaluated by leaving out Subjects (b) (6). These subjects had vomitted during Periods 4, 4 and 1 respectively of the study at times relatively shortly after dosing as shown in Table 1.

Table 1 Occurrence of vomiting relative to time of dosing

Subject No.	Treatment	Period No.	Dosing date/time	Start vomiting date/time	Start vomiting after dosing (h:min)
(b) (6)	1x80 mg	4		(b) (6)	3:39
	1x80 mg	4			3:29
	1x80 mg	1			1:34

As can be seen from Tables 2-4, the results for Org 33062 are similar with or without Subjects (b) (6). The same holds true for the metabolites 1-PP and 3'-OH-gepirone (these results are shown in the Appendix). Details on the statistical analyses without Subjects (b) (6) can be found in the Appendix.

Table 2 Comparison 1x40 mg versus 2x20 mg for Org 33062

Dose-normalized Parameter	All subjects			Without subjects (b) (6)		
	Point Estimate	90 % Confidence Interval	Conclusion	Point Estimate	90 % Confidence Interval	Conclusion
$AUC_{0\text{-}tlast}$	1.12	0.98 – 1.28	Indeterminant	1.15	0.99 – 1.33	Indeterminant
$AUC_{0\text{-}\infty}$	1.11	0.97 – 1.27	Indeterminant	1.13	0.98 – 1.31	Indeterminant
C_{max}	1.16	1.02 – 1.32	Indeterminant	1.17	1.02 – 1.35	Indeterminant

Table 3 Comparison 1x80 mg versus 4x20 mg for Org 33062

Dose-normalized Parameter	All subjects			Without subjects (b) (6)		
	Point Estimate	90 % Confidence Interval	Conclusion	Point Estimate	90 % Confidence Interval	Conclusion
$AUC_{0\text{-}tlast}$	1.03	0.90 – 1.18	Bioequivalent	0.98	0.85 – 1.14	Bioequivalent
$AUC_{0\text{-}\infty}$	1.02	0.89 – 1.16	Bioequivalent	0.97	0.84 – 1.12	Bioequivalent
C_{max}	1.17	1.02 – 1.33	Indeterminant	1.10	0.96 – 1.26	Indeterminant

Table 4 Dose Proportionality Testing for Org 33062

Dose-normalized Parameter	p-value comparison 1 x 40 mg versus 1 x 80 mg	
	All subjects	Without subjects (b) (6)
$AUC_{0\text{-}tlast}$	0.2840	0.5219
$AUC_{0\text{-}\infty}$	0.4358	0.7060
C_{max}	0.1113	0.2317

As a result of an inspection of Study 28718 by the Division of Scientific Investigation, the sponsor re-analyzed the data without some subjects whom experienced emesis following drug administration (See Amendment above). The results of the re-

evaluation did not change the original outcome. Thus, the average bioequivalence criterion was not met for both C_{max} and AUC when 1 x 40 mg and 2 x 20 mg tablets were compared, as well as the 1 x 80 mg *vs*. the 4 x 20 mg tablets.

The incidence of adverse events was higher following intake of 1 x 80 mg gepirone (93 AEs observed in 82% of the subjects) and after 4 x 20 mg (93 AEs observed in 89% of the subjects) than after 1 x 40 mg (36 AEs observed in 63% of the subjects) and after 2 x 20 mg (34 AEs observed in 52% of the subjects). These differences were particularly observed for CNS, gastro-intestinal, and general disorders.

Conclusions.

The bioequivalence criteria were not met for the test tablets (20 vs. 40 mg and 20 vs. 80 mg). Dose proportionality could not be adequately assessed because only two doses were considered in the statistical analysis. The 40 mg and 80 mg ER strengths of gepirone are not approvable based on the results of this study.

3. Protocol FK-GBE-001: Bioequivalence of Bristol-Myers Squibb Gepirone 20 mg ER Tablets and Fabre-Kramer Pharmaceuticals Inc. (b) (4) 20 mg MR Tablets ((b) (4)).

Objectives.

The objective of this study was to compare the pharmacokinetics of gepirone 20 mg MR (manufactured by (b) (4)) with that of gepirone 20 mg ER (manufactured by BMS) in normal healthy males under fasted conditions.

Study Design and Methods:

This study consisted of an open-label, randomized, single dose, 2-period, crossover design, which was balanced for first order residual effects (Fig. 5). Each period was separated by a 5-day washout period between doses. Gepirone was administered in the morning following a 10-h overnight fast and no food was permitted until 4 h after administration. Serial blood samples were collected over a 48-h period following each dose and were assayed for gepirone and 1-PP concentration utilizing a validated LC/MS method. The schedule of study assessments is shown in Table 8.

Figure 5. Study Design.

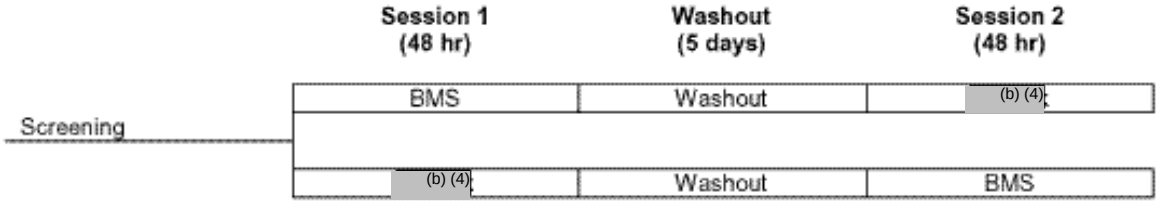


Table 8. Schedule of Study Assessments.

Period Visit	Screening [a] 1	Period 1 2	Period 2 [b] 3
Informed Consent	X		
Medical History	X		
Complete Physical Examination	X		X
12-lead Electrocardiogram	X		
Brief Physical Examination		X	X
Vital Signs	X	X	X
Clinical Laboratory (hematology, chemistry, urinalysis)	X		X
HIV Screen	X		
Hepatitis Screen	X		
Urine Drug Screen	X	X	X
Admission to Clinic (evening prior to dose)		X	X
Assessment of Adverse Experiences		X	X
Dose Administration		X	X
Blood Sample Collection [c]		X	X

(a) conducted 7 – 21 days prior to Period 1
(b) conducted 7 days after dose administration during Period 1
(c) collected at: 0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, and 48 hours after dose administration

Subjects:

Thirty-six healthy male volunteers plus four alternates (age range: 18 - 50 yrs; 30 Caucasian, 1 Black, and 7 Hispanic) were recruited. Thus, 38 subjects were enrolled and 36 completed the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone was supplied to the investigator by either (b) (4) or Bristol-Myers Squibb, which included:

- (b) (4) ER tablet formulation, product #(b) (4) (Lot # 98-013T), containing 20 mg of gepirone HCl. Each subject received a total daily dose of 20 mg.
- BMS ER tablet formulation, product #(b) (4) (Lot # E92B325), containing 20 mg of gepirone HCl. Each subject received a total daily dose of 20 mg.

Assay Validation:

An LC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curves in plasma were linear for the concentration range from 0.025 – 2.5 ng/ml for gepirone and 0.20-10.0 ng/ml for 1-PP ($r \geq 0.997$ for gepirone and $r \geq 0.994$ for 1-PP). Low, medium, and high QC samples were prepared at concentrations of 0.075 0.75, and 2.0 ng/ml for gepirone and 0.3, 3.5, and 9.0 ng/ml for 1-PP. The deviations from the mean for gepirone were within 9.8% for the low QCs, 10.9% for the medium QCs, and 11.8% for the high QCs. The corresponding values for 1-PP were 10.1%, 9.1%, and 10.5%, respectively.

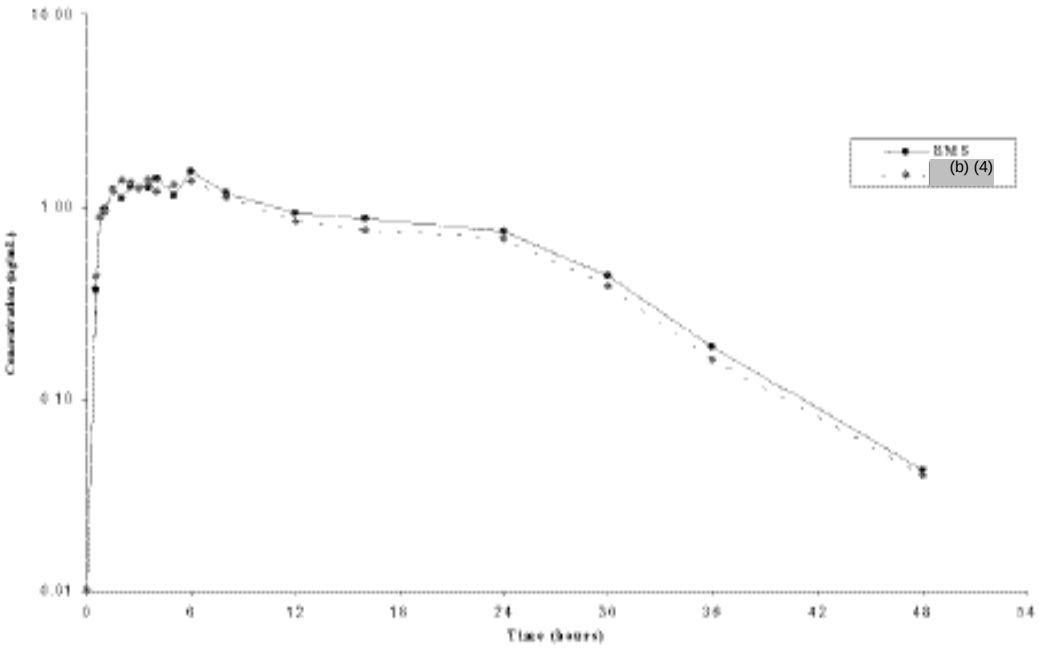
Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of C_{max}, t_{max}, and AUC in order to evaluate the bioequivalence of the two formulations. Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Statistical analysis was performed using a two, one-sided t-test procedure on ln-transformed pharmacokinetic parameters. The lower and upper 90% confidence limits were calculated for both C_{max} and AUC.

Results.

Figure 6. Mean Gepirone Plasma Concentrations.



BEST AVAILABLE COPY

Table 9. Gepirone and 1-PP Bioequivalence Results.

Parameter	Gepirone MR ([redacted] (b) (4)) (1)	Gepirone ER (BMS) (1)	Ratio Test/Ref.	Lower 90% C.I.	Upper 90% C.I.
Gepirone					
AUC_{24} (ng-h/ml)	19.7	20.3	0.97	0.89	1.06
AUC_t (ng-h/ml)	21.6	22.7	0.95	0.87	1.05
AUC (ng-h/ml)	22.5	24.2	0.93	0.83	1.04
C_{max} (ng/ml)	1.50	1.49	1.01	0.86	1.18
1-PP					
AUC_{24} (ng-h/ml)	78.9	74.8	1.06	0.96	1.16
AUC_t (ng-h/ml)	91.1	86.7	1.05	0.95	1.17
AUC (ng-h/ml)	105	98.8	1.06	0.94	1.19
C_{max} (ng/ml)	5.62	5.65	0.99	0.92	1.08

(1) Geometric least-square means from ANOVA

(2) Ratio = exponent of the difference (test – ref.) between ln-transformed means

(3) Upper and lower 90% confidence limits are for the difference between test and reference.

For gepirone, plasma concentrations peaked between 3 and 8 h (Fig. 6). For both products, the wide range in t_{max} values was due to the observation of multiple peaks for each individual. The terminal elimination phase of gepirone was longer relative to that seen for an immediate release formulation, which was characteristic for the absorption rate being slower than the elimination rate for an extended release formulation. The mean ratios for AUC and C_{max} were 0.93 and 1.01 for gepirone and 1.06 and 0.99 for 1-PP, respectively (Table 9). For the formulations, the test C_{max} and AUC for gepirone and 1-PP were within 80-125% of the reference product.

Table 10. Test and Reference Product Dissolution Results.

	% of Labeled Claim Dissolved		
Time (hr)	Gepirone MR ([redacted]) Mean (range)[1]	Gepirone ER (BMS) Mean (range)[2]	Gepirone ER (BMS) Mean [3]
1	17 [redacted]	19 ([redacted])	16
3	34	-	
5	46	50 ([redacted])	48
8	60	-	
10	70	-	
12	76	77 ([redacted])	74
15	84	-	
18	91	-	
20	93	97 ([redacted])	92
Total Recovered	99 ([redacted]	-	

[1] mean (range) of 12 units tested
[2] mean (range) of 6 units tested by BMS at the time of manufacture
[3] mean of 6 units re-tested by [redacted] in January 1998 (range not reported)

Dissolution testing was performed utilizing USP Apparatus 2 (Paddle) at 50 rpm in 900 ml 0.01 N HCL. The release specifications were 15-25% at 1 h, [redacted]% at 5 h, [redacted]% at 12 h, and ≥ [redacted]% at 20 h. The test and reference products were tested under the same specifications and both products passed (Table 10). Thus, the dissolution profiles were similar between both products.

Conclusions.

In conclusion, the gepirone extended release product manufactured by BMS and the one produced by [redacted] were bioequivalent based on similar concentration-time profiles of the parent drug and its metabolite.

4. Protocol FK-GBE-002: Effect of Food on the Bioavailability of Gepirone 20 mg ER Tablets ([redacted]).

Investigator.

[redacted]

Objectives.

The objective of this study was to compare the bioavailability of gepirone under fed and fasted conditions following a 20 mg dose.

Study Design and Methods:

This study was an open label, randomized, single-dose, two-way crossover design that was balanced for first order residual effects (Fig. 7). Each 48 h treatment period was separated by a five-day interval. During one session, doses were administered in the morning following a 10 h overnight fast and no food was permitted until 4 h after dose

administration. In the alternate session, the subjects fasted overnight and received a standard high fat breakfast in the morning; the dose of gepirone was administered within 15 min after completing the meal. Serial blood samples were collected over a 48 h period following each dose (Table 11) and were assayed for gepirone, 1-PP, and 3-OH gepirone utilizing a validated LC/MS method.

During the session when gepirone was administered with food, all subjects received the same, standardized high fat breakfast, which consisted of:

- One buttered english muffin
- One fried egg
- One slice American cheese
- One slice Canadian bacon
- One serving of hash–brown potatoes
- Six fluid ounces of orange juice
- Eight fluid ounces of whole milk

Figure 7. Study Design.

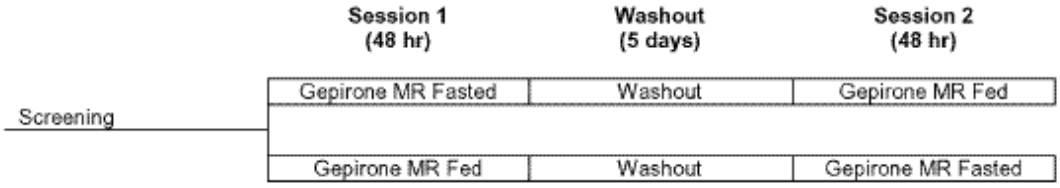


Table 11. Schedule of Study Assessments.

Period Visit	Screening [a] 1	Period 1 2	Period 2 [b] 3
Informed Consent	X		
Medical History	X		
Complete Physical Examination	X		X
12-lead Electrocardiogram	X		
Vital Signs	X	X	X
Clinical Laboratory (hematology, chemistry, urinalysis)	X		X
HIV Screen	X		
Hepatitis Screen	X		
Urine Drug Screen	X	X	X
Admission to Clinic (evening prior to dose)		X	X
Assessment of Adverse Experiences		X	X
Dose Administration		X	X
Blood Sample Collection [c]		X	X

(a) conducted within 1 to 3 weeks prior to Period (Session) 1
(b) conducted 7 days after dose administration during Period 1
(c) collected at: 0, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36, and 48 hours after dose administration

Subjects:

Twenty-seven healthy male volunteers (age range: 18-50 yrs; weight range: 65-91 kg) were recruited into the study and 24 completed it.

Test Product, Dose, and Mode of Administration:

The MR tablet formulation of gepirone that was supplied to the investigator by the (b) (4) included:

- Gepirone HCl was prepared as modified release tablet formulation containing 20 mg of gepirone, product # (b) (4) (Lot # 98-013T).

Assay Validation:

An LC/MS assay was used to quantitate gepirone and 1-PP in this study. For each run, the calibration curves were linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.998$ for gepirone, $r \geq 0.996$ for 1-PP, and $r \geq 0.992$ for 3-OH). Low medium, and high QC samples were prepared at concentrations of 0.15, 1.5, and 3.0 ng/ml for gepirone, at 1.5, 7.5, and 15 ng/ml for 1-PP, and at 0.75, 4, and 8 ng/ml for 3-OH. The between day variability for the QC samples in all runs did not exceed 11.2% for gepirone, 9.0% for 1-PP, and 15% for 3-OH. For the accuracy of the method, the deviations from the mean for gepirone did not exceed 0.8% for the low QC sample, 1.4% for the medium QC sample and 6.9% for the high QC sample. For 1-PP, the deviations from the mean were 0.2% for the low QC sample, 0.5% for the medium QC sample, and 4.2% for the high QC sample. For 3-OH, the deviations from the mean were 3.3% for the low QC sample, 0.5% for the medium QC sample, and 9.1% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0-\infty}$), half-life ($t_{1/2}$) and mean residence time (MRT).

Mean pharmacokinetic parameters were tested for differences due to sequence, period, subject within sequence, and treatment utilizing an analysis of variance. Statistical analysis was performed using two, one-sided t-test procedure on ln-transformed C_{max} and AUC and significance was set at the α=0.05 level.

Results.

Figure 8. Mean Gepirone Plasma Concentrations.

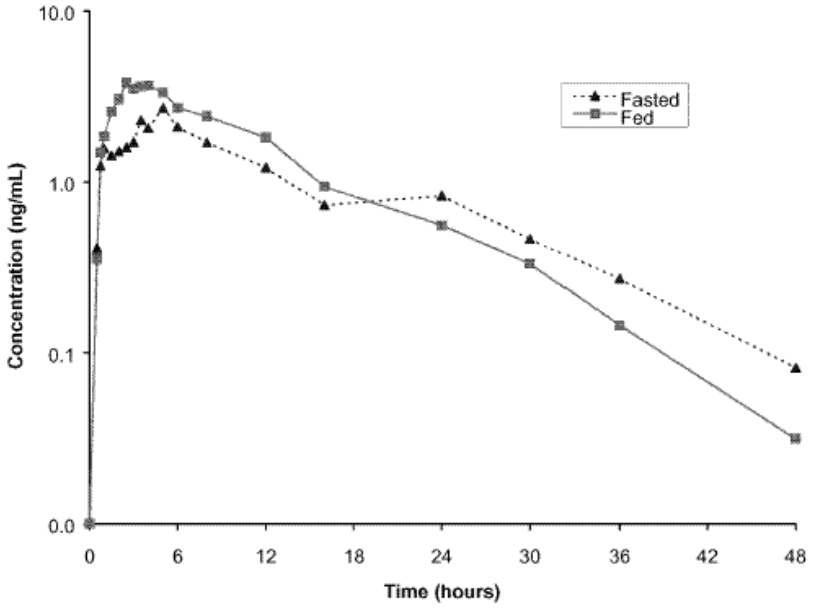


Table 12. Gepirone Bioequivalence Results (analysis of ln-transformed data).

Parameter	Gepirone MR Fed [1]	Gepirone MR Fasted [1]	Ratio Fed/Fasted	Lower 90% C.I.	Upper 90% C.I.
AUC (ng•hr/mL)	38.71	31.14	1.24	1.08	1.44
AUCT (ng•hr/mL)	37.19	29.38	1.27	1.10	1.46
C_{max} (ng/mL)	4.13	2.55	1.62	1.38	1.90

[1] geometric least-square means from analysis of variance
Ratio = exponent of the difference (test – reference) between ln-transformed means
Upper and Lower 90% confidence limits are for the difference between test and reference

Figure 9.

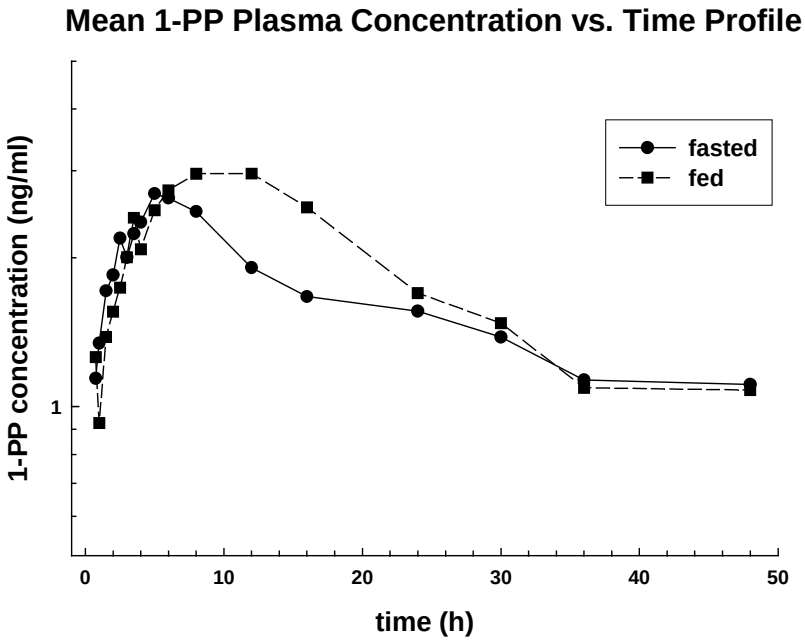


Table 13. 1-PP Bioequivalence Results (analysis of ln-transformed data).

Parameter	Gepirone MR Fed [1]	Gepirone MR Fasted [1]	Ratio Fed/Fasted	Lower 90% C.I.	Upper 90% C.I.
AUC (ng•hr/mL)	52.77	55.39	0.95	0.83	1.09
AUCT (ng•hr/mL)	39.49	37.70	1.05	0.93	1.17
C_{max} (ng/mL)	3.21	2.80	1.15	1.05	1.26

[1] geometric least-square means from analysis of variance
Ratio = exponent of the difference (test – reference) between ln-transformed means
Upper and Lower 90% confidence limits are for the difference between test and reference

Figure 10. Mean 3-OH Gepirone Plasma Concentrations.

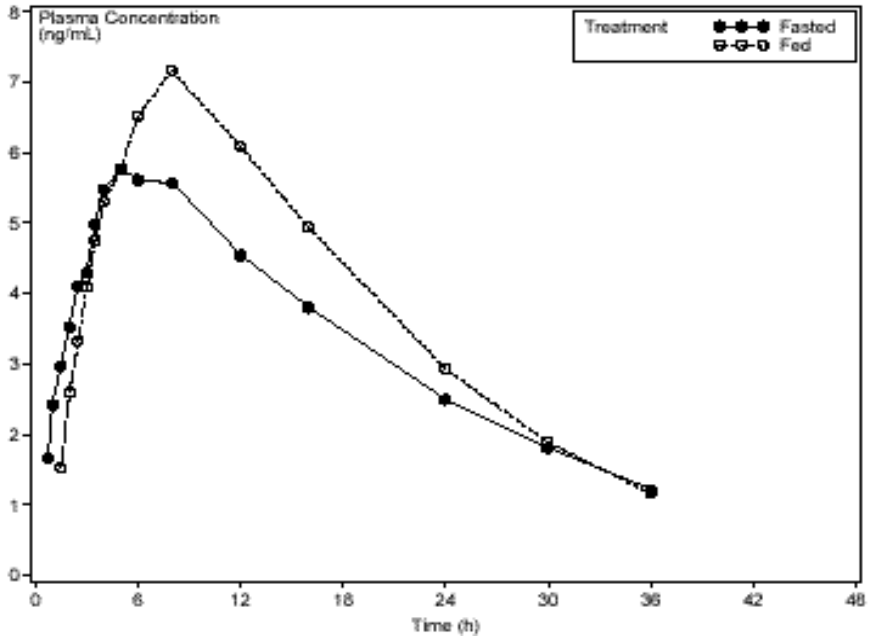


Table 14. Mean (s.d.) PK Parameters for 3-OH Gepirone.

Parameter	Fed[1] (Test)	Fasted[1] (Reference)	Point Estimate	90% Confidence Interval
C_{max}	7.50	6.37	1.18	1.11 - 1.25
AUC_{0-24}	113	93.1	1.22	1.13 - 1.32
AUC_{0-last}	143	119	1.20	1.08 - 1.33
$AUC_{0-\infty}$	151	128	1.18	1.06 - 1.31

Data were taken from Analyses 9-1 - 9-4 in Appendix BI: Pharmacokinetics B.9

[1] Geometric least-squares means

Following drug administration in the fasted state, two gepirone peaks were observed at 3 and 5 h, with corresponding peaks of 3-OH gepirone at 5 and 7 h (Figs. 8, 10). The second peak may have resulted from the effect of food on the bioavailability of the drug since food consumption was allowed after 4 h. Conversely, a second peak was not observed in the subjects that took the drug with food. At 24 h, another peak was observed in both the gepirone and 1-PP plasma profiles. The t_{max} for gepirone decreased with food intake (Fig. 8). The plasma levels of gepirone following food consumption exceeded those in the fasted state up to 16 h following drug administration. Following food intake with drug administration, the bioavailability and peak plasma concentrations of gepirone increased by 24% and 62%, respectively (Table 12). In addition, food consumption increased the C_{max} and AUC of 3-OH gepirone by 18% (Table 14). Alternatively, the rate (C_{max}) and extent (AUC) of absorption of 1-PP was unaffected by food intake (Table 13).

Conclusions.

Following food consumption, the rate and extent of absorption of gepirone was increased by 62 and 24%, respectively. In addition, the C_{max} and AUC of 3-OH gepirone increased by 18%, while they were unchanged for 1-PP. It is difficult to make a dosing recommendation due to continuous absorption of the drug from the ER product, .

Note: The breakfast consumed by the subjects in this study deviates slightly from the FDA recommended breakfast, but it seems reasonable. (The sponsor did not provide caloric and fat content of meal).

5. Protocol CN105-046: Effect of Food (Timing of Meal) on the Bioavailability of Extended Release Gepirone in Healthy male Volunteers.

Investigator.

(b) (4)

Objectives.

The objective of this study was to evaluate the effect of timing of food intake on the pharmacokinetics of gepirone and 1-PP following administration of a 20 mg dose of extended release (ER) gepirone using a 10 mg strength.

Study Design and Methods:

This study was an open label, randomized, single-dose, four-way crossover design that was balanced for first order residual effects (Table 15). Each treatment period was separated by a seven-day washout period. The drug was administered in the following treatments, (1) 20 mg after an overnight fast, and a 10 h additional fast after dosing, (2) 20 mg gepirone 1 h prior to a standard meal, (3) 20 mg gepirone 15 min after a standard meal, and (4) 20 mg gepirone 2 h after a standard meal. Except for the treatment meal, the subjects did not receive food for 10 h after the dose. Serial blood samples were collected over a 30 h period following each dose and were assayed for gepirone and 1-PP utilizing a validated GC/MS method.

During the session when gepirone was administered with food, all subjects received the same, standardized high fat breakfast, which was similar to the FDA standard breakfast.

Subjects:

Twenty-eight healthy male volunteers (age range: 18 –40 yrs.; 27 Caucasian, and 1 Hispanic) participated in the study and were randomized into one of four treatment groups consisting of 7 subjects/group.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- ER tablet formulation, product # (b) (4) (Lot #E89F090), containing 10 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h). In the study, each subject received a total dose of 20 mg (2 x 10 mg tablets).

Table 15. Dose Schedule

		Session/Treatment Code**			
Group	Subject #*	Session 1	Session 2	Session 3	Session 4
A	(b) (6)	1	2	4	3
B		2	3	1	4
C		3	4	2	1
D		4	1	3	2

*The subjects were numbered according to the randomization schedule. Subjects (b) (6) replaced subjects (b) (6).

**Treatment # (See above).

- Treatment 1: gepirone after an overnight fast
- Treatment 2: gepirone given 1 h before food
- Treatment 3: gepirone given 15 min after food
- Treatment 4: gepirone given 2 h after food

Assay Validation:

The GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.992$ for gepirone and $r \geq 0.997$ for 1-PP). Low and high QC samples were prepared at concentrations of 2.0 and 20.0 ng/ml for gepirone and at 2.18 and 21.8 ng/ml for 1-PP. The between day variability for the QC samples did not exceed 8.74% for gepirone and 8.97% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were $\leq$ 4.96% for the low QC sample and $\leq$ 5.19% for the high QC sample. For 1-PP, the deviations from the mean were $\leq$ 6.19% for the low QC sample and $\leq$ 2.5% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), and area under the curve ($AUC_{0\text{-}30\ h}$). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

An ANOVA, incorporating sequence, subjects within sequence, period and treatment effects, interaction between period and treatment, and residual error was used for the statistical analysis of various pharmacokinetic parameters for both gepirone and 1-PP. If statistically significant treatment, period, or sequence effects were observed in the ANOVA, then Tukey's multiple comparisons procedure was used to compare the group means (α=0.05). Levene's test evaluated homogeneity of variance at p=0.001 level.

Results.

Figure 11. Mean Plasma Concentrations of Gepirone For the Four Treatments.

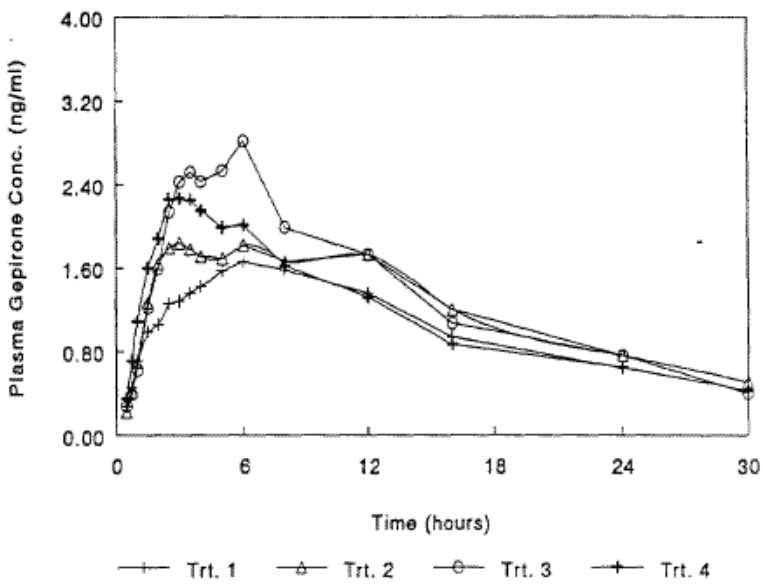


Figure 12. Mean Plasma Concentrations of 1-PP For the Four Treatments.

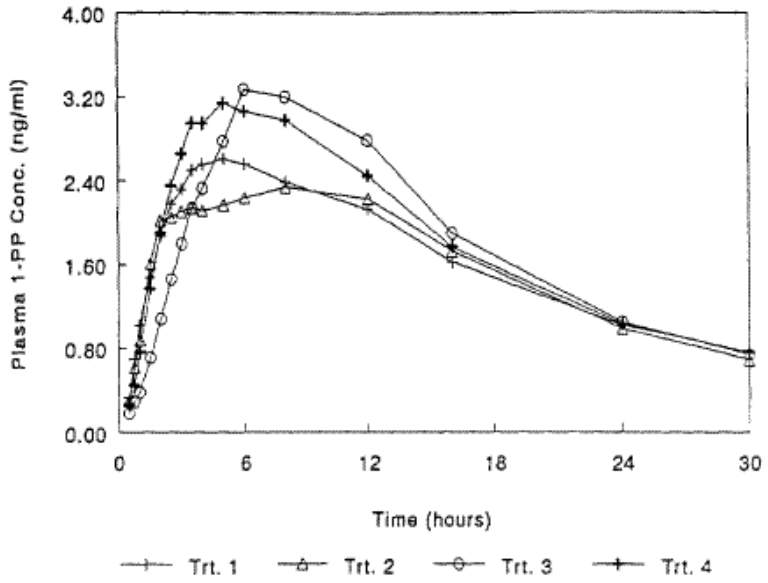


Table 16. Mean Pharmacokinetic Parameters (±S.D.)

	Treatment[2]			
PK Parameter	Trt 1 Overnight fast	Trt 2 1 h before food	Trt 3 15 min after food	Trt 4 2 h after food
Gepirone				
C_{max} (ng/ml)	1.92 ± 0.96	2.36 ± 1.10	3.25 ± 1.71	2.59 ± 1.33
t_{max} (h)[1]	6.0 ± 1.5, 12	5.0 ± 1.5, 16	5.5 ± 2.5, 12	3.0 ± 1.0, 12
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	29.8 ± 15.3	35.7 ± 19.6	39.3 ± 20.6	33.2 ± 14.6
1-PP				
C_{max} (ng/ml)	2.75 ± 0.93	2.78 ± 1.03	3.49 ± 1.06	3.34 ± 1.17
t_{max} (h)[1]	5.0 ± 2.5, 12	6.0 ± 1.5, 12	6.0 ± 5.0, 12	5.0 ± 3.0, 8
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	49.0 ± 21.5	48.0 ± 17.9	55.0 ± 21.6	54.7 ± 23.4

[1]median reported with minimum and maximum

[2]Tukey's procedure based on log transformed data for C_{max} and AUC; statistical significance at $p \leq 0.05$.

Following administration of gepirone, in conjunction with food intake, C_{max} and AUC of gepirone increased by 69% and 32%, respectively following treatment 3 compared with treatment 1. C_{max} was achieved between 3-6 h, and was significantly greater for treatments 2, 3, and 4 compared to treatment 1 (Fig. 11, Table 16). After treatments 2, 3, and 4, two peaks were observed, occurring at 3 and 6 h. This two peak

phenomenon was more pronounced for treatment 3, which suggested that the time of food intake influenced this observation. One possible explanation was that food was directly interacting with the release characteristics of the ER formulation. Since plasma concentrations of gepirone in treatments 2, 3, and 4 did not fall below the levels observed in treatment 1, the sponsor suggested that rapid release of the parent drug was not probable.

For 1-PP, both C_{max} and AUC were greater following treatments 3 and 4, compared with treatments 1 and 2 (Fig. 12, Table 16). T_{max} was observed between 5-6 h following all regimens. In addition, only one peak plasma concentration was observed.

