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RESEARCH**

*APPLICATION NUMBER:*

**21-763**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW

<b>NDA:</b>	21-763
<b>Brand Name:</b>	TRADENAME
<b>Generic Name:</b>	Citalopram Hydrobromide
<b>Sponsor:</b>	Biovail Laboratories, Inc.
<b>Type of Dosage Form:</b>	Orally Disintegrating Tablet (ODT)
<b>Strengths:</b>	10 mg, 20 mg, 40 mg
<b>Indications:</b>	Treatment of Depression
<b>OCPB Reviewer:</b>	Ta-Chen Wu, Ph.D.
<b>OCPB Team Leader:</b>	Ramana S. Uppoor, Ph.D.
<b>OCPB Division:</b>	DCPB-I HFD-860
<b>OND Division:</b>	Neurology Drug Products HFD-120
<b>Submission Date:</b>	June 23, 2005 December 12, 2005 (e-mail re: labeling)
<b>Type of Submission:</b>	Complete Response to AE Letter

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## 1. EXECUTIVE SUMMARY

### Background:

Citalopram Hydrobromide orally disintegrating tablets (ODT) of 10 mg, 20 mg, and 40 mg strengths were developed by the Biovail Laboratories, Inc. for the treatment of depression. The original NDA 505(b)(2) application was submitted on April 14, 2004, and was considered to be approvable. The current submission contains sponsor's complete response to the approvable letter dated February 14, 2005 for NDA 21-763.

In the original NDA submission the Sponsor proposed specifications of  $Q = \text{---}$  in  $\text{---}$  minutes in 900 ml of pH 6.5 phosphate buffer for 40 mg ODT and 500 ml of pH 6.5 phosphate buffer for 10 mg and 20 mg ODT, using USP Apparatus 2 (paddles) at the 100-rpm agitation speed. With the proposed dissolution method, the highest agitation speed at 100 rpm generated overlapping dissolution profile with that from  $\text{---}$  rpm, and hence did not demonstrate that the 100 rpm agitation speed was necessary for the ODT formulations. In addition, a particular biobatch of the 20 mg strength (Lot#: PR-04-064R used in Study 2914) manufactured at Biovail Dorado, PR, showed that  $\text{---}$  was dissolved in 30 minutes. All three strengths manufactured at Biovail Dublin, Ireland, indicated near complete dissolution in 30 minutes and were shown to have similar dissolution profiles using F2 testing to batches of the same strength from Dorado.

Upon reviewing the provided dissolution profiles of the biobatches in the original submission, OCPB has made the following recommendations for interim dissolution method and specifications and a Phase IV commitment, as stated in the AE Letter conveyed to the sponsor:

1. Based on the dissolution profiles of the biobatches, we accept the choice of the dissolution medium but believe that the method should be modified (especially the agitation speed) and the dissolution specifications need to be tightened. Following are the interim dissolution method and specifications recommended by the Agency:

Method: USP Apparatus 2 (Paddles)

Speed: 100 rpm

Medium: 900 ml of pH 6.5 phosphate buffer for 40 mg ODT;

500 ml of pH 6.5 phosphate buffer for 10 mg and 20 mg ODT

Specification:  $Q = \text{---}$  in 30 minutes

2. A Phase IV commitment was agreed upon during the teleconference of January 28, 2005, in which you agreed to:
  - Optimize the dissolution method and specifications using a lower agitation speed ( $\text{---}$  rpm with paddle) and a different dissolution medium if needed.
  - Generate data on biobatches and the next 3 production batches for all 3 strengths using the more optimized dissolution method. This data should be submitted to the Agency within 1 year from the date of approval for selecting a final dissolution specification for this product.

There was no new study included in the present submission pertinent to OCPB issues. The sponsor agrees to the Phase IV commitment but proposes to retain the current specification of Q = 10 in 15 min as an interim specification. The sponsor's responses to OCPB's recommendations are summarized as follows:

**Sponsor's Response:**

Response to OCPB Comment #1:

Study 2914 (2 x 10 mg vs. 1 x 20 mg) has demonstrated the in vivo bioequivalence between batches 0307015 (10 mg, Dublin) and PR-04-064R (20 mg, Dorado), as seen in the original NDA review. In current submission, Biovail has included additional comparative in vitro dissolution profiles of these 2 batches across the physiological pH range generated at the time of dosing.

Data for both batches in 0.1N HCl, pH 5 acetate buffer, and pH 7 phosphate buffer are shown in Figures 1-3 and Tables 1-3.

Figure 1: Comparison of the dissolution profiles for Dublin Batch No. 0307015 and Dorado Batch No. PR-04-064R in 0.1N HCl

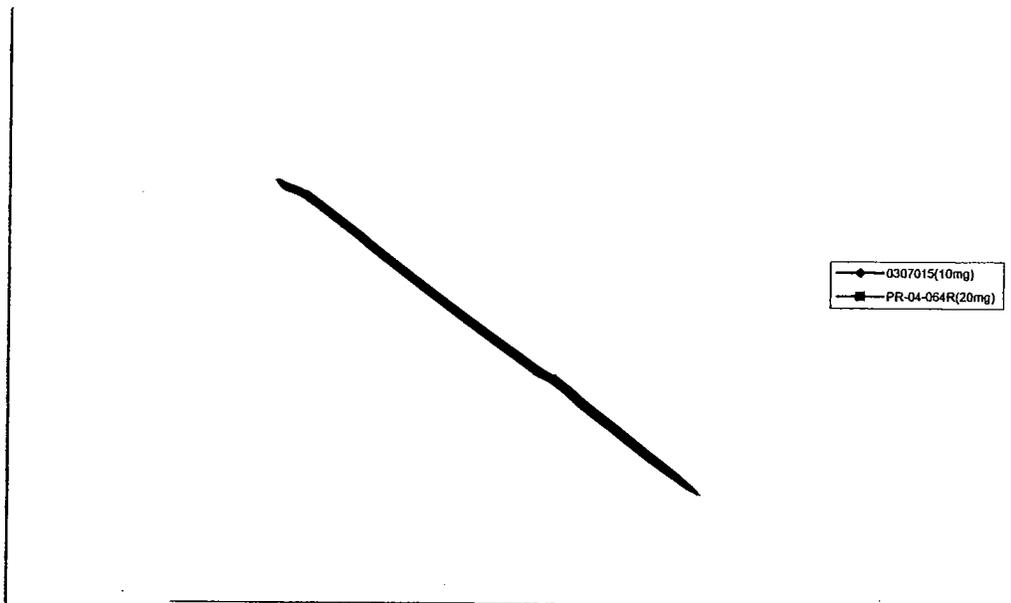


Table 1: Dissolution data in 0.1N HCl

Time (min.)	0307015				PR-04-064R			
	Mean	Max	Min	%RSD	Mean	Max	Min	%RSD
5	[REDACTED]							
10								

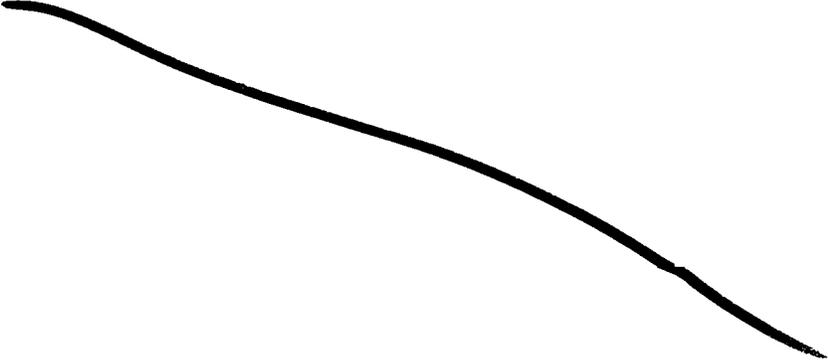
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Response to OCPB Comment #2:

Biovail agrees to optimize the dissolution method using lower agitation speed and different medium if needed. We will generate data on biobatches and the next three production batches for all strengths using the more optimized dissolution method and will submit one year from the date of approval.

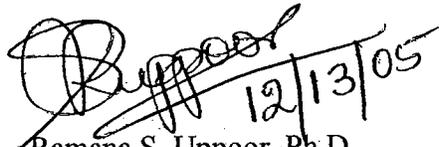
**1.1. RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the current submission and finds the Sponsor's response to OCPB's recommendations to be acceptable.

While it is OCPB's position that the proposed dissolution specifications need to be optimized, we accept the Sponsor's proposal to retain the specification of Q= [REDACTED] in [REDACTED] minutes as the interim specification based on the in vivo BE results and the provided dissolution profiles of the biobatches from both manufacturing sites. Since the Sponsor has agreed to optimize the dissolution method, we recommend that the Sponsor specifically obtain dissolution data at earlier timepoints in addition to [REDACTED] minutes on biobatches and next 3 production batches for all 3 strengths using the more optimal dissolution method.

In addition, Office of Clinical Pharmacology and Biopharmaceutics has reviewed the final proposed labeling for Citalopram HBr ODT and found the changes and justification acceptable from an OCPB perspective (see page 9).

  
Ta-Chen Wu, Ph.D. 12/13/05  
Reviewer, Neurology Drug Products, DCPB-I  
Office of Clinical Pharmacology and Biopharmaceutics

  
Concurrence: ~~Ramana S. Uppoor, Ph.D.~~ 12/13/05  
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Draft Labeling

Deliberative Process

Withheld Track Number: Clin Pharm/Bio-

2



following Tables. [reanalysis done only on parent citalopram since bioequivalence decision is based only on parent moiety]

**Study 2730 (with Subject 7):**

Parameter	Citalopram		
	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	97.02% - 102.64%	99.79%	6.05%
AUC <sub>0-inf</sub>	95.98% - 101.09%	98.50%	5.21%
C <sub>max</sub>	91.41% - 99.53%	95.38%	9.14%

**Study 2730 (without Subject 7):**

Parameter	Citalopram		
	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	96.41% - 101.59%	100.32%	5.87%
AUC <sub>0-inf</sub>	97.55% - 103.16%	98.97%	5.11%
C <sub>max</sub>	91.26% - 99.74%	95.40%	9.33%

Similar BE results were obtained following exclusion of data from Subject 7. It is concluded that the 40 mg Citalopram HBr ODT is bioequivalent to the reference 40 mg Celexa®.

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 Reviewer, Neuropharmacological Drug Section, DPE I  
 Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana S. Uppoor, Ph.D.  
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 HFD-860 /DD DPEI/M. Mehta, A. Rahman

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2/9/05 04:18:38 PM  
BIOPHARMACEUTICS

Ramana S. Uppoor  
2/9/05 04:28:22 PM  
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

<b>NDA:</b>	21-763	
<b>Brand Name:</b>	TRADENAME	
<b>Generic Name:</b>	Citalopram Hydrobromide	
<b>Sponsor:</b>	Biovail Laboratories, Inc.	
<b>Type of Dosage Form:</b>	Orally Disintegrating Tablet (ODT)	
<b>Strengths:</b>	10 mg, 20 mg, 40 mg	
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<b>OCPB Reviewer:</b>	Ta-Chen Wu, Ph.D.	
<b>OCPB Team Leader:</b>	Ramana S. Uppoor, Ph.D.	
<b>OCPB Division:</b>	DPE-I HFD-860	
<b>OND Division:</b>	Division of Neuropharmacological Drug Products HFD-120	
<b>Submission Date:</b>	April 14, 2004	December 13, 2004
	August 13, 2004	December 14, 2004
	August 23, 2004	December 21, 2004
	October 04, 2004	January 20, 2005
	October 11, 2004	January 31, 2005
	November 22, 2004	
<b>Type of Submission:</b>	505(b)(2), Standard	

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## ***1. Executive Summary***

On April 14, 2004, Biovail Laboratories, Inc. submitted an original NDA 505(b)(2) for Citalopram Hydrobromide orally disintegrating tablets (ODT) 10 mg, 20 mg, and 40 mg to seek approval for the treatment of depression.

Three tablet strengths (10, 20, and 40 mg) were developed to match commercially available Celexa™ film-coated tablets (Forest Laboratories, Inc.). Celexa™ is indicated for the treatment of depression. In support of the application the Sponsor has included in the original submission one pilot study using prototype formulation and four Phase I studies using to-be-marketed (TBM) formulation, with supporting *in vitro* dissolution profiles for TBM ODT formulation of different strengths in various media of different pH values, including deionized water.

An *in vivo* bioequivalence study was conducted to evaluate the TBM ODT formulation and the commercially available Celexa™ tablet of the highest dose strength 40 mg. Results indicated that the 40 mg ODT of highest strength is bioequivalent to the reference Celexa™ 40 mg tablet. Dosage strength equivalency was evaluated between the highest 40 mg strength and the lowest 10 mg strength; 10 mg ODT was found to be bioequivalent to the 40 mg ODT. In support of the proposed label claim that citalopram ODT formulation can be given without regards to food and water effects, the Sponsor conducted studies to show no effect on the rate and extent of citalopram absorption from 40 mg ODT formulation, in the presence or absence of high-fat meal, and with or without the administration with water. On Dec. 14, 2004, the Sponsor submitted an additional BE study (Study 2914) to support the application for 20 mg formulation since this strength was not proportionally similar in composition to other strengths. Dosage strength equivalency was established between 10 mg and 20 mg strengths.

The following studies are included in the Clinical Pharmacology program, but only the 5 definitive studies pertinent to the application and labeling were reviewed:

- Study 26022: Pilot BE study comparing prototype 40 mg ODT with the Reference List Drug (RLD) Celexa™ (NDA 20-822)
- Study 2730: BE study between 40 mg ODT and RLD Celexa™
- Study 2731: Food effect study with 40 mg ODT
- Study 2732: BE study with 40 mg ODT for effect of administration with water
- Study 2750: Dosage strength equivalence study between 4 x 10 mg ODT and 1 x 40 mg ODT
- Study 2914: Dosage strength equivalence study between 1 x 20 mg ODT and 2 x 10 mg ODT.

OCPB has requested a DSI inspection for the BE study sites (pivotal BE study of the 40 mg strength, Study #2730). Inspection has been scheduled, however, the report is unavailable at the time of this review.

### ***1.1. Recommendations***

Office of Clinical Pharmacology and Biopharmaceutics has reviewed the submission and found that NDA 21-763 is acceptable from an OCPB perspective, pending inspection report from DSI and provided that the Sponsor agrees with the dissolution specifications recommended by the Agency (along with the Phase IV commitment).

Based on the dissolution profiles of the biobatches, we accept the choice of the dissolution medium but believe that the method should be modified (especially the agitation speed) and the dissolution specifications need to be tightened. Following are the interim dissolution method and specifications recommended by the Agency:

Method: USP apparatus 2 (Paddle)

Speed: 100 rpm

Medium: 900 ml of pH 6.5 phosphate buffer for 40 mg ODT; 500 ml of pH 6.5 phosphate buffer for 10 mg and 20 mg ODT

Specification: Q =  in 30 minutes

The above Recommendations and the labeling changes (starts on page 30) pertinent to the Clinical Pharmacology and Biopharmaceutics should be conveyed to the Sponsor.

### ***1.2. Phase IV Commitments***

As communicated during the teleconference of January 28, 2005, the Sponsor should commit to:

- Optimize the dissolution method and specifications using a lower agitation speed ( rpm with paddle) and a different dissolution medium if needed.
- Generate data on biobatches and next 3 production batches for all 3 strengths using the more optimized dissolution method. This data should be submitted to the Agency within 1 year from the date of approval for selecting a final dissolution specification for this product.

### ***1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings***

#### **Bioequivalence between Citalopram HBr ODT and the RLD Celexa™:**

Relative bioavailability of the highest strength 40 mg citalopram HBr ODT was compared to the equivalent strength of reference Celexa™ tablets. A two-way crossover study was conducted in 36 healthy subjects under fasting conditions. The 40 mg citalopram ODT is shown to be bioequivalent to 40 mg Celexa™ tablet based on acceptance criteria for BE, i.e., 80-125% CI based on parent moiety. Similar pharmacokinetic profiles from ODT formulation and Celexa™ tablet were observed for both metabolites, demethylcitalopram and didemethylcitalopram.

#### **Effects of food:**

Effects of high-fat food on relative bioavailability of citalopram HBr ODT was evaluated using highest 40 mg ODT formulation in a randomized, single-dose, two-way crossover design in 36 normal, healthy subjects.. High-fat food had no effect on the rate and extent of absorption of citalopram. The ratios of geometric mean of  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram were 97.60%, 97.94%, and 98.47%, respectively.  $T_{max}$  was increased by 1 hour in fed state. Similar food effects were observed on the pharmacokinetics of 2 metabolites.

#### Effects of administration with water:

A randomized, single-dose, open-label, two-way crossover design was conducted in 36 normal, healthy subjects to evaluate the effect of administration with or without water when citalopram HBr 40 mg ODT formulation was given under fasting conditions (product was allowed to dissolve on tongue and then swallowed with or without water). No significant effect of water on BA was observed.

#### Biowaiver for Citalopram HBr 20 mg ODT:

According to the SUPAC-IR, the Level 3 difference in composition of the lower strength of 20 mg ODT, compared to the 40 mg and 10 mg ODT, requires an *in vivo* study being conducted for showing bioequivalence. Therefore, a biowaiver, as the Sponsor originally sought, could not be granted for the lower strength of 20 mg ODT formulation solely based on *in vitro* dissolution study. In response to OCPB's request, the Sponsor has submitted results of an additional study on December 14, 2004, to establish the dosage strength equivalency between 20 mg and 10 mg ODT.

#### Dosage strength equivalency:

The relative bioavailability of citalopram and its metabolites were evaluated in two similarly designed studies comparing single doses of 1 x 40 mg ODT vs. 4 x 10 mg ODT and 1 x 20 mg ODT vs. 2 x 10 mg ODT. BE was demonstrated in these two studies. Therefore, the dosage strength equivalency has been established between 10 mg, 20 mg, and 40 mg of citalopram HBr ODT.

#### Dissolution Specifications:

OCPB does not accept the dissolution specification proposed by the Sponsor ( $Q = \text{---}$  in  $\text{---}$  minutes). Based on the drug release profiles of the biobatches, we believe that the method should be modified and the dissolution specifications need to be tightened. Following are the interim dissolution methods and specifications recommended by the Agency:

Method: USP Apparatus 2 (paddle)

Speed: 100 rpm

Media: 900 ml of pH 6.5 phosphate buffer for 40 mg ODT; 500 ml of pH 6.5 phosphate buffer for 10 mg and 20 mg ODT

Specification: Q= [redacted] in 30 minutes

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On Original

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CSO/R. Gujral  
/Biopharm/T.C. Wu  
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HFD-860 /DD DPEI/M. Mehta, A. Rahman

## 2. Question-Based Review (QBR)

### 2.1. General Attributes of the Drug

**What pertinent regulatory background or history contributes to the current assessments of this drug?**

On April 14, 2004, Biovail Laboratories, Inc. submitted an original 505(b)(2) NDA for Citalopram Hydrobromide (HBr) orally disintegrating tablets (ODT) of 10 mg, 20 mg, and 40 mg strengths to seek approval for the treatment of depression.