Table 17. Mean (±S.D.) Molar 1-PP to Gepirone Ratios Based on C_{max} and AUC Values.

	Treatment			
PK Parameter	Trt 1 Overnight fast	Trt 2 1 h before food	Trt 3 15 min after food	Trt 4 2 h after food
C_{max} ratio	4.85 ± 4.91	3.68 ± 2.67	3.43 ± 2.83	4.55 ± 4.58
$AUC_{0\text{-}30\ h}$ ratio	5.32 ± 4.55	4.62 ± 4.05	4.32 ± 2.90	5.25 ± 4.39

Since food consumption increases hepatic blood flow, resulting in a decrease in metabolism of high extraction drugs, such as gepirone, the sponsor stated that the metabolic ratio of C_{max} and AUC should decrease in the presence of food. As a result, the metabolic ratio of 1-PP to gepirone suggested that this value was decreased in the presence of food (treatments 2 and 3), but was not statistically significant (Table 17).

Conclusions.

When gepirone ER was administered with food, the systemic exposure of gepirone and 1-PP were higher than that observed under fasting conditions. The greatest augmentation was observed following treatment 3 (drug administered within 15 min after food consumption), where C_{max} and AUC increased by 69% and 32%, respectively. In addition, the incidences of adverse effects were lower in the presence of food (data not shown). This is not a pivotal study since the 10 mg ER tablet is not proposed to be marketed.

6. Protocol 59B4B-001-2587: Effect of Food on Gepirone IR Bioavailability.

Objectives.

The objective of this study was to evaluate the effect of food on the pharmacokinetics of gepirone and 1-PP following administration of a 20 mg dose of gepirone IR.

Study Design and Methods:

This study was an open label, randomized, single-dose, two-way crossover design that was balanced for first order residual effects (Table 18). Each treatment period was separated by a seven-day washout period. Each subject was administered a single 20 mg dose of gepirone with or without food. Except for the treatment meal, the subjects did not receive food for 4 h after the dose. Serial blood samples were collected over a 48 h period following each dose and were assayed for gepirone and 1-PP utilizing a validated GC/MS method.

During the session when gepirone was administered with food, all subjects received the same, standardized high fat breakfast, which was similar to the FDA standard breakfast.

Subjects:

Twenty-one healthy male volunteers (age range: 18 –39 yrs.; 27 Caucasian, and 1 Hispanic) were enrolled and 20 completed the study. Each subject was randomized to two treatment groups, consisting of 10/group.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone IR capsules was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR tablet formulation, product # (b) (4) (Lot #E87C071), containing 5 mg of gepirone HCl was a no. 0 opaque gray capsule. In the study, each subject received a total dose of 20 mg (4 x 5 mg tablets).

Table 18. Dose Schedule

		Session/Treatment Code**	
Group	Subject #*	Session 1	Session 2
A	(b) (6)	1	2
B		2	1

*The subjects were numbered according to the randomization schedule. Subject (b) (6), replaced subject (b) (6).

**Treatment # (See above).

- Treatment 1: gepirone given 15 min after food
- Treatment 2: gepirone after an overnight fast

Assay Validation:

The GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.992$ for gepirone and $r \geq 0.990$ for 1-PP). Low and high QC samples were prepared at concentrations of 2.0 and 20.0 ng/ml for both gepirone and 1-PP. The between day variability for the QC samples did not exceed 8.36% for gepirone and 4.77% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were 14.1% for the low QC sample and 4.94% for the high QC sample. For 1-PP, the deviations from the mean were 9.44% for the low QC sample and 3.73% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), mean residence time (MRT), and area under the curve ($AUC_{0\text{-}30\ h}$). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

An ANOVA, incorporating sequence, subjects within sequence, food effect, interaction between sequence and food, and residual error was used for the statistical analysis of various pharmacokinetic parameters for both gepirone and 1-PP. In order to provide insight into the relative magnitude of the difference (with and without food), and the variability in the data, 95% confidence intervals were calculated for the ratios of the two means for C_{max}, $t_{1/2}$, MRT and AUC. In addition, Wilcoxon's signed rank test was used to compare t_{max}.

Results.

Figure 13. Mean Plasma Concentrations of Gepirone.

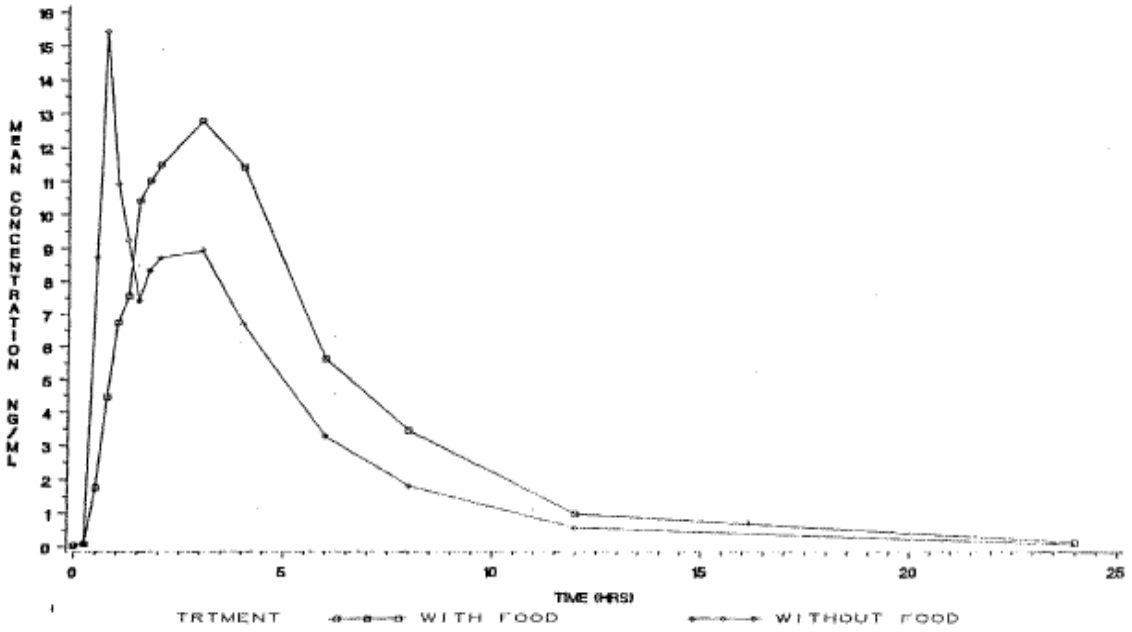


Figure 14. Mean Plasma Concentrations of 1-PP.

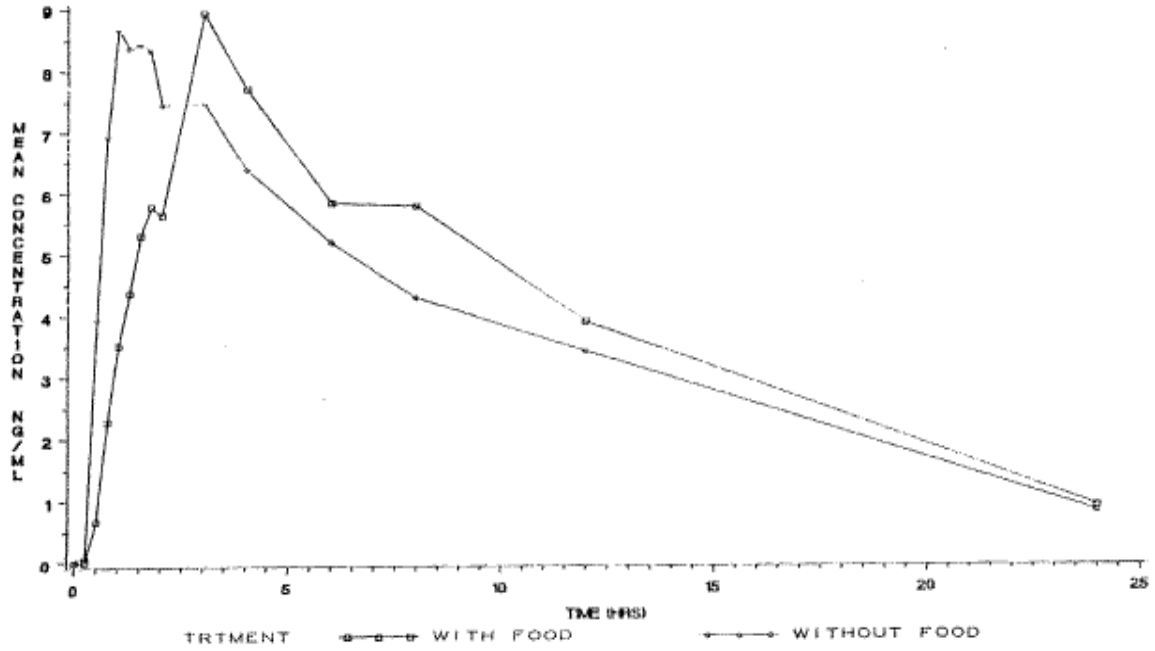


Table 19. Mean Pharmacokinetic Parameters (±S.D.)

PK Parameter	With Food	Without Food	Point Estimate of Ratio	95% Confidence Interval
Gepirone				
C_{max} (ng/ml)	17.0 ± 8.12	18.7 ± 10.3	100%	(75%, 133%)
$T_{1/2}$ (h)	3.32 ± 1.84	2.94 ± 0.905	104%	(81%, 133%)
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	75.7 ± 42.8	55.3 ± 35.7	148%	(112%, 196%)
MRT (h)	5.37 ± 1.21	4.31 ± 0.78	123%	(108%, 141%)
t_{max} (h)[1]	2.00 (0.75, 4.00)	0.75 (0.50, 3.00)		
1-PP[2]				
C_{max} (ng/ml)	12.6 ± 6.22	12.0 ± 4.53	101%	(77%, 131%)
$T_{1/2}$ (h)	6.06 ± 1.75	5.76 ± 1.75	106%	(90%, 124%)
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	99.2 ± 40.1	93.0 ± 47.5	114%	(97%, 133%)
MRT (h)	10.5 ± 2.89	9.32 ± 2.68	114%	(99%, 130%)
t_{max} (h)[1]	3.00 (0.75, 12.0)	1.25 (0.50, 3.00)		

[1]median reported with minimum and maximum

[2]$t_{1/2}$, AUC, and MRT were calculated with only 19 subjects.

Following administration of the immediate release gepirone formulation, the drug was rapidly absorbed without food consumption, indicated by the short t_{max}. In conjunction with food, the AUC of gepirone increased by 48%. C_{max} was achieved at approximately 2 h compared to 0.75 h in the fasted state, but the values were not significantly different from each other (Fig. 13, Table 19). In addition, two peaks were observed following the treatment without food, occurring at 1 and 2.5 h. This two-peak phenomenon was not observed in the fed state. With or without food intake, the $t_{1/2}$ of gepirone and 1-PP were approximately 3 and 6 h, respectively.

For 1-PP, both C_{max} and AUC were not significantly different between the fed and fasting states (Fig. 14, Table 19). T_{max} was observed at approximately 1.25 h without food intake, and at 3 h with food.

Conclusions.

These results suggested that a delay in the onset of absorption as well as a slower rate of absorption of gepirone was associated with food intake. The presence of food also resulted in a 48% increase in the extent of absorption (AUC) of gepirone.

7. Protocol CN105-026: Relative Bioavailability of Gepirone ER Tablets and IR Capsules (BMS).

Objectives.

The objectives of this study were (1) to compare the pharmacokinetics of gepirone and its metabolite, 1-PP, following administration of gepirone either as an immediate release (IR) capsule or extended release (ER) tablet formulation, and (2) to determine whether a 20 or 25 mg ER tablet dosed once a day could replace a 10 mg IR capsule dosed twice daily (q12h).

Study Design and Methods:

This study consisted of an open, randomized, 4-session crossover design balanced for first order residual effects. Each session was separated by a 7 day interval. Each subject qualified for study entry based on medical history and the inclusion/exclusion criteria. All subjects fasted the night prior to dosing and were administered gepirone as specified in the protocol. The subjects were allowed to consume food at 4 h following drug administration. Serial blood samples were collected pre-dose and up to 30 h following gepirone dosing for the determination of pertinent pharmacokinetic parameters. Following administration of the IR formulation, the 12 h blood sample was collected prior to dosing. All samples were analyzed to determine the content of gepirone and 1-PP, one of the major circulating metabolites.

Subjects:

Twelve healthy male volunteers (age range: 19 –36 yrs.; 10 Caucasian, 1 black and 1 oriental) participated in the study and were divided into 4 groups consisting of 3 subjects/group.

Test Product, Dose, and Mode of Administration:

The formulations of gepirone ER tablets and an IR capsule that were supplied to the investigator by the Pharmaceutical Product Development Division of Bristol-Myers Squibb Co. include:

- For treatment 1, product # (b) (4) (Lot #E89F089), was a tablet containing 10 mg of gepirone HCl for extended release ((b) (4) (time where (b) (4) % of the drug is released) = (b) (4) h). In the study, each subject received a total dose of 20 mg (2 x 10 mg tablets).
- For treatment 2, product # (b) (4) (Lot #E89F090), was a tablet containing 10 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h). In the study, each subject received a total dose of 20 mg (2 x 10 mg tablets).
- For treatment 3, product # (b) (4) (Lot #E89F091), was a tablet containing 25 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h). In the study, each subject received a total dose of 25 mg.
- For treatment 4, a no. 0 opaque gray capsule containing 5 mg of gepirone HCl, product # (b) (4) (Lot #E89C663), was supplied for the immediate release formulation. In the study, each subject received a total dose of 20 mg (2 x 5 mg tablets b.i.d.).

Table 20. Dose Schedule.

		Session/Treatment Code**			
Group	Subject #*	Session 1	Session 2	Session 3	Session 4
A	(b) (6)	1	2	4	3
B		2	3	1	4
C		3	4	2	1
D		4	1	3	2

*The subjects will be numbered according to the randomization schedule.

**Treatment # (See above).

Assay Validation:

The GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds (r > 0.996). Low and high QC samples were prepared at concentrations of 2.17 and 20.68 ng/ml for gepirone and at 1.92 and 18.28 ng/ml for 1-PP. The between day variability for the QC samples was determined, which did not exceed 6.03% for gepirone and 7.73% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were 10.8% for the low QC sample and 10.1% for the high QC sample. For 1-PP, the deviations from the mean were 7.96% for the low QC sample and 5.46% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0\text{-}30\ h}$), elimination half-life ($t_{1/2}$), and the fraction of gepirone absorbed over time. Non-compartmental methods were used in the determination of various pharmacokinetic parameters and evaluation of the absorption kinetics for gepirone was performed using the method described by Wagner and Nelson.

An ANOVA, incorporating sequence, period and treatment effects, was used for the statistical analysis of various pharmacokinetic parameters for both gepirone and 1-PP. If the test for treatment effects was significant, then all pairwise comparisons of the means were performed using Tukey's multiple comparisons procedure (α=0.05). If there was significant heterogeneity of variance, then a weighted ANOVA was performed and then treatment means were compared using unequal variance t-tests.

Results.

Figure 15. Mean Plasma Concentrations of Gepirone Following ER and IR Dosing.

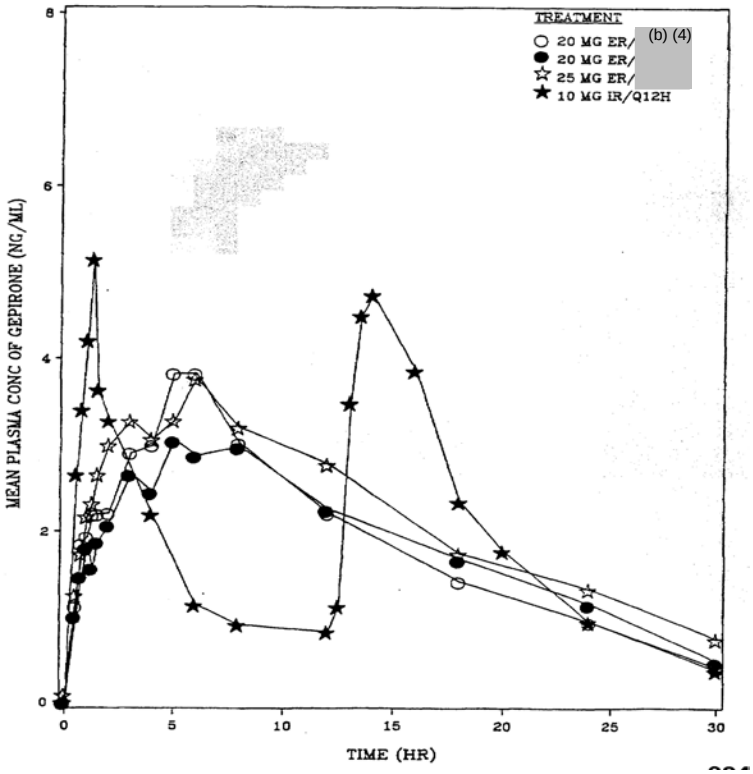


Figure 16. Mean Plasma Concentrations of 1-PP Following ER and IR Dosing.

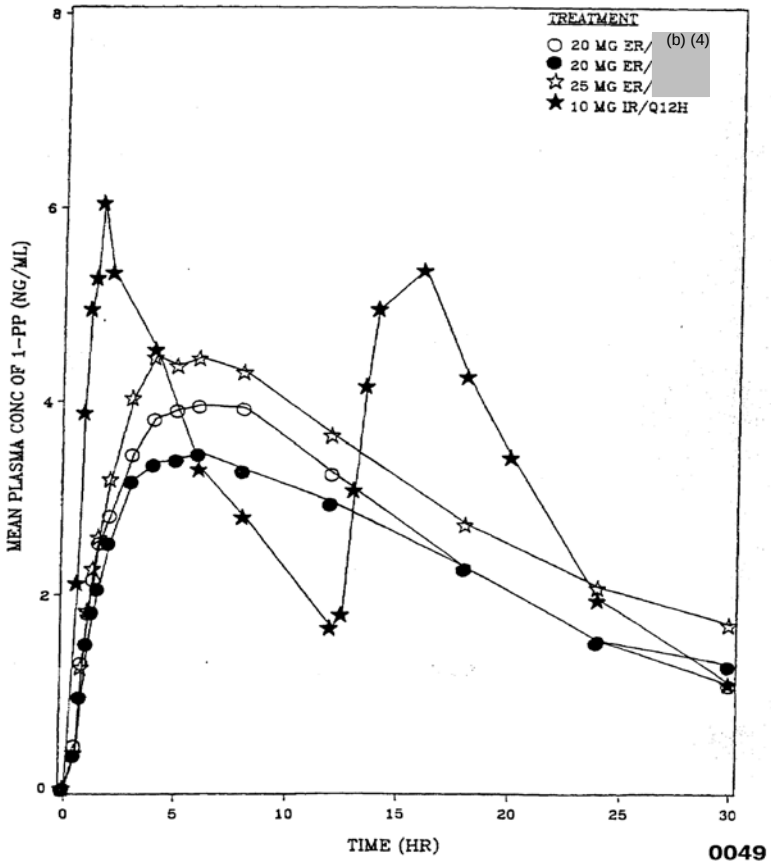


Table 21. Mean Pharmacokinetic Parameters (± S.D.)

	Treatment[A]			
PK Parameter	Trt 1	Trt 2	Trt 3	Trt 4
Gepirone				
C_{max} (ng/ml)	4.3 ± 2.8	3.7 ± 2.2	4.5 ± 2.0	6.1 ± 3.1*
DN C_{max}[C] (ng/ml)**	4.3 ± 2.8	3.7 ± 2.2	3.6 ± 1.6	12.2 ± 6.3***
t_{max} (h)	5.1 ± 1.6	5.6 ± 2.5	4.8 ± 1.9	1.3 ± 0.9*
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	55.3 ± 28.2	55.0 ± 33.7	64.7 ± 34.1	54.9 ± 25.6
DN $AUC_{0\text{-}30\ h}$[C] (ng-h/ml)**	55.3 ± 28.2	55.0 ± 33.7	51.8 ± 27.3	54.9 ± 25.6
1-PP				
C_{max} (ng/ml)	4.2 ± 1.6	3.7 ± 1.6	4.5 ± 1.8	6.3 ± 2.1*
DN C_{max} (ng/ml)**	4.2 ± 1.6	3.7 ± 1.6	3.6 ± 1.8	12.5 ± 4.3****
t_{max} (h)	5.7 ± 1.6	5.1 ± 2.0	5.6 ± 2.5	1.7 ± 0.8*
$AUC_{0\text{-}30\ h}$ (ng-h/ml)	74.0 ± 40.8	68.2 ± 40.2	84.4 ± 52.0	92.8 ± 56.8
DN $AUC_{0\text{-}30\ h}$ (ng-h/ml)**	74.0 ± 40.8	68.2 ± 40.2	67.6 ± 41.6	92.8 ± 56.8****

*C_{max} and t_{max} after the 1st dose of gepirone.

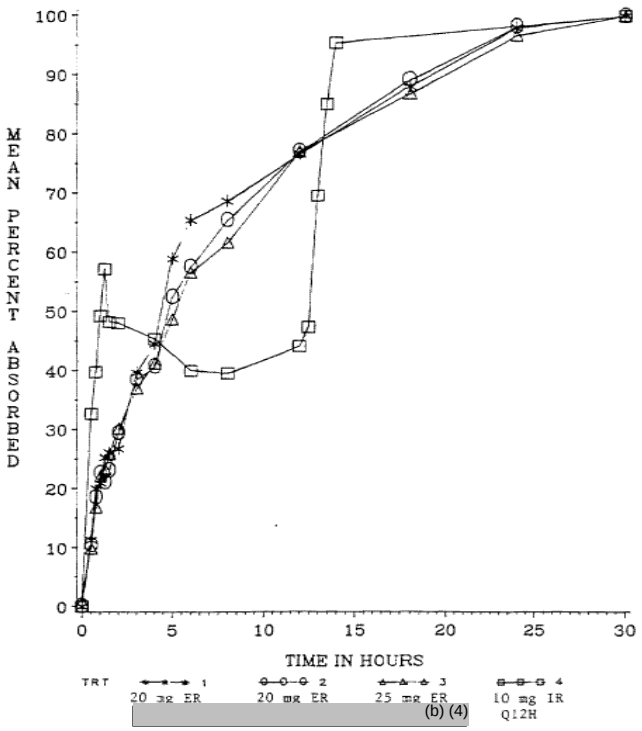
**DN C_{max} (ng/ml) and DN $AUC_{0\text{-}30\ h}$ (ng-h/ml): dose normalized to 20 mg.

***Trt 4 > Trt 1, 2 and 3, $p \leq 0.083$, unequal variance t-test.

****Trt 4 > Trt 1, 2 and 3, $p \leq 0.05$, Tukey's test.

Following administration of the ER formulation, t_{max} for both gepirone and 1-PP ranged from 4.8 – 5.6 h, compared with 1 – 2 h for the IR form (Figs 15, 16, Table 21). For both gepirone and 1-PP, the C_{max} was similar for all of the ER formulations, indicating the lack of dose-dumping or premature release. The C_{max} for the IR formulation was 3-fold greater than the ER form. The gepirone AUC was similar among all formulations. In contrast, the 1-PP AUC was statistically greater following administration of the IR formulation, compared to all ER forms. In addition, two peaks were observed following administration of the ER formulation of gepirone. Possible explanations for this phenomenon by the sponsor (BMS) included that the drug was in the distal part of the small intestine accounting for an increase in the bioavailability (Study CN105-012), increased absorption due to food consumption at 4 h after drug administration, or enterohepatic recycling of unchanged drug.

Figure 17. Mean Fraction of Gepirone Absorbed over Time (Wagner-Nelson Method).



The fraction of gepirone absorbed over time revealed that greater than 90% of the drug is not absorbed until after 20 h following administration of the ER formulation (Fig. 17). Thus, the ER form allows for continuous absorption of gepirone.

In addition, the sponsor indicated that $t_{1/2}$ values following ER dosing were approximately 21, 30, and 13 h for gepirone and 11, 13, and 15 h for 1-PP, respectively. The augmentation in $t_{1/2}$ values illustrates the phenomenon of flip-flop pharmacokinetics, which accounts for the drug being eliminated at a faster rate than it is absorbed. This observation is a typical characteristic of ER formulations.

Conclusions.

The bioavailability of gepirone following once daily dosing of the ER form was comparable to b.i.d. dosing of the IR form. But, the overall exposure (AUC) of 1-PP was not similar comparing the ER to the IR form. Following ER administration, the best rationale to explain the two peaks observed in this study may be due to food consumption. If enterohepatic recycling could explain this observation, the two peaks should be observed independent of whether gepirone was administered in the IR or ER form.

8. Protocol CN105-060: Comparative Bioavailability of Gepirone ER Tablets and Gepirone Solution.

Objectives.

The objectives of this study were (1) to provide a comparison of the oral bioavailability of the 5 mg, 10 mg, and 20 mg gepirone extended release (ER) tablets relative to a gepirone reference solution following daily dosing (20 mg) to steady-state and (2) to determine whether four 5 mg ER tablets, two 10 mg ER tablets, and one 20 mg ER tablet are bioequivalent under steady-state conditions.

Study Design and Methods:

This study consisted of a randomized, double-blind, placebo-controlled, crossover design. The study design included four 7-day treatment periods without an intervening washout period. Each session was separated by a 7-day interval. Each subject qualified for study entry based on medical history and the inclusion/exclusion criteria. All subjects fasted the night prior to each dose and were administered gepirone daily for 28 days. The subjects were allowed to consume food at 4 h following drug administration. Serial blood samples were collected pre-dose and up to 24 h following gepirone administration of the morning dose on days 7, 14, 21, and 28. The 24 h sample on days 8, 15 and 22 was taken prior to the administration of the morning dose for that day. Single blood samples were taken on days 5 and 6 (session 1), 12 and 13 (session 2), 19 and 20 (session 3), and 26 and 27 (session 4) before administration of the morning dose for determination of C_{min} data and attainment of steady-state. During the period when the solution was administered, blood samples for determination of gepirone and 1-PP concentrations were obtained immediately prior to dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 h after each dose on day 7. For the determination of pertinent pharmacokinetic parameters, all samples were analyzed to determine the concentration of gepirone and 1-PP, one of the major circulating metabolites.

Subjects:

Forty-eight healthy male volunteers (age range: 19 –36 yrs; 10 subjects completed the trial in groups A, C, and D, while 9 subjects completed the trial in group B) were enrolled and 39 completed the study and were divided into 4 groups consisting of 12 subjects/group (10 on active drug, 2 on placebo).

Test Product, Dose, and Mode of Administration:

The formulations of gepirone ER tablets and an IR solution that were supplied to the investigator by the Pharmaceutical Product Development Division of Bristol-Myers Squibb Co. include:

- For treatment 1:
  1. product # (b) (4) (Lot E90H378), was a yellow, modified oval shaped, biconvex tablet containing 5 mg of gepirone HCl for extended release (b) (4) (time

where (b) (4)% of the drug is released) = (b) (4)h). In the study, each subject received a total daily dose of 20 mg (4 x 5 mg tablets).

2. product # (b) (4), was a yellow, modified oval shaped, biconvex placebo tablet matched to the 5 mg gepirone HCl extended release tablet.

- For treatment 2:
  1. product # (b) (4) (Lot E90H380), was a light orange, modified oval shaped, biconvex tablet containing 10 mg of gepirone HCl for extended release (b) (4) = (b) (4) h). In the study, each subject received a total daily dose of 20 mg (2 x 10 mg tablets).
  2. product # (b) (4), was a light orange, modified oval shaped, biconvex placebo tablet matched to the 10 mg gepirone HCl extended release tablet.
- For treatment 3:
  1. product # (b) (4) (Lot E90H381), was a pink, modified oval shaped, biconvex tablet containing 20 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h). In the study, each subject received a total daily dose of 20 mg (1 x 20 mg tablets).
  2. product # (b) (4), was a pink, modified oval shaped, biconvex placebo tablet matched to the 20 mg gepirone HCl extended release tablet.
- For treatment 4:

1. An unpreserved oral solution of gepirone HCl containing 1 mg/ml, packaged 10 ml in a 15 ml vial, product # (b) (4) (Lot E90H351). In the study, each subject received a total daily dose of 20 mg (10 ml of a 1mg/ml solution b.i.d.).
2. A placebo solution matched to the unpreserved oral solution of gepirone HCl containing 1 mg/ml, product # (b) (4).

Table 22. Dose Schedule

		Period/Treatment Code**			
Group	#Subjects*	Period 1	Period 2	Period 3	Period 4
A (1)	12	1	2	4	3
B (2)	12	2	3	1	4
C (3)	12	3	4	2	1
D (4)	12	4	1	3	2

Treatment # (See above).

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The sponsor stated that each analytical run resulted in two output files containing the results for either gepirone or 1-PP. For each run, the calibration curves were linear for the concentration range from 0.1 – 25 ng/ml for both compounds (r > 0.991 for gepirone and r > 0.998 for 1-PP). Low and high QC samples were prepared at concentrations of 2.03

and 18.3 ng/ml for gepirone and at 1.82 and 19.8 ng/ml for 1-PP. In order to complete the study analysis, a second set of QC samples were prepared because it became apparent that the sponsor had an insufficient quantity of the original QCs. In this second set, the gepirone concentrations for the low and high QCs were 2.08 and 20.8 ng/ml, respectively. The 1-PP concentrations for the low and high QCs were 2.09 and 20.9 ng/ml, respectively. The between day variability for the QC samples in all runs did not exceed 9.0% for gepirone and 16.0% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone did not exceed 8.2% for the low QC sample and 6.3% for the high QC sample. For 1-PP, the deviations from the mean were 4.63% for the low QC sample and 3.03% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0\text{-}24\ h}$ for the ER tablets and $AUC_{0\text{-}12\ h}$ for the solution), trough plasma concentrations measured prior to drug administration (C_{min}), average plasma concentration (C_{avg}), and F.I. (fluctuation index, calculated by (C_{max}-C_{min}/C_{avg})).

An ANOVA, incorporating effects for sequence, subjects nested within sequence group, treatment, period, the adjusted period by treatment interaction and the residual error term was used for the statistical analysis of various pharmacokinetic parameters for both gepirone and 1-PP. A repeated measures ANOVA followed by appropriate multiple comparisons procedures was used to assess the attainment of steady-state. The two one-sided tests procedure, through the use of 90% confidence intervals, was used to assess the relative bioavailability of the ER formulations with respect to the IR solution, and of the 4 x 5 mg ER, 2 x 10 mg ER, and the 1 x 20 mg ER with respect to each other.

Results.

Figure 18. Mean Plasma Concentrations of Gepirone Following ER and IR Dosing.

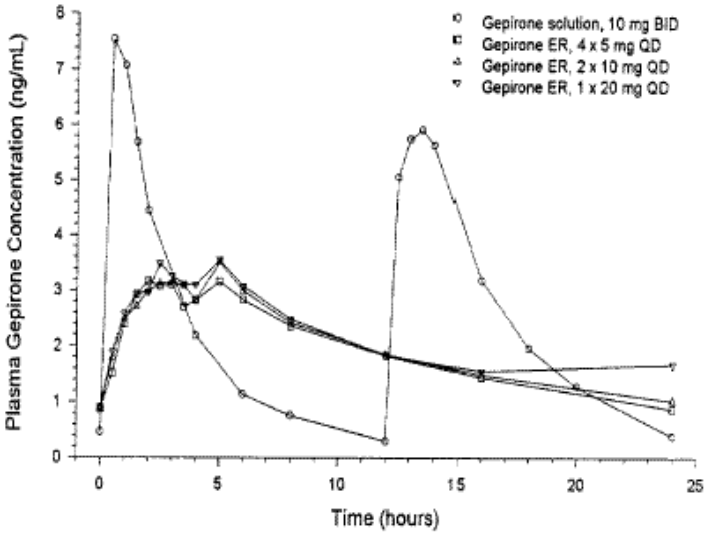


Figure 19. Mean Plasma Concentrations of 1-PP Following ER and IR Dosing.

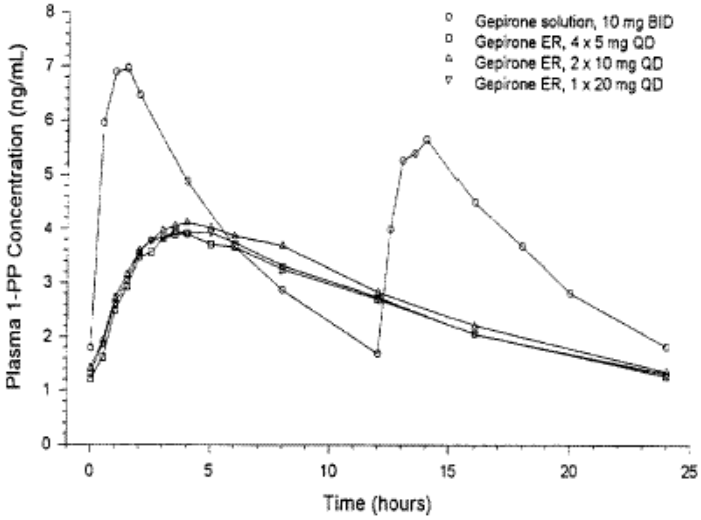


Table 23. Gepirone Bioavailability Results (Bioavailability Ratio and 90% Confidence Limits As a Percentage of Reference).