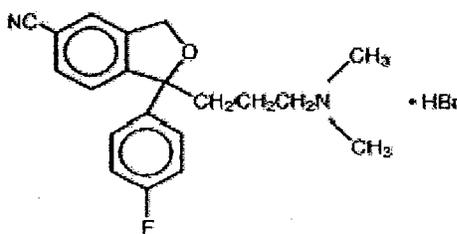
One supportive pilot study and 4 definitive biostudies were included in the original submission dated 4/14/2004. The Sponsor was seeking a biowaiver for the 20 mg strength with supporting *in-vitro* dissolution profiles, but on December 14, 2004, the Sponsor submitted additional *in-vivo* dosage strength BE study for the 20 mg ODT in response to OCPB's request. No clinical trials were conducted on this ODT dosage form. There was no related IND or prior Agency communication for PK Studies in the current submission.

Three tablet strengths (10, 20, and 40 mg) were developed to match the commercially available Celexa™ film-coated tablets (Forest Laboratories, Inc.) containing the same active moiety. Celexa™ is currently approved for the indication for the treatment of depression. According to the Orange Book, the Celexa™ 20 mg and 40 mg tablets were approved on July 17, 1998 and the Celexa™ 10 mg tablet was approved on April 27, 2000 under NDA 20-822.

**2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

TRADENAME™ (Citalopram HBr), a racemic bicyclic phthalane derivative, is an orally administered selective serotonin reuptake inhibitor (SSRI) and has a distinct chemical structure from other available antidepressant agents. Chemical structure of citalopram is shown in Figure 1.

Figure 1. Chemical structure of citalopram HBr (C<sub>20</sub>H<sub>22</sub>BrFN<sub>2</sub>O with a molecular weight of 405.35)



Citalopram HBr is sparingly soluble in water and soluble in ethanol.

TRADENAME (citalopram HBr) is formulated as orally disintegrating tablets, with appearance described as follows:

- 10 mg round orange speckled tablets with a dimple on both sides
- 20 mg round white speckled tablets with a dimple on both sides
- 40 mg round green speckled tablets with a dimple on both sides

to produce 10 mg, 20 mg, and 40-mg tablets.

Compositions of the pivotal bioequivalence studies formulation and to-be-marketed formulation are the same (see Table 5 on Page 13 for composition).

#### **2.1.2. What are the proposed mechanism of action and therapeutic indication?**

The proposed indication of TRADENAME™ (citalopram HBr) ODT formulation is for the treatment of depression.

The mechanism of action as an antidepressant is presumed to be by potentiation of the serotonergic activity in the central nervous system as a result of its inhibition of serotonin (5-HT) reuptake in CNS. The ability of citalopram to inhibit the serotonin reuptake has been demonstrated in animal studies. The inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

#### **2.1.3. What are the proposed dosages and route of administration?**

The proposed dosing regimen is similar to the RLD Celexa™ with an initial dose 20 mg/day with an increase up to 40 mg/day in increments of 20 mg at intervals of no less than one week. Dosing regimen of 20 mg/day is proposed for elderly patients and patients with hepatic impairment.

Citalopram HBr ODT is intended to be administered orally by being placed on the tongue, and subsequently swallowed with or without water and absorbed in gastrointestinal tract. The proposed ODT formulation is expected to disintegrate within 30 seconds on the tongue. The Citalopram HBr ODT can be taken without regards to food.

### **2.2. General Clinical Pharmacology**

#### **2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

The clinical pharmacology program was designed to demonstrate (1) the bioequivalence between the highest strength (40 mg) of the proposed citalopram HBr ODT and the commercially available Celexa™ tablets of the same strengths, and (2) and the bioequivalence between the highest strength of 40 mg and the lower strengths of 10 mg and 20 mg ODT.

As shown in Table 1 below, a total of six Phase I studies were designed to support such application, which included one supportive pilot study and five definitive biostudies. No clinical efficacy trials were conducted for this NDA.

<b>Protocol Number (Study No.)</b>	<b>Report Title</b>	<b>Related IND or NDA Numbers</b>	<b>Submission Date</b>
26022 B00-508PK-PRKN11	A Pilot Three-Way Crossover, Single-Dose Open-Label, Fasting, Comparative Bioavailability Study of Citalopram 40 mg Flash Dose Tablets vs. Celexa™ 40 mg (Citalopram Hydrobromide) Tablets In Normal Healthy Non-Smoking Male Volunteers	None	This submission
2730 (B03-635PK-N11F1)	A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT Versus Celexa™ 40 mg Tablets In Normal Healthy Non-Smoking Male and Female Volunteers	None	This submission
2731 (B03-636PK-N11F1)	A Two-Way Crossover, Open-Label, Single-Dose, Food Effect Study of Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male and Female Subjects	None	This submission
2732 (B03-637PK-N11F1)	A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT Without and With Water In Normal Healthy Non-Smoking Male And Female Subjects	None	This submission
2750 (B03-638PK-N11F1)	A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalence Study of 4 x Citalopram Hydrobromide 10 mg ODT Versus 1 x Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male And Female Subjects	None	This submission

2914 (B04-688PK-N11F1)	A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalence Study of Citalopram HBr Orally Disintegrating Tablets (1 x 20 mg Versus 2 x 10 mg) in Normal Healthy Non-Smoking Male And Female Subjects	None	This submission
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The pilot study using the highest 40 mg strength of the prototype formulation was conducted to characterize the pharmacokinetics and compare the bioavailability, given with or without food, with RLD Celexa™ of the same strength administered under fasting condition.

The proposed to-be-marketed formulation was used in definitive biostudies. Two pivotal bioequivalence studies were conducted to first demonstrate the bioequivalence of the ODT of the highest 40 mg strength relative to the reference list product, and then to demonstrate the bioequivalence when the proposed 40 mg ODT formulation was administered with or without water.

A food effect study was conducted for the highest 40 mg strength ODT formulation.

Two dosage strength equivalence studies were conducted to assess the dosage form proportionality between the lowest strength 10 mg ODT and the highest strength 40 mg ODT, and between 10 mg ODT and 20 mg ODT.

**2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?**

Yes, citalopram and both of its active metabolites, demethylcitalopram and didemethylcitalopram, were appropriately identified and measured.

**2.2.3. Are there major findings in exposure-response relationships?**

Exposure-Response Relationships were not evaluated. Dosing recommendation for Citalopram HBr ODT is based on the comparison of exposure measurement between the proposed ODT formulation and the reference drug product.

**2.2.4. Does this drug prolong the QT or QTc interval?**

Among the safety assessments, the 12-lead ECG monitoring was carried out in all the definitive studies prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. It was concluded by the Sponsor that the proposed citalopram HBr ODT of different strengths did not produce clinically significant ECG abnormality.

Comment: The ECG assessments were conducted at 24 hours post-dose, instead of at the  $T_{max}$  range (~5 hours post-dose); therefore the results were not conclusive. According to the reference label, there were no observed differences in QT or other ECG intervals after oral administration of Celexa™ tablet.

### **2.2.5. What are the pharmacokinetic characteristics of the drug and its major metabolite?**

In the present application, the reference is made to the information on the basic pharmacokinetics and metabolism of citalopram available in the literature and in the approved labeling for Celexa™.

According to the reference label, pharmacokinetics of citalopram following the single- and multiple-dose Celexa™ are linear and dose-proportional within the dose range of 10-60 mg/day, with a mean terminal  $T_{1/2}$  of about 35 hours. Absolute bioavailability of citalopram is about 80%. Peak time ( $T_{max}$ ) occurs at 4 hours post-dose. Volume of distribution of citalopram is about 12 L/kg and plasma protein binding of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram, is about 80%. The extent of accumulation of citalopram at steady state is 2.5 times compared to single dose. Renal clearance accounts for approximately 20% of the systemic clearance (330 mL/min). Citalopram is mainly metabolized in liver to demethylcitalopram, didemethylcitalopram, citalopram-N-oxide, and a deaminated propionic acid derivative. CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram and CYP2D6 is mainly responsible for the conversion of demethylcitalopram to didemethylcitalopram. The parent moiety citalopram is the major circulating compound in plasma and has been shown *in vitro* to be least 8 times more potent than both demethylcitalopram and didemethylcitalopram. Food does not affect the citalopram absorption.

Following a single oral dose of citalopram HBr ODT to healthy subjects,  $T_{max}$  of citalopram, demethylcitalopram, and didemethylcitalopram occurred at approximately 5, 28, and 79 hours, respectively. The plasma concentration of citalopram followed a biexponential decline from the peak with  $T_{1/2}$  values of roughly 2 and 41 hours as reported by the Sponsor. The  $T_{1/2}$  obtained from the studies for citalopram, demethylcitalopram, and didemethylcitalopram were approximately 50, 72, and 109 hours, respectively. The  $C_{max}$  for demethylcitalopram and didemethylcitalopram were approximately 13% and 2%, respectively, of those for citalopram. The corresponding AUC for demethylcitalopram and didemethylcitalopram were approximately 33% and 11%, respectively, of those for citalopram. Food and water did not affect the citalopram absorption. Overall, the pharmacokinetic characteristics of citalopram are similar between ODT formulation and the Celexa™ tablet.

### **2.3. Intrinsic Factors**

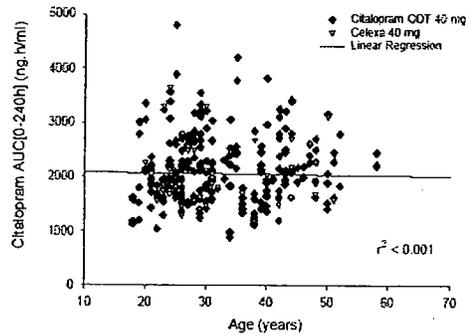
The influence of intrinsic factors on the PK of citalopram HBr ODT were evaluated based on the data obtained in 1 pilot study and 4 definitive pharmacokinetic studies in the

original submission. Data from Study 2914 are consistent with these results. No pharmacokinetic studies were conducted in special populations. Effect of smoking could not be evaluated in these studies.

### 2.3.1. What is the effect of Age?

As shown in the Figure below, the regression analysis indicated that age has no effect on PK of citalopram, metabolites, and the parent-to-metabolite ratios, which is in agreement with the approved labeling of Celexa™.

Figure 2. Scatter plot for citalopram exposure by age for citalopram HBr ODT and Celexa™



### 2.3.2. What is the effect of Gender?

Gender effects were evaluated for  $AUC_{0-t}$ ,  $C_{max}$  and  $T_{1/2}$  values for citalopram and its mono- and di-demethyl metabolites and for the corresponding metabolite/drug ratios. As shown in Table 2 and Figure 3, no significant differences in PK profiles were observed with respect to the citalopram. For demethylcitalopram and didemethylcitalopram,  $AUC_{0-t}$  and  $C_{max}$  were 17~25% and 54%, respectively, higher in females. The Sponsor attributed this observation to the smaller volume of distribution in females and concluded this is likely to be clinically insignificant.

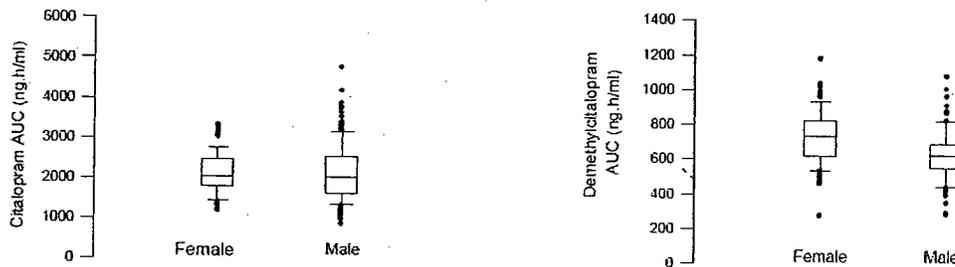
Table 2. Comparison of pharmacokinetic parameters in males and females for citalopram, demethylcitalopram, and didemethylcitalopram

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Drug or Metabolite/ Pharmacokinetic Parameter	C <sub>max</sub> (ng/mL)		AUC <sub>0-∞</sub> (ng·h/mL)		T <sub>1/2</sub> (hours)	
	Male	Female	Male	Female	Male	Female
<b>Citalopram</b>						
Mean	44.9	47.1	2140.3	2113.1	49.6	50.8
SD	9.3	9.2	697.6	507.6	13.8	11.6
Median	44.5	45.4	2045.3	2061.2	48.3	49.0
Min	22.9	24.3	877.9	1187.5	21.7	25.6
Max	89.9	76.7	4796.3	3344.1	97.2	81.2
N	180	102	180	102	178	99
F/M Ratio of Means		1.05		0.99 <sup>a</sup>		1.03
<b>Demethylcitalopram</b>						
Mean	5.2	6.5	624.1	732.3	71.2	72.0
SD	1.4	1.6	141.8	151.7	24.3	49.3
Median	5.3	6.4	623.4	734.7	66.8	64.6
Min	1.6	1.9	284.2	274.5	33.6	33.7
Max	9.4	10.4	1079.5	1180.4	178.7	478.3
N	126	102	126	102	116	95
F/M Ratio of Means		1.25		1.17		1.01
<b>Didemethylcitalopram</b>						
Mean	0.8	1.2	127.5	196.7	121.1	99.8
SD	0.6	0.9	86.9	119.4	135.1	45.9
Median	0.8	1.0	126.4	158.6	92.3	91.9
Min	0.0	0.1	0.0	11.9	39.5	46.6
Max	2.9	3.4	458.7	477.7	927.7	351.1
N	122	102	122	102	79	67
F/M Ratio of Means		1.54		1.54		1.03 <sup>a</sup>

<sup>a</sup> Three outlier values were not included.  
F/M = Female/Male.

Figure 3. Box plots for citalopram exposures in male and female subjects after a single oral dose of citalopram HBr ODT



### 2.3.3. What is the effect of Race?

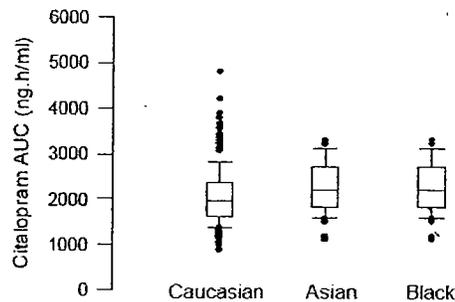
Subjects participated in all the biostudies consisted of 3 racial groups that were biased toward Caucasians. No definitive conclusions can be drawn due to the biased and limited numbers of the subjects, however, highest citalopram and lower metabolites exposures were observed in Asians. It was concluded that the observed differences are unlikely to be clinically important. The pharmacokinetic findings are summarized in Table 3 and Figure 4:

Table 3. Comparison of pharmacokinetic parameters in different races for citalopram, demethylcitalopram, and didemethylcitalopram

Statistic	C <sub>max</sub> (ng/ml)			AUC <sub>0-∞</sub> (ng·h/ml)			T <sub>1/2</sub> (hours)		
	Caucasian	Asian	Black	Caucasian	Asian	Black	Caucasian	Asian	Black
<b>Citalopram</b>									
Mean	44.7	47.7	49.7	2053.6	2569.3	2297.6	47.9	47.5	62.6
SD	9.2	6.4	10.0	623.0	665.9	575.3	12.5	6.5	11.3
Median	43.9	46.7	48.1	1960.9	2529.2	2222.8	46.9	47.0	60.3
Min	22.9	36.9	32.8	877.9	1428.0	1125.9	21.7	37.5	47.3
Max	89.9	61.6	76.0	4796.3	3811.9	3298.1	97.2	58.3	89.9
N	220	20	42	220	20	42	217	20	40
Ratio <sup>a</sup>		1.07	1.11		1.25	1.12		0.99	1.30
<b>Demethylcitalopram</b>									
Mean	6.0	4.7	5.4	689.8	553.7	657.8	71.1	64.8	76.3
SD	1.6	1.4	1.6	152.1	114.3	165.0	43.1	16.0	15.7
Median	5.8	4.6	5.4	677.9	570.5	529.2	62.0	61.1	76.4
Min	1.8	2.7	1.6	274.5	292.9	294.2	33.6	42.2	33.7
Max	10.4	7.7	8.7	1180.4	867.3	1033.6	478.3	97.1	124.2
N	166	20	42	166	20	42	152	20	39
Ratio <sup>a</sup>		0.79	0.91		0.81	0.95		0.91	1.08
<b>Didemethylcitalopram</b>									
Mean	1.1	0.6	0.7	178.9	96.9	111.9	103.9	115.6	141.2
SD	0.8	0.5	0.5	109.6	72.3	92.4	100.1	95.4	113.8
Median	1.0	0.5	0.5	161.8	95.0	86.2	90.4	81.9	111.8
Min	0.0	0.1	0.1	0.0	9.4	1.5	39.5	52.6	69.2
Max	3.4	1.3	2.6	477.7	245.4	401.8	927.7	455.6	656.2
N	162	20	42	162	20	42	167	17	28
Ratio <sup>a</sup>		0.54	0.56		0.54	0.63		1.11	1.36

<sup>a</sup> Ratio of mean values for other races compared with Caucasian.

Figure 4. Box plots for citalopram exposures in different racial groups after a single oral dose of citalopram HBr ODT



#### 2.3.4. What is the effect of Body Weight?

No perceivable effects of body weight were concluded with the analysis on pharmacokinetic parameters.

#### 2.4. Extrinsic Factors

No studies for effects of extrinsic factors, such as drug-drug interactions, were conducted.

#### 2.5. General Biopharmaceutics

The Biopharmaceutic program was designed to address only the performance of the proposed ODT formulation comparing to the approved reference product.

##### 2.5.1. What is the proposed formulation of the drug product?

The quantitative composition of the TMMS and the ODT formulation are shown in Tables 4 and 5, respectively.

Table 4. Composition of [redacted] for Citalopram 10, 20 and 40 mg ODT

Component	Function	% w/w
Citalopram hydrobromide	Active ingredient	
Glyceryl Distearate		
Stearoyl Macrogolglyceride		
Polyacrylate dispersion 30%		
Hypromellose 2910		
Talc		
<hr/>		
Total		
<sup>a</sup> Removed during processing.		

Table 5. Composition of the TBM Citalopram 10, 20 and 40 mg ODT

Component	Function	Excipient Weight per 10 mg ODT (mg)	Excipient Weight per 20 mg ODT (mg)	Excipient Weight per 40 mg ODT (mg)
Mannitol				
Microcrystalline Cellulose				
Low Substituted Hydroxypropyl Cellulose				
Crospovidone				
Sodium Stearyl Fumarate				
Silicon Dioxide				
Acesulfame Potassium				
Monoammonium Glycyrrhizinate				
Citric Acid				
Tangerine Orange Flavor				
FD&C Yellow #6				
Lemon-Lime Flavor				
Green Blend				
Tablet weight milligrams				

The Sponsor stated that the TBM 10, 20, and 40 mg ODT of the new formulation are

compositionally and quantitatively proportional, with the only difference being the amount of \_\_\_\_\_ in each of the 3 strengths.

Comment: According to the Guidance for Industry on SUPAC-IR: “Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation” (<http://www.fda.gov/cder/guidance/cmc5.pdf>), the total changes (% w/w) of excipients in lower strengths (18% for 10 mg; 26% for 20 mg), compared to the highest 40 mg strength, of finished products have exceeded 10% (i.e., Level 3 changes). For Level 3 changes, a full *in vivo* BE study and the multiple-point dissolution profile with adequate sampling points should be performed to document the bioequivalence between different dosage strengths.