Test Product	Reference Product	Test Mean	Reference Mean	Ratio (% Ref)	Lower 90% C.I.	Upper 90% C.I.
AUC (ng•hr/mL)						
5 mg ER	10 mg ER	38.30	38.89	98.5	85.7	113.2
5 mg ER	20 mg ER	38.30	39.59	96.7	84.2	111.2
10 mg ER	20 mg ER	38.89	39.59	98.2	85.5	112.9
5 mg ER	Solution	38.30	49.21	77.8	67.7	89.4
10 mg ER	Solution	38.89	49.21	79.0	68.8	90.8
20 mg ER	Solution	39.59	49.21	80.5	70.0	92.5
C_{max} (ng/mL)						
5 mg ER	10 mg ER	3.50	3.52	99.4	89.0	110.9
5 mg ER	20 mg ER	3.50	3.83	91.5	82.0	102.1
10 mg ER	20 mg ER	3.52	3.83	92.1	82.5	102.8
5 mg ER	Solution	3.50	8.05	43.5	39.0	48.6
10 mg ER	Solution	3.52	8.05	43.8	39.2	48.9
20 mg ER	Solution	3.83	8.05	47.6	42.6	53.1
C_{min} (ng/mL)						
5 mg ER	10 mg ER	0.47	0.57	83.0	61.1	112.8
5 mg ER	20 mg ER	0.47	0.53	88.1	64.8	119.7
10 mg ER	20 mg ER	0.57	0.53	106.2	78.1	144.3
5 mg ER	Solution	0.47	0.31	149.7	110.2	203.5
10 mg ER	Solution	0.57	0.31	180.4	132.7	245.2
20 mg ER	Solution	0.53	0.31	169.9	125.0	230.9
F.I.						
5 mg ER	10 mg ER	1.89	1.86	101.5	87.9	115.0
5 mg ER	20 mg ER	1.89	1.95	96.5	83.6	109.5
10 mg ER	20 mg ER	1.86	1.95	95.1	82.2	108.1
5 mg ER	Solution	1.89	3.84	49.1	42.5	55.7
10 mg ER	Solution	1.86	3.84	48.4	41.8	55.0
20 mg ER	Solution	1.95	3.84	50.9	44.3	57.5
T_{max} (hr)						
5 mg ER	10 mg ER	3.12	4.14	75.4	58.7	92.0
5 mg ER	20 mg ER	3.12	3.97	78.6	61.3	96.0
10 mg ER	20 mg ER	4.14	3.97	104.3	87.0	121.7
5 mg ER	Solution	3.12	0.83	375.1	293.3	457.8
10 mg ER	Solution	4.14	0.83	497.6	414.9	580.4
20 mg ER	Solution	3.97	0.83	476.9	394.2	559.7

*LSmeans

Table 24. Summary of Bioequivalence Results for 1-PP (Ratio and 90% C.I. Limits of Log-Transformed Data).

BEST AVAILABLE COPY

Variable	Test Product	Reference Product	Test LSmean	Reference LSmean	Ratio	Lower 90% CI	Upper 90% CI
AUC (1-PP)	05 mg	10 mg	55.45	59.04	0.939	0.866	1.019
	05 mg	20 mg	55.45	56.43	0.983	0.906	1.066
	10 mg	20 mg	59.04	56.43	1.046	0.964	1.135
	05 mg	Soln	55.45	82.86	0.669	0.617	0.726
	10 mg	Soln	59.04	82.86	0.712	0.657	0.773
	20 mg	Soln	56.43	82.86	0.681	0.628	0.739
Cmax (1-PP)	05 mg	10 mg	4.11	4.29	0.959	0.881	1.044
	05 mg	20 mg	4.11	4.26	0.965	0.886	1.050
	10 mg	20 mg	4.29	4.26	1.005	0.924	1.094
	05 mg	Soln	4.11	7.36	0.558	0.513	0.608
	10 mg	Soln	4.29	7.36	0.582	0.535	0.634
	20 mg	Soln	4.26	7.36	0.579	0.532	0.630
Cmin (1-PP)	05 mg	10 mg	0.92	1.07	0.857	0.704	1.042
	05 mg	20 mg	0.92	1.10	0.832	0.684	1.012
	10 mg	20 mg	1.07	1.10	0.972	0.799	1.182
	05 mg	Soln	0.92	1.40	0.657	0.540	0.799
	10 mg	Soln	1.07	1.40	0.767	0.631	0.933
	20 mg	Soln	1.10	1.40	0.790	0.649	0.960

The average plasma concentrations of both parent drug and metabolite were similar following administration of the three ER tablet formulations (Figs. 18, 19, Tables 23, 24). In contrast, the solution showed higher peak and lower trough concentrations. For the ER formulations, the t_{max} occurred between 3 and 4 h, while the t_{max} for the solution was less than 1 h. In addition, the plasma concentration-time profile for gepirone illustrated two peaks, occurring at approximately 3 and 5 h (Fig. 18). The ER formulations had significantly less peak-to-trough fluctuation than the reference solution (Table 23). Following b.i.d. dosing of the solution, the 2nd peak was approximately 25% less than the 1st peak (Fig. 18).

When the bioavailability results were compared, the rate (C_{max}) and extent of absorption (AUC) for both the parent drug and metabolite were similar for all ER formulations (Table 23). In comparison to the solution, all three ER formulations demonstrated lower overall bioavailability. Based on gepirone's AUC, the ER tablets were approximately 80% bioavailable relative to the solution. For 1-PP, the bioavailability estimates were only about 20% lower (Table 24).

Conclusions.

Following ER administration, two peaks were observed and the second peak occurred at approximately 1 h following food consumption. The best rationale to explain the two peaks observed in this study may be due to food consumption. (b) (4) . In addition, the rate and extent of absorption of both gepirone and 1-PP were comparable for all three ER forms. But, the overall exposure (AUC) of gepirone was not similar compared with the solution. Consistent with administration of ER formulations, all tablet strengths exhibited significantly lower peak

concentrations, higher trough concentration, and less peak-to-trough fluctuation than the solution.

9. *In Vitro/In Vivo* Correlation

(b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

11. Greenblatt Study: Human Cytochromes Mediating Gepirone Biotransformation at Low Substrate Concentrations.

Background.

Prior to this study, this group performed *in vitro* experiments to assess which CYP450 isozymes where involved in the metabolism of gepirone (von Moltke et al, 1998). The results of the study concluded that CYP450 3A4 and 2D6 were the main enzymes involved in metabolizing the parent drug. But, the experiments were performed with therapeutically irrelevant concentrations of gepirone. Thus, the following study was conducted to ascertain a similar objective at clinically relevant concentrations of the drug.

Objectives.

The objective of this study was to determine which cytochrome enzymes mediate the biotransformation of gepirone.

Study Design and Methods:

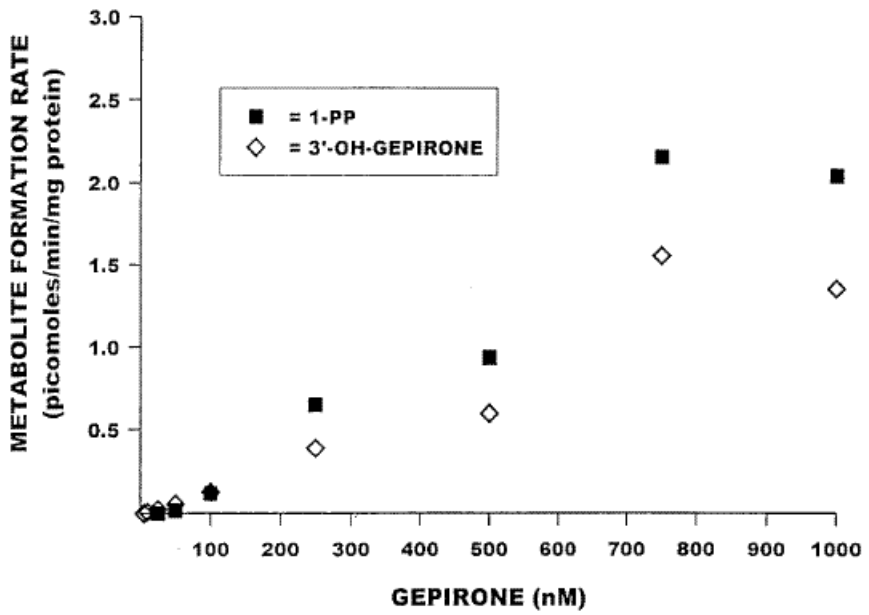
Microsomal preparations from a human liver were used for this study. The donor was established to be a CYP2D6 normal metabolizer phenotype. The microsomes were prepared by an ultracentrifugation method. Various concentrations of gepirone ranging from 0 – 1000 nM were prepared. Additional 1000 nM samples were studies with coaddition of ketoconazole (3A inhibitor) and quinidine (2D6 inhibitor). Also, microsomes containing human CYP3A4 or 2D6 expressed by cDNA-transfected human lymphoblastoid cells were used.

Assay Validation:

The LC/ESI-MS assay was developed to quantitate gepirone, 1-PP, and 3'OH gepirone in this study. The calibration curves were linear for the concentration range from 0.36 – 9 ng/ml, 10 – 500 ng/ml, and 50 – 300 ng/ml for gepirone; 0.36 – 9.0 ng/ml and 0.25 –10 ng/ml for 3'OH gepirone; and 0.25 – 10 ng/ml for 1-PP ($r > 0.995$ for all compounds). Each standard curve had a minimum of five calibration points, with a relative standard error within ±15%.

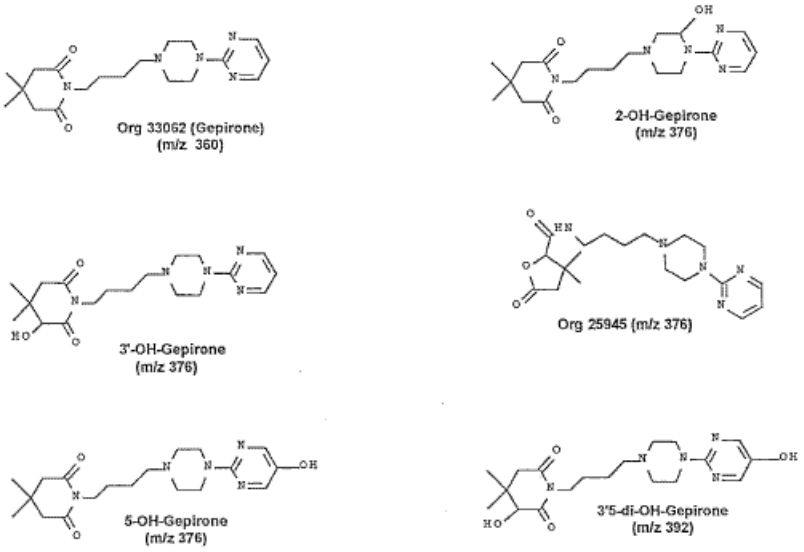
Results.

Figure 21. Formation Rates of 1-PP and 3'OH gepirone in relation to the Gepirone Concentration.



Both 1-PP and 3' OH gepirone were formed *in vitro* at substrate concentrations of 50 nM or higher, with the rate of formation for 1-PP generally exceeding those of 3'OH gepirone (Fig. 21). When gepirone was co-incubated with ketoconazole, the inhibitor completely eliminated the formation of 1-PP, and reduced the formation of 3'OH gepirone by approximately 80% (data not shown). Co-incubation of gepirone with quinidine, a potent inhibitor of CYP2D6 showed no inhibition in the formation of either 1-PP or 3'OH gepirone (data not shown).

Figure 22. Chemical Structures of Gepirone and its Hydroxylated Metabolites.



From the results of the chromatograms and LC/MS/MS analysis, the metabolites were identified as 3'OH gepirone, 5-OH gepirone, 2-OH gepirone, 3', 5 diOH gepirone, and Org 25945 (Fig. 22). The structural assignments were verified by comparison of their LC/MS/MS spectra to that of a corresponding authentic standard.

Additional chromatographic peaks identified as 5-OH and 2-OH gepirone were also observed as in vitro metabolites, but were not quantitated since reference standards were not available.

Conclusions.

Based on an *in vitro* assessment, the results showed that CYP450 3A4 and 2D6 are involved in the metabolism of gepirone at therapeutically relevant concentrations. In addition, CYP3A4 may be solely responsible for the formation of 1-PP and 3'OH gepirone. CYP2D6 plays a minimal role in the formation of 3'OH and 5-OH gepirone. Also, several mono- and di-OH metabolites of gepirone were verified *in vitro* by an LC/MS/MS assay.

12. Von Moltke Study: Gepirone and 1-PP: Cytochrome Inhibitory Effects.

Objectives.

The objective of this study was to determine the potential inhibitory activity of gepirone and 1-PP on various CYP450 isozymes.

Study Design and Methods:

Using pooled human microsomes, the potential inhibitory effect of gepirone and 1-PP on the activity of specific human cytochromes was evaluated using the following index reactions and methods: 1A2, phenacetin to acetaminophen; 2C9, phenytoin to para-OHphenyl hydantoin; 2C19, S-mephenytoin to 4-OH mephenytoin; 2D6, dextromethorphan to dextrorphan; 2E1, chlorzoxazone to 6-OH-chlorzoxazone; 3A, dextromethorphan to 3-methoxymorphinan. Varying concentrations of gepirone and 1-PP (0-250μM) were coincubated with fixed concentrations of the index substrate. Also, the studies were conducted with positive control index inhibitors (α-naphthoflavone for 1A2; sulfaphenazole for 2C9; omeprazole for 2C19; quinidine, fluoxetine, and norfluoxetine for 2D6; diethyldithiocarbamate for 2E1; and ketoconazole and norfluoxetine for 3A).

Results.

Table 25. Inhibition of CYP450s by Gepirone, 1-PP, and positive control index inhibitors.

Cytochrome P450	Mean (± SE) IC_{50}, in μM		
	Gepirone	1-PP	Positive control
1A2	>250	>250	α-Naphthoflavone: 0.29 (± 0.05)
2C9	>250	>250	Sulfaphenazole: 1.4 (± 0.3)
2C19	>250	>250	Omeprazole: 5.6 (± 0.9)
2D6	>250	>250	Quinidine: 0.3 (± 0.1)
			Fluoxetine: 2.6 (± 0.6)
			Norfluoxetine: 4.3 (± 0.8)
2E1	>250	>250	Diethyldithiocarbamate: 10.0 (± 0.9)[a]
3A	>250	>250	Ketoconazole: 1.1 (± 0.2)
			Norfluoxetine: 8.8 (± 1.5)

[a]Samples were preincubated with inhibitor prior to addition of substrate

For all of the CYP450 enzymes, the gepirone and 1-PP concentration needed to inhibit 50% of the enzyme activity exceeded 250 μM (90 μg/ml) (Table 25).

Conclusions.

Both gepirone and 1-PP appear not to inhibit any of the CYP450 enzymes at the concentrations tested. Clinically, plasma concentrations that were achieved following a dose of 80 mg (highest to be marketed dose) exceeded 40 ng/ml. Thus, the possibility that gepirone and 1-PP can inhibit the activity of CYP450s is not plausible.

13. Protocol [redacted] (b) (4) -21085: Protein Binding of Gepirone and 1-PP in Mouse, Rat, Dog, and Human Plasma.

Investigators.

[redacted] (b) (4), M.S. and [redacted] (b) (4) Ph.D., Bristol-Myers Company, Syracuse, NY.

Objectives.

The objective of this study was to determine and compare the in vitro binding of gepirone and 1-PP to plasma proteins in mouse, rat, dog, and human using an ultrafiltration method.

Study Design and Methods:

The fraction of drug bound was determined using ultrafiltration. Plasma was collected from each species. Solutions of ^{14}C-gepirone and ^{14}C-1-PP were prepared, and then an appropriate amount of each compound was added to plasma producing final drug concentrations ranging from 30 - 150 ng/ml for gepirone and 25 – 130 ng/ml for 1-PP. The samples were mixed and equilibrated for 10 min. An aliquot from each sample was centrifuged in an ultrafiltration device at 1500 x g for 30 min and analyzed for ^{14}C using a Packard 1900CA liquid scintillation analyzer (Downers Grove, Ill.). The percent of drug bound was calculated as %bound = ((dpm in retentate –dpm in ultrafiltrate)/(dpm in retentate)) x 100.

Analytes:

- gepirone: product # [redacted] (b) (4) (Lot #26560-30B).
- 1-PP: product # [redacted] (b) (4) (Lot #26560-34B).

Results.

Table 26. Protein Binding of Gepirone and 1-PP to Plasma Proteins.

Mean Plasma Concentration (ng/ml)	Percent Bound (±S.D.)			
Gepirone	**Mouse**	**Rat**	**Dog**	**Human**
30.4	73.3 ± 0.9	69.3 ± 11.7	65.9 ± 2.7	69.4 ± 7.7
60.9	75.2 ± 1.7	72.1 ± 8.4	64.1 ± 1.2	71.2 ± 5.6
152.2	72.9 ± 2.1	74.2 ± 3.2	65.5 ± 6.7	75.0 ± 5.5
Mean (±SD)	74.0 ± 1.8	72.8 ± 3.0	65.2 ± 3.7	71.8 ± 6.0
1-PP	**Mouse**	**Rat**	**Dog**	**Human**
25.5	10.1 ± 0.1	18.9 ± 2.5	39.4 ± 7.1	59.4 ± 7.3
51.0	13.7± 2.6	18.2 ± 1.1	39.9 ± 6.0	59.5 ± 4.9
127.5	11.4 ± 3.0	15.7 ± 3.2	39.4 ± 6.3	58.0 ± 5.2
Mean (±SD)	12.0 ± 2.6	17.6 ± 2.6	39.6 ± 5.6	58.9 ± 5.2

In humans, gepirone and 1-PP were approximately 72% and 59% bound to plasma proteins, respectively (Table 26). In mouse, rat, and dog, the protein binding of gepirone was similar to humans (74%, 73%, and 65%), and 1-PP was bound to a lesser extent.

Conclusions.

The results indicated that the plasma protein binding of both gepirone and 1-PP was not concentration dependent and that both compounds were not highly bound to plasma proteins.

14. Protocol (b) (4)-11887: The Effect of Gepirone on the Plasma Protein Binding of Potentially Co-Administered Drugs.

Investigators.

(b) (4), B.S. and (b) (4), Ph.D., Bristol-Myers Company, Evansville, IN.

Objectives.

The objective of this study was to determine the effect of gepirone on the plasma protein binding of potentially co-administered drugs.

Study Design and Methods:

The fraction of drug bound was determined using ultrafiltration. Plasma was collected from each species. Solutions of ^{14}C-gepirone and ^{14}C-1-PP were prepared, and then an appropriate amount of each compound was added to plasma producing final drug concentrations ranging from 30 - 150 ng/ml for gepirone and 25 – 130 ng/ml for 1-PP.

The samples were mixed and equilibrated for 10 min. An aliquot from each sample was centrifuged in an ultrafiltration device at 1500 x g for 30 min and analyzed for ^{14}C using a Packard 1900CA liquid scintillation analyzer (Downers Grove, Ill.). The percent of drug bound was calculated as %bound = ((dpm in retentate –dpm in ultrafiltrate)/(dpm in retentate)) x 100.

Analytes:

- gepirone: product # (b) (4) (Lot #26560-30B).
- 1-PP: product # (b) (4) (Lot #26560-34B).

Results.

Table 27. Effect of Gepirone on the Plasma Protein Binding of Concomitant Drugs.

	Change in Percent of Bound Drug From Control (ng/ml of gepirone)		
Drug and Concentration	**0.5**	**5.0**	**50**
Chlorpromazine; 25 ng/ml	0.3	0.3	0.7
Desipramine; 25 mg/ml	0	1.0	0.9
Diazepam; 125 ng/ml	-0.1	-0.3	-0.1
Digoxin; 0.5 ng/ml	-2.7	-3.3	-5.0
Diphenylhydantoin; 1 µg/ml	-0.2	-0.3	0.1
Haloperidol; 5 ng/ml	-6.4	-9.4	-7.5
Lidocaine; 1 µg/ml	0.6	4.2	4.9
Prazosin; 125 ng/ml	0.2	-0.1	0.2
Propranolol; 25 ng/ml	0.1	0.5	0.6
Verapamil; 25 ng/ml	-0.5	-1.1	0
Warfarin; 1 µg/ml	0	0.1	0

Concentrations of gepirone were found only to affect the plasma protein binding of digoxin, haloperidol, and lidocaine (Table 27). According to the sponsor, these drugs are only 28, 65, and 74% bound, respectively. As a result, plasma protein binding at this level is believed to be clinically insignificant.

Conclusions.

The results showed that the ability for gepirone to alter the protein binding of concomitantly administered drugs is unlikely.

15. Protocol CN105-049: Pharmacokinetics and Linearity During Single and Multiple Dose Administration of Gepirone ER.

Objectives.

The objective of this study was to evaluate the safety, tolerability and pharmacokinetics of gepirone after single and multiple dose administration as the extended release (ER) formulation.

Study Design and Methods:

This study was a double-blind parallel group, placebo-controlled design in which five groups of 12 subjects received 5 dose levels of ER gepirone (Table 28). After the low dose was judged to be safe and tolerated, the next higher dose was administered. Each treatment period was separated by a seven-day washout period. Serial blood samples were collected over a 48 h period following a single dose of gepirone ER on day 1 and for 48 h after the last dose on day 8 during the multiple dose segment of the study (days 3-8). On days 1 and 8, the subjects remained fasted for 4 h following drug administration. The samples were assayed for gepirone and 1-PP utilizing a validated GC/MS method.

Subjects:

Sixty healthy male volunteers (age range: 18 –40 yrs; 30 Caucasian, 27 black, and 3 Hispanic) were enrolled in the study. Of the sixty subjects, only two were poor metabolizers and the rest of them were extensive metabolizers of dextromethorphan. Each subject was randomized to five treatment groups, consisting of 9/treatment group and 3 subjects that received placebo.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER capsules was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- ER tablet formulation, product # (b) (4) (Lot #E89F090), containing 10 mg of gepirone HCl for sustained release ((b) (4) = (b) (4) h).
- ER tablet formulation, product # (b) (4) (Lot #E89F091), containing 25 mg of gepirone HCl for sustained release ((b) (4) = (b) (4) h).
- ER tablet formulation, product # (b) (4) (Lot #E90E847), placebo tablet containing no active ingredient.

Table 28. Dose Composition of the Treatment Subgroups.

Treatment Group	ER Gepirone			Placebo	
	Gepirone Dose (mg)	N	Dose Composition	N	Dose Composition
1	10	9	1 x 10 mg ER + 3 placebos	3	4 placebos
2	20	9	2 x 10 mg ER + 2 placebos	3	4 placebos
3	25	9	1 x 25 mg ER + 3 placebos	3	4 placebos
4	40	9	4 x 10 mg ER	3	4 placebos
5	75	9	3 x 25 mg ER + 1 placebo	3	4 placebos

Assay Validation:

The GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds (r = 0.998 for gepirone and r = 0.999 for 1-PP). Low and high QC samples were prepared at concentrations of 1.98 and 18.3 ng/ml for gepirone and 2.18 and 20.1 ng/ml for 1-PP. In addition, QC samples were prepared just prior to sample analysis at 2 and 20 ng/ml for both compounds. The between day variability for the QC samples did not exceed 4.62% for gepirone and 4.51% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were 5.5% for the low QC sample and 6.93% for the high QC sample. For 1-PP, the deviations from the mean were 4.86% for the low QC sample and 4.57% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), trough concentration (C_{min}), area under the curve ($AUC_{0\text{-}24\ h}$), and an accumulation ratio for Cmax and AUC (AR). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Dose linearity and proportionality of C_{max} and AUC was evaluated statistically by weighted linear regression. The test for dose linearity was based on the t-test for a linear trend across doses. Statistical assessment of the attainment of steady-state by C_{min} data was conducted in a randomized block ANOVA model. Differences in the AR were evaluated using a one-way ANOVA. All tests of significance were performed at the p = 0.05 level.

Results.

Figure 23. Mean Plasma Concentrations of Gepirone on Day 1.

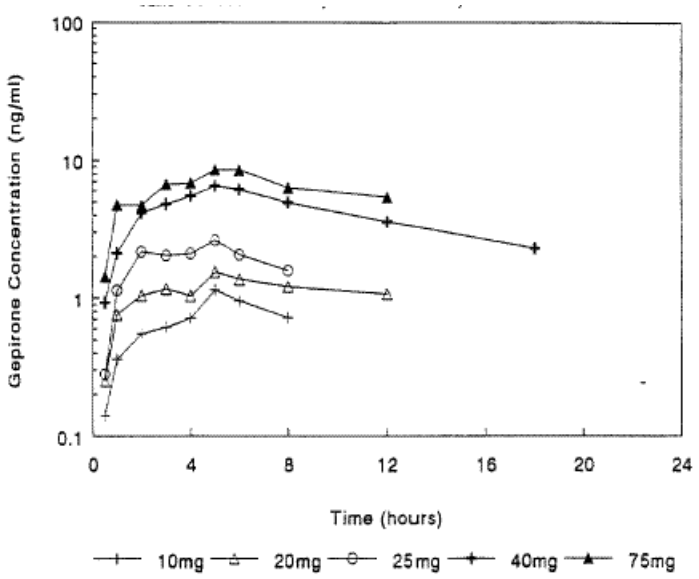


Figure 24. Mean Steady-state Plasma Concentrations of Gepirone on Day 8.

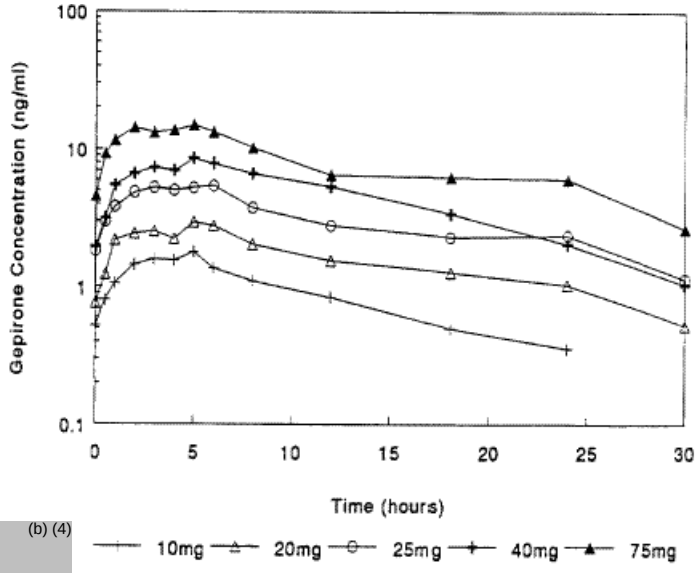


Table 29. Mean Pharmacokinetic Parameters of Gepirone Following a Single Dose (Day 1) and on Dosing to Steady State (Day 8).

ER Gepirone Dose (mg)	Trt. Group #	Study Day	N	Pharmacokinetic Parameter Values			
				CMAX (ng/ml)	TMAX[a] (hr)	AUC(0-24 hr)[b] (hr.ng/ml)	THALF (hr)
10	1	1	9	1.20 (0.55)	5 (4,12)	14.4 (6.93)	11.1 (8.42)
		8	9	1.86 (0.81)	5 (2,6)	21.3 (9.22)	9.92 (3.27)
20	2	1	9	1.65 (0.64)	5 (3,6)	21.7 (10.0)	10.0 (5.84)
		8	9	3.16 (1.30)	5 (2,6)	41.4 (20.2)	11.9 (6.45)
25	4	1	9	2.82 (1.31)	5 (2,6)	33.7 (16.2)	8.24 (5.00)
		8	9	5.92 (2.72)	6 (2,6)	79.4 (47.8)	11.5 (10.9)
40	3	1	9	6.79 (4.46)	5 (0.5,6)	83.1 (53.6)	8.40 (5.52)
		8	9	8.83 (3.22)	5 (2,6)	121 (45.6)	12.3 (13.2)
75	5	1	9	9.14 (3.72)	5 (3,6)	121 (69.9)	4.37 (1.99)
		8	9	16.4 (7.81)	4 (1,5)	210 (119)	6.08 (2.87)
Tukey Comparisons[c]		Dose:		1 2 4 3 5	NS[d]	1 2 4 3 5	5 4 3 1 2
		Day:		8>1	NS[d]	8>1	NS[d]

[a]Median reported with minimum and maximum
[b]Trapezoidal AUC(0-24hr)
[c]Numbers not connected by a common line are significantly different
[d]Not significant

Following once daily dosing of gepirone ER, an initial peak plasma concentration occurred at approximately 2-3 h, but an increase in absorption following food intake at 4 h resulted in a t_{max} at 5h on both days 1 and 8 (Figs. 23, 24, Table 29). The apparent $t_{1/2}$ for gepirone ranged from 4 –11 h on day 1, and 6 –12 h at steady state (day 8). For gepirone, linear regression analysis of C_{max} and AUC vs. dose on day 1 revealed a lack of fit for C_{max} and a suggestion of linearity for AUC ($r^2 = 0.453$). The relationship between dose and AUC or C_{max} improved at steady state ($r^2 = 0.64, 0.63$). Modest accumulation of gepirone levels was observed following once daily dosing of the ER formulation.

Table 30. Mean Pharmacokinetic Parameters of 1-PP Following a Single Dose (Day 1) and on Dosing to Steady State (Day 8).

ER Gepirone Dose (mg)	Trt. Group #	Study Day	N	Pharmacokinetic Parameter Values			
				CMAX (ng/ml)	TMAX[a] (hr)	AUC(0-24 hr)[b] (hr.ng/ml)	THALF (hr)
10	1	1	9	1.51 (0.44)	5 (4,8)	23.0 (7.20)	9.28 (4.03)
		8	9	2.26 (0.76)	5 (2,12)	33.5 (12.8)	10.5 (2.74)
20	2	1	9	2.78 (0.91)	5 (3,6)	41.1 (18.0)	10.2 (4.79)
		8	9	3.01 (1.16)	3 (2,5)	45.3 (20.0)	9.88 (1.92)
25	4	1	9	4.16 (1.20)	5 (2,6)	58.5 (22.8)	8.12 (3.29)
		8	9	5.21 (2.08)	4 (3,5)	82.1 (43.4)	7.62 (2.53)
40	3	1	9	5.60 (1.82)	5 (3,12)	85.3 (37.9)	10.2 (8.55)
		8	9	7.91 (2.50)	4 (4,8)	118 (55.4)	16.0 (25.1)
75	5	1	9	11.9 (6.22)	5 (4,12)	195 (137)	7.43 (2.23)
		8	9	16.8 (9.17)	4 (2,8)	243 (168)	7.59 (2.53)
Tukey Comparisons[c]		Dose:		1 2 4 3 5	NS[d]	1 2 4 3 5	NS[d]
		Day:		8>1	8<1	8>1	NS[d]

[a]Median reported with minimum and maximum
[b]Trapezoidal AUC(0-24hr)
[c]Numbers not connected by a common line are significantly different
[d]Not significant

For 1-PP, C_{max} was achieved at 5 h independent of single dose or steady state conditions (Fig. 24, Table 30). The apparent $t_{1/2}$ ranged from 7.5 – 10.5 h. AUC and C_{max} were marginally proportional to escalating doses on both days 1 and 8, respectively (r^2 = 0.706 and 0.585 for C_{max}, r^2 = 0.582 and 0.448 for AUC). No differences were observed in the metabolic ratio, thus suggesting that disposition of gepirone and 1-PP was not influenced by the dose administered.

Conclusions.

Based on C_{min} values, steady state conditions were achieved on day 2 (data not shown). Modest accumulation of gepirone and 1-PP following once daily dosing was observed. In addition, assessment of dose linearity with C_{max} and AUC after single dose and steady state conditions was inconclusive due to high pharmacokinetic variability and multiple plasma peaks of gepirone. One possible explanation for the variability observed in this study could be due to the effect of food consumption, resulting in an alteration of the bioavailability of the parent compound.

16. Protocol CN105-068: Steady-State Pharmacokinetics of Gepirone ER Tablets in Young and Elderly Healthy Male and Female Subjects.

Objectives.

The objectives of this study were to evaluate the effects of age and gender on the steady-state pharmacokinetics of gepirone and 1-PP following administration of gepirone ER.

Study Design and Methods:

This study consisted of a double-blind, placebo-controlled, parallel treatment design. All subjects fasted 10 h prior to dosing and were administered ER gepirone as specified in the protocol. Each subject received 20 mg (1 x 20 mg tablet) or matching placebo for days 1-7, 40 mg (2 x 20 mg tablets) or matching placebo for days 8-14, and 80 mg (4 x 20 mg tablets) or matching placebo for days 15-21. There was no washout period between dose levels. On all study days except days 7, 14, and 21, the subjects continued to fast for 2 h after dosing. On days 7, 14, and 21, the subjects continued to fast for 4 h after dosing. Serial blood samples were collected pre-dose and up to 24 h following gepirone administration of the morning dose on days 7, 14, and 21. Additional blood samples were taken on days 4, 5, 6; 11, 12, 13; and 18, 19, and 20 to check the attainment of steady-state. The pre-dose samples on days 7, 14, and 21 also were used as C_{min} samples. All samples were analyzed to determine the concentration of gepirone and 1-PP, one of the major circulating metabolites.

Subjects:

Sixty healthy volunteers, 15 men and 15 women in the age range of 18-40 years, and 15 men and 15 women in the age range of 65-80 years participated in the trial. Of the 15 subjects in each demographic group, 12 received gepirone ER and 3 received matching placebo tablets.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- ER tablet formulation, product # (b) (4) (Lot #E90H381), was a pink, modified oval-shaped, biconvex tablet containing 20 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h).
- Placebo tablet, product # (b) (4), was used to match the gepirone ER tablet.

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.990$). Multiple QC samples were prepared at concentrations of 2, 8, 20, and 40 ng/ml for both gepirone and 1-PP. For gepirone, the between day and within day

assay variability were less than 3.6% and 7.0%, respectively. The corresponding values for 1-PP were 5.4% and 3.4%, respectively.

Criteria for Evaluation:

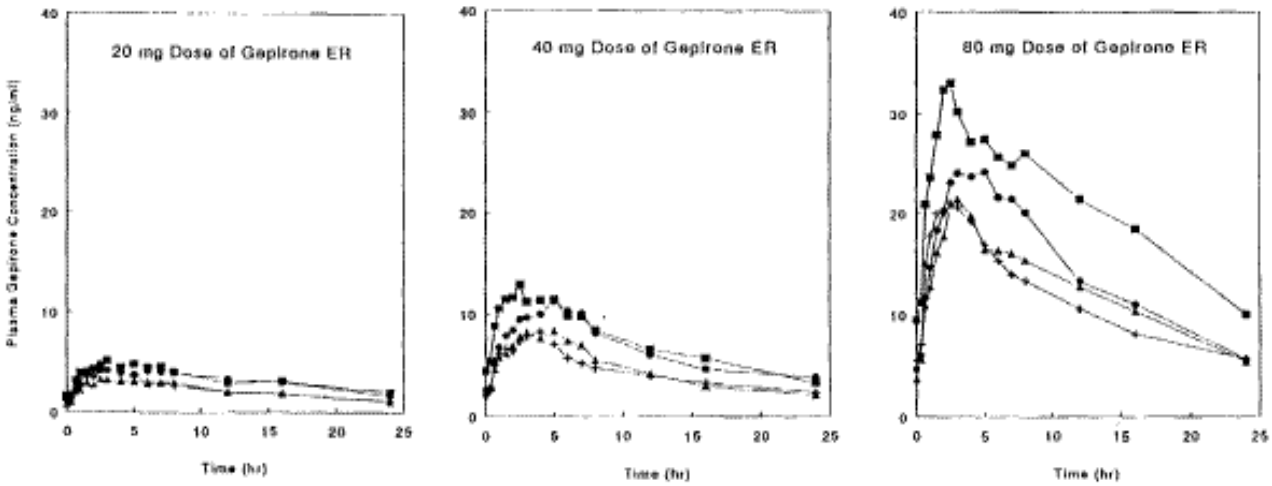
Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), and a metabolic ratio for C_{max} and AUC. Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

In order to assess the age and gender effects on the pharmacokinetics, an ANOVA, incorporating the appropriate covariates was performed. Weighted linear regression was used to test the dose proportionality of C_{max} and AUC, and a subsequent t-statistic was conducted to determine significance. For the determination of the onset of steady-state, a randomized block ANOVA was used for assessment of C_{min} values. With the exception of Levene's test, significance was set at p=0.05 level.

Results.

Figure 25. Mean Plasma Gepirone Concentrations (Day 1 and 7).

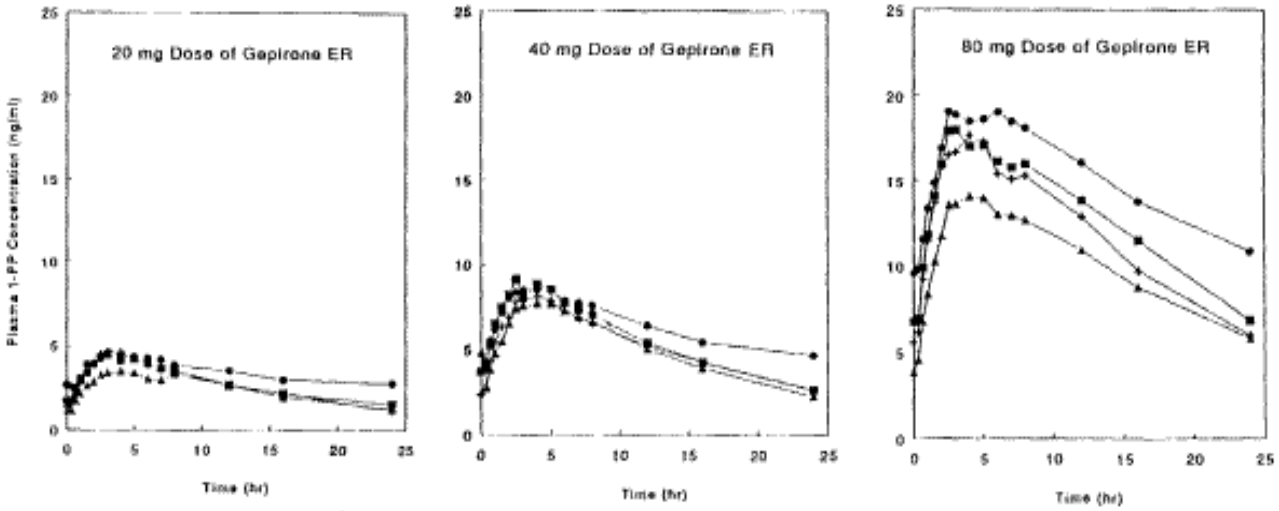
BEST AVAILABLE COPY



Legend: Filled squares; elderly women, filled squares; elderly men, filled triangles; young males, plus signs; young females.

BEST AVAILABLE COPY

Figure 26. Mean Plasma 1-PP Concentrations (Day 1 and 7).



Legend: Filled squares; elderly women, filled squares; elderly men, filled triangles; young males, plus signs; young females.

Table 31. Mean (SD) Pharmacokinetic Parameters of Gepirone.

Pharmacokinetic Parameter	Elderly Male, N = 12 ER Gepirone Dose			Young Male, N = 12 ER Gepirone Dose		
	20 mg	40 mg	80 mg	20 mg	40 mg	80 mg
CMAX (ng/mL)	5.14 (3.08)	12.4 (6.30)	27.5 (15.9)	3.90 (1.55)	9.06 (4.86)	23.0 (15.9)
TMAX (hours)[a]	3.50 (1.5-12)	5.00 (2.5-7)	3.50 (1.5-7)	4.50 (1.5-8)	3.00 (1.0-7)	2.50 (1.5-4)
TAUC(0-τ) (hr ng/mL)	75.0 (48.7)	156 (94.0)	344 (231)	51.4 (23.6)	108 (81.5)	296 (210)

[a]Values are median (min,max)

Pharmacokinetic Parameter	Elderly Female, N = 12 ER Gepirone Dose			Young Female, N = 12 ER Gepirone Dose		
	20 mg	40 mg	80 mg	20 mg	40 mg	80 mg
CMAX (ng/mL)	5.73 (2.44)	13.9 (5.50)	36.8 (19.3)	4.71 (1.84)	8.81 (5.56)	22.9 (11.5)
TMAX (hours)[a]	4.50 (0.7-7)	2.75 (1.0-7)	2.50 (2.0-12)	3.00 (1.0-4)	4.00 (2.5-6)	2.50 (1.0-5)
TAUC(0-τ) (hr ng/mL)	80.0 (45.2)	174 (96.8)	498 (274)	54.9 (22.6)	105 (61.3)	273 (133)

[a]Values are median (min,max)

Table 32. Mean (SD) Pharmacokinetic Parameters for 1-PP.

Pharmacokinetic Parameter	Elderly Male, N = 12 ER Gepirone Dose			Young Male, N = 12 ER Gepirone Dose		
	20 mg	40 mg	80 mg	20 mg	40 mg	80 mg
CMAX (ng/mL)	4.90 (5.25)	9.00 (8.43)	20.7 (22.4)	3.99 (2.32)	8.20 (4.16)	14.9 (7.52)
TMAX (hours)[a]	4.00 (2.0-7)	4.00 (2.0-12)	4.00 (3.0-7)	4.00 (2.5-12)	4.00 (2.5-6)	4.50 (2.5-12)
TAUC(0-τ) (hrng/mL)	82.1 (102)	151 (186)	364 (513)	58.3 (36.6)	119 (76.4)	241 (151)

[a]Values are median (min,max)

Pharmacokinetic Parameter	Elderly Female, N = 12 ER Gepirone Dose			Young Female, N = 12 ER Gepirone Dose		
	20 mg	40 mg	80 mg	20 mg	40 mg	80 mg
CMAX (ng/mL)	4.61 (1.87)	9.40 (3.98)	19.2 (5.50)	4.76 (2.11)	8.31 (3.55)	18.4 (6.66)
TMAX (hours)[a]	3.00 (2.5-6)	3.00 (2.5-5)	3.00 (2.5-12)	3.50 (2.5-6)	4.00 (2.5-6)	4.00 (2.0-8)
TAUC(0-τ) (hrng/mL)	67.2 (36.6)	134 (64.0)	307 (112)	66.4 (31.5)	125 (67.2)	284 (139)

[a]Values are median (min,max)

Figure 27. Mean (SD) C_{min} Values of Gepirone for the 4 Demographic Groups.

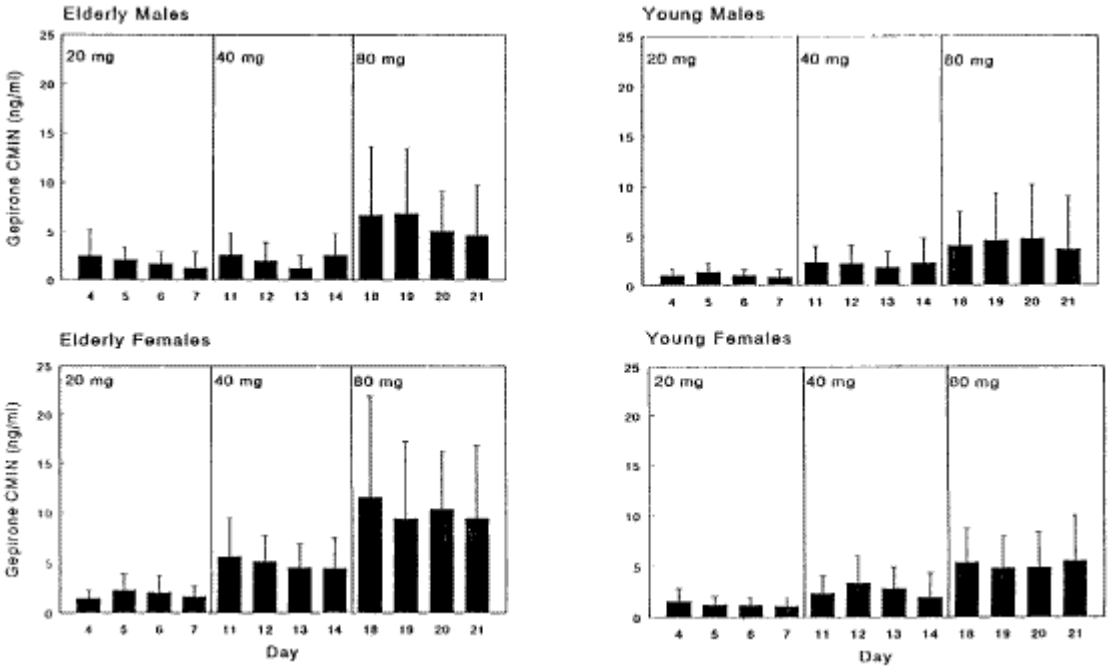
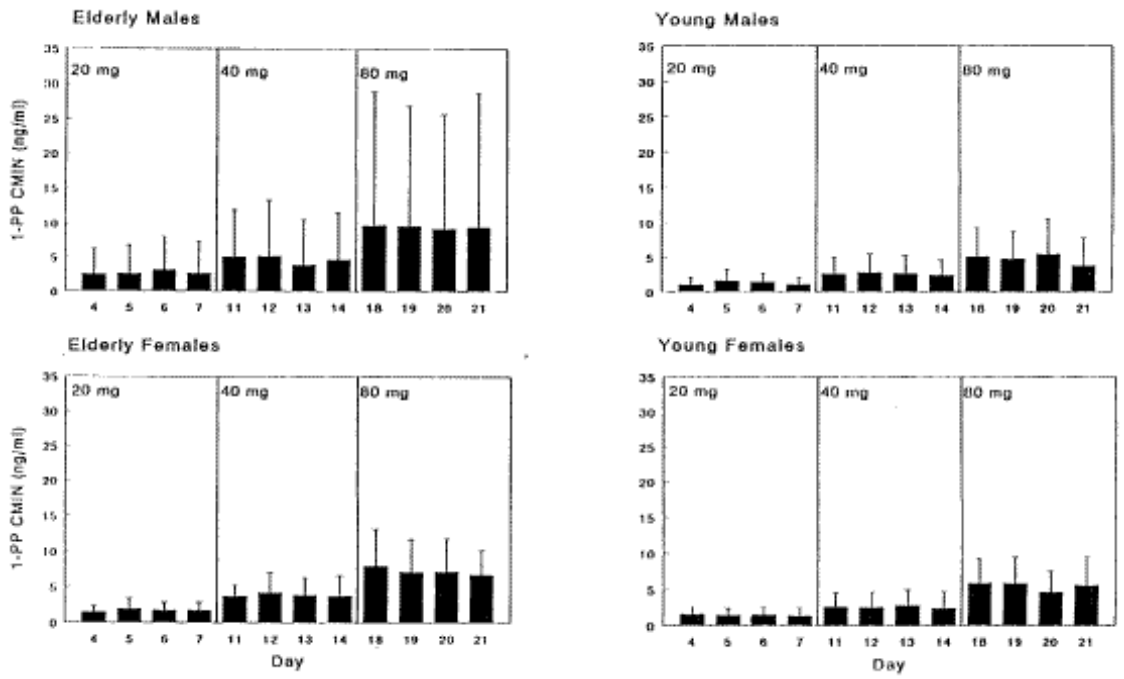


Figure 28. Mean (SD) C_{min} Values of 1-PP for the 4 Demographic Groups.



The pharmacokinetics of gepirone were analyzed in four demographic groups (elderly male and female and young male and female) at the dose levels of 20, 40, and 80 mg. For gepirone, the t_{max} ranged from 2.5-5 h and trough concentrations were stable at each dose level (Fig. 25, Table 31). As a result, day 7, 14, and 21 were representative of steady-state data for both gepirone and 1-PP (Figs 27, 28). Following the 80 mg dose, a trend was observed that C_{max} and AUC exhibited a greater than proportional increase with respect to dose (Fig. 25, Table 31). Due to high variability in the population, no statistically significant differences were observed in dose corrected C_{max} and AUC. The AUC values in elderly females at the three doses were 7, 12, and 45% greater compared with those observed with young females. In contrast, no gender effect was observed with steady state AUCs in the young population. Thus, differences in C_{max} and AUC were age related, and not gender related.

For 1-PP, the t_{max} ranged from 2.5 –5 h also (Fig. 26, Table 32). In contrast to gepirone, both C_{max} and AUC were proportional with respect to dose over the entire dose range. As a result, the pharmacokinetics of 1-PP were not influenced by age and gender. Although, a decrease in the 1-PP/gepirone molar ratio was observed at higher doses, suggesting that metabolic saturation may have occurred.

The most common adverse events following gepirone administration were lightheadedness and headache. In addition, systolic hypotension was prevalent in 11/13 young males, 6/12 elderly females, and 12/13 young females on active drug. Diastolic hypotension was prominent in 9/13 young females on active drug.

Conclusions.

Statistical analysis of the gepirone data, in conjunction with high variability in the data, showed that both C_{max} and AUC were dose proportional over the 20-80 mg dose range, with the exception of the relationship between C_{max} and dose in elderly females. Also, no gender differences were observed, but the data revealed an age difference in pharmacokinetic parameters, with the elderly exhibiting higher C_{max} and AUC values compared with the young subjects. For 1-PP, dose proportionality was demonstrated in all four treatment groups, and neither age nor gender differences were observed in 1-PP pharmacokinetic parameters. Since the metabolic ratio decreased at higher doses, a decrease in the metabolism of gepirone could occur at higher doses. It is recommended that the maximum daily dose of gepirone should not exceed 40 mg in the elderly.

17. **Protocol FK-GBE-005: Single Dose Pharmacokinetics of Gepirone 20 mg MR Tablets ((b) (4)) in Normal and Hepatically Impaired Volunteers.**

Objectives.

The objective of this study was to compare the pharmacokinetics of gepirone and its major metabolites in normal and hepatically impaired patients.

Study Design and Methods:

This study consisted of an open-label, single-dose, two-treatment design. In session 1, 12 hepatically impaired patients received a single 20 mg dose of gepirone ER following a 10 h fast. In session 2, 12 matched control subjects were administered a single dose of 20 mg of gepirone ER. Serial blood samples were collected over 48 h and urine was collected for 24 h. All samples were assayed for gepirone, 1-PP, and 3'OH-gepirone content using LC/MS. In addition, the sponsor made an effort to more fully define the presence of additional metabolites.

Subjects:

Twenty-five subjects (age 18-70; 12 Caucasian and 13 Hispanic), with hepatic impairment as well as healthy subjects, were enrolled in the study. Twenty-four subjects completed the study, consisting of two groups of 12/group. The hepatically impaired subjects included 7 subjects with Grade A, 5 subjects with Grade B, and 1 subject with Grade C hepatic impairment based on the Child-Pugh scores recorded for each subject.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the (b) (4), which included:

- MR tablet formulation, product #(b) (4) (Lot #98-013T), containing 20 mg of gepirone HCl.

Assay Validation:

An LC/MS/MS assay was used to quantitate gepirone, 1-PP, and 3'OH-gepirone in this study. The calibration curves were linear for the concentration range from 0.025-9.0 ng/ml for gepirone, 0.1 – 10 ng/ml for 1-PP, and 0.25-15 ng/ml for 3'OH-gepirone ($r \geq 0.996$, $r \geq 0.996$, and $r \geq 0.997$ for gepirone, 1-PP, and 3'OH). Low, medium, and high QC samples were prepared at concentrations of 0.5, 1.0, and 2.0 ng/ml for gepirone and 1-PP, and 0.25, 5.0, and 10 ng/ml for 3'OH-gepirone. The deviations from the mean for gepirone were within 14.0% for the low QCs, 6.8% for the medium QCs, and 7.2% for the high QCs. The corresponding values for 1-PP were 8.1%, 11.4%, and 12.1%, respectively. The corresponding values for 3'OH-gepirone were 7.0%, 10.2%, and 10.1%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), half-life ($t_{1/2}$), and the terminal elimination rate constant (K_e). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

An ANOVA, incorporating group, gender, weight, and age was utilized in order to compare C_{max}, $t_{1/2}$, AUC, and K_e. In addition, C_{max} and AUC also were log-transformed for comparison of the two groups. In all tests, differences were considered significant if $p \leq 0.05$ (2-tailed test). Also for practical considerations, 24 subjects (12/group) were employed to show an effect difference of 50%.

Results.

Figure 29. Mean Plasma Concentrations of Gepirone, 1-PP, and 3'OH gepirone in Hepatically Impaired and Healthy Volunteers.

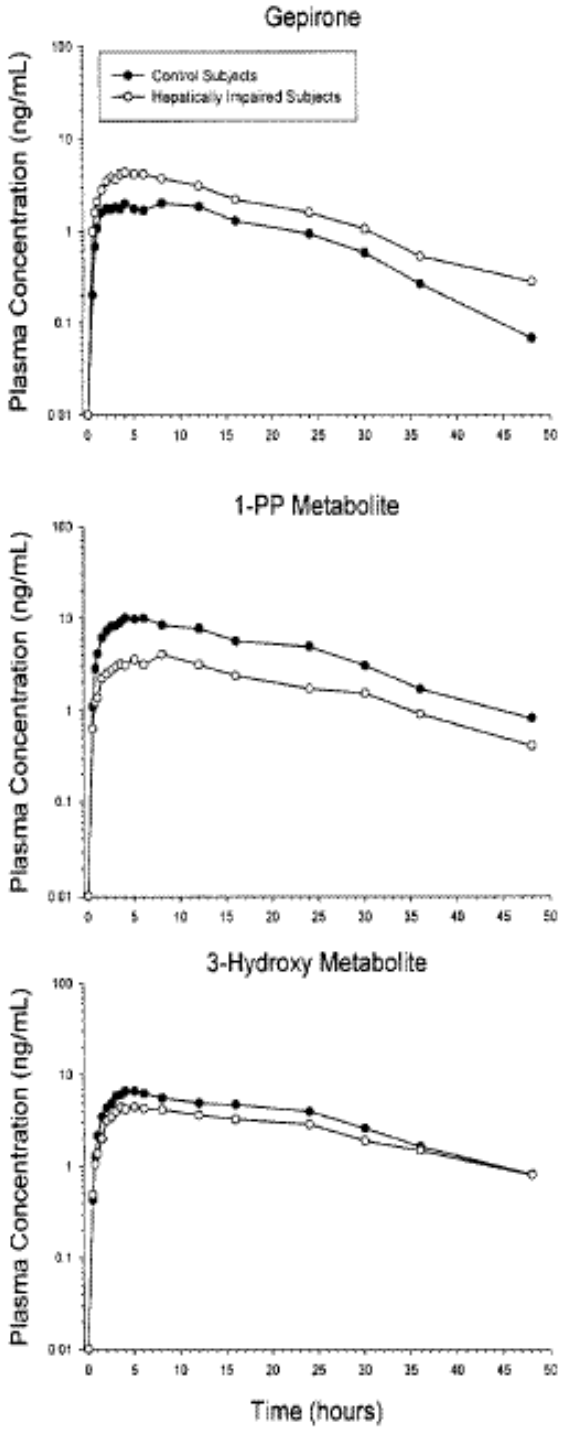


Table 33. Mean (SD) Pharmacokinetic Parameters for Gepirone, 1-PP, and 3'Hydroxy Gepirone in Hepatically Impaired and Healthy Volunteers.

Variable	Hepatically Impaired	Healthy Volunteers	p-Value
Gepirone			
AUC (ng-h/ml)	91.6 (69.7)	46.0 (27.0)	0.046
C_{max} (ng/ml)	5.25 (2.63)	2.41 (1.15)	0.0023
K_e (h^{-1})	0.12 (0.0865)	0.12 (0.041)	0.930
$T_{1/2}$ (h)	9.25 (8.74)	6.73 (3.02)	0.3543
Ln-AUC (ng-h/ml)	70.6	39.7	0.0490
Ln-C_{max} (ng/ml)	4.59	2.18	0.0019
1-PP			
AUC (ng-h/ml)	96.5 (56.1)	229 (138)	0.0055
C_{max} (ng/ml)	4.49 (2.05)	12.5 (5.22)	0.0001
K_e (h^{-1})	0.08 (0.0289)	0.10 (0.0497)	0.232
$T_{1/2}$ (h)	10.2 (5.42)	8.20 (3.14)	0.271
Ln-AUC (ng-h/ml)	80.7	193	0.0033
Ln-C_{max} (ng/ml)	4.09	11.4	0.0000
3'OH-gepirone			
AUC (ng-h/ml)	147 (84.8)	178 (62.8)	0.321
C_{max} (ng/ml)	5.40 (1.88)	7.69 (1.71)	0.0049
K_e (h^{-1})	0.06 (0.0292)	0.08 (0.0271)	0.107
$T_{1/2}$ (h)	16.7 (11.2)	10.6 (5.03)	0.103
Ln-AUC (ng-h/ml)	126	168	0.175
Ln-C_{max} (ng/ml)	5.08	7.51	0.0055

For gepirone, both C_{max} and AUC were significantly higher in the hepatically impaired population compared to the healthy volunteers (Fig. 29, Table 33). In the subjects with hepatic impairment, AUC was increased approximately 2-fold compared with normal volunteers. The sponsor suggested that this increase is primarily attributable to high AUC values for subjects 1, 3, and 5, which comprise 60% (3/5) of the subjects with Grade B hepatic impairment.

In contrast to gepirone, both the AUC and C_{max} for 1-PP in hepatically impaired subjects were reduced significantly compared to healthy volunteers. The AUC and C_{max} were approximately one-half and one-third that in the healthy volunteers. In addition, the metabolic ratio of AUCs for 1-PP indicated an approximate 4-fold reduction in the ability of hepatically impaired patients to convert gepirone to 1-PP.

For 3'OH-gepirone, the AUC and C_{max} were also lower in the hepatically impaired group. The molar ratio of the AUC revealed a 2-fold reduction in the ability of the hepatically impaired subjects to metabolize gepirone to 3'OH-gepirone.

Table 34. Comparison of 24-Hour Excretion of Gepirone and Its Metabolites in Hepatically Impaired and Healthy Subjects.

Analyte	Hepatically impaired		Healthy Volunteers		p-Value
Total Amount Excreted	**(nmol/24 hr)**	**(% of Total)**	**(nmol/24 hr)**	**(% of Total)**	
Gepirone	276.89	5.5	186.03	3.5	0.3007
1-PP	381.01	7.6	913.56	17.0	0.0174
3-Hydroxy gepirone	541.04	10.7	660.27	12.3	0.5157
5-Hydroxy gepirone	666.86	13.2	462.08	8.6	0.0915
3, 5-Dihydroxy gepirone	3180.46	63.0	3137.12	58.5	0.9510
Urine Metabolite Ratios					
1-PP to gepirone	2.73	N/A	7.11	N/A	0.0495
3-Hydroxy gepirone to gepirone	1.97	N/A	5.37	N/A	0.0318
5-Hydroxy gepirone to gepirone	4.06	N/A	4.54	N/A	0.7520
3, 5-Dihydroxy gepirone to gepirone	19.22	N/A	30.16	N/A	0.2209

N/A = Not applicable

In order to understand more fully the presence of metabolites, urine was analyzed using the LC/MS assay (Table 34). The samples were hydrolyzed overnight, thus resulting in total concentrations, free plus conjugated. The results showed that 60% of the total analytes present in the urine consisted of 3, 5-dihydroxy gepirone. Also, the amount of drug recovered in the urine during the first 24 h in severely impaired patients was less than that of the other groups.

Conclusions.

Based on the individual patient data, Grade B (moderate) hepatic impairment results in a decrease in the first pass metabolism of gepirone. As a result, hepatic dysfunction can contribute to elevated and decrease levels of gepirone (2-fold elevation in exposure) and 1-PP (3- and 2-fold reduction in C_{max} and AUC), respectively. The maximum daily dose of gepirone should not exceed 40 mg in moderately impaired patients since the liver plays a major role in the metabolic pathway of the drug. The pharmacokinetics of gepirone have not been adequately characterized in severe hepatic impairment. It is not recommended that gepirone is administered to these patients.

18. Protocol 28708: A Single Dose Study to Assess the Effect of Renal Impairment on the Pharmacokinetics of Gepirone and its Metabolites.

Investigator.

(b) (4)

Objectives.

The objectives of this study were (1) to compare the pharmacokinetic parameters of gepirone and its major metabolites (1-PP and 3'OH-gepirone) following a single dose of 40 mg gepirone MR in subjects with different levels of renal function and (2) to assess the relative safety of gepirone in these subjects.

Study Design and Methods:

This study consisted of an open-labeled, single dose, parallel design. Gepirone was administered under fasting conditions as a single 40 mg dose of a modified release formulation. Subjects were not allowed to consume food until 4 h after drug administration. Blood samples were collected over 96 h and urine was collected for 48 h. Samples were analyzed for gepirone, 1-PP, and 3'OH-gepirone by LC/MS/MS.

Subjects:

Thirty-seven male or female Caucasian subjects (age 35-65), with different degrees of renal function as well as healthy subjects, were enrolled in the study. Thirty-six completed the study, consisting of four groups of 9/group. The subjects were allocated to their respective study groups according to the GFR as follows:

Table 35. Renal Function of Subjects.

Group 1 (n=9)	mild renal insufficiency with GFR $\geq$ 52 and < 78 ml/min/1.73 m^2 of body surface.
Group 2 (n=9)	moderate renal insufficiency with GFR $\geq$ 32 and < 48 ml/min/1.73 m^2 of body surface.
Group 3 (n=9)	severe renal insufficiency with GFR < 28 ml/min/1.73 m^2 of body surface.
Group 4 (n=9)	Normal renal function with GFR $\geq$ 82 ml/min/1.73 m^2 of body surface.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the (b) (4), which included:

- MR tablet formulation, product #(b) (4) (Lot #0581394), containing 20 mg of gepirone HCl. Each subject received a total dose of 40 mg (2 x 20 mg tablets).

Assay Validation:

A LC/MS/MS assay was used to quantitate gepirone, 1-PP, and 3'OH-gepirone in this study. The calibration curves were linear for the concentration range from 0.1 – 10 ng/ml for all of the compounds ($r \geq 0.995$, $r \geq 0.993$, and $r \geq 0.990$ for gepirone, 1-PP, and 3'OH). Low, medium, and high QC samples were prepared at concentrations of 0.3, 4.0, 8.0 ng/ml for gepirone and 3'OH-gepirone and 0.6, 4.0, and 8.0 ng/ml for 1-PP. The deviations from the mean for gepirone were within 17.9% for the low QCs, 9.3 for the medium QCs, and 7.66% for the high QCs. The corresponding values for 1-PP were 16.5%, 13.0%, and 13.0%, respectively. The corresponding values for 3'OH-gepirone were 19.4%, 11.5%, and 10.1%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), half-life ($t_{1/}2$), apparent clearance (CL_{app}), and apparent volume of distribution during the terminal phase (V_{app}). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

A one-way ANOVA with group as a fixed factor was utilized on the log transformed values of the parameters C_{max}, $t_{1/2}$, $AUC_{0-\infty}$, and weight normalized CL. For the log-transformed parameters, 90% confidence intervals for the true ratio of mild, moderate and severe renal impairment geometric mean versus control were calculated. The acceptance ranges were (b) (4) (C_{max}) or (b) (4) for other parameters. For t_{max}, the non-parametric Kruskal-Wallis test was performed. Correlation analysis was performed between GFR and CL_{app}, wn-CL_{app}, terminal elimination rate constant, and C_{max}. In all tests, differences were considered significant if $p \leq 0.05$ (2-tailed test). Also for practical considerations, 36 patients (9/group) were employed to show an effect difference of 50%.

Results.

Figure 30. Mean Plasma Gepirone Concentrations.

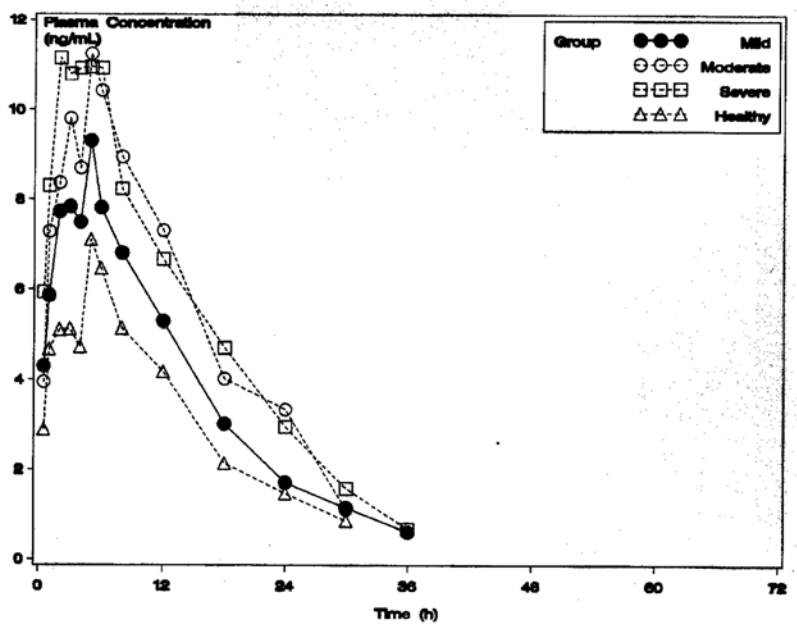


Figure 31. Mean Plasma 1-PP Concentrations.

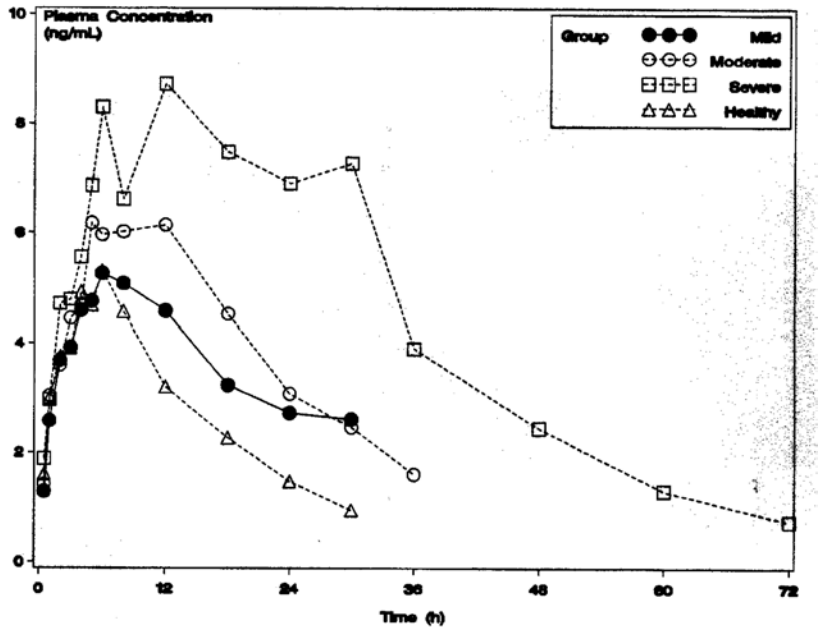


Figure 32. Mean Plasma Concentrations of 3'OH-gepirone.

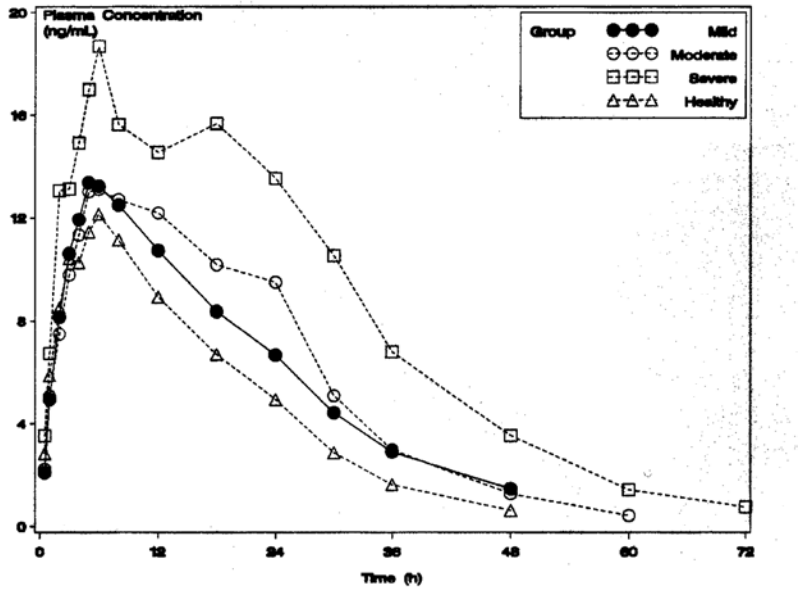


Table 36. Mean Pharmacokinetic Parameters of Gepirone.