**2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?**

The proposed to-be-marketed formulation and the pivotal clinical (biostudy) formulation are exactly the same, and hence no study for relative bioavailability is necessary.

**2.5.3. Is the to-be-marketed ODT formulation bioequivalent to the RLD formulation of same strength?**

To establish bioequivalence between the TBM citalopram ODT and the reference Celexa™ tablets of same strength, two studies were conducted by the Sponsor to evaluate the relative bioavailability of the highest strength 40 mg citalopram HBr ODT:

- Study 26022 was a 3-way crossover pilot study in 18 healthy non-smoking male subjects. A 40-mg citalopram HBr ODT from a pilot batch was administered under fasting conditions or with high-fat meal.
- Study 2730 was a 2-way crossover study design that compared a 40 mg citalopram HBr ODT from a commercial-scale batch with a 40 mg Celexa™ tablets in 36 healthy non-smoking male and female subjects under fasting conditions. Pharmacokinetic parameters and statistics are summarized in Tables 6 and 7.

Table 6. Pharmacokinetic parameters for citalopram and its mono- and di-demethyl metabolites (Study 2730)

Drug or Metabolite/ Pharmacokinetic Parameter	Citalopram HBr ODT 40 mg (n=27) (mean ± SD)	Celexa™ Tablets 40 mg (n=27) (mean ± SD)
<b>Citalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	2188.88 ± 614.27	2188.31 ± 630.21
AUC <sub>0-∞</sub> (ng·h/mL)	2297.89 ± 679.94 <sup>a</sup>	2310.07 ± 682.00 <sup>b</sup>
C <sub>max</sub> (ng/mL)	46.67 ± 8.77	48.53 ± 13.91
T <sub>max</sub> (h)	5.38 ± 2.24 [5.03] <sup>f</sup>	5.21 ± 2.41 [6.00] <sup>f</sup>
T <sub>1/2</sub> (h)	51.70 ± 13.41 <sup>a</sup>	52.64 ± 9.94 <sup>b</sup>
<b>Demethylcitalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	723.41 ± 170.80	722.94 ± 157.81
AUC <sub>0-∞</sub> (ng·h/mL)	853.34 ± 358.58 <sup>d</sup>	827.97 ± 224.89 <sup>a</sup>
C <sub>max</sub> (ng/mL)	6.16 ± 1.71	6.04 ± 1.60
T <sub>max</sub> (h)	31.80 ± 15.30 [38.00] <sup>f</sup>	29.12 ± 12.25 [36.00] <sup>f</sup>
T <sub>1/2</sub> (h)	88.29 ± 85.22 <sup>d</sup>	71.99 ± 20.42 <sup>a</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.3883 ± 0.1031 <sup>e</sup>	0.3995 ± 0.1384 <sup>a</sup>
<b>Didemethylcitalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	154.01 ± 105.23	158.65 ± 108.70
AUC <sub>0-∞</sub> (ng·h/mL)	275.36 ± 139.64 <sup>f</sup>	222.88 ± 149.64 <sup>e</sup>
C <sub>max</sub> (ng/mL)	0.98 ± 0.84	1.00 ± 0.78
T <sub>max</sub> (h)	78.26 ± 29.86 [72.67] <sup>f</sup>	85.87 ± 35.53 [86.00] <sup>f</sup>
T <sub>1/2</sub> (h)	130.93 ± 134.45 <sup>f</sup>	99.49 ± 34.11 <sup>e</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.1537 ± 0.0932 <sup>f</sup>	0.1212 ± 0.0674 <sup>e</sup>

Table 7. Relative bioavailability analysis of citalopram and its mono- and di-demethyl metabolites after single oral dose of 40 mg citalopram HBr ODT and 40 mg Celexa™ Tablets (Study 2731)

Drug or Metabolite/ Pharmacokinetic Parameter	90% Confidence Interval	Ratio of Means
<b>Citalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	97.02% - 102.64%	99.79%
AUC <sub>0-∞</sub> (ng·h/mL)	85.86% - 101.08%	98.50%
C <sub>max</sub> (ng/mL)	91.41% - 99.53%	95.38%
<b>Demethylcitalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	98.47% - 103.21%	99.78%
AUC <sub>0-∞</sub> (ng·h/mL)	98.09% - 111.95%	104.79%
C <sub>max</sub> (ng/mL)	97.31% - 106.88%	101.69%
<b>Didemethylcitalopram</b>		
AUC <sub>0-∞</sub> (ng·h/mL)	88.00% - 99.80%	93.71%
AUC <sub>0-∞</sub> (ng·h/mL)	78.49% - 117.99%	95.00%
C <sub>max</sub> (ng/mL)	85.78% - 99.27%	92.28%

Bioavailability, as reflected by rate and extent of absorption, of a single oral dose of 40 mg citalopram ODT (test) was similar to the Celexa™ tablet (reference) of same strength. Statistical analysis of exposures measurements, AUC and C<sub>max</sub>, revealed that the 40 mg citalopram ODT is bioequivalent to 40 mg Celexa™ tablet (based on acceptance criteria for BE, i.e., 80-125% CI based on parent moiety) under single-dose fasting conditions.

Similar pharmacokinetic profiles were observed for the metabolites, demethylcitalopram and didemethylcitalopram, following oral administration of 40 mg citalopram ODT or 40 mg Celexa™ formulation.

For didemethylcitalopram the lower limit of the 90% CI of the geometric mean ratio for AUC<sub>0-∞</sub> fell outside the bioequivalence boundary of 80-125%. Didemethylcitalopram, though an active moiety, is a minor metabolite of citalopram. Therefore, this small difference with respect to didemethylcitalopram is not considered critical. BE decision is based only on parent citalopram.

#### 2.5.4. Does food affect the bioavailability of citalopram ODT formulation?

Two studies were conducted by the Sponsor to evaluate the effects of high-fat food on bioavailability of citalopram HBr ODT:

- Study 26022 was an open-label, fasting, comparative bioavailability pilot study of prototype Citalopram 40 mg tablets vs. reference Celexa™ 40 mg tablets in 18 normal healthy non-smoking male volunteers.
- Study 2731 was a randomized, two-way crossover, open-label, single-dose, fed and fasting design in 36 normal, healthy, non-smoking male and female subjects. TBM Citalopram HBr 40 mg ODT was administered either under fasting condition or with high-fat food. Pharmacokinetic parameters and statistics are summarized in Tables 8 and 9.

Table 8. Pharmacokinetic parameters for citalopram and its mono- and di-demethyl metabolites (Study 2731)

Drug or Metabolite/ Pharmacokinetic Parameter	Citalopram HBr ODT 40 mg Immediately After Food (n=31)	Citalopram HBr ODT 40 mg Fasting Condition (n=31)
<b>Citalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	2233.49 ± 785.58	2270.78 ± 755.49
AUC <sub>0-∞</sub> (ng·h/mL)	2352.97 ± 888.84	2364.81 ± 841.01
C <sub>max</sub> (ng/mL)	45.07 ± 19.62	45.51 ± 10.15
T <sub>max</sub> (h)	6.03 ± 2.28 [5.00] <sup>a</sup>	4.90 ± 1.90 [5.00] <sup>a</sup>
T <sub>1/2</sub> (h)	55.81 ± 15.00	54.20 ± 13.04
<b>Demethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	601.17 ± 138.88	638.03 ± 132.85
AUC <sub>0-∞</sub> (ng·h/mL)	688.88 ± 185.07	729.12 ± 173.65 <sup>c</sup>
C <sub>max</sub> (ng/mL)	5.03 ± 1.15	5.44 ± 1.38
T <sub>max</sub> (h)	27.87 ± 13.75 [36.00] <sup>a</sup>	25.41 ± 15.17 [18.00] <sup>a</sup>
T <sub>1/2</sub> (h)	73.59 ± 21.78 <sup>b</sup>	71.90 ± 21.89 <sup>c</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.3507 ± 0.1248 <sup>b</sup>	0.3605 ± 0.1228 <sup>c</sup>
<b>Didemethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	141.43 ± 74.40	158.72 ± 86.18
AUC <sub>0-∞</sub> (ng·h/mL)	207.14 ± 89.89 <sup>d</sup>	235.76 ± 103.73 <sup>e</sup>
C <sub>max</sub> (ng/mL)	0.85 ± 0.48	0.95 ± 0.55
T <sub>max</sub> (h)	78.34 ± 35.51 [96.00] <sup>a</sup>	78.88 ± 32.71 [72.00] <sup>a</sup>
T <sub>1/2</sub> (h)	136.77 ± 182.72 <sup>d</sup>	123.20 ± 115.40 <sup>e</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.1248 ± 0.0781 <sup>d</sup>	0.1353 ± 0.0875 <sup>e</sup>

Table 9. Relative bioavailability analysis of citalopram and its mono- and di-demethyl metabolites after single oral dose of 40 mg citalopram HBr ODT (Study 2731)

Drug or Metabolite	90% Confidence Interval	Ratio of Means
<b>Citalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	93.30% - 102.09%	97.60%
AUC <sub>0-∞</sub> (ng·h/mL)	93.79% - 102.29%	97.94%
C <sub>max</sub> (ng/mL)	91.58% - 105.87%	96.47%
<b>Demethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	89.40% - 97.92%	93.57%
AUC <sub>0-∞</sub> (ng·h/mL)	89.76% - 98.89%	94.22%
C <sub>max</sub> (ng/mL)	86.63% - 99.71%	92.94%
<b>Didemethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	84.08% - 103.75%	93.39%
AUC <sub>0-∞</sub> (ng·h/mL)	80.33% - 100.91%	90.03%
C <sub>max</sub> (ng/mL)	83.00% - 101.35%	91.72%

Similar pharmacokinetic profiles of citalopram were observed following oral administration of Citalopram HBr 40 mg ODT after high-fat breakfast or without food. High-fat food had no effect on the rate and extent of absorption of citalopram. There was a slight increase in mean T<sub>max</sub> by 1 hour in the presence of food; however, the slight delay in time to reach C<sub>max</sub> is not likely to have clinical significance. Similar results were observed with demethylcitalopram and didemethylcitalopram.

#### 2.5.5. Was the dosage form equivalence established for the to-be-marketed formulations?

The Sponsor has conducted two definitive studies to demonstrate the dosage strength equivalency for the TBM citalopram HBr ODT formulation.

Study 2750 was a 2-way crossover design to evaluate dosage strength equivalency between 4 x 10-mg and 1 x 40-mg citalopram HBr ODT from commercial-scale batches in 36 healthy non-smoking male and female subjects under fasting conditions. Pharmacokinetic parameter and statistics are summarized in Tables 10 and 11.

Table 10. Pharmacokinetic parameters for citalopram and its mono- and di-demethyl metabolites (Study 2750)

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Drug or Metabolite/ Pharmacokinetic Parameter	Citalopram HBr ODT 4 x 10 mg (n=26)	Citalopram HBr ODT 1 x 40 mg (n=28)
<b>Citalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	2127.73 ± 543.86	1992.39 ± 472.16
AUC <sub>0-∞</sub> (ng·h/mL)	2205.91 ± 581.06	2082.57 ± 515.85
C <sub>max</sub> (ng/mL)	44.52 ± 7.70	41.93 ± 5.43
T <sub>max</sub> (h)	4.88 ± 1.78 [5.00] <sup>a</sup>	5.25 ± 1.60 [5.00] <sup>a</sup>
T <sub>1/2</sub> (h)	49.04 ± 12.64	50.00 ± 11.95
<b>Demethylcitalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	659.02 ± 136.81	614.49 ± 107.79
AUC <sub>0-∞</sub> (ng·h/mL)	735.58 ± 194.08 <sup>b</sup>	685.27 ± 153.40 <sup>b</sup>
C <sub>max</sub> (ng/mL)	5.85 ± 1.52	5.50 ± 1.48
T <sub>max</sub> (h)	23.84 ± 15.13 [16.00] <sup>a</sup>	22.04 ± 12.06 [16.00] <sup>a,c</sup>
T <sub>1/2</sub> (h)	60.04 ± 23.22 <sup>b</sup>	67.49 ± 29.46 <sup>b</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.3678 ± 0.1001 <sup>b</sup>	0.3621 ± 0.0925 <sup>b</sup>
<b>Didemethylcitalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	147.10 ± 113.39	142.31 ± 116.00
AUC <sub>0-∞</sub> (ng·h/mL)	224.76 ± 125.43 <sup>c</sup>	218.47 ± 140.72 <sup>c</sup>
C <sub>max</sub> (ng/mL)	0.99 ± 0.91	0.93 ± 0.90
T <sub>max</sub> (h)	81.16 ± 32.91 [72.00] <sup>a</sup>	66.28 ± 20.49 [72.00] <sup>a,d</sup>
T <sub>1/2</sub> (h)	108.87 ± 86.90 <sup>c</sup>	90.87 ± 34.04 <sup>c</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.1318 ± 0.0849 <sup>c</sup>	0.1356 ± 0.0913 <sup>c</sup>

<sup>a</sup> Median value.  
<sup>b</sup> n=27.  
<sup>c</sup> n=20.  
<sup>d</sup> n=25.

Table 11. Relative bioavailability analysis of citalopram and its mono- and di-demethyl metabolites after single dosing with 4 x 10-mg and 1 x 40 mg citalopram HBr ODT (Study 2750)

Drug or Metabolite/ Pharmacokinetic Parameter	90% Confidence Interval	Ratio of Means
<b>Citalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	102.43% - 110.70%	105.48%
AUC <sub>0-∞</sub> (ng·h/mL)	102.58% - 110.88%	106.65%
C <sub>max</sub> (ng/mL)	100.53% - 110.88%	105.58%
<b>Demethylcitalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	102.20% - 111.19%	106.60%
AUC <sub>0-∞</sub> (ng·h/mL)	101.54% - 111.67%	105.49%
C <sub>max</sub> (ng/mL)	101.99% - 111.24%	105.51%
<b>Didemethylcitalopram</b>		
AUC <sub>0-1</sub> (ng·h/mL)	99.47% - 121.28%	109.84%
AUC <sub>0-∞</sub> (ng·h/mL)	94.01% - 118.54%	105.56%
C <sub>max</sub> (ng/mL)	110.75% - 119.67%	109.80%

Based on the results of parent citalopram moiety, it is concluded that the dosage strength equivalency is established between two strengths (4 x 10 mg vs. 1 x 40 mg) of citalopram HBr ODT under single-dose fasting conditions. Similar results were observed with demethylcitalopram and didemethylcitalopram.

Study 2914, submitted on December 14, 2004, was a similar study design to evaluate dosage strength equivalency between 2 x 10 mg ODT and 1 x 20 mg ODT in 36 healthy non-smoking male and female subjects under fasting conditions. Pharmacokinetic parameter and statistics are summarized in Table 12.

Table 12. Relative bioavailability analysis of citalopram HBr 1 x 20 mg ODT formulation and 2 x 10 mg ODT formulation for citalopram, demethylcitalopram, and didemethylcitalopram (Study 2914)

Parameter	Citalopram			
	90% CI		Ratio of Means	
AUC <sub>0-t</sub>	94.73% - 101.16%		97.89%	
AUC <sub>0-inf</sub>	94.75% - 101.06%		97.85%	
C <sub>max</sub>	96.81% - 102.46%		99.59%	
	Demethylcitalopram		Didemethylcitalopram	
	90% CI	Ratio of Means	90% CI	Ratio of Means
AUC <sub>0-t</sub>	95.65% - 102.47%	99.00%	97.64% - 106.87%	102.15%
AUC <sub>0-inf</sub>	96.80% - 103.93%	100.30%	94.03% - 106.76%	100.19%
C <sub>max</sub>	94.64% - 102.68%	98.58%	99.93% - 111.90%	105.75%

Based on the results of parent citalopram moiety, the dosage form equivalency is established between two strengths (1 x 20 mg vs. 2 x 10 mg) of Citalopram HBr ODT under single-dose fasting conditions. Similar results were observed with demethylcitalopram and didemethylcitalopram.

#### 2.5.6. What is the effect of administration with water?

Study 2732 was conducted to evaluate the effect of administration with or without water when citalopram HBr 40 mg ODT formulation was given under fasting conditions.

- Treatment A: 40 mg ODT; no water was ingested after the ODT was completely dissolved on the tongue and swallowed
- Treatment B: 40 mg ODT; 240 mL of water was ingested after the ODT was completely dissolved on the tongue

Pharmacokinetic parameters and statistics are summarized in Tables 13 and 14.

Table 13. Pharmacokinetic parameters for citalopram and its mono- and di-demethyl metabolites (Study 2732)

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Drug or Metabolite/ Pharmacokinetic Parameter	Fasting Administration Without Water (n=28)	Fasting Administration With Water (n=28)
<b>Citalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	2301.71 ± 780.35	2105.83 ± 842.81
AUC <sub>0-∞</sub> (ng·h/mL)	2444.05 ± 842.76 <sup>a</sup>	2352.40 ± 776.15 <sup>b</sup>
C <sub>max</sub> (ng/mL)	47.70 ± 7.30	48.28 ± 9.25
T <sub>max</sub> (h)	5.11 ± 1.45 [5.00] <sup>b</sup>	4.74 ± 1.73 [5.00] <sup>b</sup>
T <sub>1/2</sub> (h)	50.14 ± 11.84 <sup>c</sup>	53.33 ± 12.00 <sup>c</sup>
<b>Demethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	728.13 ± 179.59	707.85 ± 185.90
AUC <sub>0-∞</sub> (ng·h/mL)	845.32 ± 359.52 <sup>c</sup>	814.77 ± 105.05 <sup>d</sup>
C <sub>max</sub> (ng/mL)	8.25 ± 1.88	8.08 ± 1.88
T <sub>max</sub> (h)	34.42 ± 31.82 [24.05] <sup>b</sup>	29.36 ± 21.76 [24.00] <sup>b</sup>
T <sub>1/2</sub> (h)	69.85 ± 38.58 <sup>e</sup>	64.07 ± 18.73 <sup>e</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.3631 ± 0.1554 <sup>c</sup>	0.3938 ± 0.0957 <sup>d</sup>
<b>Didemethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	194.32 ± 134.58 <sup>e</sup>	184.77 ± 128.26 <sup>e</sup>
AUC <sub>0-∞</sub> (ng·h/mL)	280.62 ± 168.48 <sup>f</sup>	237.44 ± 156.17 <sup>g</sup>
C <sub>max</sub> (ng/mL)	1.24 ± 0.60 <sup>e</sup>	1.20 ± 0.87 <sup>e</sup>
T <sub>max</sub> (h)	82.76 ± 30.97 [90.00] <sup>b</sup>	79.08 ± 43.93 [72.00] <sup>b,e</sup>
T <sub>1/2</sub> (h)	103.34 ± 70.25 <sup>f</sup>	96.05 ± 33.04 <sup>g</sup>
M/P Ratio (AUC <sub>0-∞</sub> )	0.1536 ± 0.1148 <sup>f</sup>	0.1347 ± 0.1001 <sup>g</sup>

<sup>a</sup> n=27.  
<sup>b</sup> Median value.  
<sup>c</sup> n=25.  
<sup>d</sup> n=24.  
<sup>e</sup> n=26.  
<sup>f</sup> n=20.  
<sup>g</sup> n=17.