Parameter	Group			
	Healthy	Mild	Moderate	Severe
C_{max} (ng/mL)	7.60 (2.49)	9.73 (4.36)	12.4 (6.98)	14.2 (7.12)
t_{max}[1] (h)	5.0 (1.0 - 8.0)	5.0 (0.5 – 8.0)	4.0 (1.0 – 6.0)	4.0 (1.0 – 6.0)
$AUC_{0\text{-}tfix}$ (ng.h/mL)	79.6 (27.4)	107 (44.5)	137 (59.8)	142 (69.8)
$AUC_{0\text{-}tlast}$(ng.h/mL)	103 (40.2)	144 (58.9)	180 (82.5)	188 (98.0)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	107 (42.5)	147 (59.0)	182 (82.4)	194 (100)
$t_{½}$ (h)	6.03 (3.74)	6.09 (3.71)	4.60 (1.61)	6.23 (4.10)
CL_{app} (L/h)	387 (144)	298 (162)	241 (108)	239 (115)
wn-CL_{app} (L/h/kg)	4.86 (1.53)	3.77 (2.12)	3.06 (1.38)	3.43 (2.11)
$V_{z.app}$ (L)	3092 (1719)	2265 (1118)	1502 (703)	2178 (2153)
wn-$V_{z.app}$(L/kg)	39.5 (22.3)	29.0 (15.7)	19.3 (9.68)	34.7 (45.4)

Data were taken from Table 9-2 in Appendix BI: Pharmacokinetics, BI.9.
[1] median (range)

Table 37. Mean Pharmacokinetic Parameters of 1-PP.

Parameter	Group			
	Healthy	Mild	Moderate	Severe
C_{max} (ng/mL)	5.84 (2.28)	5.93 (2.77)	7.65 (3.10)	11.1 (6.07)
t_{max}[1] (h)	5.0 (4.0 – 6.0)	6.0 (1.0 – 30.0)	8.0 (5.0 – 12.0)	12.0 (3.0 – 30)
$AUC_{0\text{-}tfix}$ (ng.h/mL)	76.0 (33.7)	93.1 (53.9)	116 (62.0)	167 (83.4)
$AUC_{0\text{-}tlast}$(ng.h/mL)	91.7 (50.1)	138 (120)	166 (120)	324 (205)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	97.5 (53.7)	144 (123)	169 (121)	335 (210)
$t_{½}$ (h)	7.17 (2.70)	8.06 (2.33)	7.26 (3.11)	15.5 (8.19)
CL_{app} (L/h)	486 (239)	419 (266)	324 (214)	158 (98.4)
wn-CL_{app} (L/h/kg)	6.16 (2.95)	5.16 (3.34)	4.05 (2.62)	2.21 (1.78)
$V_{z,app}$ (L)	4324 (1192)	4235 (2166)	2956 (1669)	3449 (3292)
wn-$V_{z,app}$(L/kg)	55.1 (14.2)	52.3 (27.6)	70.0 (101)	46.2 (40.0)

Data were taken from Table 9-4 in Appendix BI: Pharmacokinetics, BI.9.

[1] median (range)

Table 38. Mean Pharmacokinetic Parameters of 3'OH-gepirone.

Parameter	Group			
	Healthy	Mild	Moderate	Severe
C_{max} (ng/mL)	13.3 (5.79)	15.7 (8.89)	15.6 (2.94)	21.2 (11.2)
t_{max}[1] (h)	5.0 (4.0 – 8.0)	5.0 (5.0 – 8.0)	8.0 (4.0-24.0)	6.0 (4.0 – 24.0)
$AUC_{0\text{-}tfix}$ (ng.h/mL)	235 (95.1)	285 (112)	323 (67.3)	471 (207)
$AUC_{0\text{-}tlast}$(ng.h/mL)	252 (103)	324 (138)	362 (80.8)	583 (248)
$AUC_{0\text{-}\infty}$ (ng.h/mL)	256 (103)	331 (139)	367 (81.6)	591 (248)
$t_{½}$ (h)	7.03 (2.16)	8.62 (2.09)	10.1 (4.87)	12.1 (2.95)
CL_{app} (L/h)	163 (66.7)	129 (53.1)	104 (28.2)	81.2 (60.4)
wn-CL_{app} (L/h/kg)	2.04 (0.698)	1.58 (0.590)	1.33 (0.367)	1.05 (0.654)
$V_{z,app}$ (L)	1597 (629)	1570 (648)	1445 (548)	1479 (1308)
wn-$V_{z,app}$(L/kg)	20.1 (7.26)	19.3 (7.59)	18.4 (6.83)	18.9 (14.2)

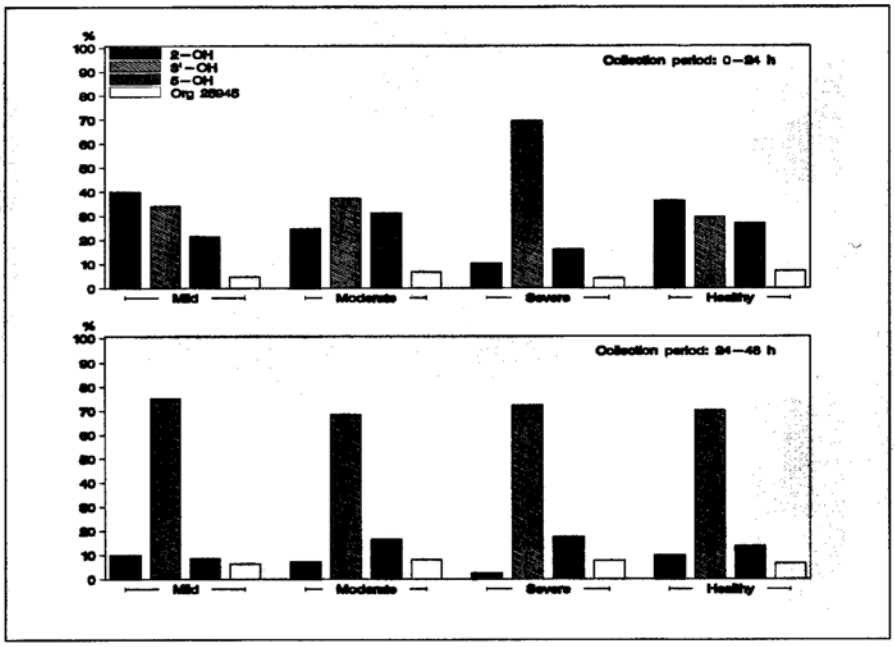
Data were taken from Table 9-6 in Appendix BI: Pharmacokinetics, BI.9.

[1] median (range)

Table 39. Mean Urine Gepirone, 1-PP, and 3'OH-gepirone Amounts.

Group	Org 33062		1-PP		3'-OH	
	0-24 h	24-48 h	0-24 h	24-48 h	0-24 h	24-48 h
Healthy	195 (127)	48 (46)	492 (313)	101 (92)	556 (210)	205 (104)
Mild	224(153)	62 (33)	391 (422)	186 (244)	496 (322)	263 (151)
Moderate	285 (169)	76 (88)	420 (354)	202 (171)	481 (215)	247 (146)
Severe	140 (124)	53 (58)	264 (161)	275 (202)	252 (146)	193 (104)

Figure 33. Profile of Minor Metabolites in Urine.



Note: data expressed as percentage of the total peak area of these four metabolites (3',5-OH metabolite not shown)

For gepirone, an increased AUC by 65-71%, and consequently a decreased CL_{app} by 60-62% were observed for the moderately and severely impaired patient groups (Fig. 30, Table 36). Also, a 74% increase in C_{max} was observed in severely impaired subjects compared with healthy subjects. No change in $t_{1/2}$ was observed for gepirone among all of the groups.

For 1-PP, an increased C_{max} (by 79%), AUC (by 112-226%) and a prolonged t1/2 was observed in the severely impaired patients (Fig. 31, Table 37). As a result of the increase in exposure, a 68% decrease in CL_{app} was observed in this group.

For 3'OH-gepirone, the results for the comparison of severe vs. healthy subjects were similar to those for 1-PP, an increased C_{max}, (by 50%), AUC (by 90-121%), and $t_{1/2}$ (by 74%) (Fig. 32, Table 38). As a result, CL_{app} decreased by 52%. For the moderately impaired patients, an increased $t_{1/2}$ (by 38%) and a decreased CL_{app} (by 43%) were observed.

Also, the amount of drug recovered in the urine during the first 24 h in severely impaired patients was less than that of the other groups (Fig. 33, Table 39). Thus, these findings support the changes in plasma pharmacokinetic parameters found in renal impaired patients.

Conclusions.

Overall, plasma levels of gepirone, 1-PP, and 3'OH-gepirone increased with respect to the level of renal impairment. The overall effect of renal insufficiency was more pronounced for the metabolites and parent drug in the moderately and severely impaired groups, resulting in prolonged exposure and half-lives. Thus, the maximum daily dose should not exceed 40 mg in both moderate and severely impaired patients since the kidneys play a major role in the elimination of the metabolites of gepirone.

19. Protocol 28717: Single and Multiple Dose Pharmacokinetic Interaction Study Between Gepirone and Ketoconazole in Healthy Male Volunteers.

Investigator.

(b) (4)

Objectives.

The objectives of this study were (1) to compare the pharmacokinetics of gepirone and its metabolites (1-PP and 3'OH-gepirone) after single and multiple dose administration with and without pre-and co-administration of ketoconazole, and (2) assess the tolerability of the combined administration of a single dose of gepirone and ketoconazole.

Study Design and Methods:

This study consisted of an open-label, randomized, single and multiple dose, two-period crossover, design. Between gepirone dosing regimens, a 14-day washout phase was implemented. Subjects were dosed in two groups according to the treatment sequence:

1) Group 1: gepirone alone/gepirone + ketoconazole
2) Group 2: gepirone + ketoconazole/gepirone alone

Because of the high incidence of adverse events indicating a strong interaction between ketoconazole and gepirone, the drug interaction was assessed with a single dose of gepirone only. In addition, the gepirone dose that was administered with ketoconazole in group 1 was reduced to 20 mg. The actual dosing schedule was according to the following:

A) A single dose of 40 mg gepirone on day 1 followed by a multiple dose regimen of 40 mg gepirone once daily on days 5-9. All 24 subjects received treatment A.

B1) A single dose of 40 mg gepirone on day 1 with pre-and co-administration of 200 mg ketoconazole b.i.d. Dosing with ketoconazole started on the evening of day –3, and continued up to an including the morning dose on day 1. Twelve subjects received this treatment.

B2) a single dose of 20 mg gepirone on day 1 with pre- and co-administration of 200 mg ketoconazole b.i.d. Dosing with ketoconazole commenced in the evening of day –3, and continued up to and including the evening dose on day 4. Twelve subjects received this treatment.

Doses were administered following a light meal except for days 1 and 9, when the morning doses were given after a 10 h fasting period. Serial blood samples were collected over a 96-h period on days 1 and 9. Extra samples (up to 192 h) were collected after the single dose combination treatment in period 1. Urine was collected for 48 h after the last gepirone dose in both periods. All samples were analyzed by a LC/MS assay to determine the concentration of gepirone, 1-PP, and 3'OH-gepirone. In addition, during both periods, a day 1 and 9 urine sample was collected for the determination of 6β-hydroxycortisol as a marker for CYP3A4 inhibition.

Subjects:

Twenty-four healthy male volunteers (age range: 18 - 45 yrs; all Caucasians) were enrolled and completed the study. All subjects received treatment A. 12 subjects received treatment B1 and 12 subjects received treatment B2.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone was supplied to the investigator by (b) (4), which included:

- ER tablet formulation, product #(b) (4) (Lot # 0581393), containing 20 mg of gepirone HCl. Each subject received a total daily dose of 40 mg (2 x 20 mg tablets).

For ketoconazole (Nizoral®), the formulation was supplied by Janssen Pharmaceuticals, which included:

- Tablet formulation (Lot # 98H07/356), containing 200 mg of ketoconazole. Each subject was administered 200 mg b.i.d.

Assay Validation:

An LC/MS assay was used to quantitate gepirone, 1-PP, and 3'OH-gepirone in this study. The calibration curves in plasma were linear for the concentration range from 0.1–10 ng/ml for gepirone, 0.2-5.0 ng/ml for 1-PP, and 0.25-10 ng/ml for 3'OH-gepirone ($r \geq 0.988$ for gepirone, $r \geq 0.984$ for 1-PP, and $r \geq 0.989$ for 3'OH-gepirone). Several QC samples were prepared at concentrations of 0.15-8.0 ng/ml for gepirone, 0.6-4.0 ng/ml for 1-PP, and 0.75-8.0 ng/ml for 3'OH-gepirone. The deviations from the mean for gepirone, 1-PP, and 3'OH were less than 13.2%, 17.6%, and 17.2%.

For urine, the calibration curves were linear for the concentration range from 2.5-100 ng/ml for the low concentration range and 50-600 ng/ml for the high concentration

range for all analytes ($r \geq 0.995$ for gepirone, $r \geq 0.991$ for 1-PP, and $r \geq 0.986$ for 3'OH). Several QCs were prepared to cover the low and high concentration ranges, and as a result the deviations from the mean for gepirone, 1-PP, and 3'OH were less than 13%, 25%, and 20%.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of various parameters including a lag time (t_{lag}), peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), area under the curve ($AUC_{0\text{-}t,\infty}$), minimum observed plasma concentration (C_{min}), steady-state pharmacokinetic parameters, and an accumulation ratio for AUC (day 8)/AUC (day 1). In addition, 6β-OHcortisol/cortisol ratios in urine were calculated. Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

For C_{max} and AUC, the parametric point estimates were calculated with 90% confidence intervals derived from the ANOVA on log-transformed data. The ANOVA incorporated sequence, subject, treatment, period, and residual error effects. Effects were considered significant if $p \leq 0.05$. In addition, a paired t-test was performed on the log-transformed AUC and $t_{1/2}$.

Results.

Figure 34. Mean Single Dose Gepirone Curves.

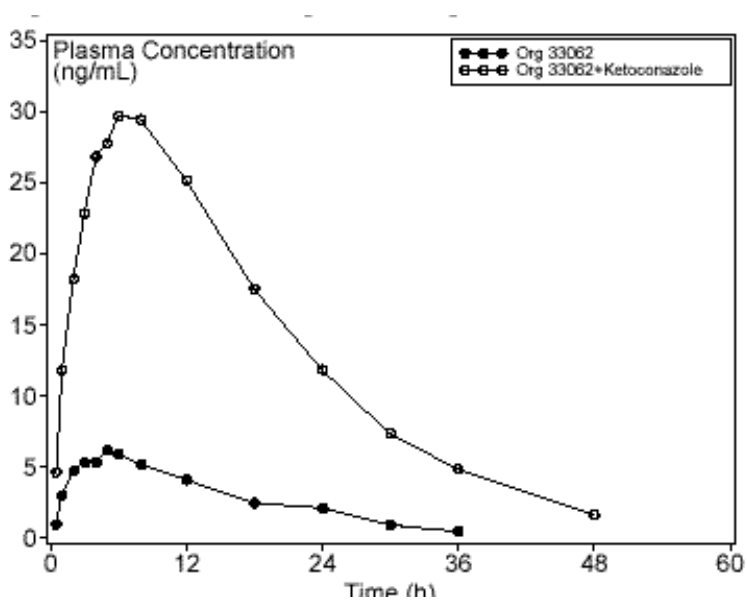


Figure 35. Mean Single Dose 1-PP Curves.

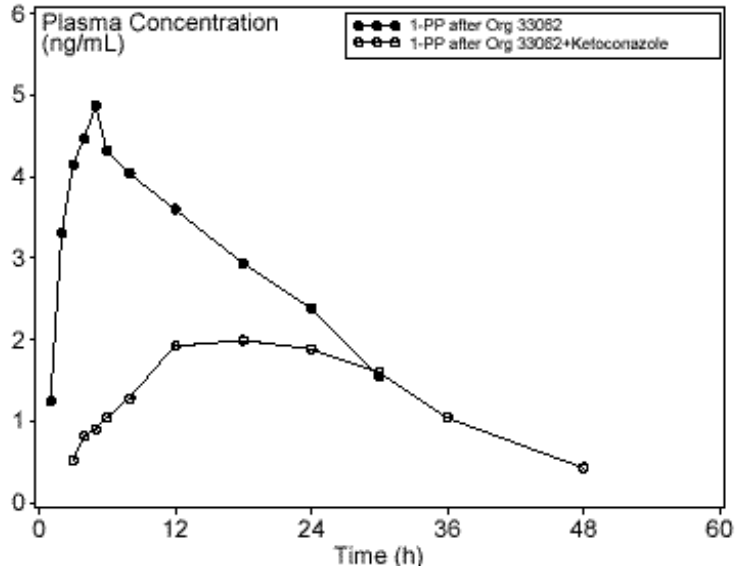
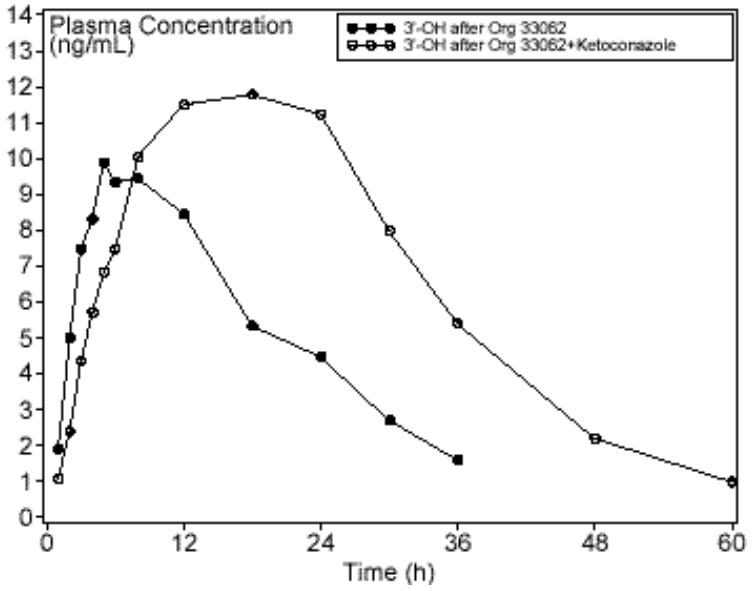


Figure 36. Mean Single Dose 3'OH-gepirone Curves.



Note: For Figs. 34-36, data from the 20 mg gepirone + ketoconazole treatment were normalized to a 40 mg dose before taking the average.

Figure 37. Mean Multiple Dose Gepirone, 1-PP, and 3'OH-gepirone Plasma Curves after treatment with Gepirone Alone.

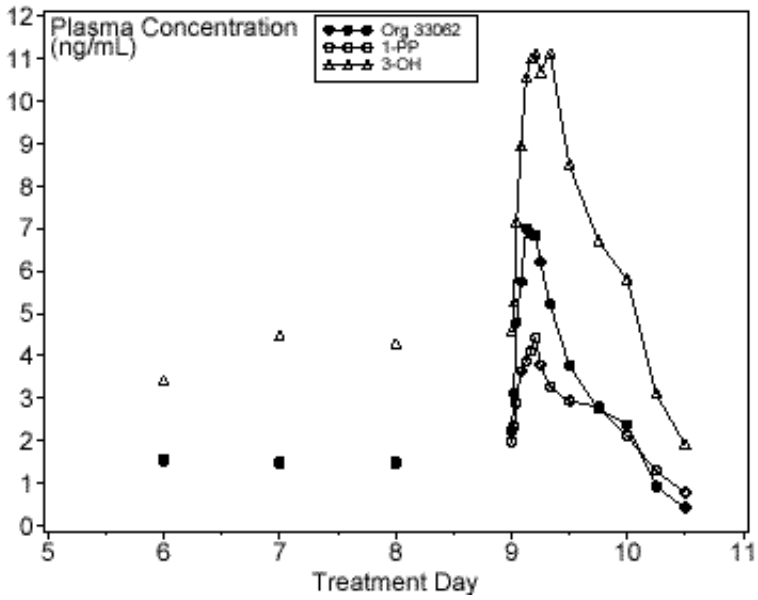


Table 40. Mean (SD) Single Dose Parameters for Gepirone.

Parameter	Units	Treatment	
		Org 33062	Org 33062+Ketoconazole
$t_{sd,lag}$[1]	h	0.104 (0-0.500)	0.042 (0-0.500)
$t_{sd,max}$[1]	h	6.25 (2.00-18.0)	5.75 (3.00-8.00)
$C_{sd,max}$	ng/mL	7.18 (3.74)	34.8 (14.1)
$t_{sd,½}$	h	6.96 (3.93)	7.58 (3.51)
$AUC_{sd,0-\infty}$	ng.h/mL	109 (53.2)	659 (338)
$AUC_{sd,0-12}$	ng.h/mL	56.7 (28.7)	289 (108)
wn-$CL_{sd,app}$	L/h/kg	5.29 (3.10)	0.854 (0.389)
wn-$V_{sd,z,app}$	L/kg	57.0 (65.5)	8.44 (3.96)

Table 41. Mean (SD) Single Dose Parameters for 1-PP.

Parameter	Units	Treatment	
		Org 33062	Org 33062+Ketoconazole
$t_{sd,lag}$[1]	h	0.188 (0-0.500)	2.44 (0.500-8.00)
$t_{sd,max}$[1]	h	5.21 (2.00-12.0)	15.9 (4.00-30.0)
$C_{sd,max}$	ng/mL	5.76 (3.67)	2.26 (1.37)
$t_{sd,½}$	h	11.7 (9.26)	12.1 (6.81)
$AUC_{sd,0-\infty}$	ng.h/mL	122 (96.8)	70.4 (44.8)
$AUC_{sd,0-12}$	ng.h/mL	43.7 (27.3)	10.9 (7.60)
wn-$CL_{sd,app}$	L/h.kg	7.49 (7.86)	9.52 (6.95)
wn-$V_{sd,z,app}$	L/kg	108 (107)	151 (117)

Table 42. Mean (SD) Single Dose Parameters for 3'OH.

Parameter	Units	Treatment	
		Org 33062	Org 33062+Ketoconazole
$t_{sd,lag}$[1]	h	0.417 (0-1.00)	0.542 (0-2.00)
$t_{sd,max}$[1]	h	6.46 (3.00-12.0)	16.9 (8.00-30.0)
$C_{sd,max}$	ng/mL	11.3 (6.86)	14.1 (4.51)
$t_{sd,½}$	h	9.83 (6.47)	9.47 (3.41)
$AUC_{sd,0-\infty}$	ng.h/mL	223 (117)	397 (139)
$AUC_{sd,0-12}$	ng.h/mL	91.4 (49.0)	81.4 (33.1)
wn-$CL_{sd,app}$	L/h/kg	2.53 (1.24)	1.34 (0.660)
wn-$V_{sd,z,app}$	L/kg	32.3 (16.6)	18.2 (11.3)

Table 43. Mean (SD) Multiple Dose Parameters after administration of Gepirone Alone.

Parameter	Units	Treatment = Org 33062		
		Org 33062	1-PP	3'-OH
$t_{ss,max}$[1]	h	3.46 (0-8.00)	4.65 (0.50-12.0)	5.54 (1.00-12.0)
$C_{ss,max}$	ng/mL	8.22 (4.87)	5.25 (5.03)	12.6 (6.98)
$C_{ss,max,corr}$	ng/mL	7.34 (4.77)	4.59 (4.27)	9.21 (4.73)
$t_{ss,½}$	h	7.81 (6.69)	10.3 (3.64)	9.67 (4.03)
$AUC_{ss,0-12}$	ng.h/mL	64.6 (37.4)	41.1 (35.3)	117 (61.4)
$AUC_{ss,0-24}$	ng.h/mL	99.6 (56.7)	73.0 (72.1)	200 (102)
wn-$CL_{ss,app}$	L/h/kg	6.59 (4.92)	12.6 (16.1)	2.94 (2.20)
wn-$V_{ss,z,app}$	L/kg	107 (203)	154 (188)	44.5 (43.7)
DF	%	143 (52.2)	138 (64.3)	96.0 (27.2)
RA1	-	1.22 (0.503)	0.947 (0.343)	1.24 (0.420)
RA2	-	1.18 (0.526)	0.986 (0.538)	1.34 (0.473)
$C_{ss,min,av}$	ng/mL	1.82 (1.38)	1.78 (1.65)	4.76 (2.88)

Table 44. Comparison between Predose and Single Dose/Multiple Dose 6β-hydroxycortisol Ratios.

Treatment	Regimen	Ratio 6β-hydroxycortisol /cortisol	
		Mean (-)	p-value
Org 33062	Predose	2.27	-
	Single Dose	1.89	**0.0098**
	Multiple Dose	1.66	**0.0018**
Org 33062 + Ketoconazole	Predose	1.89	-
	Single Dose, Seq.1	0.866	**0.0001**
	Single Dose, Seq.2	0.469	**0.0001**

Following co-administration with ketoconazole, both the C_{max} and AUC of gepirone increased significantly by approximately 5- and 6-fold, respectively (Fig 34, Table 40). As a result, the C_{max} and AUC of 1-PP decreased approximately 2.5- and 2-

fold, respectively (Fig. 35, Table 41). Peak concentration s of both metabolites shifted to a later time point (Figs. 35, 36, Tables 41, 42). Following multiple dose administration, trough concentrations of gepirone and its metabolites did not increase (Fig. 37, Table 43). Therefore, steady state conditions were achieved following one day of multiple dosing for gepirone and 1-PP, and two days for 3'OH. For 1-PP, a significantly lower AUC and C_{max} was observed after multiple dose treatment of gepirone alone. In addition, co-administration of ketoconazole increased the amount of gepirone in urine 5-fold (data not shown). The ratio of 6b-hyroxycortisol/cortisol in urine was significantly decreased after co-administration with ketoconazole (Table 44).

Conclusions.

As a result of co-administration of gepirone with ketoconazole, gepirone plasma concentrations increased 5-fold, while 1-PP concentrations decreased by approximately 3-fold, in line with the metabolic formation of 1-PP by CYP3A4. Since gepirone and 3'OH levels were elevated, a wide range of adverse events, including dizziness, nausea, and vomiting, was observed following co-administration. In addition, the decrease in the 6β-hyroxycortisol metabolic ratio was indicative of an inhibiting effect of gepirone on CYP3A4. Thus, potential drug interactions may exist among concomitant medications for the treatment of depression and gepirone, if the administered drugs are metabolized via CYP3A4. As a result, gepirone administration is not warranted with ketoconazole. Caution needs to be exercised and a gepirone dose reduction may be warranted when it is co-administered with other CYP3A4 inhibitors.

20. Protocol FK-GBE-004: The Pharmacokinetics of Gepirone 20 mg MR Tablets ([redacted] (b) (4)) in Male Asians, Caucasians, and Blacks.

Objectives.

The objective of this study was to evaluate and compare the single and multiple dose pharmacokinetics of gepirone in male Caucasians, Asians, and Blacks.

Study Design and Methods:

This study consisted of an open-label, single center, single and multiple dose design. After an overnight fast, doses were administered in the morning on days 1 and 3-8 and no food was permitted until five h after administration. Serial blood samples were collected over a 48-h period on days 1 and 8. A 24-h urine sample was also collected on day 8. All samples were analyzed by a LC/MS assay to determine the concentration of gepirone, 1-PP, and 3'OH gepirone.

Subjects:

Thirty-six healthy male volunteers (age range: 18 - 50 yrs; 12 Caucasians and 12 Blacks and 5 Asians) were enrolled in the study and 29 completed the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone was supplied to the investigator by (b) (4), which included:

- ER tablet formulation, product #(b) (4) (Lot # 98-009T), containing 20 mg of gepirone HCl. Each subjects received a total daily dose of 20 mg.

Assay Validation:

A LC/MS assay was used to quantitate gepirone, 1-PP, and 3'OH-gepirone in this study. The calibration curves in plasma were linear for the concentration range from 0.1 – 4.5 ng/ml for gepirone, 0.10-9.0 ng/ml for 1-PP, and 0.25-10 ng/ml for 3'OH-gepirone ($r \geq 0.995$ for gepirone, $r \geq 0.995$ for 1-PP, and $r \geq 0.994$ for 3'OH-gepirone). Several QC samples were prepared at concentrations of 0.5. 1.0, and 2.0 ng/ml for both gepirone and 1-PP, and 0.25, 5.0, and 10 ng/ml for 3'OH-gepirone. The deviations from the mean for gepirone were within 7.7% for the low QCs, 7.8% for the medium QCs, and 10.0% for the high QCs. The corresponding values for 1-PP were 7.7%, 8.5%, and 8.8%, respectively. The corresponding values for 3'OH-gepirone were 5.6%, 8.1%, and 9.6%, respectively.

For urine, the calibration curves were linear for the concentration range from 2.5-75 ng/ml for both gepirone and 1-PP ($r \geq 0.991$ and $r \geq 0.991$).

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), area under the curve ($AUC_{0\text{-}12\ h,\ \infty}$), minimum observed plasma concentration (Cmin), and an accumulation ratio for AUC (day 8)/AUC (day 1). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Statistical analysis was performed using a one-way ANOVA with group as the main effect. Three bioequivalence ratios of least square means were constructed, treating the Caucasian group as the reference, and the Asian and Black groups as test groups. The lower and upper 90% confidence limits were calculated for each ratio.

Results.

Figure 38. Mean Plasma Concentrations (Day 1 and Day 8).

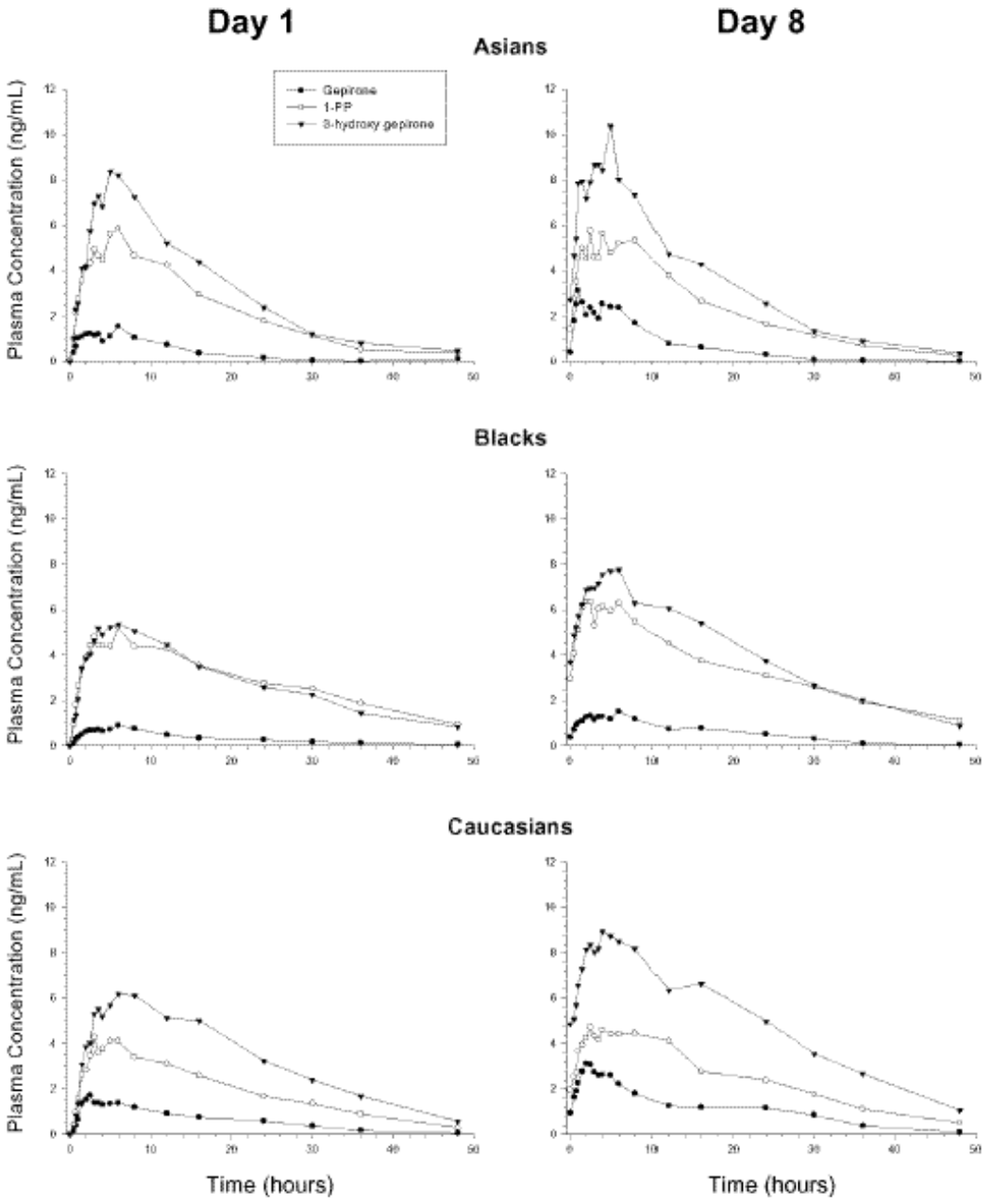


Table 45. Comparison of Mean Pharmacokinetics Results across Race on Day 1.

Analyte Variable	Caucasians	Blacks	Asians	P-value**
Gepirone				
ln-AUC (ng•hr/mL)*	26.79	14.67	17.59	0.0242
ln-AUCT (ng•hr/mL)*	24.24	13.07	16.46	0.0240
ln-Cmax (ng/mL)*	1.93	0.95	1.48	0.0011
λ_z (hr^{-1})	0.14	0.16	0.25	0.1778
T 1/2 (hr)	7.35	7.03	4.07	0.3811
1-PP				
ln-AUC (ng•hr/mL)*	75.89	132.77	106.87	0.0933
ln-AUCT (ng•hr/mL)*	70.74	119.16	101.87	0.1230
ln-Cmax (ng/mL)*	4.65	5.66	6.41	0.3802
λ_z (hr^{-1})	0.13	0.07	0.15	0.1618
T 1/2 (hr)	7.56	9.69	5.83	0.0919
3-OH-gepirone				
ln-AUC (ng•hr/mL)*	153.91	137.15	151.55	0.6552
ln-AUCT (ng•hr/mL)*	144.16	128.35	143.85	0.6141
ln-Cmax (ng/mL)*	6.55	6.22	8.96	0.0645
λ_z (hr^{-1})	0.09	0.09	0.08	0.8926
T 1/2 (hr)	8.71	8.69	9.50	0.8629

*geometric least square means presented for ln-transformed data
**p-value for test across racial groups

Table 46. Comparison of Mean Pharmacokinetic Parameters across Race on Day 8.