Table 14. Relative bioavailability analysis of citalopram and its mono- and di-Demethyl metabolites after single oral dose of citalopram HBr 40 mg ODT (Study 2732)

Drug or Metabolite/ Pharmacokinetic Parameter	90% Confidence Interval	Ratio of Means
<b>Citalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	97.53% - 110.53%	103.83%
AUC <sub>0-∞</sub> (ng·h/mL)	97.39% - 110.56%	103.76%
C <sub>max</sub> (ng/mL)	93.20% - 108.73%	99.74%
<b>Demethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	95.83% - 111.38%	103.32%
AUC <sub>0-∞</sub> (ng·h/mL)	93.94% - 109.21%	101.29%
C <sub>max</sub> (ng/mL)	96.16% - 112.34%	103.93%
<b>Didemethylcitalopram</b>		
AUC <sub>0-4</sub> (ng·h/mL)	94.03% - 121.16%	106.73%
AUC <sub>0-∞</sub> (ng·h/mL)	85.05% - 116.43%	99.51%
C <sub>max</sub> (ng/mL)	92.01% - 120.55%	105.32%

As shown in the above results, ingesting 240 mL water immediately after the ODT disintegrated on the tongue appeared not to affect the rate or extent of citalopram absorption. Therefore, it is concluded that water has no effect on absorption of citalopram following oral administration of the citalopram HBr 40 mg ODT.

Comment:

Study 2732 for the effect of administration with water is not very valuable to evaluate the effect of swallowing vs. allowing to dissolve/disintegrate, since in both treatment groups

the 40 mg citalopram ODT was allowed to disintegrate/dissolve in oral cavity prior to swallowing. It would be a more optimal study design to detect the effect of swallowing water by instructing the subjects in Treatment group B (with water) to swallow the tablet directly with 240 mL water without intentionally letting the ODT to disintegrate/dissolve on the tongue and sucking on the tablet prior to the swallowing. However, through Studies 2732 and 2730, since the ODT has been shown to be BE to reference tablet (when let to dissolve without water), label claim with and without water can be allowed.

#### 2.5.7. Is the dissolution method appropriate for citalopram ODT formulation?

The Sponsor has proposed the following dissolution test method and specification, with justification, for citalopram ODT formulation:

Apparatus: USP apparatus 2 (Paddle)

Stirring Speed: 100 rpm

Dissolution Medium: pH 6.5 phosphate buffer

Volume of Medium: 900 mL for 40 mg ODT; 500 mL for 10 mg and 20 mg ODT

Temperature:  $37.0 \pm 0.5$  °C

Specification:  $Q =$  in minutes

(Complies with USP <711> Unit Sample Acceptance Criteria)

Dissolution Analytical Method:

Withdraw an aliquot of the dissolution medium at each sampling point and analyze by HPLC with UV detection. Calculate the percent citalopram HBr dissolved, applying a volume correction.

Submission dated April 14, October 11, November 13, and December 21, 2004, included results (biowaiver and release data) of *in vitro* dissolution studies for 10 mg (Lot#: 0307015), 20mg (Lot#: 0307018), and 40 mg ODT (Lot#: 0306011), used in definitive clinical studies.

The assessments for effects of dissolution media and the choice of paddle speed were evaluated, and the Sponsor has provided justifications for the selections. As shown in Figures 6-8, *In vitro* dissolution testing was first performed for all 3 strengths in Acetate Buffer, pH 6.5 Phosphate Buffer, Phosphate Buffer, and Deionized Water, at 100 rpm paddle speed. Samples were collected at 5, 10, 15, 30 and 60 minutes.

Figure 5. Dissolution profiles of Citalopram 40 mg ODT in various media

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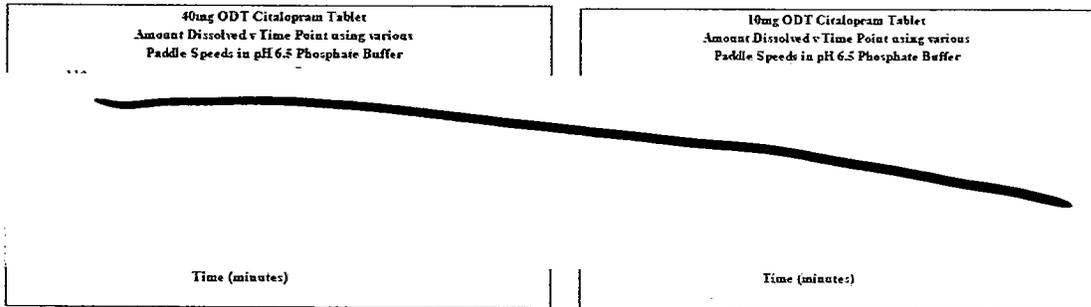
Draft Labeling

Deliberative Process

slower release of drug or dissolution profile compared to other media. The choice of dissolution medium was justified.

To justify the selection of paddle speed, the Sponsor conducted further studies with 10 mg and 40 mg ODT at 50 rpm, 75 rpm, and 100 rpm paddle speeds using pH 6.5 Phosphate Buffer. No study was conducted for 20 mg formulation. Dissolution profiles based on mean data are shown in Figure 9.

Figure 8. Dissolution profiles of Citalopram 40 mg and 10 mg ODT using various paddle speeds in pH 6.5 Phosphate Buffer



The dissolution profiles from 100 rpm and 75 rpm were essentially overlapping for the highest and the lowest strengths and were concluded being equivalent. The Sponsor has chosen the 100 rpm paddle speed for its robustness and to prevent the potential variation associated with the slower stirring rate.

Comment:

1. Based on the above dissolution profiles provided by the Sponsor under different conditions, the choice of pH 6.5 Phosphate Buffer as dissolution medium is acceptable.
2. According to the FDA Guidance, the mild agitation conditions commonly at 50-75 rpm paddle speeds should be maintained during dissolution testing to allow maximum discriminating ability. The paddle speed at 75 rpm seemed to allow the maximum discriminating ability for the lowest strength, 10 mg, and the highest strength, 40 mg. Therefore, the 75 rpm is preferred. However, since mean dissolution data at 30 minutes for both 40 mg and 10 mg were less than 50% when using pH 6.5 Phosphate Buffer and at 50 rpm, and both 75 rpm and 100 rpm were concluded to be equivalent, the 75 rpm paddle speed maybe appropriate for the dissolution testing.

A second set of dissolution studies were conducted for the pivotal batches, 10 mg (0307015), 20 mg (0307018), and 40 mg (0306011), manufactured at Biovail Dublin, Ireland. Additional release data were included in the submission dated December 14 for the 20 mg strength (Lot#: PR-04-064R) used in Study 2914 and manufactured at another proposed commercial site (Biovail Dorado, PR). Comparative dissolution data based on mean values are shown in the following Table:

Table 15. Comparative dissolution data using pH 6.5 Phosphate Buffer at 100 rpm

Strength	Lot Number	Time (Minutes)	Numbers of Tablets	% Label Claim		
				Mean	Minimum	Maximum
10 mg	0307015	5	12			
		30	12			
		60	12			
20 mg	0307018	5	12			
		30	12			
		60	12			
40 mg	0306011	5	12			
		30	12			
		60	12			
20 mg	PR-04-064R	5	12			
		30	12			
		60	12			

The above results show the essentially complete dissolution at 30 minutes for all the pivotal batches manufactured at Biovail Dublin, Ireland. On the other hand, only  $\frac{1}{2}$  was dissolved at 30 minutes for the 20 mg ODT (Lot#: PR-04-064R) manufactured at Biovail Dorado, PR.

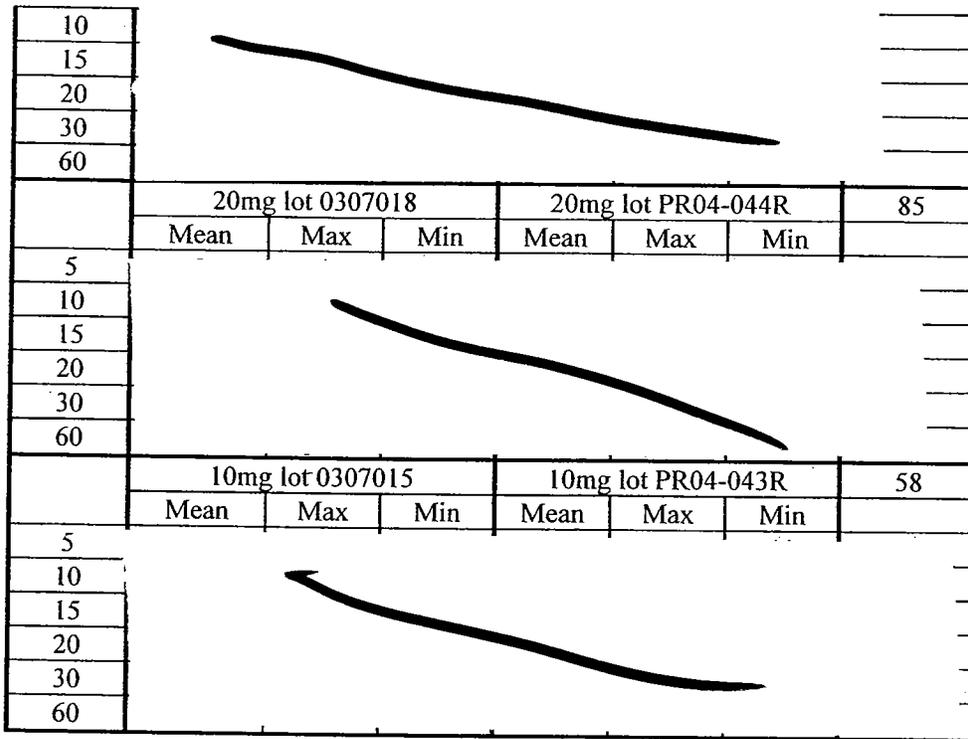
Comment:

- The *in vitro* dissolution data for all three pivotal strengths manufactured at Biovail Dublin, Ireland, indicated that more than  $\frac{1}{2}$  was dissolved at 30 minutes according to the proposed specifications. However only  $\frac{1}{2}$  was dissolved in 30 minutes for 20 mg biobatch (made in Dorado). Therefore, the dissolution specifications should be tightened to  $Q = \frac{1}{2}$  at 30 minutes.

Since there are 2 proposed manufacturing sites (PR and Ireland), a tabulated comparative dissolution data, including statistics, for all 3 strengths manufactured from both sites have been requested on December 30, 2004. On January 20, 2005, the Sponsor submitted the requested tabulated comparative dissolution profiles for all strengths from both manufacturing sites. Mean dissolution data and the f2 (similarity factor) values calculated by this reviewer are shown in the following Table:

Table 16. Comparative Dissolution Data and f2 values

Time (sec)	Dublin, Ireland			Dorado, PR			F2
	Mean	Max	Min	Mean	Max	Min	
5	40mg lot 0306011			40mg lot PR04-045R			61



Data n=6 for Dublin n=12 for Dorado

The f2 value for each strength shows the similarity in the dissolution profiles of the batches manufactured from both Dublin and Dorado manufacturing sites.

### 2.5.8. Is there *In vivo-In vitro* Correlation?

No *in vitro-in vivo* correlation studies have been conducted with citalopram HBr ODT. The Sponsor states that the *in vitro* disintegration of the ODT formulation occurred in less than 60 seconds and the mean *in vivo* disintegration time ranged from 16 seconds for the 10-mg tablet to 15.5 seconds for the 40-mg tablet.

### In Vivo Disintegration Time

The *in vivo* disintegration time for citalopram HBr ODT formulation was defined by the Sponsor as “The time interval between placing the tablet on the tongue to the onset of disintegration”, and was measured in two studies:

1. Study 2837 (B04-666-PK-N11F1): “Assessment of *in-vivo* disintegration time of 10 mg and 40 mg strengths of citalopram HBr orally disintegrating tablets in healthy males and females subjects”. Equal numbers of 20 subjects were given either 10-mg or 40-mg citalopram HBr ODT in this study.
2. Study 2914 (B04-688PK-N11F1) included 36 healthy male and female subjects.

Table 17. *In Vivo* Disintegration Time (Seconds) of Citalopram ODT (Study 2837)

10 mg ODT		40 mg ODT	
Subject Number	In vivo DT	Subject Number	In vivo DT
2			
3			
7			
8			
11			
12			
15			
19			
20			
22			
23			
24			
28			
27			
28			
31			
32			
33			
36			
37			
Mean	16		15.5
SD	9.78		5.92
Median	12.5		14.5
Minimum			
Maximum			

*In vivo* disintegration was rapid for the 2 tablet strengths, with most of the *in vivo* disintegration occurring in less than 30 seconds. Mean *in vivo* disintegration times for the 10-mg and 40-mg citalopram HBr ODT were 16 seconds and 15.5 seconds, respectively. The maximal observed disintegration times for 10 mg and 40 mg were 42 and 32 seconds, respectively.

Table 18. *In Vivo* Disintegration Time of Citalopram ODT (Study 2914)

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Subject Number	Randomization Sequence	In-Vivo Disintegration Time for Treatment A (seconds)	In-Vivo Disintegration Time for Treatment B (seconds)
001			
002			
003			
004			
005			
006			
007			
008			
009			
010			
011			
012			
013			
014			
015			
016			
017			
018			
019			
020			
021			
022			
023			
024			
025			
026			
027			
028			
029			
030			
031			
032			
033			
034			
035			
036			
Mean Disintegration Time		13	14
Range: Minimum			
Maximum			

A: Citalopram HBr 1 x 20 mg ODT (Lot #: PR-04-064R)  
B: Citalopram HBr 2 x 10 mg ODT (Batch #: 0307015)

As shown, the citalopram HBr ODT formulations disintegrated rapidly when placed on the tongue, with mean values of the *in-vivo* disintegration time of citalopram for Treatments A and B being 13 seconds (2-38 seconds) and 14 seconds (6-40 seconds), respectively.

The Sponsor has proposed *in vitro* disintegration time specifications of NMT ~~10~~ seconds, which will be reviewed by the chemist.

**2.5.9. What other significant, unresolved issues related to *in vitro* dissolution or *in vivo* definitive studies need to be addressed?**

None

**2.6. Analytical Section**

OCPB finds the bioanalytical methods adequate and justified.

**2.6.1. What bioanalytical methods are used to assess concentrations of citalopram and its metabolites?**

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed using a validated LC-MS/MS method. The same

method was used in all pivotal BA and BE studies with doses  $\leq 40$  mg of citalopram and was performed by \_\_\_\_\_

**2.6.2. Which metabolites have been selected for analysis and why?**

Both demethylcitalopram and didemethylcitalopram were analyzed for plasma concentrations mainly because they are active metabolites of the parent compound, citalopram.

**2.6.3. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?**

An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. Plasma samples were properly diluted for the analyte concentrations to fall within the range of standard curves. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Correlation coefficient for 3 analytes were \_\_\_\_\_. The standard curves for citalopram, demethylcitalopram, and didemethylcitalopram ranged from \_\_\_\_\_ respectively.

**2.6.4. What are the lower and upper limits of quantification (LLOQ/ULOQ)?**

Lower and upper limits of quantification (LLOQ–ULOQ) with respect to analysis of citalopram, demethylcitalopram, and didemethylcitalopram are \_\_\_\_\_ respectively.

**2.6.5. What are the accuracy, precision, and selectivity at these limits?**

Samples were found to be free of significant interfering peaks. The precision and accuracy based on six duplicates for these 3 analytes at LLOQ were \_\_\_\_\_ and at ULOQ were \_\_\_\_\_. These assays were validated with the intra-assay and inter-assay precision and accuracy within \_\_\_\_\_ and are found acceptable.

**2.6.6. What is the sample stability under the conditions used in the study?**

Sample stability was tested under various conditions. Freeze-thaw stability for three analytes in human plasma was tested at  $-70^\circ\text{C} \pm 10^\circ\text{C}$  and  $-25^\circ\text{C} \pm 10^\circ\text{C}$  controlled at QC Low and QC High levels. Short-term stability was tested at room temperature for 4 hours and found stable. Long-term stability was tested at  $-70^\circ\text{C} \pm 10^\circ\text{C}$  and  $-25^\circ\text{C} \pm 10^\circ\text{C}$  and at QC Low and QC High levels, and was found to be stable for 84–87 days.

**2.6.7. What is the QC sample plan?**

Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples. Three QC samples for citalopram consisted of [redacted] (QC Low), [redacted] (QC Med), and [redacted] (QC High); for demethylcitalopram [redacted] (QC Low), [redacted] (QC Med), and [redacted] (QC High); and for didemethylcitalopram [redacted] (QC Low), [redacted] (QC Med), [redacted] (QC High).

### ***3. Detailed Labeling Recommendations***

Office of Clinical Pharmacology and Biopharmaceutics has reviewed the proposed labeling for Citalopram HBr ODT and found it acceptable provided that revision is made to the labeling language.

#### Labeling comments to the Medical Officer:

1. The "ANIMAL TOXICOLOGY" section should be moved to the end of the label as in the labeling of Celexa™.
2. Labeling statements taken from Celexa™ label should state Celexa™ (instead of citalopram) where appropriate.

#### Labeling recommendation to be sent to the Sponsor:

The following describes the proposed changes: the underlined text is the proposed change to the label language; the ~~strike through~~ is recommendation for deletion from the perspective of OCPB.

### ***4. Appendices***

#### ***4.1. Package insert (Sponsor proposed and annotated with agency recommendation)***

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#### 4.2. *Clinical pharmacology and biopharmaceutics individual study reviews*

Only the definitive studies will be reviewed in this section.

##### **Study 2730 (B03-635PK-N11F1)**

#### **A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT Versus Celexa™ 40 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects**

Study Period: August 1, 2003 - September 9, 2003

##### **Objectives:**

- To compare the rate and extent of absorption of citalopram HBr from the proposed to-be-marketed citalopram HBr 40 mg ODT vs. the reference Celexa™ 40 mg Tablets under fasting conditions.
- To assess the relative bioavailability of these formulations for citalopram and its metabolites, demethylcitalopram and didemethylcitalopram.

**Test formulation:** Citalopram HBr 40 mg ODT, Batch #: 0306011

Batch size:

**Reference formulation:** Celexa™ 40 mg Tablets, Lot #: M0201J (Forest Pharmaceuticals, Inc.)

##### **Study Design:**

This study was a randomized, open-label, single-dose, two-way crossover design in 36 normal, healthy, non-smoking male and female subjects (with possible equal numbers of each gender) under fasting conditions. Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 19 and 26 kg/m<sup>2</sup>, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of two 11-day periods with a 4-week washout between these two periods. Subjects received one of the following treatments in the morning on Day 1 of each period as follows:

**Treatment A:** Following an overnight fast of at least 10 hours each subject received one Citalopram HBr 40 mg ODT administered orally. The test product was placed directly on each subject's tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

**Treatment B:** Following an overnight fast of at least 10 hours each subject was given one Celexa™ 40 mg Tablet administered with 240 mL of ambient temperature water.

All subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic until the 24-hour blood sampling in each study period.

**Safety Assessments:**

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine and saliva alcohol testing). In addition, pregnancy tests were performed on all female subjects. A hemoglobin test was repeated for all subjects prior to Period II dosing. The 12-lead ECG monitoring was carried out prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. Adverse events were monitored throughout the study.

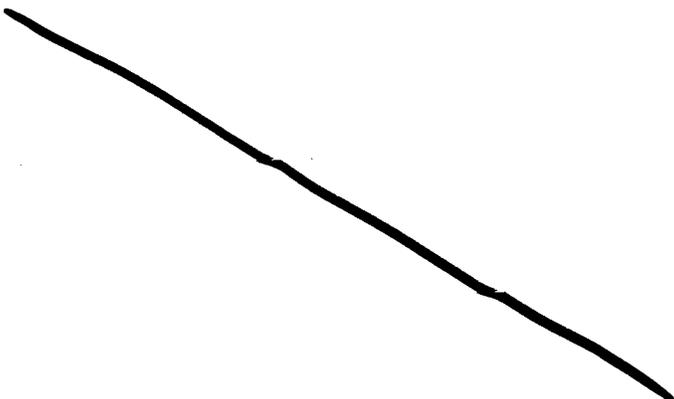
**Pharmacokinetics Assessments:**

A total of 25 blood samples were collected from each subject for determination of citalopram, demethylcitalopram, and didemethylcitalopram at pre-dose, 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. No urine samples were collected. Plasma samples were stored frozen at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until assayed.

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed by a validated LC-MS/MS method. An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

Table 19. Assay validation for Study 2730

	Citalopram	Demethyl-citalopram	Didemethyl-citalopram
<b>Method:</b>	LC-MS/MS	LC-MS/MS	LC-MS/MS

<b>Standard curve</b>	Range:	Precision: Accuracy:	
	Linearity:		
<b>LOQ</b>	LLOQ: ULOQ:		
<b>QC</b>	Low:	Precision: Accuracy:	
	Med:	Precision: Accuracy:	
	High:	Precision: Accuracy:	

**Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for citalopram, demethylcitalopram, and didemethylcitalopram from both Treatment groups were calculated by standard non-compartmental methods:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$ , and the M/P (Metabolite/Parent) ratio for  $AUC_{0-inf}$ .

**Statistical Analysis:**

Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of citalopram, demethylcitalopram, and didemethylcitalopram at each sampling time and for each formulation. The ANOVA was performed using SAS on pharmacokinetic parameters and included period, sequence, subjects nested within sequence, and treatment as factors.

For the bioequivalence determination, the intra-subject CV and the relative ratios of the geometric means between the test and reference, and the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram, demethylcitalopram, and didemethylcitalopram.

**RESULTS**

**Demographics of Subjects:**

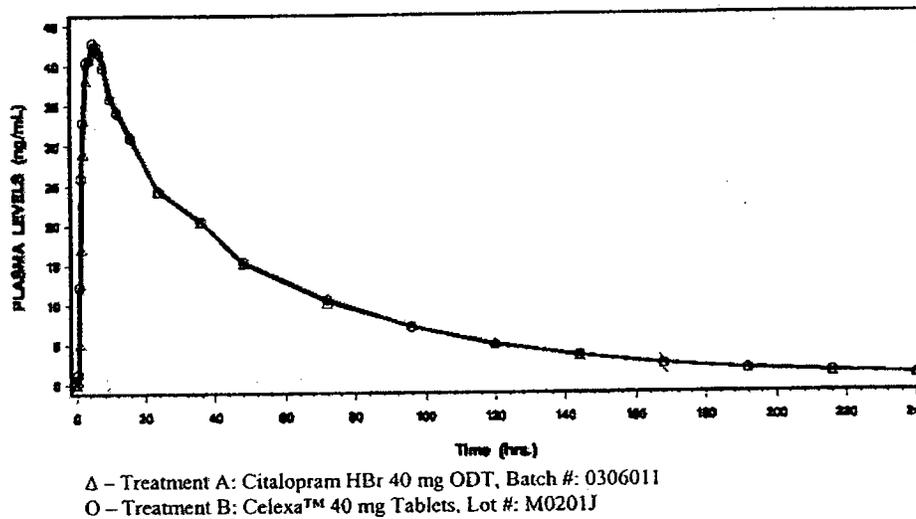
Thirty-six subjects (12 males and 24 females) were enrolled into the study and were dosed in period I. The mean age was 35 years (20-51 years of age) and the mean BMI was 23.0 kg/m<sup>2</sup> (19.4-26.0 kg/m<sup>2</sup>). The subjects consisted of 30 Caucasians, 4 Asians and 2 Blacks. The initial pharmacokinetic and statistical analyses were performed on the 28 subjects who completed the study. Three out of 8 subjects who dropped out of the study were due to the adverse events. Subject #27 was excluded from the statistical analysis due to the non-

compliance with study restrictions. Therefore, final pharmacokinetic and statistical analyses were performed on 27 subjects who completed the study.

**Pharmacokinetic Summary:**

Mean citalopram, demethylcitalopram, and didemethylcitalopram plasma concentration-time profiles following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations under fasting condition are shown in Figures 9-11. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 20-22.

**Figure 9.** Mean citalopram plasma concentration-time profiles following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations (N = 27)



**Table 20.** Summary of pharmacokinetic results for citalopram following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations:

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Pharmacokinetic Parameters	Citalopram HBr 40 mg ODT (A) (n=27) (mean ± SD)	Celexa™ 40 mg Tablets (B) (n=27) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	2188.66 ± 614.27	2198.31 ± 636.21
AUC <sub>0-inf</sub> (ng·hr/mL)	2297.99 ± 679.94†	2310.07 ± 682.00‡
C <sub>max</sub> (ng/mL)	45.67 ± 8.77	48.53 ± 13.91
T <sub>max</sub> (hr)	5.38 ± 2.24 5.03*	5.21 ± 2.41 6.00*
t <sub>1/2</sub> (hr)	51.70 ± 13.41†	52.64 ± 9.94‡
K <sub>el</sub> (hr <sup>-1</sup> )	1.43E-02 ± 4.01E-03†	1.37E-02 ± 2.81E-03‡

\* median values

† n = 25

‡ n = 26

Figure 10. Mean demethylcitalopram plasma concentration-time profiles following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations (N = 27)

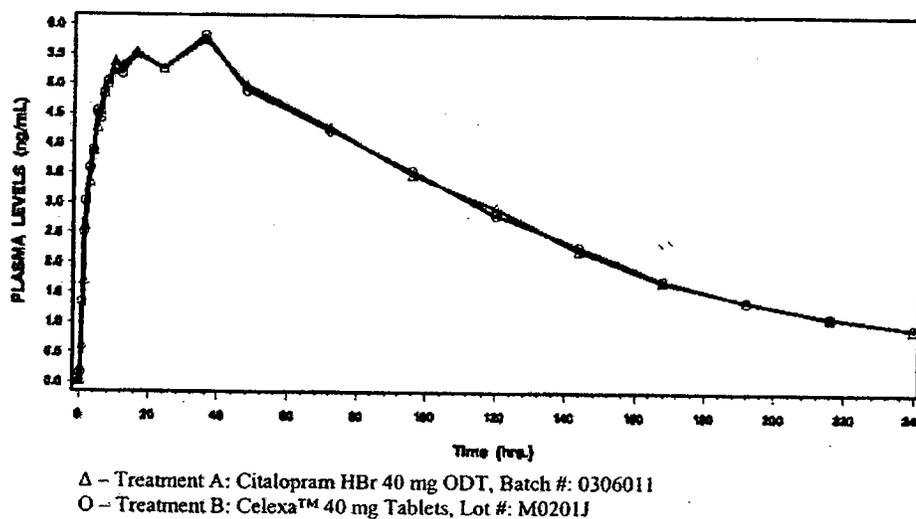


Table 21. Summary of pharmacokinetic results for demethylcitalopram following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations:

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Pharmacokinetic Parameters	Citalopram HBr 40 mg ODT (A) (n=27) (mean ± SD)	Celexa™ 40 mg Tablets (B) (n=27) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	723.41 ± 170.60	722.94 ± 157.81
AUC <sub>0-inf</sub> (ng·hr/mL)	853.34 ± 358.58†	827.97 ± 224.89‡
C <sub>max</sub> (ng/mL)	6.16 ± 1.71	6.04 ± 1.60
T <sub>max</sub> (hr)	31.60 ± 15.30 36.00*	29.12 ± 12.25 36.00*
t <sub>1/2</sub> (hr)	88.29 ± 85.22†	71.96 ± 20.42‡
K <sub>el</sub> (hr <sup>-1</sup> )	1.01E-02 ± 3.43E-03†	1.04E-02 ± 2.93E-03‡
M/P Ratio (AUC <sub>0-inf</sub> )	0.3883 ± 0.1081**	0.3995 ± 0.1384‡

\* median values

\*\* n = 22

† n = 24

‡ n = 25

Figure 11. Mean didemethylcitalopram plasma concentration-time profiles following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations (N = 27)

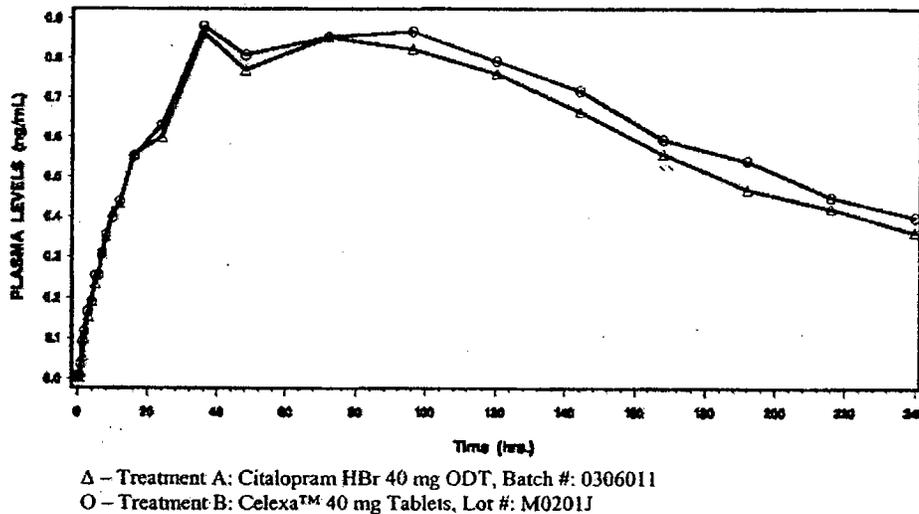


Table 22. Summary of pharmacokinetic results for didemethylcitalopram following single oral doses of 40 mg test (Treatment A) and reference (Treatment B) formulations:

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Pharmacokinetic Parameters	Citalopram HBr 40 mg ODT (A) (n=27) (mean ± SD)	Celexa™ 40 mg Tablets (B) (n=27) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	151.01 ± 105.23	158.65 ± 106.70
AUC <sub>0-inf</sub> (ng·hr/mL)	275.36 ± 139.64‡	222.98 ± 149.64†
C <sub>max</sub> (ng/mL)	0.96 ± 0.84	1.00 ± 0.78
T <sub>max</sub> (hr)	78.26 ± 29.66 72.07*	85.87 ± 35.53 96.00*
t <sub>1/2</sub> (hr)	130.93 ± 134.45‡	99.49 ± 34.11†
K <sub>el</sub> (hr <sup>-1</sup> )	7.34E-03 ± 2.94E-03‡	7.75E-03 ± 2.61E-03†
M/P Ratio (AUC <sub>0-inf</sub> )	0.1537 ± 0.0932‡	0.1212 ± 0.0974†

\* median values

† n = 13

‡ n = 16

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> are summarized in Table 23.

**Table 23.** Relative bioavailability analysis of citalopram HBr 40 mg ODT (Treatment A) vs. Celexa™ 40 mg tablets (Treatment B) for citalopram, demethylcitalopram, and didemethylcitalopram

Parameter	Citalopram					
	90% CI		Ratio of Means	Intra-Subject CV		
AUC <sub>0-t</sub>	97.02% - 102.64%		99.79%	6.05%		
AUC <sub>0-inf</sub>	95.98% - 101.09%		98.50%	5.21%		
C <sub>max</sub>	91.41% - 99.53%		95.38%	9.14%		
	Demethylcitalopram			Didemethylcitalopram		
	90% CI	Ratio of Means	Intra-Subject CV	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	96.47% - 103.21%	99.78%	7.26%	88.00% - 99.80%	93.71%	13.53%
AUC <sub>0-inf</sub>	98.09% - 111.95%	104.79%	12.50%	76.49% - 117.99%	95.00%	14.08%
C <sub>max</sub>	97.31% - 106.68%	101.89%	9.89%	85.78% - 99.27%	92.28%	15.70%

#### CONCLUSION:

- The 40 mg citalopram ODT is bioequivalent to 40 mg Celexa™ tablet (based on acceptance criteria for BE, i.e., 80-125% CI based on parent moiety) under single-dose fasting conditions.

- Similar pharmacokinetic profiles were observed with metabolites, demethylcitalopram and didemethylcitalopram, following oral administration of 40 mg citalopram ODT (test) or 40 mg Celexa™ (reference) formulation.
- For didemethylcitalopram the lower limit of the 90% CI of the geometric mean ratio for  $AUC_{0-inf}$  fell outside the bioequivalence boundary of 80-125%. Didemethylcitalopram, though an active moiety, is a minor metabolite of citalopram. Therefore, not being able to meet the bioequivalence criteria with respect to didemethylcitalopram is not considered critical.

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## Study 2731 (B03-636PK-N11F1)

### A Two-Way, Crossover, Open-Label, Single-Dose, Food Effect Study of Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male and Female Subjects



Study Period: August 14, 2003 - September 22, 2003

#### Objectives:

- To compare the effect of food on the rate and extent of absorption of citalopram HBr from a test formulation of citalopram HBr 40 mg ODT.
- To assess the relative bioavailability of these formulations for citalopram and its metabolites, demethylcitalopram and didemethylcitalopram.

**Test formulation:** Citalopram HBr 40 mg ODT, Batch #: 0306011 (Biovail Technologies Ltd., Ireland)

#### Study Design:

This was a randomized, two-way crossover, open-label, single-dose, fed and fasting design in 36 normal, healthy, non-smoking male and female subjects (with possible equal numbers of each gender). Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 19 and 26 kg/m<sup>2</sup>, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of two 11-day periods with a 4-week washout between these two periods. Subjects received one of the following treatments in the morning on Day 1 of each period as follows:

**Treatment A (Fed):** Following an overnight fast of at least 10 hours each subject received high-fat breakfast. Within 5 minutes following the completion of a high-fat breakfast, one Citalopram HBr 40 mg ODT will be placed directly on the tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

The high-fat breakfast was per Agency's food-effect guidance and contained two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight fluid ounces (240 mL) of whole milk.

**Treatment B (Fasting):** Following an overnight fast of at least 10 hours each subject received one Citalopram HBr 40 mg ODT administered orally. The subject will have the tablet placed directly on the tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

All subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic until the 24-hour blood sampling in each study period.

#### **Safety Assessments:**

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine and saliva alcohol testing). In addition, pregnancy tests were performed on all female subjects. A hemoglobin test was repeated for all subjects prior to Period II dosing. The 12-lead ECG monitoring was carried out prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. Adverse events were monitored throughout the study.

#### **Pharmacokinetics Assessments:**

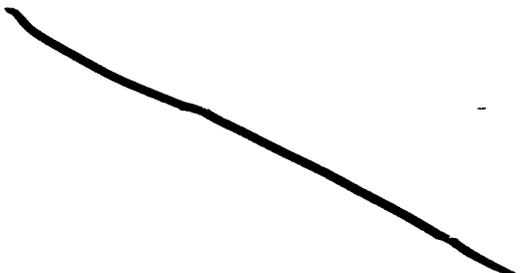
A total of 25 blood samples were collected from each subject for determination of citalopram, demethylcitalopram, and didemethylcitalopram at pre-dose, 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. No urine samples were collected. Plasma samples were stored frozen at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until assayed.

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed by a validated LC-MS/MS method. An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

Table 24. Assay validation for Study 2731

	Citalopram	Demethyl- citalopram	Didemethyl- citalopram
Method:	LC-MS/MS	LC-MS/MS	LC-MS/MS

<b>Standard curve</b>	Range:	Precision: Accuracy:
	Linearity:	
<b>LOQ</b>	LLOQ: ULOQ:	
<b>QC</b>	Low:	Precision: Accuracy:
	Med:	Precision: Accuracy:
	High:	Precision: Accuracy:



### **Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for citalopram, demethylcitalopram, and didemethylcitalopram from both Treatment groups were calculated by standard non-compartmental methods:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$ , and the M/P (Metabolite/Parent) ratio for  $AUC_{0-inf}$ .

### **Statistical Analysis:**

Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of citalopram, demethylcitalopram, and didemethylcitalopram at each sampling time and for each formulation. The ANOVA was performed using SAS on pharmacokinetic parameters and included period, sequence, subjects nested within sequence, and treatment as factors.

For the bioequivalence determination, the intra-subject CV and the relative ratios of the geometric means between the fed and fasted treatments, and the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram, demethylcitalopram, and didemethylcitalopram.

## **RESULTS**

### **Demographics of Subjects:**

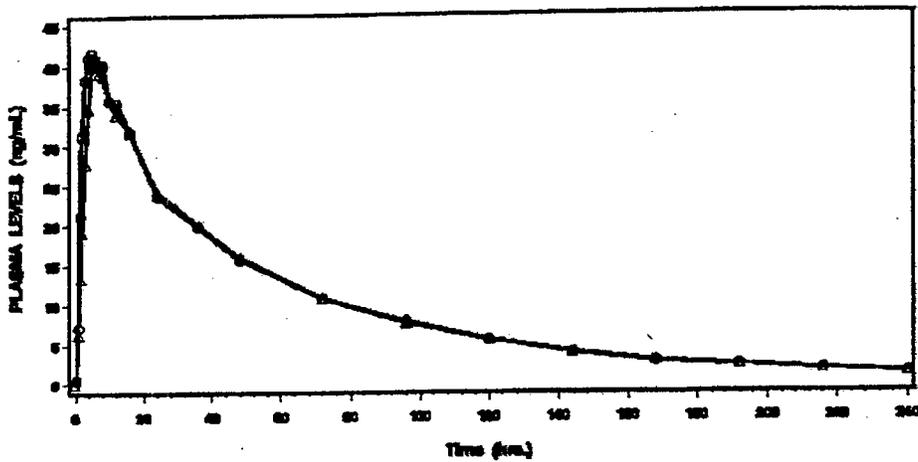
Thirty-four subjects (23 males and 11 females) were enrolled into the study and were dosed in period I, of whom 31 actually completed the study. The mean age was 34 years (18-58 years of age) and the mean BMI was 23.5  $kg/m^2$  (19.4-25.7  $kg/m^2$ ). The subjects consisted of 23 Caucasians, 4 Asians and 7 Blacks. Among the 3 subjects dismissed from the study, subject #08 was removed from the study and excluded from the pharmacokinetic and statistical analyses due to the adverse events, but was included in analysis for potential

contributor for adverse events. Therefore, final pharmacokinetic and statistical analyses were performed on 31 subjects who completed the study.