Analyte Variable	Caucasians	Blacks	Asians	P-value**
Gepirone				
ln-AUC_{ss} (ng•hr/mL)*	37.49	19.40	25.60	0.0039
ln-Cmax (ng/mL)*	3.27	1.73	3.01	0.0023
λ_z (hr^{-1})	0.12	0.17	0.25	0.0190
T 1/2 (hr)	7.00	5.49	3.40	0.1055
F.I.avg	1.60	1.90	2.74	0.0573
F.I.min	2.66	4.25	3.39	0.1469
1-PP				
ln-AUC_{ss} (ng•hr/mL)*	72.47	102.31	85.34	0.2243
ln-Cmax (ng/mL)*	5.61	7.41	7.21	0.2937
λ_z (hr^{-1})	0.09	0.08	0.12	0.2332
T 1/2 (hr)	11.49	10.81	6.80	0.3510
F.I.avg	1.37	1.10	1.74	0.1353
F.I.min	4.20	2.39	5.74	0.2632
3-OH-gepirone				
ln-AUC_{ss} (ng•hr/mL)*	155.51	135.48	130.37	0.3995
ln-Cmax (ng/mL)*	9.25	8.85	10.27	0.5971
λ_z (hr^{-1})	0.08	0.07	0.07	0.7702
T 1/2 (hr)	9.65	10.35	9.65	0.8220
F.I.avg	0.77	0.95	1.50	0.0176
F.I.min	1.51	2.35	3.60	0.2048

*geometric least square means presented for ln-transformed data
**p-value for test across racial groups

Table 47. Comparison of Mean AUC Metabolic Ratios.

Analyte Variable	Day	Caucasian	Black	Asian	P-Values Day	Race	Day x Race
AUC* gepirone (nmol•hr/L)	1	84.58	44.86	53.59	0.0156	0.0000	0.8234
	8	109.31	59.73	79.23			
AUC* 1-PP (nmol•hr/L)	1	586.59	918.7	667.7	0.1261	0.0498	0.6668
	8	516.11	669.5	529.2			
AUC* 3-OH-gepirone (nmol•hr/L)	1	439.20	381.2	405.6	0.5722	0.1943	0.8599
	8	439.87	370.3	353.6			
1-PP:gepirone	1	7.32	23.23	15.34	0.0027	0.0000	0.1788
	8	4.97	13.00	8.38			
3-OH-gepirone:gepirone	1	5.87	9.20	9.14	0.0023	0.0004	0.5965
	8	4.23	7.24	5.52			
3-OH-gepirone:1-PP	1	0.99	0.52	0.64	0.4836	0.0025	0.9661
	8	1.13	0.62	0.69			

results are least square means
*AUC on Day 1 and AUC_{ss} on Day 8

During multiple dose administration, gepirone and its 3'OH metabolite accumulated in all treatment groups (Fig. 38, Tables 45, 46). Similar accumulation was observed for gepirone, but 3'OH gepirone accumulated more in Blacks and Caucasians compared to Asian subjects. At steady state, trough levels were stable for the three analytes. Following both single and multiple dose administration, the exposure of gepirone was significantly greater in Caucasians (1.5-2-fold) compared to Blacks and Asians. In addition, a trend for higher exposure of 1-PP was observed in Blacks and Asians, but was not significantly different. The Black subjects had lower concentrations of gepirone and higher concentrations of 1-PP following single and multiple dose administration. The same trend was observed in Asian subjects, but the magnitude of the difference was less compared to Caucasians. Also, these differences are reflected in the values of each population's metabolic ratios (Table 47).

Conclusions.

In conclusion, comparison of AUC values at steady-state and on day 1 revealed that gepirone and 3'OH-gepirone accumulated in the plasma following multiple dose administration, which were similar among all treatment groups. The data suggests that the difference in the extent of gepirone bioavailability is due to a higher conversion of gepirone to 1-PP in Black and Asian Subjects. No dose adjustment is recommended based on race since patients will be dose-titrated to achieve optimal response.

21. Protocol CN105-085: Multiple Dose Pilot Study Evaluating the Safety, Tolerance, and Single Dose and Steady-State Pharmacokinetics of Gepirone ER 120 mg in Healthy Male Subjects.

Objectives.

The objectives of this study were to establish a safety and tolerability profile, and evaluate the pharmacokinetics of gepirone extended release (ER) at a dosage of 120 mg once daily in healthy male volunteers.

Study Design and Methods:

This study consisted of a randomized, double-blind, placebo-controlled design. The study design included a 7-day treatment period. All subjects fasted the night prior to dosing and were administered 120 mg of ER gepirone as specified in the protocol. The subjects were allowed to consume food between 2-4 h following drug administration. Serial blood samples were collected pre-dose and up to 24 h following gepirone administration of the morning dose on days 1 and 7. Additional blood samples were taken on days 3, 4, 5 and 6 to check the attainment of steady-state. All samples were analyzed to determine the concentration of gepirone and 1-PP, one of the major circulating metabolites.

Subjects:

Seventeen healthy male volunteers (age range: 18 - 40 yrs.; 11 Caucasian, 4 Black, 1 Hispanic and 1 Oriental) participated in the trial. Thirteen subjects received gepirone ER and four received placebo.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- ER tablet formulation, product # (b) (4) (Lot #E90H381), was a pink, modified oval-shaped, biconvex tablet containing 20 mg of gepirone HCl for extended release ((b) (4) = (b) (4) h). In the study, each subject received a total dose of 120 mg (6 x 20 mg tablets).
- Placebo tablet, product # (b) (4), was used to match the gepirone ER tablet.

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.995$). Multiple QC samples were prepared at concentrations ranging from 1 – 40 ng/ml for both gepirone and 1-PP. For gepirone, the between day and within day assay variability were less than 5.8% and 11.7%, respectively. The corresponding values for 1-PP were 4.6% and 9.0%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0\text{-}24\ h}$), trough concentration (C_{min}), and an accumulation ratio (AR; the ratio of AUC (day 6)/AUC (day 1)). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

For the determination of the onset of steady-state, qualitative assessment of C_{min} values and a comparison of the least squares means over time using an ANOVA, incorporating time and subject. The results for AUC, C_{max}, and the ratio of metabolite-to-parent AUC on days 1 and 7 were compared using an ANOVA, incorporating subject and day as covariates.

Results.

Figure 39. Mean Plasma Gepirone Concentrations (Day 1 and 7).

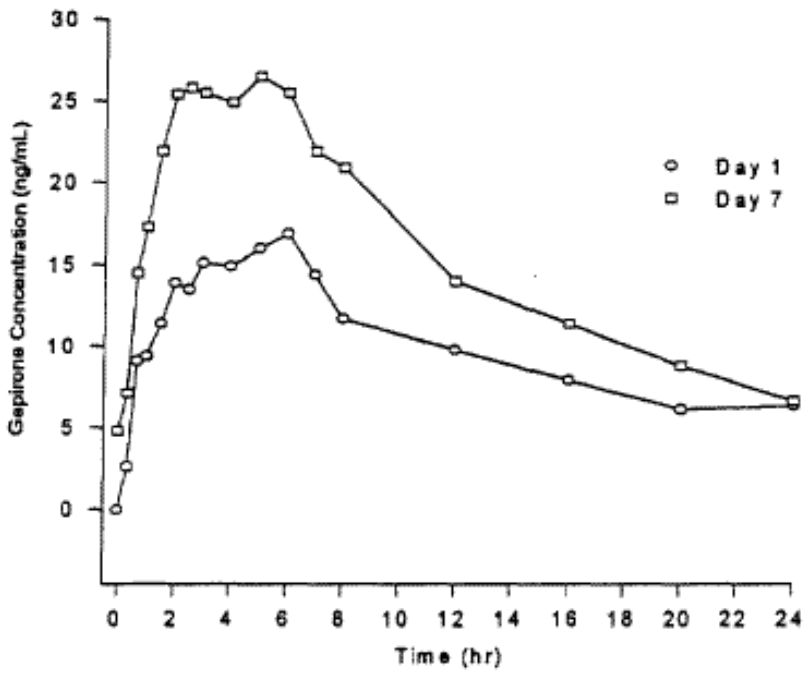


Figure 40. Mean Plasma 1-PP Concentrations (Day 1 and 7).

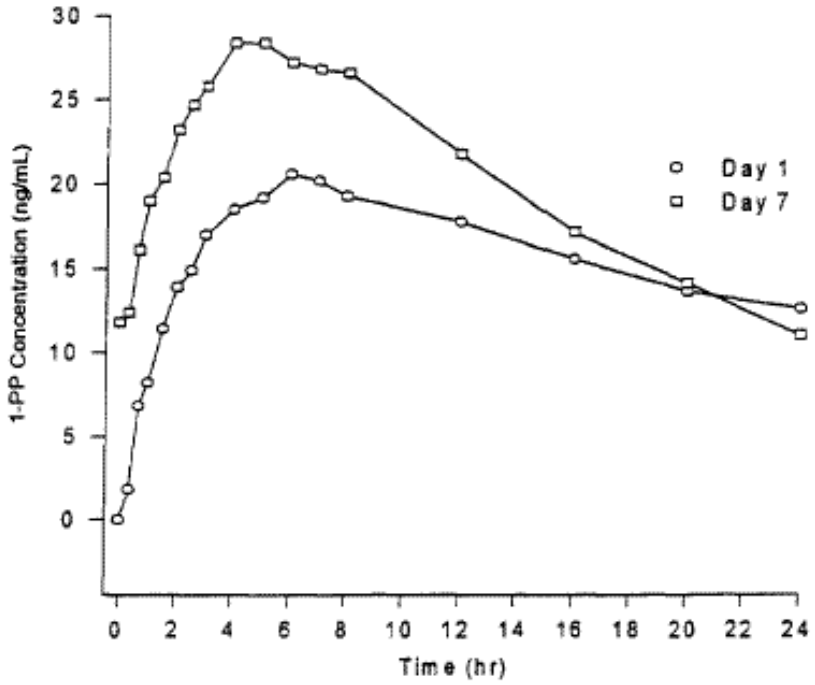


Table 48. Trough Concentrations of Gepirone and 1-PP (LSMEANS in ng/ml).

Time (h)	Gepirone (ng/ml)	1-PP (ng/ml)
24	6.30	12.7
48	4.61	15.6
72	4.23	12.1
96	6.40	14.1
120	6.68	13.5
144	4.76	11.8
168	6.59	11.1
p-values (time)	0.293	0.150

Table 49. Comparison of AUC and C_{max} on Days 1 and 7.

Variable	Day 1	Day 7	P-value*
AUC (ng-h/ml) (gepirone)	238 (31.3)	372 (56.4)	0.0088
C_{max} (ng/ml) (gepirone)	18.7	30.5 (4.2)	0.0031
Tmax (h) (gepirone)	3.78 (0.53)	3.89 (0.66)	
AUC (ng-h/ml) (1-PP)	380 (43.2)	485 (55.7)	0.0043
C_{max} (ng/ml) (1-PP)	22.2	29.5 (2.1)	0.0007
Tmax (h) (1-PP)	7.31 (0.93)	5.11 (0.35)	
AUC ratio (1-PP/gep)	1.64 (0.29)	1.56 (0.26)	
AR (gepirone)	1.63 (0.17)		
AR (1-PP)	1.30 (0.06)		
*Pairwise comparisons; only includes subjects that completed entire study.			

Four of 13 subjects that received gepirone withdrew from the study due to adverse events, associated with dizziness and nausea. Thus, the pharmacokinetic parameters were calculated based on 9 subjects.

Following drug administration, the AUC and C_{max} values were increased significantly for both the parent and metabolite on day 7 compared with day 1 (Table 49). An apparent 63% and 30% accumulation in AUC for gepirone and 1-PP was observed (Figs. 39, 40, Table 49). No statistical differences were observed for t_{max} and the metabolic ratio between days 1 and 7. On days 1 and 7, the t_{max} values for gepirone and 1-PP were approximately 4 and 6 h, respectively. The trough concentrations for both gepirone and 1-PP were variable, resulting in no clear trend following the first and last dose (Table 48).

Conclusions.

As a result of 4 subjects withdrawing from the study, the 120 mg dose of gepirone ER was not tolerated well. Steady-state conditions were achieved by the end of the dosage interval for both the parent drug and metabolite. No accumulation in trough levels was observed over the seven day treatment. The accumulation in AUC and Cmax values appeared to be due to the characteristics of the extended release formulation, and not saturation of metabolic pathways of gepirone.

22. Protocol FK-GBE-003: A Pilot Study to Evaluate the Pharmacokinetic Profile After a Single Dose of Gepirone MR ([redacted] (b) (4)) Tablets in Normal Male Subjects Under Fasting and Fed Conditions.

Objectives.

The objective of this pilot study was to compare the pharmacokinetics of gepirone MR 20 mg tablets under fasting and nonfasting conditions.

Study Design and Methods:

This study consisted of an open label, single dose, one period, two treatment design. Subjects 1 and 2 fasted 10 h prior to dosing and 4 h following drug administration. Subjects 3 and 4 were fasted for 9.5 h and fed a standardized high fat breakfast. Blood samples were collected over 36 h after drug administration. All samples were analyzed for gepirone and 1-PP content.

Subjects:

Four healthy male volunteers (age range: 18 - 40 yrs., 1 Caucasian, 3 Black) were enrolled and completed the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone ER tablets was supplied to the [redacted] (b) (4), which included:

- MR tablet formulation, product #[redacted] (b) (4) (Lot #662-001), containing 20 mg of gepirone HCl.

Two subjects received gepirone with food and two received it without food.

Assay Validation:

A LC/MS assay was used to quantitate both gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.2 – 4.5 ng/ml for both gepirone ($r \geq 0.998$) and 1-PP ($r \geq 0.997$). Low, medium, and high QC samples were prepared at concentrations of 0.5, 1, and 2 ng/ml for both gepirone and 1-PP. The overall variability for the QC samples did not exceed 3.21% for gepirone and 5.59% for 1-PP.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), and half-life ($t_{1/2}$). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Results.

Figure 41. Mean Plasma Gepirone Concentrations on Day 1.

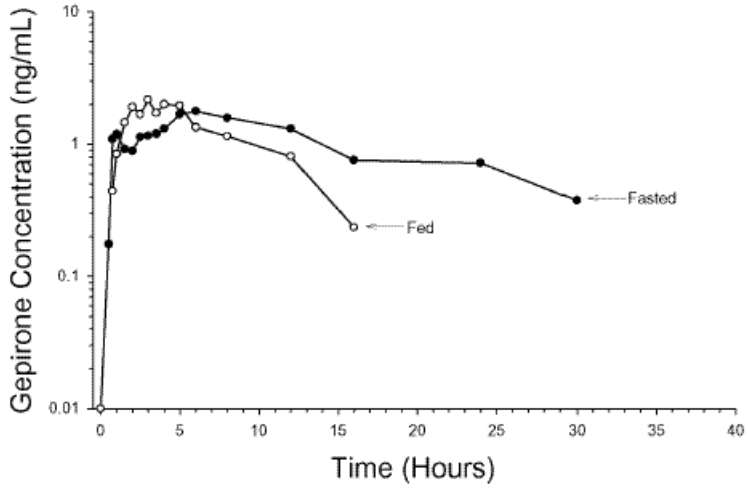


Table 50. Summary of Pharmacokinetic Parameters.

	C_{max} (ng/mL)	T_{max} (hr)	AUC_T (ng*hr/mL)	$AUC_{(0-\infty)}$ (ng*hr/mL)	$T_{½}$ (hr)
Fasted Subjects					
Subject (b) (6)	1.73	5.0	29.58	34.52	7.8
Subject	1.93	8.0	31.37	33.69	5.2
Fed Subjects					
Subject (b) (6)	3.38	3.0	27.34	28.17	2.6
Subject	1.26	2.0	9.45	11.4	5.3

For gepirone, t_{max} ranged from 2-3 h in the fasted state and 5-8 h in the fed state (Fig. 41, Table 50). Because of the limited sample size, no formal analysis of the gepirone and 1-PP data was conducted.

Conclusions.

Because of the limited sample size, the effect of food on the bioavailability of gepirone MR is inconclusive.

23. Protocol CN105-007: Pharmacokinetics and Disposition of ^{14}C-Gepirone in humans following intravenous and oral administration.

Investigator.

(b) (4).

Objectives.

The objectives of this study were to describe the absorption, elimination and pharmacokinetics of gepirone following IV and oral administration and to determine the systemic bioavailability of the oral dose as unchanged drug and as total radiolabel.

Study Design and Methods:

This study consisted of an open, randomized, 3-period crossover design. This study incorporated an initial session 1 to screen the potential subjects for adverse events prior to admission of the subjects into the crossover segment (sessions 2, 3, and 4) of the study (Table 51). Each subject qualified for study entry based on medical history and the inclusion/exclusion criteria. All subjects fasted the night prior to dosing and were administered gepirone as specified in the protocol. Serial blood samples were collected pre-dose and up to 24 h following gepirone dosing for the determination of pertinent pharmacokinetic parameters. Urine and feces were collected from all subjects in sessions 2, 3, and 4 at various time intervals up to 144 h post-dose. All samples were analyzed to determine the content of gepirone and 1-PP, one of the major circulating metabolites.

Subjects:

Thirteen healthy male volunteers were recruited into session 1 of the study (age range; 18-39 yrs) (Table 51). Of the 13 subjects, 9 subjects who exhibited the least side effects were selected to continue into sessions 2, 3, and 4 of the 3-way crossover segment of the study. This approach was used since emesis is a common adverse effect associated with gepirone administration. These 9 subjects completed all 4 sessions of the study.

Test Product, Dose, and Mode of Administration:

The ^{14}C-gepirone HCL, lots #27017-15B and 27017-17B, which were used in the preparation of the intravenous and oral solution formulations, respectively, were labeled in the 2-position of the pyrimidinyl moiety.

The formulations of gepirone hydrochloride that were supplied to the investigator by the Pharmaceutical Product Development Division of Bristol-Myers Squibb Co. include:

- For treatment 1, ^{14}C-gepirone HCl, product # (b) (4) (Lot #E88D099), was supplied as a sterile solution for intravenous injection containing 1 mg/ml of compound. The assay amount of ^{14}C that the formulation contained was 12.39 μCi/ml. In the study, each subject received a total dose of 1 mg IV equivalent to 12.4 μCi. The radiochemical purity of this solution was 97.5%.

- For treatment 2, a sterile solution was supplied containing 1.05 mg/ml of ^{14}C-gepirone HCl, product # (b) (4) (Lot #E88D103). The assay amount of ^{14}C that this formulation contained was 3.28 µCi/ml. In the study, each subject received a total oral dose of 21 mg equivalent to 65.6 mCi. The radiochemical purity of this solution was 99.7%.
- For treatment 3, a no. 0 opaque gray capsule containing 5 mg of gepirone HCl, product # (b) (4) (Lot #E87C070), was supplied for oral administration.

Table 51

		Treatment Schedule/Treatment Code*			
Group	Subject #	Session 1	Session 2	Session 3	Session 4
1	(b) (6)	3	1	2	3
2		3	2	3	1
3		3	3	1	2

*Treatment 1: 10 minute IV infusion of 1 mg of ^{14}C-gepirone (12.39 µCi)
Treatment 2: 21 mg oral dose of ^{14}C-gepirone solution (65.6 µCi)
Treatment 3: 20 mg oral dose (4 x 5 mg capsules) of unlabelled gepirone

In session 1 (Table 51), all 13 subjects received a single 20 mg oral dose (4 x 5 mg capsules) of unlabelled gepirone. The 9 subjects selected to continue the study received in a crossover fashion, determined from the rows of a 3 x 3 latin square, a 10 minute IV infusion of 1 mg ^{14}C-gepirone, a 21 mg oral solution dose of ^{14}C-gepirone, and a 20 mg oral dose (4 x 5 capsules) of unlabelled gepirone. Sessions 1 and 2 were separated by a 4 day interval, sessions 2, 3, and 4 were separated by a 7 day interval to allow for complete elimination of the radiolabel.

Assay Validation.

The assay used to quantitate gepirone and 1-PP was either the use of a scintillation counter to determine the amount of ^{14}C in each sample or a GC/MS assay. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r > 0.996$). The between day variability was determined for the QC samples at concentrations of 2.40, 22.4, and 98.2 ng/ml and did not exceed 8.5% for gepirone and 5.0% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were 4.7% for the low QC sample, 4.85% for the intermediate QC sample, and 3.85% for the high QC sample. For 1-PP, the deviations from the mean were 3.5% for the low QC sample, 4.3% for the intermediate QC sample, and 5.28% for the high QC sample.

Criteria for Evaluation:

Non-compartmental methods were used in the determination of various pharmacokinetic parameters for gepirone. The evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0-24\ h}$), elimination half-life ($t_{1/2}$), mean residence time (MRT), volume of distribution at steady-state and in the terminal elimination phase (V_{ss} or V_{β}, respectively), systemic clearance (CL_s), and the absolute bioavailability (F).

For statistical analysis of the data, a regression model was used to evaluate cumulative urinary and fecal elimination of radioactivity expressed as percent of ^{14}C-gepirone dose. The parameters C_{max}, AUC, $t_{1/2}$, and MRT were evaluated in the context of an analysis of variance appropriate for a 3-period crossover design with 3 sequence groups. All tests of significance were conducted at the α=0.05 level.

Results.

Figure 42. Plasma Concentration-Time Profile for Gepirone Following Either IV of Oral Administration.

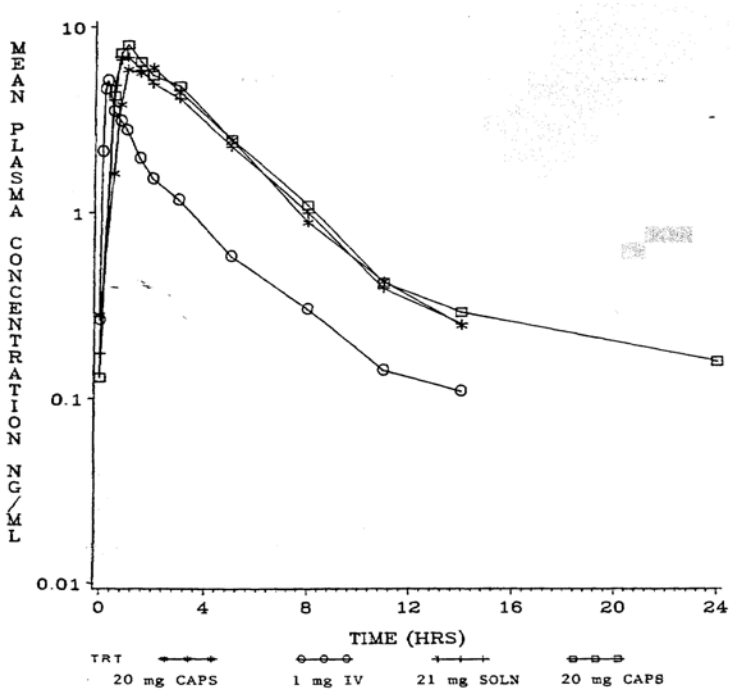


Figure 43. Plasma Concentration-Time Profile for 1-PP following Either IV of Oral Administration of Gepirone.

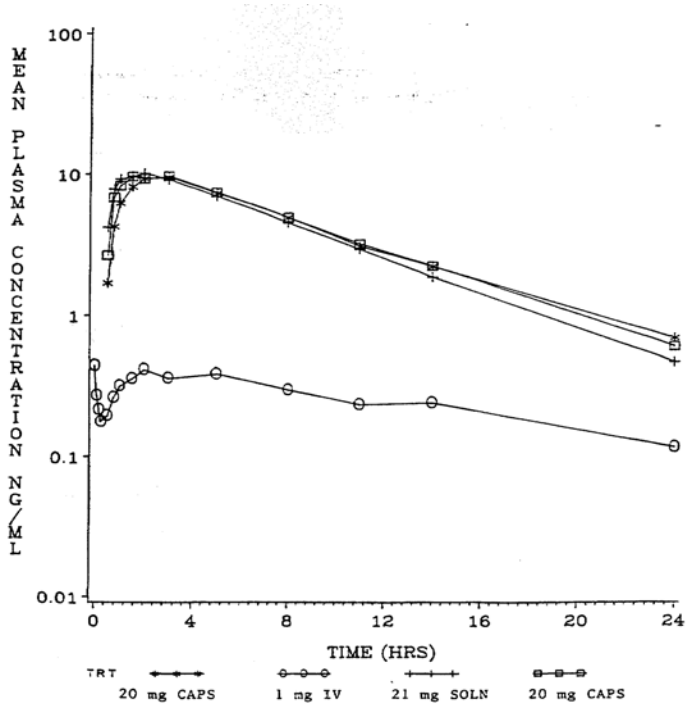


Table 52. Mean Pharmacokinetic Parameters (± S.D.)

	Gepirone			1-PP	
PK Parameter	IV 1 mg	PO (sol) 21 mg	PO (caps) 20 mg	PO (sol)	PO (caps)
C_{max} (ng/ml)	5.9 (1.2)	9.3* (5.0)	10.7 (4.4)	10.6* (2.8)	11.1 (3.3)
t_{max} (h)	0.2 (0.04)	0.8 (0.5)	1.1 (0.7)	1.7 (0.8)	2.1 (0.9)
MRT (h)	3.4 (0.7)	4.0 (0.8)	4.1 (0.9)	8.6 (3.3)	9.1 (3.0)
$t_{1/2}$ (h)	2.9 (1.0)	2.6 (0.25)	2.9 (0.8)	5.4 (2.1)	5.8 (1.7)
$AUC_{0-\infty}$ (ng-h/ml)	11.4 (2.9)	31.3* (11.8)	36.6 (13.4)	108.2* (70.6)	120.5 (72.1)
$V_d(\beta)$ (L)	385.7 (181)				
V_{ss} (L)	313.3 (94.5)				
CL_s (L/h)	92.6 (23.4)				
F		0.14 (0.05)	0.17 (0.08)		

*Mean was normalized to a 20 mg dose.

The results of this study indicated that independent of the route of administration, the dose of gepirone was accounted for quantitatively in both urine and feces (data not shown). After IV dosing, 89% of the dose was recovered in urine and 13.3% in feces 6

days after dosing. Following oral administration, 80.8% and 13% of the dose was recovered in urine and feces, respectively. The majority of the radioactivity was eliminated in urine within 24 h and urinary and fecal elimination was essentially complete within 96 h following administration of the drug. The percentage of radioactivity in plasma that was unchanged gepirone at any time after oral administration was less than 9% and after IV administration, it was 50%. Gepirone was extensively metabolized following oral administration, resulting in a low oral bioavailability of 14–17% (Table 52). The parent drug exhibited a large volume of distribution, a high rate of systemic clearance, and a relatively short half-life (2.6-2.9 h) (Figs 42, 43, Table 52). In contrast to gepirone, 1-PP had a longer $t_{1/2}$ and MRT of approximately 6 and 9 h, respectively. In addition, the AUC for 1-PP is 3-fold greater than that of gepirone.

Conclusions.

Following administration of ^{14}C-gepirone both orally and intravenously, the total radioactivity was recovered independent of the route of administration. Gepirone was subjected to an extensive 1st pass effect following oral absorption, resulting in a poor bioavailability. In addition, the parent drug exhibited a large volume of distribution and a high systemic clearance, with values approaching that of hepatic blood flow.

24. Protocol CN105-025: Single and Multiple Dose Pharmacokinetics of Gepirone IR in Poor and Extensive Metabolizers of Dextromethorphan.

Objectives.

The objective of this study was to evaluate and compare the single and multiple dose pharmacokinetics of gepirone and 1-PP following oral administration of gepirone to male subjects phenotyped as poor or extensive metabolizers of dextromethorphan.

Study Design and Methods:

This study consisted of an open-label, single and multiple dose, parallel group design. After an overnight fast, both groups received a single 15 mg dose of gepirone on day 1 followed by a collection of blood samples for 48 h. On days 3 through 7, all subjects received 15 mg of gepirone every 12 h. On day 8, only the morning dose was administered followed by a collection of blood samples over 48 h. Additional blood samples were collected prior to the morning dose on days 3-7 for determining C_{min} values. All samples were analyzed by a GC/MS assay to determine the concentration of gepirone and 1-PP.

Subjects:

Twelve subjects (6 poor and 6 extensive metabolizers of dextromethorphan) (age range: 18 - 35 yrs; 11 Caucasians and 1 Asian) were enrolled in the study and divided into two groups.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR capsule formulation, product # (b) (4), was a no. 3 capsule containing 5 mg of gepirone HCl. Each subjects received a total dose of 15 mg (3 x 5 mg) b.i.d. for eight days.

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.991$ for gepirone and $r \geq 0.998$ for 1-PP). Several QC samples were prepared at concentrations ranging from 2.12-104 ng/ml for both gepirone and 1-PP. The between day and within day variability for the QC samples did not exceed 6.2% and 17.3% for gepirone and 11.8% and 3.8% for 1-PP.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), area under the curve ($AUC_{0\text{-}12\ h,\ \infty}$), minimum observed plasma concentration (Cmin), and an accumulation ratio for AUC (day 8)/AUC (day 1). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Due to the small sample size, no formal statistical analysis was performed. Only a paired t-test ($p < 0.05$) was used to compare the accumulation ratios of poor and extensive metabolizers.

Results.

Figure 44. Mean Plasma Gepirone Concentrations in Poor and Extensive Metabolizers of Dextromethorphan (Day 1 and Day 8).

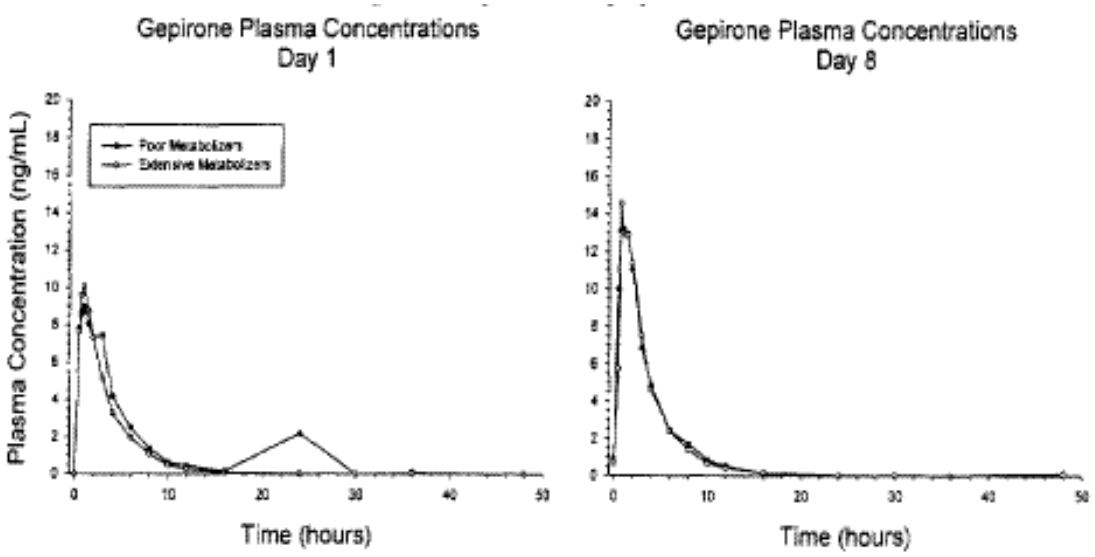


Figure 45. Mean Plasma 1-PP Concentrations in Poor and Extensive Metabolizers of Dextromethorphan (Day 1 and Day 8).

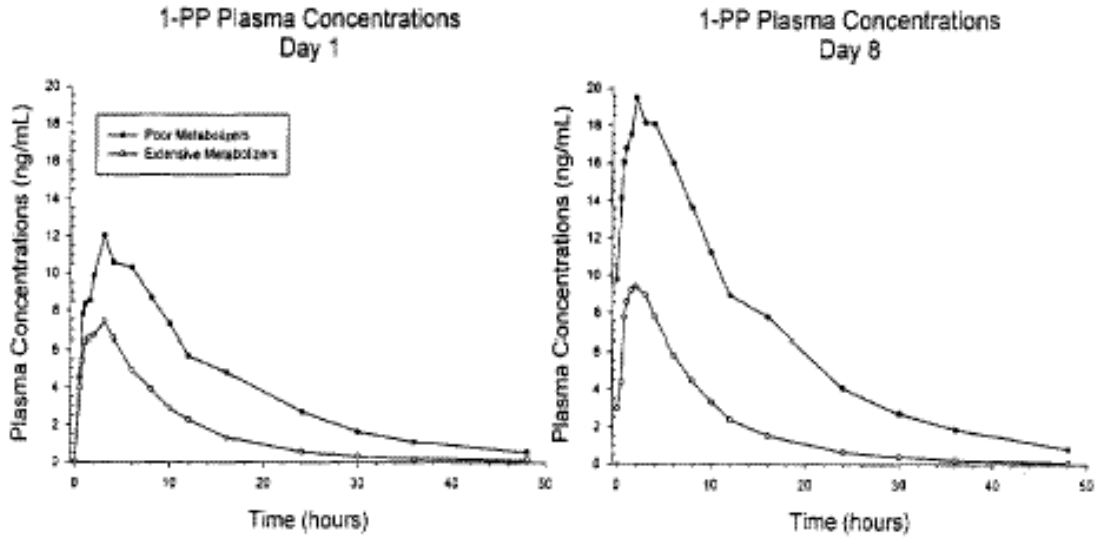


Figure 46. Mean Trough Concentrations for Gepirone and 1-PP in Poor and Extensive Metabolizers of Dextromethorphan on Days 3-7.