**Pharmacokinetic Summary:**

Mean citalopram, demethylcitalopram, and didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition are shown in Figures 12-14. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 25-27.

**Figure 12.** Mean citalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31)



▲▲▲ TREATMENT A: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fed)  
○○○ TREATMENT B: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fasting)

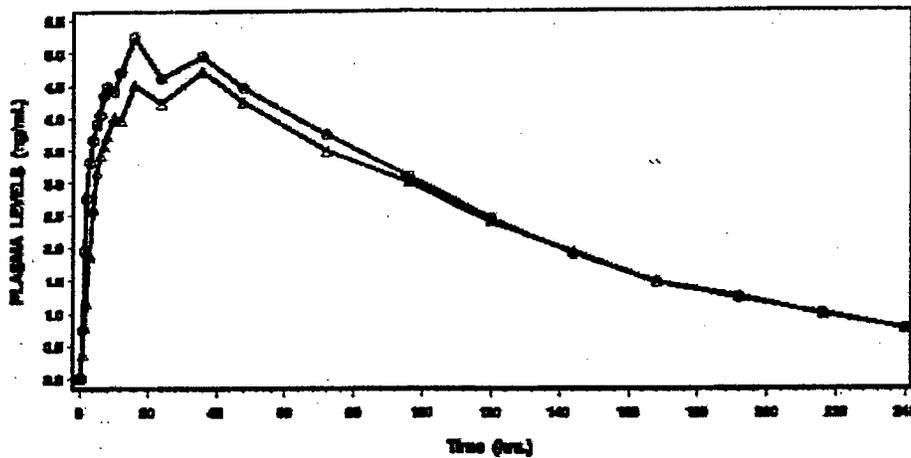
**Table 25.** Summary of pharmacokinetic results for citalopram following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31):

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Pharmacokinetic Parameter	Citalopram HBr 40 mg ODT (Fed) (A) n = 31 Mean ± SD	Citalopram HBr 40 mg ODT (Fasting) (B) n = 31 Mean ± SD
	AUC <sub>0-4</sub> (ng·hr/mL)	2233.49 ± 785.58
AUC <sub>0-24</sub> (ng·hr/mL)	2352.87 ± 868.84	2384.81 ± 841.01
C <sub>max</sub> (ng/mL)	45.07 ± 10.62	45.51 ± 10.15
T <sub>max</sub> (hr)	6.03 ± 2.28 5.00†	4.90 ± 1.90 5.00†
t <sub>1/2</sub> (hr)	55.81 ± 15.00	54.20 ± 13.04
K <sub>e1</sub> (hr <sup>-1</sup> )	1.33E-02 ± 3.57E-03	1.35E-02 ± 3.18E-03

†This is the median value.

Figure 13. Mean demethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31)



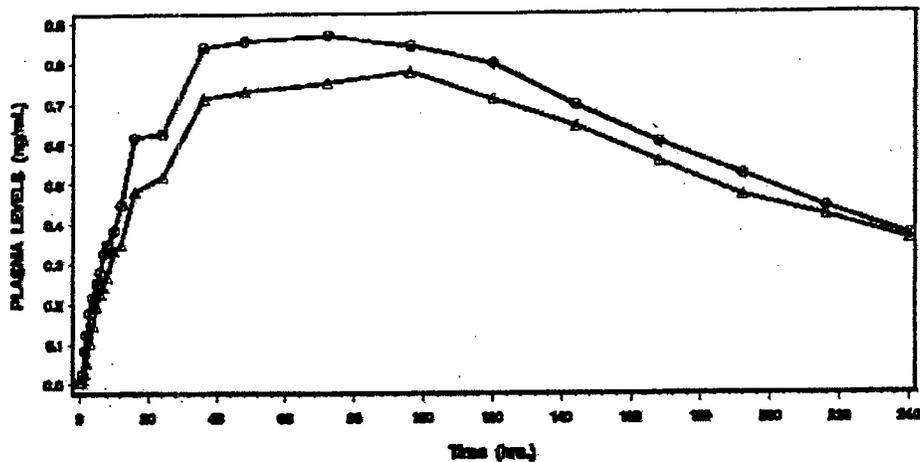
▲▲▲ TREATMENT A: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fed)  
 ○○○ TREATMENT B: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fasting)

Table 26. Summary of pharmacokinetic results for demethylcitalopram following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31):

Pharmacokinetic Parameter	Citalopram HBr 40 mg ODT (Fed) (A) n = 31 Mean ± SD	Citalopram HBr 40 mg ODT (Fasting) (B) n = 31 Mean ± SD
	AUC <sub>0-t</sub> (ng·hr/mL)	601.17 ± 138.69
AUC <sub>0-inf</sub> (ng·hr/mL)	688.66 ± 185.07*	729.12 ± 173.65**
C <sub>max</sub> (ng/mL)	5.03 ± 1.15	5.44 ± 1.38
T <sub>max</sub> (hr)	27.87 ± 13.75 36.00†	25.41 ± 15.17 16.00†
t <sub>1/2</sub> (hr)	73.59 ± 21.79*	71.90 ± 21.99**
K <sub>el</sub> (hr <sup>-1</sup> )	1.02E-02 ± 2.92E-03*	1.04E-02 ± 2.74E-03**
M/P ratio (AUC <sub>0-inf</sub> )	0.3507 ± 0.1249*	0.3605 ± 0.1226**

\*n = 29, \*\* n = 30; †This is the median value.

Figure 14. Mean didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31)



▲▲▲ TREATMENT A: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fed)  
 ○○○ TREATMENT B: CITALOPRAM HBr ODT, 1 x 40 mg, Batch #: 0306011 (fasting)

Table 27. Summary of pharmacokinetic results for didemethylcitalopram following single oral doses of citalopram HBr 40 mg ODT formulation under fed (Treatment A) and fasting (Treatment B) condition (N = 31):

Pharmacokinetic Parameter	<b>Citalopram HBr 40 mg</b>	<b>Citalopram HBr 40 mg</b>
	<b>ODT (Fed) (A)</b> n = 31 Mean ± SD	<b>ODT (Fasting) (B)</b> n = 31 Mean ± SD
AUC <sub>0-t</sub> (ng·hr/mL)	141.43 ± 74.40	158.72 ± 86.18
AUC <sub>0-inf</sub> (ng·hr/mL)	207.14 ± 89.89*	235.76 ± 103.73**
C <sub>max</sub> (ng/mL)	0.85 ± 0.46	0.95 ± 0.55
T <sub>max</sub> (hr)	78.34 ± 35.51 96.00†	78.68 ± 32.71 72.00†
t <sub>1/2</sub> (hr)	136.77 ± 182.72*	123.20 ± 115.40**
K <sub>el</sub> (hr <sup>-1</sup> )	7.20E-03 ± 2.27E-03*	7.22E-03 ± 2.52E-03**
M/P ratio (AUC <sub>0-inf</sub> )	0.1248 ± 0.0781*	0.1353 ± 0.0875**

\*n = 21, \*\*n = 25; †This is the median value.

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> are summarized in Table 28.

**Table 28.** Relative bioavailability analysis of citalopram HBr 40 mg ODT under fed (Treatment A) vs. fasting (Treatment B) condition for citalopram, demethylcitalopram, and didemethylcitalopram

Parameter	Citalopram					
	90% CI		Ratio of Means		Intra-Subject CV	
AUC <sub>0-t</sub>	93.30% - 102.9%		97.60%		10.42%	
AUC <sub>0-inf</sub>	93.79% - 102.29%		97.94%		10.05%	
C <sub>max</sub>	91.58% - 105.87%		98.47%		16.79%	
	Demethylcitalopram			Didemethylcitalopram		
	90% CI	Ratio of Means	Intra-Subject CV	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	89.40% - 97.92%	93.57%	10.54%	84.06% - 103.75%	93.39%	24.37%
AUC <sub>0-inf</sub>	89.76% - 98.89%	94.22%	10.83%	80.33% - 100.91%	90.03%	18.17%
C <sub>max</sub>	86.63% - 99.71%	92.94%	16.28%	83.00% - 101.35%	91.72%	23.13%

#### CONCLUSION:

- Similar pharmacokinetic profiles of citalopram were observed following oral administration of Citalopram HBr 40 mg ODT after high fat breakfast (Treatment A) or without food (Treatment B). Food had no effect on the rate and extent of absorption of citalopram. The ratios of geometric mean of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for citalopram were 97.60%, 97.94%, and 98.47%, respectively. There was a slight

increase in mean  $T_{\max}$  by 1 hour in the presence of food; however, the slight delay in time to reach  $C_{\max}$  is not likely to have clinical significance.

- Similar results were observed with demethylcitalopram and didemethylcitalopram.

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**Study 2732 (B03-637PK-N11F1)**

**A Two-Way, Crossover, Open-Label, Single-Dose, Fasting, Comparative Bioavailability Study of Citalopram Hydrobromide 40 mg ODT, Without and With Water in Normal Healthy Non-Smoking Male and Female Subjects**



Study Period: August 7, 2003 - September 22, 2003

**Objectives:**

- To compare the rate and extent of absorption of citalopram HBr from a test formulation of citalopram HBr 40 mg Orally Dissolving Tablets (ODT) when administered without and with water under fasting conditions.
- To assess the relative bioavailability of these formulations for citalopram and its metabolites, demethycitalopram and didemethylcitalopram.

**Test formulation:** Citalopram HBr 40 mg ODT, Batch #: 0306011 (Biovail Technologies Ltd., Ireland)

**Study Design:**

This was a randomized, single-dose, open-label, two-way crossover design under fasting condition in 36 normal, healthy, non-smoking male and female subjects (with possible equal numbers of each gender). Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 19 and 26 kg/m<sup>2</sup>, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of two 11-day periods with a 4-week washout between these two periods. Subjects received one of the following treatments in the morning on Day 1 of each period as follows:

**Treatment A (Without Water):** Following an overnight fast of at least 10 hours each subject received one Citalopram HBr 40 mg ODT administered orally. The test product was placed directly on each subject's tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. No water was ingested after the ODT was completely dissolved and swallowed. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

**Treatment B (With Water):** Following an overnight fast of at least 10 hours each subject received one Citalopram HBr 40 mg ODT administered orally. The subject placed the tablet directly on the tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

All subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic until the 24-hour blood sampling in each study period.

**Safety Assessments:**

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine and saliva alcohol testing). In addition, pregnancy tests were performed on all female subjects. A hemoglobin test was repeated for all subjects prior to Period II dosing. The 12-lead ECG monitoring was carried out prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. Adverse events were monitored throughout the study.

**Pharmacokinetics Assessments:**

A total of 25 blood samples were collected from each subject for determination of citalopram, demethylcitalopram, and didemethylcitalopram at pre-dose, 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. No urine samples were collected. Plasma samples were stored frozen at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until assayed.

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed by a validated LC-MS/MS method. An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

Table 29. Assay validation for Study 2732

	Citalopram	Demethyl-citalopram	Didemethyl-citalopram
<b>Method:</b>	LC-MS/MS	LC-MS/MS	LC-MS/MS
<b>Standard curve</b>			

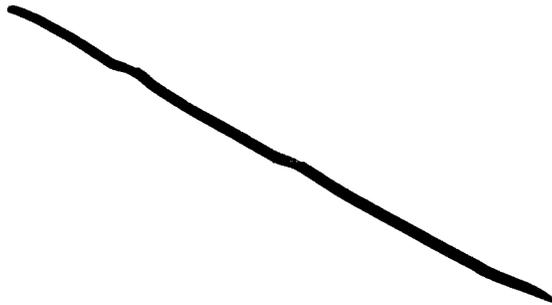
Range:

Precision:

Accuracy:



Linearity:	
LOQ	
	LLOQ:
	ULOQ:
QC	
Low:	Precision:
	Accuracy:
Med:	Precision:
	Accuracy:
High:	Precision:
	Accuracy:



**Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for citalopram, demethylcitalopram, and didemethylcitalopram from both Treatment groups were calculated by standard non-compartmental methods:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$ , and the M/P (Metabolite/Parent) ratio for  $AUC_{0-inf}$ .

**Statistical Analysis:**

Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of citalopram, demethylcitalopram, and didemethylcitalopram at each sampling time and for each formulation. The ANOVA was performed using SAS on pharmacokinetic parameters and included period, sequence, subjects nested within sequence, and treatment as factors.

For the bioequivalence determination, the intra-subject CV and the relative ratios of the geometric means between the test and reference treatments, and the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram, demethylcitalopram, and didemethylcitalopram.

**RESULTS**

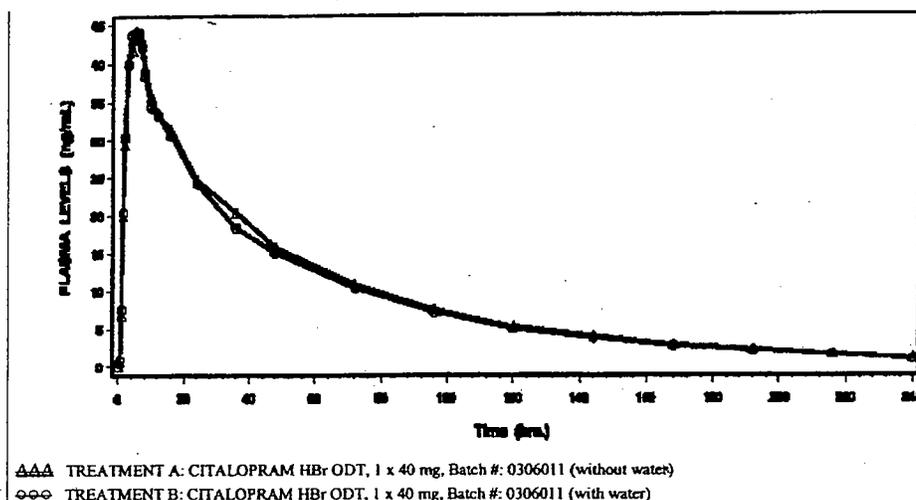
**Demographics of Subjects:**

Thirty-four subjects (13 males and 22 females) were enrolled into the study and were dosed in period I, of whom 28 actually completed the study. The mean age was 34 years (18-50 years of age) and the mean BMI was 23.2 kg/m<sup>2</sup> (20.1-25.9 kg/m<sup>2</sup>). The subjects consisted of 24 Caucasians, 2 Asians, 7 Blacks, and 1 Native. Among the 6 subjects dismissed from the study, subjects #03, #06, #08, #27, and #36 were removed from the study and excluded from the pharmacokinetic and statistical analyses due to the adverse events, but were included in analysis for potential contributor for adverse events. Therefore, final pharmacokinetic and statistical analyses were performed on 28 subjects who completed the study.

**Pharmacokinetic Summary:**

Mean citalopram, demethylcitalopram, and didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) are shown in Figures 15-17. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 30-32.

**Figure 15.** Mean citalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)

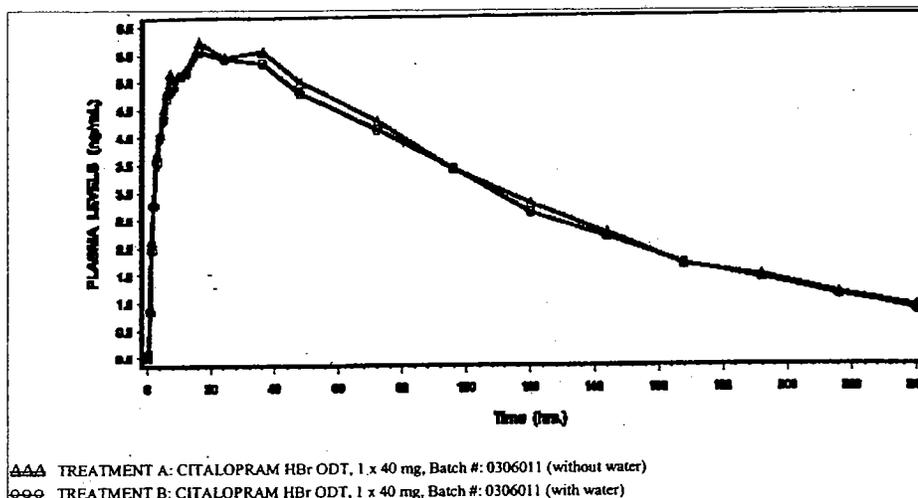


**Table 30.** Summary of pharmacokinetic results for citalopram following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)

Pharmacokinetic Parameter	Citalopram HBr 40 mg ODT (Without water) (A)	Citalopram HBr 40 mg ODT (With water) (B)
	n = 28 Mean ± SD	n = 28 Mean ± SD
AUC <sub>0-t</sub> (ng·hr/mL)	2301.71 ± 790.35	2195.83 ± 642.91
AUC <sub>0-inf</sub> (ng·hr/mL)	2444.05 ± 842.76*	2352.40 ± 776.15*
C <sub>max</sub> (ng/mL)	47.70 ± 7.30	48.28 ± 9.25
T <sub>max</sub> (hr)	5.11 ± 1.45 5.00†	4.74 ± 1.73 5.00†
t <sub>1/2</sub> (hr)	50.14 ± 11.84*	53.33 ± 12.00*
K <sub>e1</sub> (hr <sup>-1</sup> )	1.46E-02 ± 3.67E-03*	1.36E-02 ± 2.76E-03*

\*n = 27; †This is the median value.

**Figure 16.** Mean demethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)

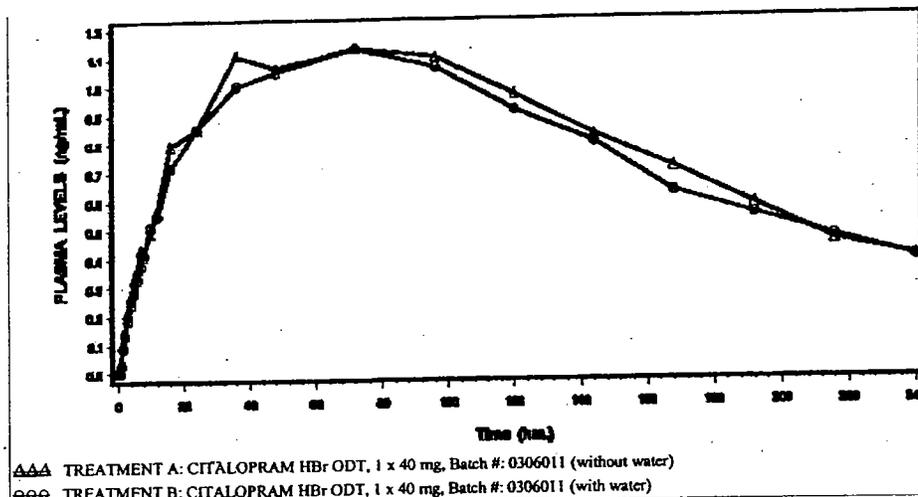


**Table 31.** Summary of pharmacokinetic results for demethylcitalopram following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)

Pharmacokinetic Parameter	Citalopram HBr 40 mg ODT (Without water) (A)	Citalopram HBr 40 mg ODT (With water) (B)
	n = 28 Mean ± SD	n = 28 Mean ± SD
AUC <sub>0-t</sub> (ng·hr/mL)	728.13 ± 179.59	707.85 ± 165.99
AUC <sub>0-inf</sub> (ng·hr/mL)	845.32 ± 358.52*	814.77 ± 165.05**
C <sub>max</sub> (ng/mL)	6.25 ± 1.89	6.08 ± 1.96
T <sub>max</sub> (hr)	34.42 ± 31.82 24.05†	29.36 ± 21.76 24.00†
t <sub>1/2</sub> (hr)	69.85 ± 39.58*	64.07 ± 18.73**
K <sub>el</sub> (hr <sup>-1</sup> )	1.16E-02 ± 3.76E-03*	1.19E-02 ± 3.90E-03**
M/P ratio (AUC <sub>0-inf</sub> )	0.3931 ± 0.1554*	0.3936 ± 0.0957**

\*n = 25, \*\*n = 24; †This is the median value.

**Figure 17.** Mean didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)



**Table 32.** Summary of pharmacokinetic results for didemethylcitalopram following single oral doses of citalopram HBr 40 mg ODT formulation without water (Treatment A) and with water (Treatment B) (N = 28)

Pharmacokinetic Parameter	<u>Citalopram HBr 40 mg ODT</u> <u>(Without water)</u> <u>(A)</u> n = 28 Mean ± SD	<u>Citalopram HBr 40 mg ODT</u> <u>(With water)</u> <u>(B)</u> n = 28 Mean ± SD
	AUC <sub>0-t</sub> (ng·hr/mL)	194.32 ± 134.56*
AUC <sub>0-inf</sub> (ng·hr/mL)	260.62 ± 168.48**	237.44 ± 156.17***
C <sub>max</sub> (ng/mL)	1.24 ± 0.90*	1.20 ± 0.87*
T <sub>max</sub> (hr)	82.76 ± 30.97* 96.00†	79.08 ± 43.93* 72.03†
t <sub>1/2</sub> (hr)	103.34 ± 70.25**	96.05 ± 33.04***
K <sub>el</sub> (hr <sup>-1</sup> )	8.70E-03 ± 3.93E-03**	8.07E-03 ± 2.91E-03***
M/P ratio (AUC <sub>0-inf</sub> )	0.1536 ± 0.1146**	0.1347 ± 0.1001***

\*n = 26, \*\*n = 20, \*\*\*n = 17; †This is the median value.

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> are summarized in Table 33.

**Table 33.** Relative bioavailability analysis of citalopram HBr 40 mg ODT without water (Treatment A) and with water (Treatment B) for citalopram, demethylcitalopram, and didemethylcitalopram

Parameter	Citalopram					
	90% CI		Ratio of Means		Intra-Subject CV	
AUC <sub>0-t</sub>	97.53% - 110.53%		103.83%		13.69%	
AUC <sub>0-inf</sub>	97.39% - 110.56%		103.76%		13.56%	
C <sub>max</sub>	93.20% - 106.73%		99.74%		14.82%	
	Demethylcitalopram			Didemethylcitalopram		
	90% CI	Ratio of Means	Intra-Subject CV	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	95.83% - 111.38%	103.32%	16.45%	94.03% - 121.16%	106.73%	26.63%
AUC <sub>0-inf</sub>	93.94% - 109.21%	101.29%	14.24%	85.05% - 116.43%	99.51%	24.42%
C <sub>max</sub>	96.16% - 112.34%	103.93%	17.02%	92.01% - 120.55%	105.32%	28.38%

### CONCLUSION:

- Citalopram exhibited similar pharmacokinetic profiles following oral administration of Citalopram HBr 40 mg ODT without water (Treatment A) or with water (Treatment B) under fasting condition. The rate and extent of absorption of citalopram from two treatments were similar. The ratios of geometric mean of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for citalopram were 103.83%, 103.76%, and 99.74%, respectively.
- Similar results were observed with demethylcitalopram and didemethylcitalopram.
- The 90% CI of the geometric mean ratios of AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> for citalopram were within the range of 80-125%. It was concluded that water had no effect on the rate and extent of absorption of citalopram following oral administration of the citalopram HBr 40 mg ODT.

### Comment:

Study 2732 for the effect of administration with water is not very valuable to evaluate the effect of swallowing vs. allowing to disintegrate/dissolve, since in both treatment groups the 40 mg citalopram ODT was allowed to disintegrate/dissolve in oral cavity prior to swallowing. It would be a more optimal study design to detect the effect of swallowing water by instructing the subjects in Treatment group B (with water) to swallow the tablet directly with 240 mL water without intentionally letting the ODT disintegrate/dissolve on the tongue and sucking on the tablet prior to the swallowing. However, through Studies 2732 and 2730, since the ODT has been shown to be BE to reference tablet (when let to dissolve without water), label claim with and without water can be allowed.

**Study 2750 (B03-638PK-N11F1)**

**A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalency Study of 4 x Citalopram Hydrobromide 10 mg ODT Versus 1 x Citalopram Hydrobromide 40 mg ODT in Normal Healthy Non-Smoking Male and Female Subjects**

Study Period: September 12, 2003 – November 14, 2003

**Objectives:**

- To determine the dosage strength equivalence between two strengths of citalopram HBr Orally Dissolving Tablets (ODT) (4 x 10 mg vs. 1 x 40 mg) under fasting conditions.
- To assess the relative bioavailability of these formulations for citalopram and its metabolites, demethycitalopram and didemethylcitalopram.

**Test formulation:** Citalopram HBr 40 mg ODT, Batch #: 0306011 (Biovail Technologies Ltd., Ireland)

**Reference formulation:** Citalopram HBr 10 mg ODT, Batch #: 0307015 (Biovail Technologies Ltd., Ireland), Batch size: 

**Study Design:**

This was a randomized, open-label, single-dose, two-way crossover design in 36 normal, healthy, non-smoking male and female subjects (with possible equal numbers of each gender) under fasting condition. Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 19 and 26 kg/m<sup>2</sup>, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of two 11-day periods with a 4-week washout between these two periods. Subjects received one of the following treatments in the morning on Day 1 of each period as follows:

**Treatment A (4 x 10 mg):** Following an overnight fast of at least 10 hours each subject received a single oral dose of four Citalopram HBr 10 mg ODT. The 10 mg ODT formulation was administered in two sequences. After placing 2 test tablets directly on the tongue, not below the tongue, the subject was instructed to suck on the tablets for 15 seconds. Following that the subject received the remaining 2 test tablets placed directly on the tongue, not below the tongue and was instructed to suck on the tablets for one minute or longer, until all tablets have completely dissolved in the mouth. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of

ambient temperature water within one minute. The actual dosing time will be recorded when the first 2 tablets were given to the subject.

**Treatment B (1 x 40 mg):** Following an overnight fast of at least 10 hours each subject received one Citalopram HBr 40 mg ODT administered orally. The subject had the tablet placed directly on the tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

All subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic until the 24-hour blood sampling in each study period.

**Safety Assessments:**

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine and saliva alcohol testing). In addition, pregnancy tests were performed on all female subjects. A hemoglobin test was repeated for all subjects prior to Period II dosing. The 12-lead ECG monitoring was carried out prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. Adverse events were monitored throughout the study.

**Pharmacokinetics Assessments:**

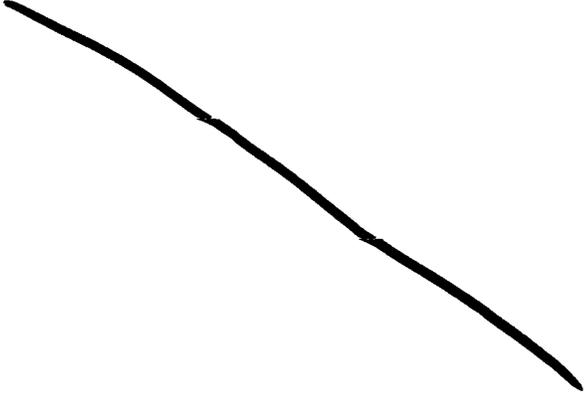
A total of 25 blood samples were collected from each subject for determination of citalopram, demethylcitalopram, and didemethylcitalopram at pre-dose, 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. No urine samples were collected. Plasma samples were stored frozen at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until assayed.

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed by a validated LC-MS/MS method. An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

Table 34. Assay validation for Study 2750

	Citalopram	Demethyl- citalopram	Didemethyl- citalopram
Method:	LC-MS/MS	LC-MS/MS	LC-MS/MS
Standard			

curve	Range:	Precision:
		Accuracy:
	Linearity:	
LOQ	LLOQ:	
	ULOQ:	
QC	Low:	Precision:
		Accuracy:
	Med:	Precision:
		Accuracy:
	High:	Precision:
		Accuracy:



### **Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for citalopram, demethylcitalopram, and didemethylcitalopram from both Treatment groups were calculated by standard non-compartmental methods:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$ , and the M/P (Metabolite/Parent) ratio for  $AUC_{0-inf}$ .

### **Statistical Analysis:**

Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of citalopram, demethylcitalopram, and didemethylcitalopram at each sampling time and for each formulation. The ANOVA was performed using SAS on pharmacokinetic parameters and included period, sequence, subjects nested within sequence, and treatment as factors.

For the bioequivalence determination, the intra-subject CV and the relative ratios of the geometric means between the test and reference treatments, and the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram, demethylcitalopram, and didemethylcitalopram.

## **RESULTS**

### **Demographics of Subjects:**

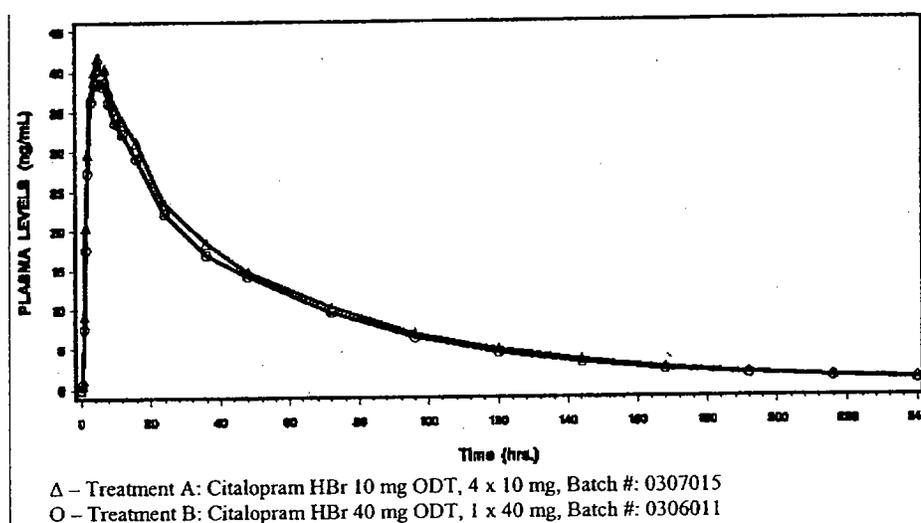
Thirty-six subjects (27 males and 9 females) were enrolled into the study and were dosed in period I, of whom 28 actually completed the study. The mean age was 31 years (19-48 years of age) and the mean BMI was 23.8 kg/m<sup>2</sup> (20.7-26.0 kg/m<sup>2</sup>). The subjects consisted of 26 Caucasians, 4 Asians, and 6 Blacks. Among the 8 subjects either withdrawn or dismissed from the study, subjects #14, #15, #20, #26, #30, #34, and #36 were removed from the study and excluded from the pharmacokinetic and statistical analyses due to the adverse events, but were included in analysis for potential contributor for adverse events. Therefore, final

pharmacokinetic and statistical analyses were performed on 28 subjects who completed the study.

**Pharmacokinetic Summary:**

Mean citalopram, demethylcitalopram, and didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) are shown in Figures 18-20. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 35-37.

**Figure 18.** Mean citalopram plasma concentration-time profiles following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)



**Table 35.** Summary of pharmacokinetic results for citalopram following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)

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Pharmacokinetic Parameters	Citalopram HBr 10 mg ODT	Citalopram HBr 40 mg ODT
	(A) (n=28) (mean ± SD)	(B) (n=28) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	2127.73 ± 543.86	1992.39 ± 472.16
AUC <sub>0-inf</sub> (ng·hr/mL)	2205.91 ± 591.06	2062.57 ± 515.85
C <sub>max</sub> (ng/mL)	44.52 ± 7.70	41.93 ± 5.43
T <sub>max</sub> (hr)	4.88 ± 1.79 5.00*	5.25 ± 1.69 5.00*
t <sub>1/2</sub> (hr)	49.94 ± 12.64	50.00 ± 11.95
K <sub>el</sub> (hr <sup>-1</sup> )	1.47E-02 ± 3.60E-03	1.46E-02 ± 3.30E-03

\* median values

Figure 19. Mean demethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)

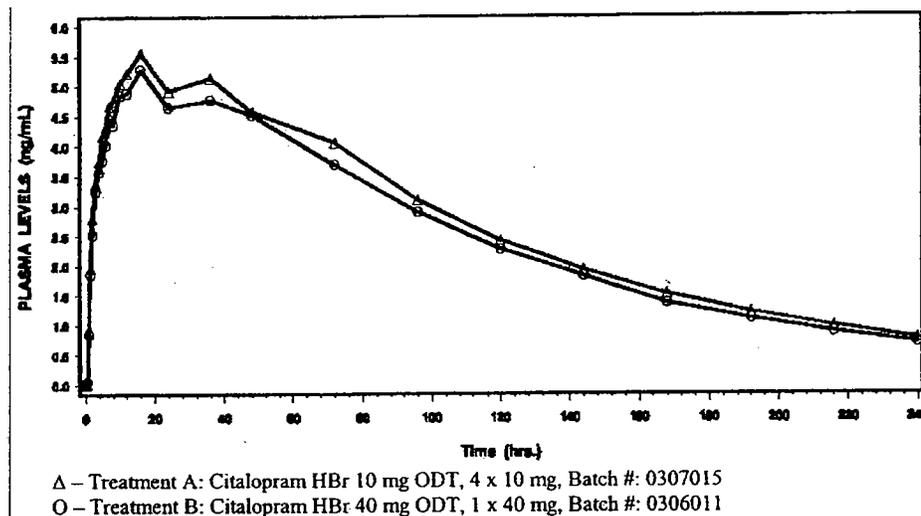


Table 36. Summary of pharmacokinetic results for demethylcitalopram following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)

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Pharmacokinetic Parameters	Citalopram HBr 10 mg ODT (A) (n=28) (mean ± SD)	Citalopram HBr 40 mg ODT (B) (n=28) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	659.02 ± 136.61	614.49 ± 107.79
AUC <sub>0-inf</sub> (ng·hr/mL)	735.58 ± 194.08†	685.27 ± 153.40†
C <sub>max</sub> (ng/mL)	5.85 ± 1.52	5.50 ± 1.48
T <sub>max</sub> (hr)	23.64 ± 15.13 16.00*	22.04 ± 12.06 16.00*
t <sub>1/2</sub> (hr)	66.04 ± 23.22†	67.49 ± 29.46†
K <sub>el</sub> (hr <sup>-1</sup> )	1.15E-02 ± 3.24E-03†	1.16E-02 ± 3.66E-03†
M/P Ratio (AUC <sub>0-inf</sub> )	0.3678 ± 0.1001†	0.3621 ± 0.0925†

\* median values

† n = 27

Figure 20. Mean didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)

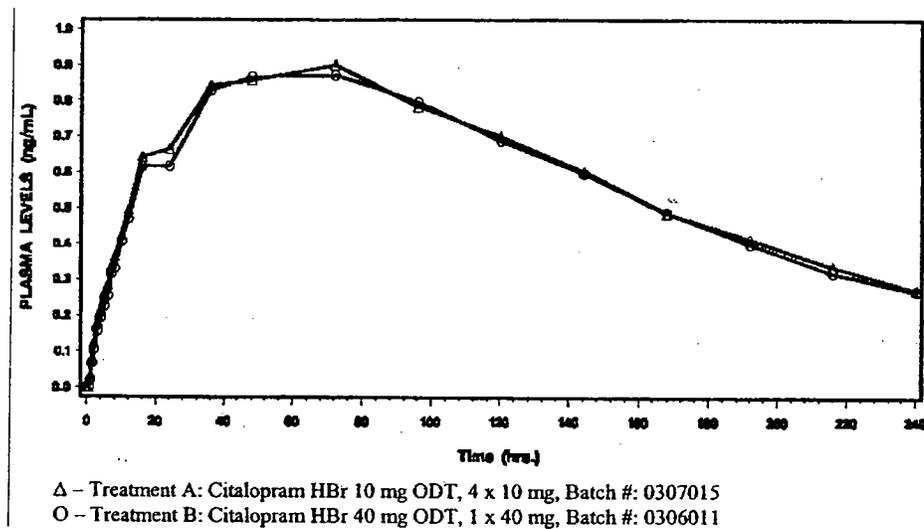


Table 37. Summary of pharmacokinetic results for didemethylcitalopram following single oral doses of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) (N = 28)

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Pharmacokinetic Parameters	Citalopram HBr 10 mg ODT	Citalopram HBr 40 mg ODT
	(A) (n=28) (mean ± SD)	(B) (n=28) (mean ± SD)
AUC <sub>0-t</sub> (ng·hr/mL)	147.10 ± 113.39	142.31 ± 116.00
AUC <sub>0-inf</sub> (ng·hr/mL)	224.76 ± 125.43†	218.47 ± 140.72†
C <sub>max</sub> (ng/mL)	0.99 ± 0.81	0.93 ± 0.80
T <sub>max</sub> (hr)	81.16 ± 32.91‡ 72.02*	66.28 ± 20.49‡ 72.00*
t <sub>1/2</sub> (hr)	108.87 ± 86.90†	90.87 ± 34.04†
K <sub>e1</sub> (hr <sup>-1</sup> )	8.18E-03 ± 3.20E-03†	8.49E-03 ± 2.62E-03†
M/P Ratio (AUC <sub>0-inf</sub> )	0.1318 ± 0.0849†	0.1356 ± 0.0913†

\* median values

† n = 20

‡ n = 25

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> are summarized in Table 38.

**Table 38.** Relative bioavailability analysis of citalopram HBr 4 x 10 mg ODT formulation (Treatment A) and 1 x 40 mg ODT formulation (Treatment B) for citalopram, demethylcitalopram, and didemethylcitalopram

Parameter	Citalopram					
	90% CI		Ratio of Means		Intra-Subject CV	
AUC <sub>0-t</sub>	102.43% - 110.70%		106.48%		8.49%	
AUC <sub>0-inf</sub>	102.58% - 110.88%		106.65%		8.51%	
C <sub>max</sub>	110.53% - 110.88%		105.58%		10.72%	
	Demethylcitalopram			Didemethylcitalopram		
	90% CI	Ratio of Means	Intra-Subject CV	90% CI	Ratio of Means	Intra-Subject CV
AUC <sub>0-t</sub>	102.20% - 111.19%	106.60%	9.23%	99.47% - 111.29%	109.84%	20.44%
AUC <sub>0-inf</sub>	101.54% - 111.67%	106.49%	9.98%	94.01% - 118.54%	105.56%	19.92%
C <sub>max</sub>	101.99% - 111.24%	106.51%	9.50%	100.75% - 191.67%	109.80%	17.74%

#### CONCLUSION:

- As shown, citalopram exhibited similar pharmacokinetic profiles following oral administration of 40 mg test (4 x 10 mg) or reference (1 x 40 mg) ODT formulation under fasting condition. The rate and extent of absorption of citalopram from two treatments were similar. The ratios of geometric mean of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, and C<sub>max</sub> for citalopram were 106.48%, 106.65%, and 105.58%, respectively. The 90% CI of

the geometric mean ratios of  $AUC_{0-t}$  and  $AUC_{0-inf}$  for citalopram were within the range of 80-125%.