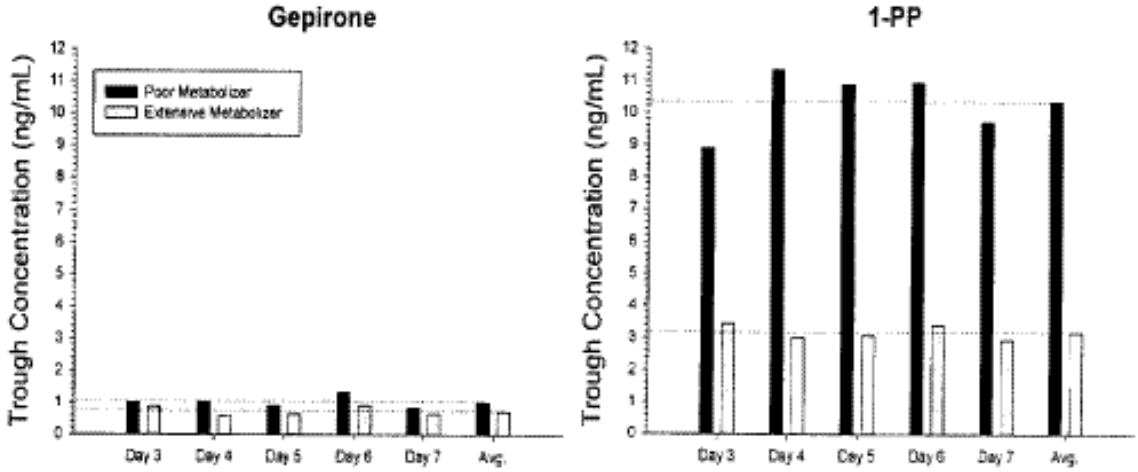


Table 53. Comparison of Mean (S.D.) AUC and C_{max} for Poor and Extensive Dextromethorphan Metabolizers on Days 1 and 8.

PK Parameter	Day 1		Day 8	
Gepirone	Poor Metabolizers	Extensive Metabolizers	Poor Metabolizers	Extensive Metabolizers
C_{max} (ng/ml)	11.6 (6.27)	11.8 (5.83)	14.5 (7.02)	16.5 (5.80)
T_{max} (h)	1.4 (1.0)	0.8 (0.2)	0.8 (0.2)	1.0 (0.4)
$T_{1/2}$ (h)	2.92 (1.02)	3.38 (2.39)	2.36 (0.29)	3.22 (1.23)
$AUC_{(0\text{-}12\ h,\ \infty)}$ (ng-h/ml)	43.3 (13.9)	37.3 (13.1)	51.7 (19.0)	49.4 (14.9)
1-PP				
C_{max} (ng/ml)	12.4 (1.86)	8.29 (1.56)	19.3 (2.15)	9.57 (3.25)
T_{max} (h)	3.1 (1.6)	2.0 (1.2)	2.0 (1.1)	1.4 (0.5)
$T_{1/2}$ (h)	9.81 (1.25)	7.26 (2.33)	9.69 (1.40)	6.35(1.24)
$AUC_{(0\text{-}\infty)}$ (ng-h/ml)	173 (22.7)	71.0 (30.5)	177 (26.2)	69.1 (30.9)

*AUC was calculated up to infinity on day 1 and 12 h on day 8.

Following drug administration, the plasma concentration of gepirone reached a peak level between 1 and 2 h (Fig. 44, Table 53). The plasma concentrations of both analytes were similar in characteristics, but higher on day 8 than on day 1. Neither C_{max} nor AUC for gepirone differed between the poor and extensive metabolizers on days 1 and 8. Both AUC and C_{max} were increased on day 8, with an accumulation ratio of 1.31 for poor metabolizers and 1.37 for extensive metabolizers of dextromethorphan. In

addition, trough concentrations for gepirone were relatively stable between days 3-8 (Fig. 3).

For 1-PP, poor metabolizers had both an increased AUC and C_{max} compared to extensive metabolizers (Fig. 45, Table 53). The increase in AUC for poor metabolizers on days 1 and 8 was approximately 2.5 fold. Mean trough concentrations in the poor metabolizer group were about 3-fold higher than those of the extensive metabolizer group (Fig. 46).

Conclusions.

No change was observed in C_{max} and AUC for gepirone in subjects with reduced activity of CYP2D6, but a 2.5 fold increase was shown in the AUC for 1-PP. As a result, poor metabolizers of dextromethorphan compensated for the reduced metabolism of gepirone through the 2D6 pathway with an increase in the conversion of gepirone to 1-PP probably *via* the 3A4 metabolic route.

25. Protocol CN105-012: Gepirone Site of Gastrointestinal Absorption in Man.

Investigator.

(b) (4)

Objectives.

The objectives of this study were (1) to use an intubation method for dosing gepirone to the region of interest of the GI tract, (2) to assess and compare the absorption of gepirone from the distal and proximal regions of the intestines to that of an oral solution dose, and (3) to determine and compare the bioavailability of gepirone when given as 4 consecutive doses of 5 mg at hourly intervals or as a single 20 mg dose.

Study Design and Methods:

This was an open study in which healthy male volunteers were administered three single doses of 20 mg gepirone HCL and a 20 mg dose divided into 4 consecutive doses of 5 mg each given every hour. Each subject qualified for study entry based on medical history and the inclusion/exclusion criteria. The study was carried over 4 sessions, with a 1 week washout between doses. All subjects fasted the night prior to drug administration. The subjects were allowed to eat lunch at 5 h following dosing. In session 1, 9 subjects received a 20 mg dose of gepirone and then they were subsequently screened for potential side effects prior to admission into the intubation segments (sessions 2 and 3) of the study. Seven subjects received 20 mg of gepirone into the distal segment of the intestine in session 2 and the proximal segment of the GI tract in session 3. In session 4, the seven subjects received 4 consecutive doses of 5 mg one hour apart. Serial blood and urine samples were collected for 30 h following drug administration. All samples were analyzed to determine the content of gepirone and 1-PP.

Subjects:

Nine healthy male volunteers (age range: 19 –36 yrs; weight range: 65-91 kg) were recruited into session 1 and as a result, the 7 subjects that showed the best tolerance to the drug were selected to complete all 4 sessions.

Test Product, Dose, and Mode of Administration:

The formulations of gepirone oral solution that were supplied to the investigator by the Pharmaceutical Product Development Division of Bristol-Myers Squibb Co. include:

1. Gepirone HCl oral solution: containing 1 mg/ml, packaged 5 ml in a 10 ml vial, product # (b) (4).
2. Gepirone HCl oral solution: containing 1 mg/ml, packaged 20 ml in a 30 ml vial, product # (b) (4).

Table 54. Flow Chart

BEST AVAILABLE COPY

Study Day	Dose	Blood Samples	Urine Samples	Admit to Clinic	Vital Signs	ECG	History	Phys. Exam	Clin Lab Test	Intuba-tion	Fluoro-scopy	Discharge from Clinic
Preestudy[a]					X	X	X	X	X[b]			
Sessions 2 and 3 - Intestinal intubation												
0				X					X[c]	X	X	
1											X	
2	X	X	X		X						X	
3		X	X		X[e]				X[d,e]			X
Sessions 1 and 4 - Oral dosing												
0				X					X[c]			
1	X	X	X		X							
2		X	X		X[f]	X[g]			X[d,f]			X

a) 1-3 weeks prior to day 0 of Session 1.
b) Hematology/Chemistry/Urinalysis; HIV testing; Drugs of Abuse; Urine for Oxidative Phenotyping.
c) Hematology/Chemistry/Urinalysis; Drugs of Abuse.
d) Hematology/Chemistry/Urinalysis.
e) Prior to discharge after Sessions 2 and 3.
f) Prior to discharge after Sessions 1 and 4.
g) Prior to discharge after Session 4 only.

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The sponsor stated that each analytical run resulted in two output files containing the results for either gepirone or 1-PP. For each run, the calibration curves were linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.995$ for gepirone and $r \geq 0.997$ for 1-PP). Low and high QC samples were prepared at concentrations of 1.98 and 18.8 ng/ml for both gepirone and 1-PP. Another QC sample of 97.8 ng/ml was also prepared for samples that were diluted. The between day variability for the QC samples in all runs did not exceed 8.4% for gepirone and 10.4% for 1-PP. For the accuracy of the

method, the deviations from the mean for gepirone did not exceed 6.3% for the low QC sample and 6.5% for the high QC sample. For 1-PP, the deviations from the mean were 10.8% for the low QC sample and 7.34% for the high QC sample.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve ($AUC_{0-\infty}$), half-life ($t_{1/2}$) and mean residence time (MRT).

The effect of site/treatment on C_{max}, MRT, $t_{1/2}$, and AUC was evaluated by a randomized block ANOVA, with subjects as the blocks, including a residual error term for both gepirone and 1-PP. Tukey's multiple comparisons procedure was used at the α=0.05 level.

Results.

Figure 47. Mean Plasma Concentrations of Gepirone Following Dosing in Sessions 1-4 in Subject #(b)(6)

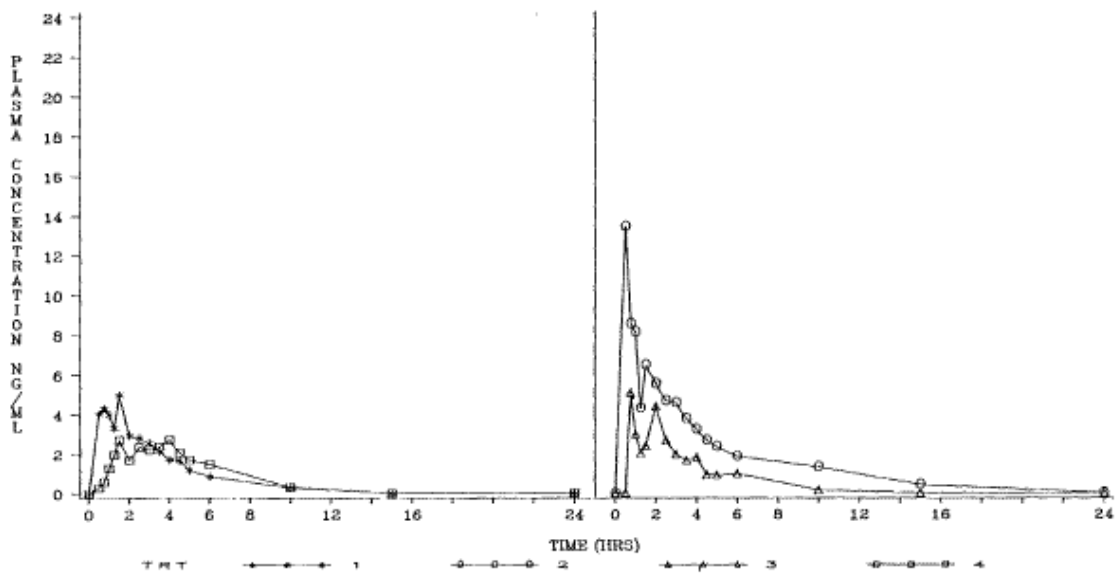


Figure 48. Mean Plasma Concentrations of 1-PP Following Gepirone Dosing in Sessions 1-4 in Subject # (b) (6)

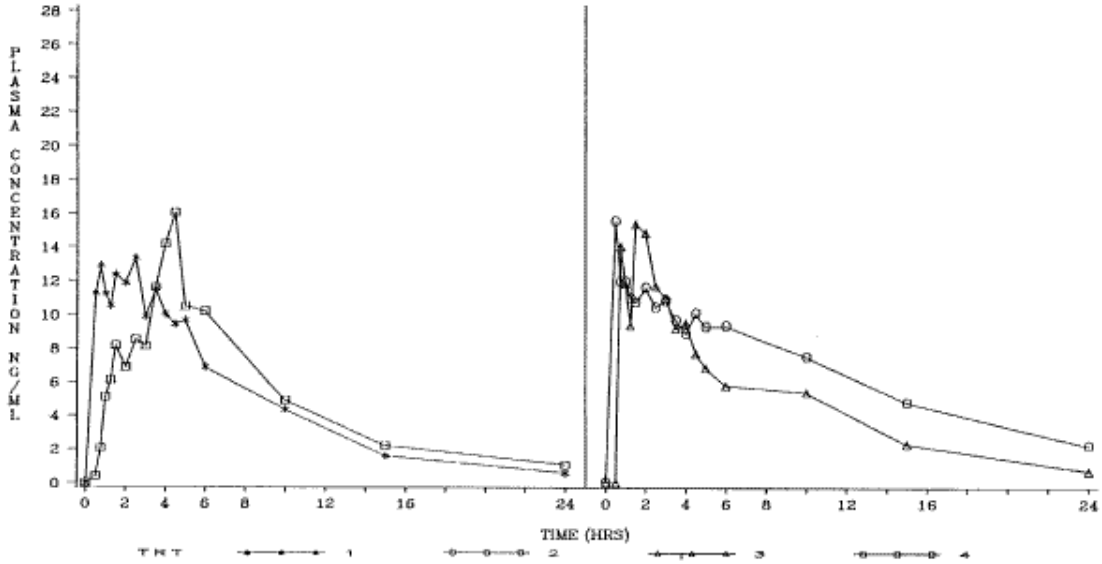


Table 55. Mean Pharmacokinetic Parameters (S.D.).

Gepirone:	Treatment			
Parameter	Trt 1	Trt 2	Trt 3	Trt4
CMAX (ng/ml)	6.8 (3.5)	12.9 (7.2)	6.3 (2.3)	4.4 (2.1)
TMAX (hr)	1.1 (0.6)	0.6 (0.2)	0.6 (0.1)	2.8 (1.1)
T-HALF (hr)	2.8 (0.6)	3.2 (0.9)	3.3 (1.7)	3.0 (1.1)
MRT(INF) (hr)	4.1 (0.4)	4.1 (1.2)	4.6 (1.7)	* *
AUC(INF) (ng.hr/ml)	18.1 (6.1)	29.8 (17.4)	17.7 (7.7)	26.2 (13.6)
1-PP:				
CMAX (ng/ml)	13.6 (3.3)	19.3 (6.6)	15.6 (4.3)	12.3 (3.1)
TMAX (hr)	1.3 (0.8)	0.9 (0.5)	0.8 (0.4)	3.6 (1.0)
T-HALF (hr)	4.9 (1.0)	4.9 (1.6)	5.6 (1.0)	6.7 (3.0)
MRT(INF) (hr)	7.1 (1.3)	7.3 (2.5)	8.1 (1.1)	* *
AUC(INF) (ng.hr/ml)	84.0 (44.0)	102.4 (48.0)	97.5 (29.3)	108.6 (38.2)

* MRT(INF) for Trt 4 omitted due to different treatment design
Trt 1: 20 mg solution administered orally
Trt 2: 20 mg solution administered to distal GI tract
Trt 3: 20 mg solution administered to proximal GI tract
Trt 4: 4x5 mg solution/hr administered orally
Statistical analysis:
Gepirone: CMAX and AUC(INF): Trt 2 > Trt 1 and 3
1-PP: CMAX: Trt 2 > Trt 1

Following administration into the distal portion of the GI tract (Treatment 2) (Figs. 47, 48, Table 55), both C_{max} and AUC of gepirone and 1-PP were significantly greater than treatments 1 and 3 (proximal GI). In contrast, no differences in AUC or C_{max} were observed between treatments 1 and 3. The half-lives for gepirone and 1-PP were similar across all treatment regimens. The formation of 1-PP was rapid, indicated by its short t_{max} and the rate of metabolite formation was similar across all treatments.

In addition, treatment 4 was designed to mimic a sustained release dosage form. When this regimen was compared with treatment 1, the overall amount of drug absorbed was similar, thus suggesting that the bioavailability of an ER dosage form would not be affected.

Conclusions.

Gepirone was absorbed throughout the entire length of the small intestine and no apparent specific window of absorption exists. Thus, GI absorption of gepirone should not be affected when the drug is released from an extended release dosage form.

26. Protocol CN105-005: Pharmacokinetics of Gepirone IR Following Single and Multiple Dosing in Young Adult and Elderly Men and Women.

Objectives.

The objective of this study was to evaluate differences in gepirone single and multiple dose pharmacokinetics that may be associated with the subject's age and /or gender.

Study Design and Methods:

This study consisted of an open-labeled, parallel group design. All subjects fasted the night prior to dosing. On days 1 and 7, the subjects were administered 10 mg of drug (Table 56). On days 3-6, the subjects were dosed with 10 mg t.i.d. Blood and urine samples were collected over 48 h on days 1 and 7. Single blood samples also were collected for C_{min} determinations immediately prior to the morning dose on days 4 and 7. Samples were analyzed for gepirone and 1-PP by GC/MS. Urine samples were not analyzed.

Table 56. Treatment Schedule.

	Study Day/Gepirone Dose (mg)				
Group	**Description**	**Age (yrs)**	**1**	**3-6**	**7**
1	Young Male	18-40	10	10 (t.i.d.)	10
2	Elderly Male	≥65	10	10 (t.i.d.)	10
3	Young Female	18-40	10	10 (t.i.d.)	10
4	Elderly Female	≥65	10	10 (t.i.d.)	10

Subjects:

Forty-eight healthy subjects were enrolled in the study. These groups consisted of 4 groups of 12 subjects/group and all subjects completed the entire study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone IR tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR capsule formulation, product # (b) (4) (Lot #E87C071), was a no. 0 gray, opaque capsule containing 5 mg of gepirone HCl. The total dose that each subject received was 10 mg (2 x 5 mg capsules).

Assay Validation:

A GC/MS assay was used to quantitate both gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both gepirone ($r \geq 0.991$) and 1-PP ($r \geq 0.996$). Low, medium, and high QC samples were prepared at concentrations of 2.2, 18.4 and 97.6 ng/ml for gepirone and 2.3, 19.5 and 97.6 ng/ml for 1-PP. The between day variability for the QC samples did not exceed 6.38% for gepirone and 6.40% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were within 8.80 % for the low QCs, 7.825 for the medium QCs and 2.63% for the high QCs. The corresponding values for 1-PP were 7.22%, 4.20 and 1.12%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), half-life ($t_{1/2}$), trough concentrations (C_{min}), mean residence times (MRT), and an accumulation ratio (R). Non-compartmental methods were used in the determination of various pharmacokinetic parameters. Assuming constant CL and V_d during the multiple dosing period, gepirone and 1-PP plasma concentrations were extrapolated to steady-state from single dose data obtained on day 1 by the method of superpositioning.

In comparing the single and multiple dose pharmacokinetics, repeated measures ANOVA was utilized to compare the C_{max}, C_{min}, $t_{1/2}$, $MRT_{0-\infty}$, AUC, t_{max} (rank transformed) and the metabolic ratio (MR). With the exception of Levene's test (p=0.001), which was used to test homogeneity of variance for $t_{1/2}$ and MRT, the significance level was set at p=0.05. In addition, a t-statistic was used to evaluate the predictability of steady-state values from single dose data.

Results.

Figure 49. Mean Plasma Gepirone Concentrations on Day 1.

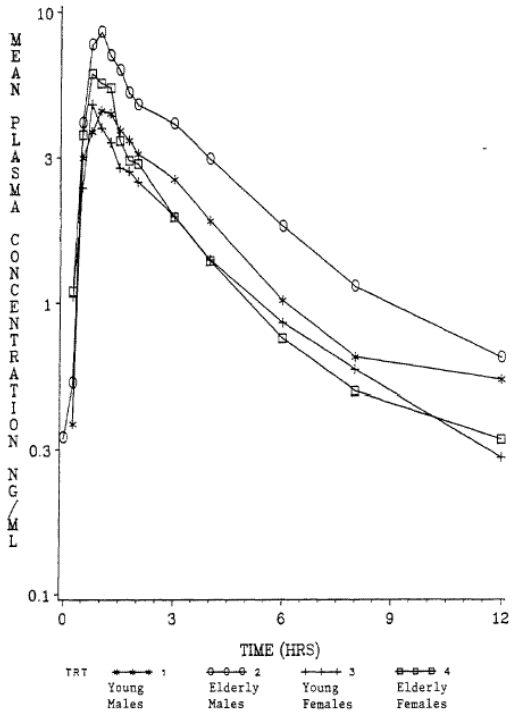


Figure 50. Mean Plasma Gepirone Concentrations on Day 7.

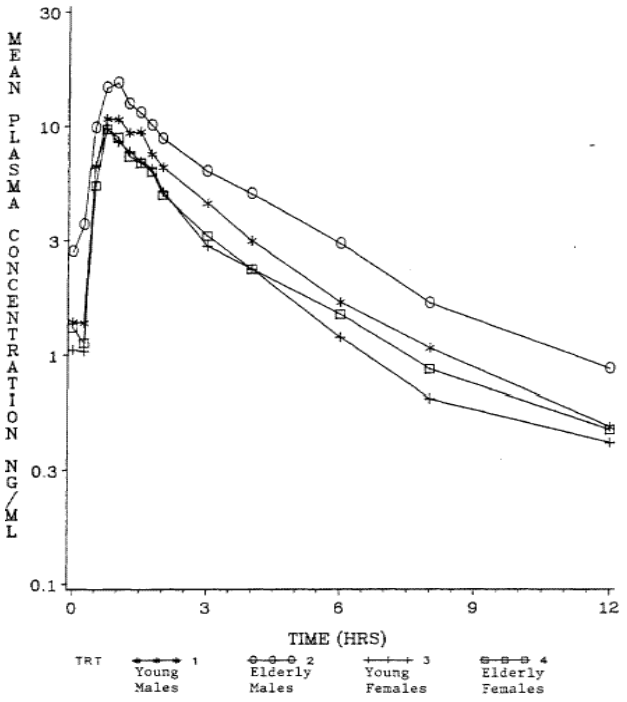


Figure 51. Mean Plasma Concentrations of 1-PP on Day 1.

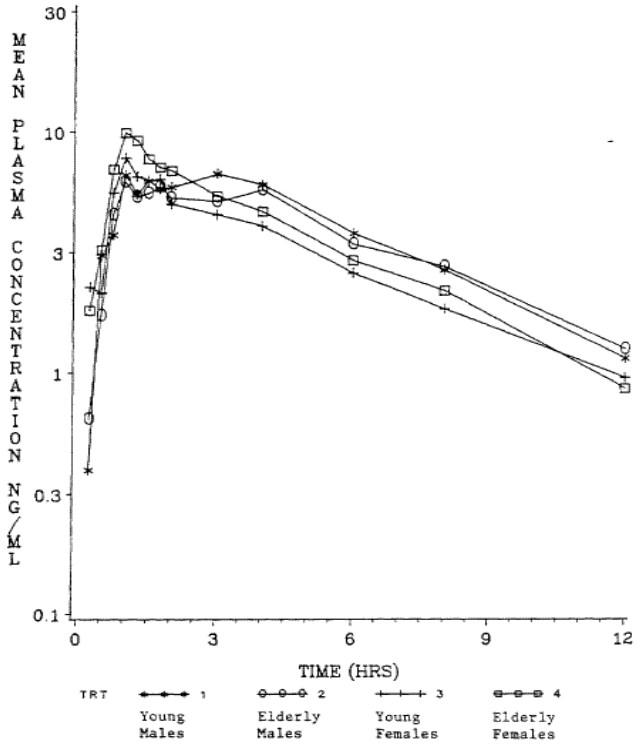


Figure 52. Mean Plasma Concentrations of 1-PP on Day 10.

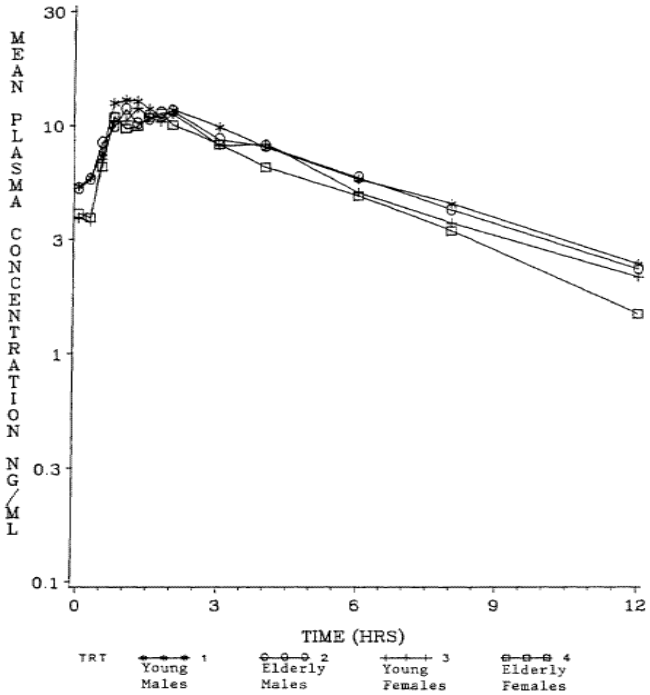


Table 57. Mean Pharmacokinetic Parameters of Gepirone.

GROUP	CMAX (ng/ml)	TMAX (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(0-8)[1] (hr.ng/ml)	AUC(INF) (hr.ng/ml)
SINGLE DOSE - DAY 1						
Young Males	6.10 (2.82)	0.96 (0.46)	3.60 (1.08)	2.74 (1.01)	- -	20.22 (9.01)
Elderly Males	11.24 (5.88)	1.08 (0.73)	4.77 (1.14)	4.18 (2.48)	- -	39.06 (18.84)
Young Females	5.64 (2.66)	1.13 (0.65)	3.74 (0.85)	3.31 (1.09)	- -	16.44 (6.62)
Elderly Females	7.83 (4.13)	0.83 (0.46)	3.61 (1.22)	3.37 (2.65)	- -	20.55 (12.12)
MULTIPLE DOSE - DAY 7						
Young Males	12.96 (5.67)	0.85 (0.25)	3.95 (0.73)	3.71 (1.55)	35.45 (14.27)	41.46 (17.85)
Elderly Males	18.94 (9.11)	0.94 (0.32)	4.94 (1.39)	4.62 (2.17)	55.18 (28.49)	70.51 (40.60)
Young Females	11.64 (3.94)	0.90 (0.45)	3.71 (0.35)	3.84 (1.58)	26.62 (8.23)	30.95 (10.27)
Elderly Females	11.98 (5.56)	0.92 (0.36)	4.56 (0.90)	4.52 (2.00)	29.74 (15.08)	36.73 (19.29)

[1] Trapezoidal AUC from 0-8 hrs.

CMAX: Elderly > Young; Male > Female (day 7); Day 7 > Day 1 (all groups)
AUC: Elderly > Young; Male > Female; Day 7 > Day 1 (all groups)
T-HALF: Day 7 > Day 1 (all groups)
MRT: Elderly > Young

Table 58. Mean Pharmacokinetic Parameters of 1-PP.

GROUP	CMAX (ng/ml)	TMAX (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(0-8)[1] (hr.ng/ml)	AUC(INF) (hr.ng/ml)
SINGLE DOSE - DAY 1						
Young Males	11.13 (4.04)	2.33 (1.54)	7.60 (3.29)	5.40 (3.05)	- -	64.61 (27.44)
Elderly Males	8.61 (2.71)	2.46 (1.19)	9.38 (5.42)	6.05 (3.52)	- -	66.61 (41.94)
Young Females	8.91 (4.15)	1.63 (0.99)	7.00 (2.61)	5.52 (3.31)	- -	54.08 (39.75)
Elderly Females	13.32 (5.50)	1.21 (0.37)	5.96 (2.45)	5.21 (3.62)	- -	52.85 (14.10)
MULTIPLE DOSE - DAY 7						
Young Males	17.18 (6.31)	1.13 (0.43)	8.71 (3.99)	6.92 (3.49)	70.98 (26.97)	123.13 (72.03)
Elderly Males	18.25 (7.47)	1.94 (1.06)	9.31 (4.01)	7.92 (3.07)	73.78 (39.08)	139.82 (121.07)
Young Females	15.32 (8.18)	1.60 (0.88)	7.76 (2.89)	5.95 (1.91)	67.32 (35.41)	116.05 (96.87)
Elderly Females	15.41 (6.36)	1.79 (2.02)	6.11 (1.50)	5.60 (3.32)	59.79 (21.29)	80.60 (30.53)

[1] Trapezoidal AUC from 0-8 hrs

CMAX, AUC, T-HALF: Day 7 > Day 1 (all groups)
No significant age/gender differences
MRT: Male > Female; No significant age/day differences
TMAX: Males > Female (day 1); Day 1 > Day 7 (young males)

For gepirone, t_{max} was approximately 1 h, indicating that absorption was rapid, and independent of the multiple dosing regimen (Figs. 49, 50, Table 57). The $t_{1/2}$ ranged from 2.7-4.6 h following single and multiple dose administration. Based on C_{min}, C_{max}, and AUC data, steady-state conditions were achieved after 2 days of t.i.d. dosing. C_{min} values were unchanged for both gepirone and 1-PP. C_{max} and AUC_{ss} on day 7 were significantly greater than the values on day 1 in all groups, indicating some accumulation of gepirone following multiple dosing. As a result, plasma concentrations of gepirone accumulated less than 3-fold. C_{max}, AUC, and MRT values were greater in the elderly subjects. Also, male subjects had greater values for C_{max} and AUC (15-25% elevation) compared with females.

For 1-PP, plasma levels were observed within 15 min (Figs. 51, 52, Table 58). The $t_{1/2}$ ranged from 5-8 h following single and multiple dose administration. For all groups, the pharmacokinetics on day 7 were greater than the values on day 1, illustrating some accumulation of 1-PP. In contrast to gepirone pharmacokinetics, no significant age or gender effects were observed for C_{max}, AUC, and $t_{1/2}$. No change in the metabolic ratio was observed in all dose groups.

Conclusions.

The results of this study showed that significant differences in gepirone pharmacokinetics were obtained based on age and/or gender as well as multiple dosing. Following multiple dose administration, plasma levels accumulated less than 3-fold. The AUC, C_{max} and MRT values were augmented in the elderly subjects after single dose and at steady-state. Thus, a dose reduction is warranted when treating the elderly with gepirone.

27. Protocol 030L1-0001-1700: Safety and Tolerance of MJ-13805 Following Single Escalating Doses of Gepirone IR in Normal Male Subjects.

Investigator.

(b) (4)

Objectives.

The objectives of this study were to examine the safety and tolerability of escalating, single oral doses of MJ-13805, and evaluate the pharmacokinetics of the compound in healthy male volunteers.

Study Design and Methods:

This study consisted of a randomized, double-blind, parallel group, placebo-controlled, "leap-frog" design. The study design included a 17-day treatment period. All subjects fasted the night prior to dosing and were administered gepirone as specified in the protocol. Doses were provided as follows:

Group 1 (Subject # (b) (6)): 5, 20, 50, 80 mg
Group 2 (Subject # (b) (6)): 10, 30, 60, 90 mg
Group 3 (Subject # (b) (6)): 15, 40, 70, 100 mg
Group 4 (Subject # (b) (6)): placebo
Subjects # (b) (6) and (b) (6) did not complete the study.

Based on this study design, a 2-day interval was placed between successive doses during which each subject received placebo. In addition, 2 days after group 3 received their 100 mg dose, all 3 groups received a final dose of 100 mg gepirone. Serial blood samples were collected pre-dose and up to 5 h following gepirone administration on days 6 and 9. Only subjects in group 2 were administered gepirone on days 6 and 9 due to the study design. On day 16, every subject in the study received 100 mg of gepirone and thus blood samples were collected up to 24 h following administration. All samples were analyzed by a GC/MS assay to determine the concentration of gepirone and 1-PP.

Subjects:

Eighteen healthy male volunteers (age range: 18 - 40 yrs.) were enrolled in the study and divided into three groups of 6/group. Four subjects in each group received gepirone and two received placebo. Three subjects discontinued before the completion of the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone IR tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR capsule formulation, product # (b) (4), was a no. 3 capsule containing 5 mg of gepirone HCl.
- IR capsule formulation, product # (b) (4), was a no. 3 capsule containing 25 mg of gepirone HCl.
- Placebo tablet, product # (b) (4), was a no. 3 capsule containing no active ingredients.

Assay Validation:

A GC/MS assay was used to quantitate gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both compounds ($r \geq 0.998$). Low, medium, and high QC samples were prepared at concentrations of 2.0, 20, and 97.6 ng/ml for gepirone and 2.12, 21.2, and 103.3 for 1-PP. The between day variability for the QC samples did not exceed 3.83% for gepirone and 4.57% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were 5.67% for the low QC, 5.83% for the middle QC, and 5.08% for the high QC. The corresponding values for 1-PP were 3.23%, 3.05%, and 10.1%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), half-life ($t_{1/2}$), and area under the curve ($AUC_{0\text{-}5,\ 24\ h}$). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

Statistical analysis was performed in the context of a randomized block design where each subject defined a block. Tests were carried out for dose linearity of gepirone and 1-PP and were based on the t-test for a linear trend across the three doses. Dose proportionality was evaluated based on a t-statistic for the significance of the intercept.

Results.

Figure 53. Mean Plasma Gepirone Concentrations Following Doses of 30, 60, and 100mg.

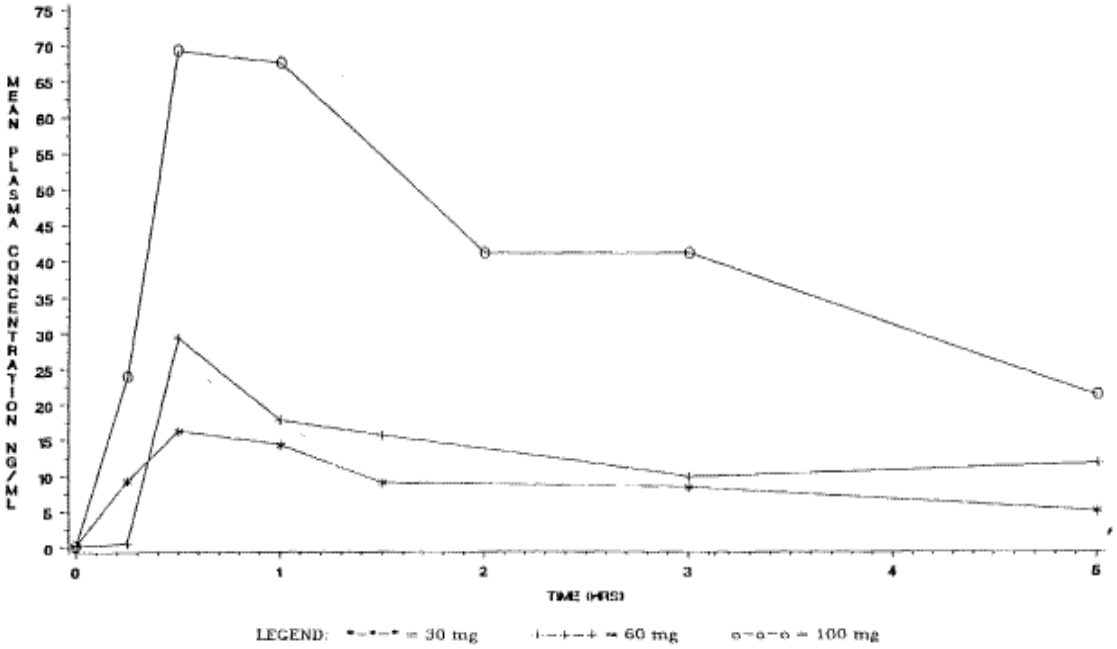


Figure 54. Mean Plasma 1-PP Concentrations Following Doses of 30, 60, and 100 mg.

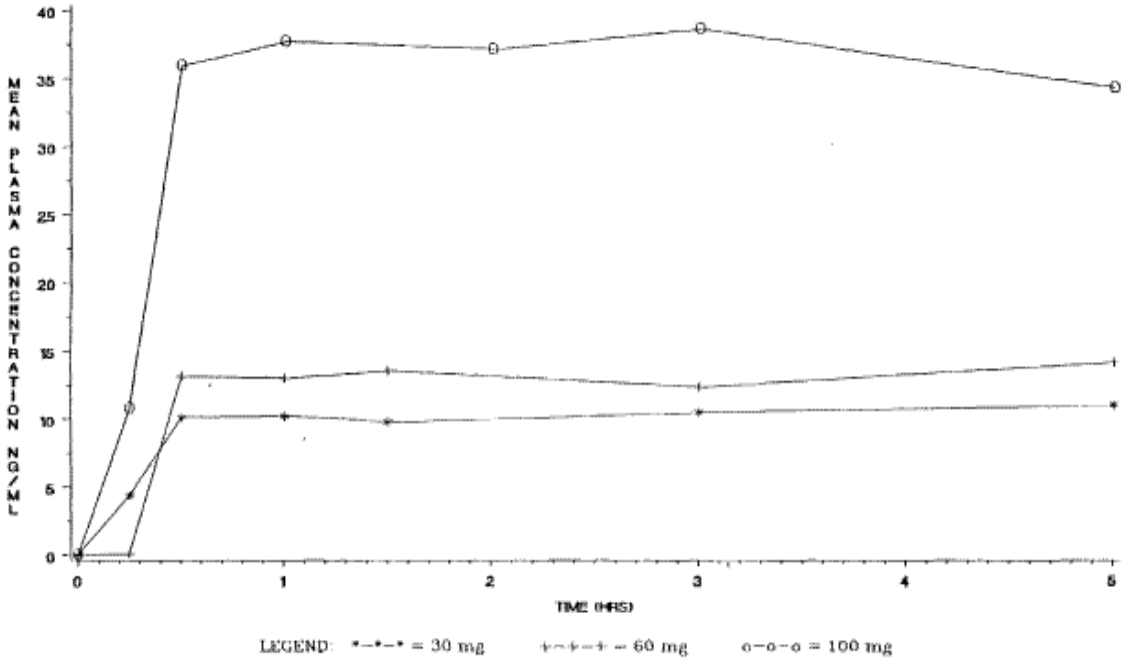


Table 59. Mean Pharmacokinetic Parameters of Gepirone and 1-PP (±S.D.).

PK Parameter	30 mg	60 mg	100 mg
Gepirone			
C_{max} (ng/ml)	19.7 (10.7)	34.6 (25.1)	93.7 (47.7)
T_{max} (h)	0.69 (0.38)	1.88 (2.14)	0.69 (0.38)
$T_{1/2}$ (h)			2.28 (0.91)
$AUC_{(0\text{-}5\ h)}$ (ng-h/ml)	44.3 (16.6)	65.1 (36.1)	193 (50.2)
*$AUC_{(0\text{-}\infty)}$ (ng-h/ml)			265.7 (80.7)
1-PP			
C_{max} (ng/ml)	13.9 (3.62)	19.6 (11.7)	41.4 (9.22)
T_{max} (h)	2.81 (2.54)	1.88 (2.14)	2.31 (1.97)
$T_{1/2}$ (h)			5.09 (1.70)
$AUC_{(0\text{-}5\ h)}$ (ng-h/ml)	49.2 (11.9)	60.8 (34.8)	150 (23.8)
*$AUC_{(0\text{-}\infty)}$ (ng-h/ml)			435 (150)

*Total AUC was calculated based on ten subjects that were administered 100 mg of gepirone on day 16.

Following drug administration, gepirone was absorbed rapidly, indicated by a short t_{max} of 0.7 – 1.9 h (Fig. 53, Table 59). T_{max} remained unchanged independent of dose for both gepirone and 1-PP (Figs 53, 54, Table 59). The parent drug also was metabolized rapidly, due to observed plasma levels of 1-PP within 15 min (Fig. 54). Following administration of the 30 and 60 mg doses, the half-lives for gepirone and 1-PP could not be determined. Thus, the $t_{1/2}$ following the 100 mg dose was 2.3 h and 5.1 h for gepirone and 1-PP, respectively. A trend for nonlinearity at the higher doses was observed between dose and AUC, but was inconclusive based on the AUC values for both compounds only representing plasma levels up to 5 h. As a result, the AUC up to 5 h represented 77% and 34% of the total AUC for gepirone and 1-PP, respectively.

Conclusions.

Overall, gepirone was well tolerated up to 80 mg. The results showed that gepirone was rapidly absorbed and metabolized following oral administration. Even though the sponsor stated that gepirone and 1-PP may exhibit nonlinear pharmacokinetics at higher doses, this assessment cannot be adequately interpreted due to a statistical comparison of AUC values only up to 5 h.

10. Protocol 030L1-0001-1869: Multiple Dose Safety and Tolerability Study of Gepirone IR in Normal Male Subjects.

Objectives.

The purpose of this study was to determine the safety and tolerability of multiple doses of MJ-13805, and obtain preliminary data on the multiple dose pharmacokinetics of the compound in healthy male volunteers.

Study Design and Methods:

This study consisted of a multiple dose, double-blind, parallel group, placebo-controlled design. All subjects fasted the night prior to dosing and were administered gepirone for 28 days followed by a 4-day washout period. On days 1 and 28, the subjects fasted until 6 h following drug administration. Subjects were randomly assigned to one of the following treatment groups (Table 60).

Table 60. Dosing Schedule.

Group	Gepirone Dose
A	10 mg q8h for 28 days
B	10 mg q8h for days 1-3, followed by 25 mg q8h from days 4-28
C	10 mg q8h for days 1-3, 25 mg q8h on days 4-6, followed by 50 mg (2 x 25 mg) q8h from days 7-28
D	Placebo capsules q8h for 28 days

Serial blood samples were collected pre-dose and up to 8 h following gepirone administration on days 1 and 28. On day 32, a blood sample was collected to ensure completion of the washout phase. All samples were analyzed by a GC/MS assay to determine the concentration of gepirone and 1-PP.

Subjects:

Twenty-four healthy male volunteers (age range: 18 - 40 yrs.) were enrolled in the study and divided into four groups of 6/group. Three groups received gepirone and one received placebo. Two subjects discontinued before the completion of the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone IR tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR capsule formulation, product # (b) (4), was a no. 3 capsule containing 5 mg of gepirone HCl.
- IR capsule formulation, product # (b) (4), was a no. 3 capsule containing 25 mg of gepirone HCl.
- Placebo tablet, product # (b) (4), was a no. 3 capsule containing no active ingredients.

Assay Validation:

A radioimmunoassay (RIA) was used to quantitate gepirone and a GC/MS assay was used for 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 5 ng/ml for gepirone ($r \geq 0.992$) and 0.2 – 25 ng/ml for 1-PP ($r \geq 0.997$). Low, medium, and high QC samples were prepared at concentrations of 0.4, 3.0, and 25 ng/ml for gepirone and 0.99, 11.9, and 21.8 ng/ml for 1-PP. The between day variability for the QC samples did not exceed 9% for gepirone and 7.25% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were within 8.69% for the low QCs, 7.98% for the middle QCs, and 5.20% for the high QCs. The corresponding values for 1-PP were 6.57%, 6.70%, and 4.05%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), and area under the curve ($AUC_{0\text{-}8\ h}$). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

A paired t-test was used to compare C_{max} values of gepirone and 1-PP for the 10 mg dose level. AUC and C_{max} were evaluated by linear regression analysis to determine if these parameters were both linear and proportional to dose following multiple doses of gepirone. An ANOVA also was used to test linearity and proportionality to evaluate AUC and Cmax normalized to a 1 mg dose. Comparisons were made at each dose level using the Tukey-Kramer multiple comparison procedure and significance was determined at the $\alpha = 0.05$ level.

Results.

Figure 55. Mean Plasma Gepirone Concentrations on Day 28.

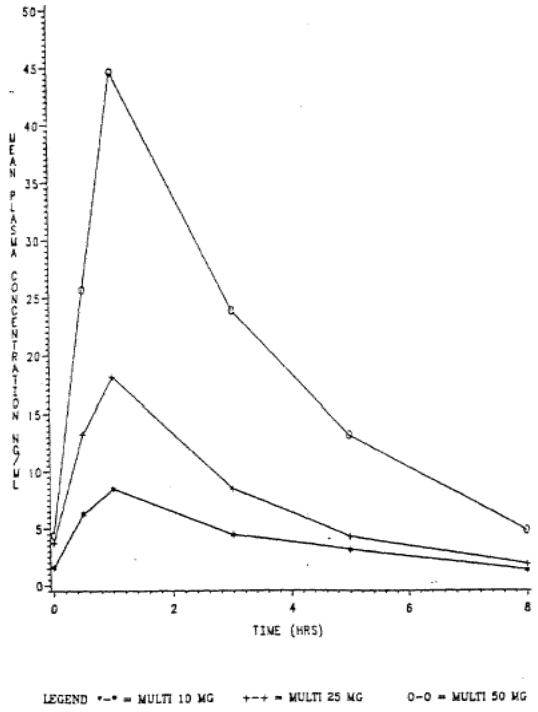


Figure 56. Mean Plasma 1-PP Concentrations on Day 28.

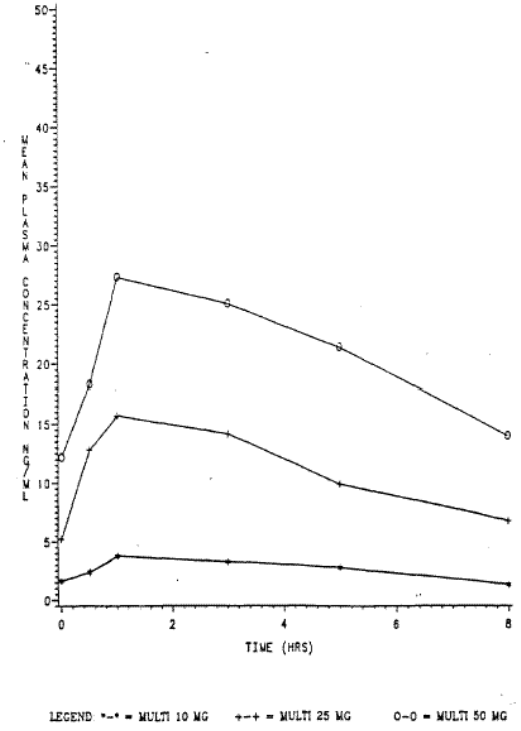


Table 61. Mean Pharmacokinetic Parameters of Gepirone and 1-PP Following Multiple Dose Administration (±S.D.).

PK Parameter	10 mg	25 mg	50 mg
Gepirone			
C^{ss}_{max} (ng/ml)	8.81 (4.90)	18.4 (6.05)	46.6 (28.6)
*DN C^{ss}_{max} (ng/ml)	0.88 (0.49)	0.74 (0.24)	0.93 (0.57)
T_{max} (h)	0.83 (0.26)	0.80 (0.27)	1.30 (0.97)
$AUC^{ss}_{(0\text{-}8\ h)}$ (ng-h/ml)	32.7 (21.2)	60.3 (21.0)	157 (66.2)
*DN $AUC^{ss}_{(0\text{-}8\ h)}$ (ng-h/ml)	3.27 (2.20)	2.41 (0.84)	3.14 (1.32)
1-PP			
C^{ss}_{max} (ng/ml)	4.35 (1.71)	16.7 (7.00)	28.7 (16.2)
*DN C^{ss}_{max} (ng/ml)	0.43 (0.17)	0.67 (0.28)	0.57 (0.32)
T_{max} (h)	1.58 (1.11)	1.30 (0.97)	1.80 (1.10)
$AUC^{ss}_{(0\text{-}8\ h)}$ (ng-h/ml)	20.2 (8.80)	90.4 (46.7)	171 (120)
*DN $AUC^{ss}_{(0\text{-}8\ h)}$ (ng-h/ml)	2.02 (0.88)	3.62 (1.87)	3.41 (2.39)

*C_{max} and AUC were normalized to a 1 mg dose.

Following drug administration, gepirone was absorbed rapidly, indicated by a short t_{max} of 0.8 – 1.3 h (Fig. 55, Table 61). T_{max} remained unchanged independent of dose for both gepirone and 1-PP (Figs. 55, 56, Table 61). The parent drug also was metabolized rapidly, due to observed plasma levels of 1-PP within 15 min (Fig. 56). Following administration of the 10, 25, and 50 mg doses, C_{max} was dose proportional for both gepirone and 1-PP. A trend for linearity was apparent between dose and AUC for both gepirone and 1-PP, and statistical analysis revealed that no significant mean differences existed between the normalized values.

Conclusions.

Following multiple dose administration, gepirone was absorbed and metabolized rapidly independent of dose, indicated by the short t_{max} values. As a result, both gepirone and 1-PP exhibited dose linear pharmacokinetics up to 50 mg.

11. Protocol 59B4A-001-2579: A Pharmacokinetic Study of Gepirone IR After Single and Multiple Dosing in Normal Male Subjects.

Objectives.

The objective of this study was to provide a more definitive picture regarding the single and multiple dose pharmacokinetics of gepirone and 1-PP in healthy male volunteers.

Study Design and Methods:

This study consisted of an open-labeled, placebo-controlled, double-blind, parallel group design. All subjects fasted the night prior to dosing and up to 5 h following administration. On days 1 and 10, the subjects were administered 5, 10, 20, or 30 mg of drug (Table 62). On days 3-9, the subjects were dosed t.i.d. with the dose they received on day 1. Blood samples were collected over 48 h on days 1 and 10, and for 8 h on day 7. Single blood samples also were collected for C_{min} determinations immediately prior to the morning dose on days 4, 5, 6, 8, and 9. Samples were analyzed for gepirone and 1-PP by GC/MS. Subjects in the 30 mg group (group 3) discontinued treatment following the second dose due to adverse events. Thus, comparisons at steady-state were made using the data from the 5, 10, and 20 mg groups.

Table 62. Dosing Schedule.

	Study Day/Gepirone Dose		
Group	1	3-9	10
1	5 mg	5 mg (t.i.d.)	5 mg
2	10 mg	10 mg (t.i.d.)	10 mg
3	20 mg	20 mg (t.i.d.)	20 mg
4	30 mg	30 mg (t.i.d.)	30 mg

Subjects:

Forty-two healthy male volunteers (age range: 18 - 40 yrs., 28 Caucasian, 14 Black) were enrolled in the study. All groups received gepirone, but only groups 1, 2, and 3, a total of 10 subjects/group completed the study. Thirteen subjects, including all of group 4, discontinued before the completion of the study.

Test Product, Dose, and Mode of Administration:

The test formulation of gepirone IR tablets was supplied to the investigator by Bristol-Myers Squibb Co., which included:

- IR capsule formulation, product # (b) (4) (Lot #E87C071), was a no. 0 gray, opaque capsule containing 5 mg of gepirone HCl.
- Placebo capsules, product # (b) (4) (Lot #E85F129), continued no active ingredients.

Each subject received 6 capsules at every dosing period, which were made up of a combination of test drug and placebo.

Assay Validation:

A GC/MS assay was used to quantitate both gepirone and 1-PP in this study. The calibration curve was linear for the concentration range from 0.1 – 25 ng/ml for both gepirone ($r \geq 0.995$) and 1-PP ($r \geq 0.993$). Low and high QC samples were prepared at concentrations of 2.0 and 20 ng/ml for gepirone and 2.12 and 21.2 ng/ml for 1-PP. The between day variability for the QC samples did not exceed 9.86% for gepirone and 5.55% for 1-PP. For the accuracy of the method, the deviations from the mean for gepirone were within 7.70 % for the low QCs and 8.90% for the high QCs. The corresponding values for 1-PP were 5.29% and 5.72%, respectively.

Criteria for Evaluation:

Pharmacokinetic evaluation included the determination of peak concentration (C_{max}), corresponding peak times (t_{max}), area under the curve (AUC_{0-t}), half-life ($t_{1/2}$), trough concentrations (C_{min}), and an accumulation ratio (R). Non-compartmental methods were used in the determination of various pharmacokinetic parameters.

In comparing the single and multiple dose pharmacokinetics, repeated measures ANOVA was utilized to compare the C_{min}, $t_{1/2}$, $MRT_{0-\infty}$, $AUC_{0-\infty}$, t_{max} (rank transformed) and AUC_{0-8} data. With the exception of Levene's test ($p=0.001$), which was used to test homogeneity of variance for $t_{1/2}$ and MRT, the significance level was set at $p=0.05$. Weighted linear regression was used to determine whether C_{min}, C_{max}, and AUC were linear or proportional to dose. Tests for linearity were conducted using the lack-of-fit t-statistic. Due to discontinuation of the 30 mg group following the second dose, the data only was included in the assessment of dose proportionality.

Results.

Figure 57. Mean Plasma Gepirone Concentrations on Day 1.

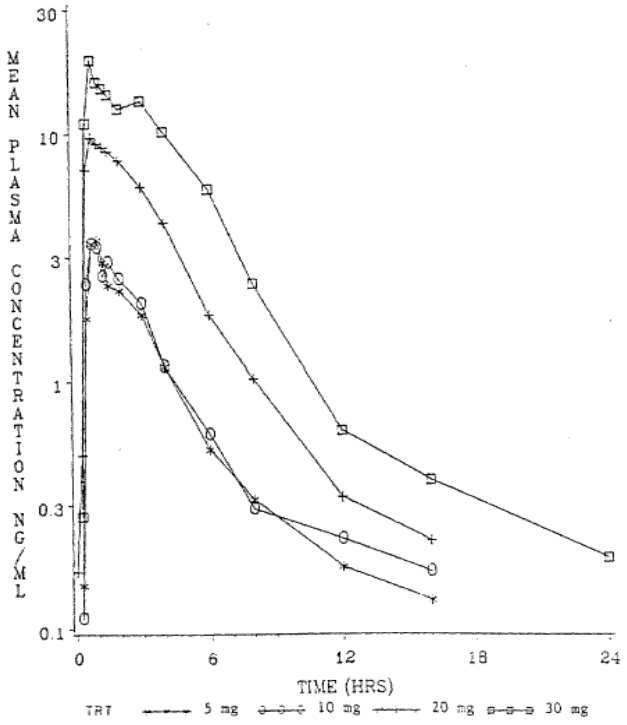


Figure 58. Mean Plasma Gepirone Concentrations on Day 10.

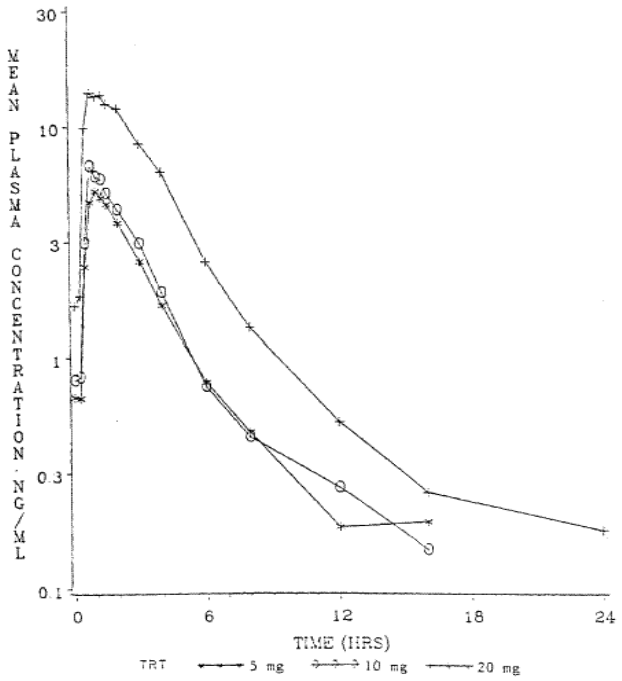


Figure 59. Mean Plasma Concentrations of 1-PP on Day 1.

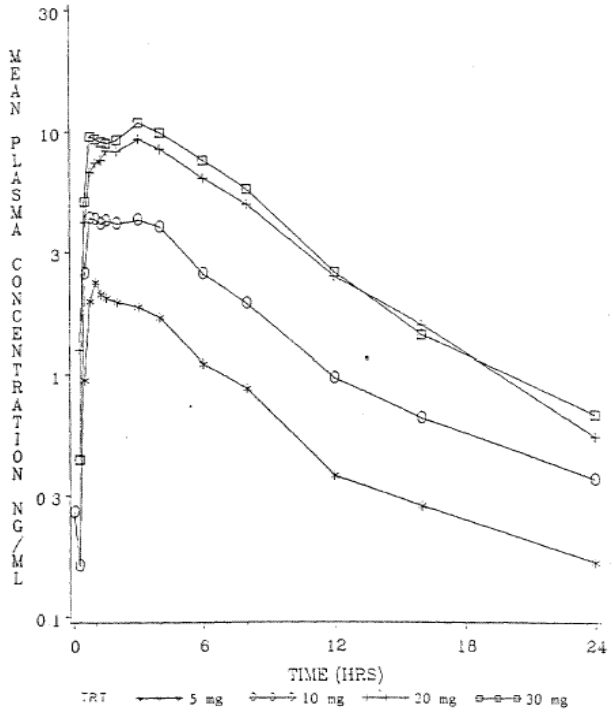
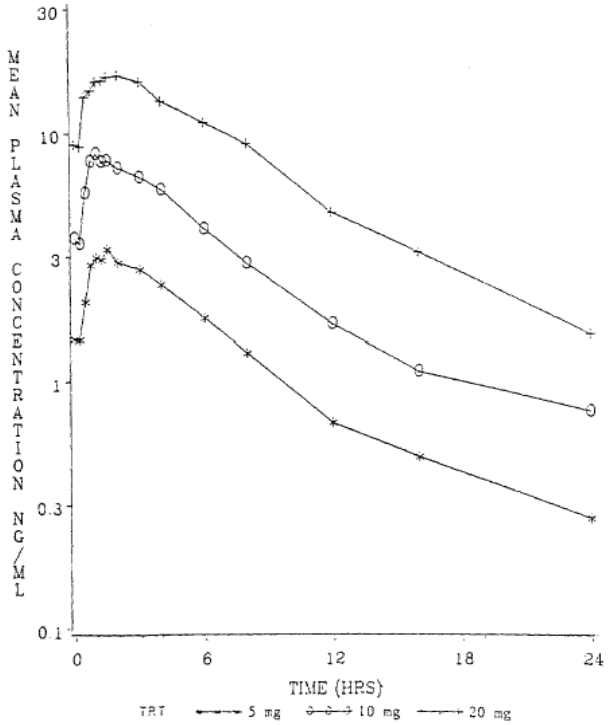


Figure 60. Mean Plasma Concentrations of 1-PP on Day 10.



BEST AVAILABLE COPY

Table 63. Mean Pharmacokinetic Parameters of Gepirone.

Dose (mg):		5	10	20	30
	n	10	10	10	8
CMAX (ng/ml)					
Day 1	Mean	4.24	6.48	14.46	28.19
	SD	1.46	5.28	10.70	14.04
Day 7	Mean	6.21	8.74	25.04	---
	SD	2.25	6.59	23.31	---
Day 10	Mean	7.17	9.69	24.21	---
	SD	3.36	5.87	18.72	---
AUC(INF) (ng.hr/ml)					
Day 1	Mean	12.09	16.37	47.03	92.93
	SD	2.90	12.32	30.51	34.75
Day 10	Mean	20.07	25.69	66.74	---
	SD	8.23	14.52	36.93	---
AUC(0-8) (ng.hr/ml)					
Day 7	Mean	15.20	20.65	60.52	---
	SD	4.86	13.17	40.21	---
Day 10	Mean	18.16	23.47	59.89	---
	SD	7.13	12.92	32.50	---
T-HALF (hr)					
Day 1	Mean	2.82	2.09	2.37	
	SD	0.62	0.49	0.31	
Day 10	Mean	2.97	2.69	3.45	
	SD	0.72	0.73	1.57	
MRT(INF) (hr)					
Day 1	n	9	9	7	
	Mean	3.40	3.09	3.48	
	SD	0.51	0.60	0.39	
Day 10	n	9	9	7	
	Mean	3.40	3.17	3.72	
	SD	0.41	0.54	0.34	
Rank(TMAX)+					
Day 1	Mean	51	39	54	
	SD	21	28	27	
Day 7	Mean	42	46	32	
	SD	25	25	20	
Day 10	Mean	56	46	44	
	SD	25	20	31	
CMIN (ng/ml)					
Days 5-10	Mean	0.63	0.76	2.17	
	SD	0.23	0.42	1.17	

+ TMAX values were replaced by ranks.

Table 64. Mean Pharmacokinetic Parameters of 1-PP.

Dose (mg):		5	10	20	30
	n	10	10	10	8
CMAX (ng/ml)					
Day 1	Mean	2.55	6.04	9.93	14.16
	SD	0.64	2.09	1.61	5.22
Day 7	Mean	4.12	10.90	22.85	---
	SD	1.36	5.94	8.87	---
Day 10	Mean	3.88	10.23	20.14	---
	SD	1.41	3.88	7.74	---
AUC(INF) (ng.hr/ml)					
Day 1	Mean	18.50	49.10	102.25	118.44
	SD	7.79	25.47	50.46	69.02
Day 10	Mean	31.54	104.31	227.45	---
	SD	16.50	80.20	192.49	---
AUC(0-8) (ng.hr/ml)					
Day 7	Mean	19.77	54.29	121.29	---
	SD	7.86	30.70	60.40	---
Day 10	Mean	19.77	51.34	114.96	---
	SD	7.36	27.32	53.85	---
T-HALF (hr)					
Day 1	Mean	5.05	6.52	6.37	
	SD	1.73	3.86	3.19	
Day 10	Mean	5.58	7.91	7.20	
	SD	1.38	4.11	2.75	
MRT(INF) (hr)					
Day 1	n	10	8	9	
	Mean	6.86	8.93	9.59	
	SD	1.95	4.92	4.75	
Day 10	n	10	8	9	
	Mean	7.23	10.51	10.28	
	SD	1.83	5.22	4.03	
Rank(TMAX)+					
Day 1	Mean	45	27	74	
	SD	24	29	17	
Day 7	Mean	46	46	27	
	SD	16	27	18	
Day 10	Mean	49	43	52	
	SD	20	23	29	
CMIN (ng/ml)					
Days 5-10	Mean	1.59	4.73	10.13	
	SD	0.77	3.05	5.87	

+ TMAX values were replaced by ranks.

For gepirone, t_{max} ranged from 0.7 – 1.1 h, indicating that absorption was rapid, similar among doses, and independent of the multiple dosing regimen (Figs. 57, 58, Table 63). The $t_{1/2}$ ranged from 2 –3.5 h following single and multiple dose administration. Based on C_{min}, C_{max}, and AUC data, steady-state conditions were achieved after 2 days of t.i.d. dosing. As a result, plasma concentrations of gepirone accumulated 1.5-1.9 fold. Also, AUC_{ss} on day 7 was significantly greater than the AUC on day 1. After a single dose of gepirone, C_{max} and AUC were linear with respect to dose up to 30 mg and 20 mg, respectively. At steady-state, both C_{max} and AUC were linear with respect to dose up to 20 mg, but the outcome is marginal due to high variability in the data.

For 1-PP, plasma levels were observed within 15 min (Figs. 59, 60). The $t_{1/2}$ ranged from 5-8 h following single and multiple dose administration (Table 64). Based on C_{max} and AUC data, plasma concentrations of 1-PP accumulated approximately 1.7 fold. In contrast to gepirone pharmacokinetics, the AUC_{ss} of 1-PP was similar to the AUC on day 1, thus suggesting that the rate of metabolite formation did not change as a result of multiple dosing of the parent compound. Both C_{max} and AUC were linear with respect to dose up to 20 mg following single and multiple dose administration, but the data was associated with high variability.

Conclusions.

Gepirone was absorbed and metabolized rapidly independent of dose, indicated by the short t_{max} values. Steady state plasma levels were obtained after 2 days of t.i.d. dosing. Following multiple dose administration, both gepirone and 1-PP profiles showed little accumulation (approximately 2-fold), which may not be clinically relevant. In addition AUC and C_{max} were linear with respect to dose up to 20 mg for both gepirone and 1-PP, but the data was highly variable. As a result of the method of superpositioning, predicted values of AUCss and C_{min} were significantly less that the values observed, resulting in that steady state pharmacokinetics of gepirone and 1-PP cannot be predicted from single dose data. One possible explanation may be due to high variability in the data or saturation of metabolic pathways at higher doses.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-164**	**Brand Name**	**ARIZA**
OCPB Division (I, II, III)	**DPE 1**	**Generic Name**	**Gepirone HCl**
Medical Division	**Neuropharmacology**	**Drug Class**	
OCPB Reviewer	**Gerald Fetterly**	**Indication(s)**	**Depression**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**20, 40, 60, and 80 mg ER tablets;**
		Dosing Regimen	**Starting dose: 20 mg/day.** **Can be titrated up to 40-80 mg/day.**
Date of Submission	**5/18/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**1/15/02**	**Sponsor**	**Organon**
PDUFA Due Date	**3/15/02**	**Priority Classification**	**10 month Original NDA Resubmission**
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	
Isozyme characterization:	**X**	**1**	**1**	
Blood/plasma ratio:	**N/A**			
Plasma protein binding:	**X**	**1**	**1**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
Single dose:	**X**	**1**	**1**	
Multiple dose:	**X**	**1**	**1**	
Patients-				
Single dose:				
Multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	
fasting / non-fasting multiple dose:	**X**	**1**	**1**	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**	**1**	**With ketoconazole and dextromethorphan**
In-vivo effects of primary drug:				

In-vitro:	**X**	**1**	**1**	• **With ketoconazole and quinidine** • **Also, *in vitro* inhibition potential of gepirone on CYP450s**
Subpopulation studies -				
ethnicity:	**X**	**1**	**1**	
gender:	**X**	**1**	**1**	
pediatrics:				
geriatrics:	**X**	**1**	**1**	
renal impairment:	**X**	**2**	**1**	
hepatic impairment:	**X**	**1**	**1**	
PD:				
Phase 2:				
Phase 3:	**X**	**2**	**0**	**2 Pivotal Efficacy studies with ER formulation**
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	**X**	**1**	**1**	
Relative bioavailability -				
solution as reference:	**X**	**1**	**1**	**Relative to BMS IR formulation**
alternate formulation as reference:	**X**	**2**	**2**	• **Relative to BMS IR** • **Study comparing** (b) (4) **vs. BMS ER formulations**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	**Comparing** (b) (4)**:** • **1 x 80 mg vs. 4 x 20 mg** • **1 x 40 mg vs. 2 x 20 mg**
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**	**1**	
Dissolution:	**X**	**1**	**1**	**All proposed marketed strengths (20, 40, 60, and 80 mg)**
(IVIVC):	**X**	**1**	**1**	(b) (4)
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	**X**	**1**	**1**	**Evaluation of 2D6 phenotype using dextromethorphan**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**26**	**23**	

Background:

Gepirone was developed initially by Bristol-Myers Squibb, Inc., but a business decision led to its termination. In 1998, Organon signed an agreement with Fabre-Kramer Pharmaceuticals to further develop the drug. During development, Organon had initially submitted an NDA for the extended-release formulation of gepirone, but the agency refused to file the NDA because the sponsor did not have two positive well-controlled efficacy trials. As a result, Organon has re-submitted the NDA for approval in the treatment of depression.

Gepirone is an azapirone derivative, which has both antidepressant and anxiolytic properties by interacting with serotonin $(5\text{-HT})_{1A}$ receptors. The drug is metabolized by both CYP450 3A4 and 2D6, thus producing the potential for a variety of drug interactions. In the current submission, the effect of inducers of various CYP450 isozymes has not been studied. The 20 mg strength is the only strength that has been used in the clinical trials, although the sponsor wants to market 20, 40, 60, and 80 mg strengths. As a result, a bioequivalency study has been submitted linking the 20, 40, and 80 mg strengths. In addition, gepirone has encountered several formulation changes throughout the drug development process.

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**X**	**We are requesting that the following comments be sent to the sponsor:** **1. The sponsor has performed a Bioequivalence study comparing the 20, 40, and 80 mg strengths. They intend to also market a 60 mg strength. The sponsor needs to provide dissolution data comparing the 60 mg tablet to other strengths and justification for not testing the 60 mg strength *in vivo*.** **2. The sponsor has included a list of all clinical pharmacology studies to date, but has not clearly indicated which extended release formulation was used in each study. Please provide an amended table to include which BMS or (b) (4) formulation was used in each study (ex. ER-1, ER-2, ER-3, ER-4, and (b) (4) ER formulation).** **3. Electronic submission of data for all clinical pharmacology, pharmacokinetic, and dose-response studies is needed.** **4. Need dissolution method development report, and data for each of the ER strengths to be marketed. Also, the pH-solubility profile for gepirone is needed. We recognize that this information may have been submitted in another volume of the NDA. Please submit hard copies and indicate the section of the electronic NDA where the information resides.**
QBR questions (key issues to be considered)	**1. Are the clinical and marketed formulations bioequivalent?** **2. Is the dose selected reasonable?** **3. Is dose adjustment needed in special populations (e.g. Patients with renal or hepatic impairment)?**	
Other comments or information not included above	**1. A DSI audit will be required for the pivotal bioequivalency study comparing three dose strengths (20, 40, and 80 mg). We request the project manager to send a consult to DSI for inspection.**	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Gerald Fetterly
2/19/02 05:38:13 PM
BIOPHARMACEUTICS

Vanitha Sekar
2/19/02 05:51:24 PM
BIOPHARMACEUTICS