- Similar results were observed with demethylcitalopram and didemethylcitalopram.
- The dosage form equivalency with respect to the rate and extent of absorption of citalopram was established between two strengths (4 x 10 mg vs. 1 x 40 mg) of citalopram HBr ODT under single-dose fasting conditions.

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## Study 2914 (B04-688PK)

### **A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Equivalency Study of Citalopram HBr Orally Disintegrating Tablets (1 x 20 mg Versus 2 x 10 mg) in Normal Healthy Non-Smoking Male and Female Subjects**

Study Period: September 15, 2004 - October 26, 2004

#### **Objectives:**

- To determine the dosage strength equivalence of 10 and 20 mg strengths of citalopram HBr Orally Disintegrating Tablets (ODT) (1 x 20 mg vs. 2 x 10 mg) under fasting conditions.
- To assess the relative bioavailability of these formulations for citalopram and its metabolites, demethycitalopram and didemethylcitalopram.

**Test formulation:** Citalopram HBr 20 mg ODT, Batch #: PR-04-064R (Biovail Technologies, Inc., Dorado, PR)

**Reference formulation:** Citalopram HBr 10 mg ODT, Batch #: 0307015 (Biovail Technologies Ltd., Ireland)

#### **Study Design:**

This was a randomized, two-way crossover, open-label, single-dose, fasting design in 36 normal, healthy, non-smoking male and female subjects (equal numbers of each gender). Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 18.5 and 29.9 kg/m<sup>2</sup>, who met the inclusion and exclusion criteria, were enrolled in the study.

The study consisted of two 12-day periods with a 4-week washout between these two periods. Subjects received one of the following treatments in the morning on Day 1 of each period as follows:

**Treatment A (1 x 20 mg):** Following an overnight fast of at least 10 hours each subject received a single oral dose of one Citalopram HBr 20 mg ODT. The subject was instructed to place the tablet directly on the tongue, not below the tongue. Following that the subject was instructed to suck on the tablets for one minute or longer, until all tablets have completely dissolved in the mouth. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time will be recorded when the tablet was given to the subject.

**Treatment B (2 x 10 mg):** Following an overnight fast of at least 10 hours each subject received two Citalopram HBr 10 mg ODTs administered orally. The subject had the tablet placed directly on the tongue, not below the tongue. Subjects were instructed to suck on the drug for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. After the subject's mouth was checked to ensure that the drug had completely dissolved, the subject was instructed to ingest 240 mL of ambient temperature water within one minute. The actual dosing time was recorded when the tablet was placed on the subject's tongue.

In addition to evaluation for bioequivalence between dosage forms, the *in vivo* disintegration times of citalopram ODT were recorded in both treatment groups. Each subject was given a timer to record the time it took for disintegration of tablet to occur in the mouth, starting the moment the ODT was placed on the tongue and stopping the moment the tablet began to break. This time interval was recorded as *in-vivo* disintegration time of citalopram ODT. The subjects will continue to suck on the tablet until the tablet drug had completely dissolved.

All subjects remained fasted for at least 4 hours post-dose. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects remained in the clinic until the 24-hour blood sampling in each study period.

#### **Safety Assessments:**

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and laboratory measurements (biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine and saliva alcohol testing). In addition, pregnancy tests were performed on all female subjects. A hemoglobin test was repeated for all subjects prior to Period II dosing. The 12-lead ECG monitoring was carried out prior to starting the study, during each study period at 24 hours post-dose, and at the completion of the study. Adverse events were monitored throughout the study.

#### **Pharmacokinetics Assessments:**

A total of 25 blood samples were collected from each subject for determination of citalopram, demethylcitalopram, and didemethylcitalopram at pre-dose, 0.5, 1.0, 1.5, 2.0, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, and 240 hours post-dose. No urine samples were collected. Plasma samples were stored frozen at  $-25^{\circ}\text{C} \pm 10^{\circ}\text{C}$  until assayed.

Plasma concentrations of citalopram and its metabolites, demethylcitalopram and didemethylcitalopram were analyzed by a validated LC-MS/MS method. An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ and ULOQ of citalopram and the metabolites. A weighed ( $1/\text{conc}^2$ ) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicated QC samples for each analyte at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

Table 39. Assay validation for Study 2914

	Citalopram	Demethyl-citalopram	Didemethyl-citalopram
<b>Method:</b>	LC-MS/MS	LC-MS/MS	LC-MS/MS
<b>Standard curve</b>			
Range:			
Precision:			
Accuracy:			
Linearity:			
<b>LOQ</b>			
LLOQ:			
ULOQ:			
<b>QC</b>			
Low:			
Precision:			
Accuracy:			
Med:			
Precision:			
Accuracy:			
High:			
Precision:			
Accuracy:			

**Pharmacokinetic Analysis:**

The following pharmacokinetic parameters for citalopram, demethylcitalopram, and didemethylcitalopram from both Treatment groups were calculated by standard non-compartmental methods:  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $t_{1/2}$ , and MRT.

**Statistical Analysis:**

Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of citalopram, demethylcitalopram, and didemethylcitalopram at each sampling time and for each formulation. The ANOVA was performed using SAS on pharmacokinetic parameters and included period, sequence, subjects nested within sequence, and treatment as factors.

For the bioequivalence determination, the intra-subject CV and the relative ratios of the geometric means between the two treatments, and the 90% confidence intervals (CI) were calculated based on the difference in means of the log-transformed  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  for citalopram, demethylcitalopram, and didemethylcitalopram.

**RESULTS**

**Demographics of Subjects:**

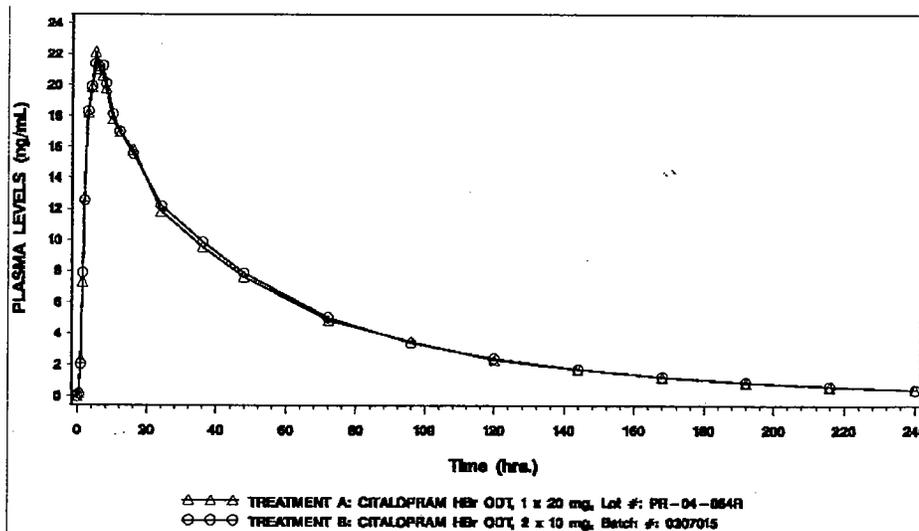
Thirty-six subjects (18 males and 18 females) were enrolled into the study and were dosed in period I, of whom 30 actually completed the study. The mean age was 38 years (18-62 years of age) and the mean BMI was 24.8 kg/m<sup>2</sup> (19-29.7 kg/m<sup>2</sup>). The subjects consisted of 21

Caucasians, 5 Asians, 5 Blacks, and 5 Hispanics. Among the 6 subjects either withdrawn or dismissed from the study, subjects #006 and #024 were removed from the study and excluded from the pharmacokinetic and statistical analyses due to the adverse events, but were included in analysis for potential contributor for adverse events. Subject #026, experienced vomiting within twice the median  $T_{max}$  and was removed per FDA guideline. Therefore, the initial pharmacokinetic determination was performed on 30 subjects who completed the study, and the final pharmacokinetic and statistical analyses were performed on 29 subjects who completed the study.

**Pharmacokinetic Summary:**

Mean citalopram, demethylcitalopram, and didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) are shown in Figures 21-23. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 40-42.

**Figure 21.** Mean citalopram plasma concentration-time profiles following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)



**Table 40.** Summary of pharmacokinetic results and statistics for citalopram following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)

PK Parameters (n=29)	A	B	Citalopram ODTs 1x20 mg (A) vs 2x10 mg (B)	
	Citalopram HBr ODT 1x20 mg (Lot# PR-04-064R)	Citalopram HBr ODTs 2x10 mg (Lot# 0307015)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval
AUC <sub>0-∞</sub> (ng*hr/mL)	1069.13 ± 319.29	1087.77 ± 306.71	97.89%	94.73% to 101.16%
AUC <sub>0-t</sub> (ng*hr/mL)	1110.56 ± 342.60	1130.29 ± 331.48	97.85%	94.75% to 101.06%
C <sub>max</sub> (ng/mL)	23.33 ± 5.24	23.39 ± 5.02	99.59%	96.81% to 102.46%
T <sub>max</sub> (hr)*	5	5		
T <sub>1/2</sub> (hr)	49.34 ± 10.83	51.02 ± 10.59		

\* Median T<sub>max</sub>

Figure 22. Mean demethylcitalopram plasma concentration-time profiles following single oral doses of citalopram-HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)

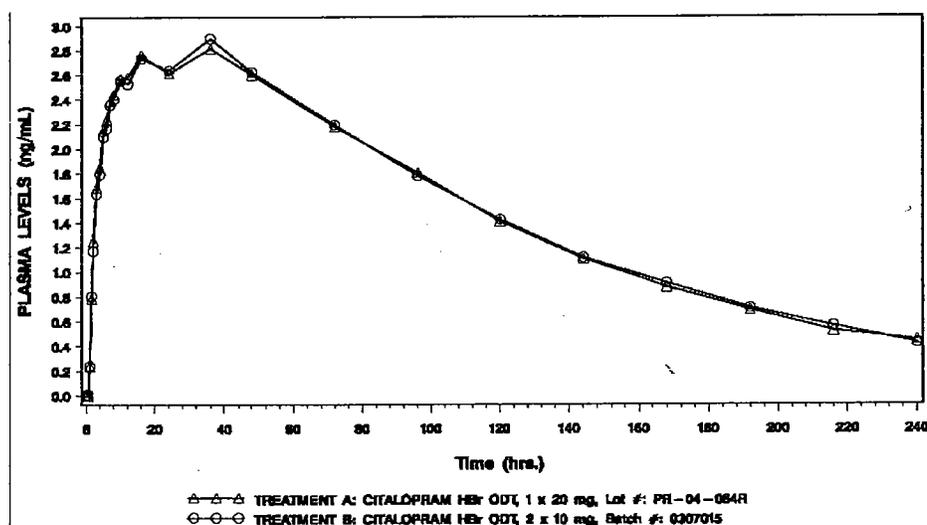
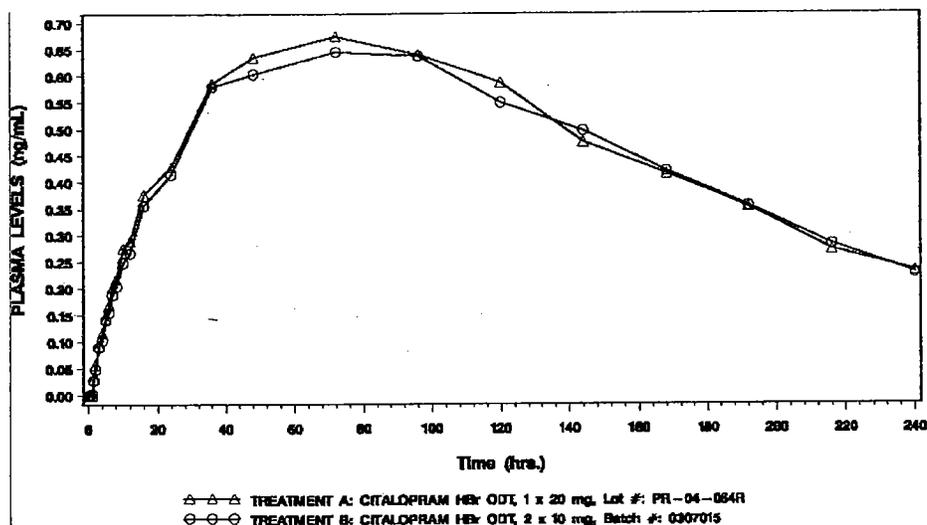


Table 41. Summary of pharmacokinetic results and statistics for demethylcitalopram following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)

PK Parameters (n=29)	A	B	Citalopram ODTs 1x20 mg (A) vs 2x10 mg (B)	
	Citalopram HBr ODT 1x20 mg (Lot# PR-04-064R)	Citalopram HBr ODTs 2x10 mg (Lot# 0307015)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval
AUC <sub>0-∞</sub> (ng*hr/mL)	363.28 ± 69.91	366.89 ± 67.80	99.00%	95.65% to 102.47%
AUC <sub>0-t</sub> (ng*hr/mL)	416.15 ± 99.47	412.85 ± 86.79	100.30%	96.80% to 103.93%
C <sub>max</sub> (ng/mL)	3.04 ± 0.75	3.06 ± 0.69	98.58%	94.64% to 102.68%
T <sub>max</sub> (hr)*	16	36		
T <sub>1/2</sub> (hr)	70.02 ± 23.40	66.24 ± 19.45		

\* Median T<sub>max</sub>

**Figure 23.** Mean didemethylcitalopram plasma concentration-time profiles following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)



**Table 42.** Summary of pharmacokinetic results for didemethylcitalopram following single oral doses of citalopram HBr 1 x 20 mg ODT formulation (Treatment A) and 2 x 10 mg ODT formulation (Treatment B) (N = 29)

PK Parameters (n=29)	A	B	Citalopram ODTs 1x20 mg (A) vs 2x10 mg (B)	
	Citalopram HBr ODT 1x20 mg (Lot# PR-04-064R)	Citalopram HBr ODTs 2x10 mg (Lot# 0307015)	Ratio of Geometric Means (%)	90% Geometric Confidence Interval
AUC <sub>0-t</sub> (ng*hr/mL)	111.88 ± 69.12	109.92 ± 66.10	102.15%	97.64% to 106.87%
AUC <sub>0-inf</sub> (ng*hr/mL)	161.01 ± 70.65	161.94 ± 65.44	100.19%	94.03% to 106.76%
C <sub>max</sub> (ng/mL)	0.72 ± 0.47	0.68 ± 0.42	105.75%	99.93% to 111.90%
T <sub>max</sub> (hr)*	72	72		
T <sub>1/2</sub> (hr)	88.00 ± 27.90	88.37 ± 29.38		

\* Median T<sub>max</sub>

**In-Vivo Disintegration Time:**

The citalopram HBr ODT formulations disintegrated rapidly when placed on the tongue, with mean values of the *in-vivo* disintegration time of citalopram for Treatments A and B being 13 seconds (2-38 seconds) and 14 seconds (6-40 seconds), respectively.

**CONCLUSION:**

- As shown in the results, citalopram exhibited similar pharmacokinetic profiles following oral administration of 20 mg test (1 x 20 mg) or reference (2 x 10 mg) ODT formulation under fasting condition. The rate and extent of absorption of citalopram from two treatments were similar. The ratios of geometric mean of AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>,

and  $C_{max}$  for citalopram were 97.89%, 97.85%, and 99.59%, respectively. The corresponding 90% CI of the geometric mean ratios of  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  were within the range of 80% -125%. Therefore, the dosage form equivalency was demonstrated between two strengths (1 x 20 mg vs. 2 x 10 mg) of Citalopram HBr ODT.

- Similar pharmacokinetic profiles were observed with demethylcitalopram and didemethylcitalopram following oral administration of 20 mg test (1 x 20 mg) or reference (2 x 10 mg) ODT formulation under fasting condition.

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4.3. Cover sheet and OCPB filing/review form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21-763	Brand Name	TRADENAME	
OCPB División (I, II, III)	DPE-I	Generic Name	Citalopram Hydrobromide	
Medical Division	HFD-120	Drug Class	Antidepressant	
OCPB Reviewer	Ta-Chen Wu, PhD	Indication(s)	Treatment of depression	
OCPB Team Leader	Ramana Uppoor, PhD	Dosage Form	Orally Disintegrating Tablets 10 mg, 20 mg, 40 mg	
		Dosing Regimen	Initial dose 20 mg/day with an increase up to 40 mg/day in increments of 20 mg at intervals of no less than one week; 20 mg/day for elderly patients and patients with hepatic impairment	
Date of Submission	April 14, 2004	Route of Administration	Oral	
Estimated Due Date of OCPB Review	12/27/04	Sponsor	Biovail Laboratories, Inc.	
PDUFA Due Date	2/14/05	Priority Classification	S	
Division Due Date	1/13/05			
Clin. Pharm. And Biopharm. Information				
<p><b>Summary:</b> This is an electronic submission for 505(B)(2) application with no desk copy provided. TRADENAME (Citalopram HBr) is a new drug formulation (orally disintegrating tablet) and is indicated for the treatment of depression. One pilot BE study (26022) using prototype 40 mg ODT formulation and two BE studies (2730, 2732) using to-be-marketed 40 mg ODT formulation were conducted in support for the bioequivalence to the RLD Celexa™ (NDA 20-822). One food effect study (2731) was conducted with highest strength of 40 mg ODT. One dosage strength equivalence study (2750) was conducted between 4 x 10 mg ODT and 1 x 40 mg ODT. In vitro dissolution profiles of to-be-marketed ODT formulation of different strengths were constructed in various media of different pH values, including deionized water.</p>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
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			• No annotated Word file
Reference Bioanalytical and Analytical Methods	X			• Validation report provided
<b>I. Clinical Pharmacology</b>	-	-	-	
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				

<b>Healthy Volunteers-</b>				
single dose:	-	-	-	
multiple dose:	-	-	-	
<b>Patients-</b>				
single dose:	-	-	-	
multiple dose:	-	-	-	
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:	-	-	-	
<b>Subpopulation studies -</b>				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
<b>PD:</b>				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
<b>Population Analyses -</b>				
Data rich:	-	-	-	
Data sparse:	-	-	-	
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:	X	5 (1 additional dosage strength equivalence study submitted later)	4	<ul style="list-style-type: none"> <li>• Pilot study (26022) – 40 mg prototype ODT formulation vs. Celexa™ 40 mg tablets</li> <li>• 2 definitive BE studies (2730 and 2732) – 40 mg ODT vs. Celexa™ 40 mg tablets in study 2730; 40 mg ODT doses with or without water in study 2732</li> <li>• 1 dosage strength equivalence study (2750) – 4 x 10 mg ODT vs. 1 x 40 mg ODT</li> <li>• Raw data for concentration-time profiles in all BE studies were provided</li> </ul>
replicate design; single / multi dose:	-	-	-	
<b>Food-drug interaction studies:</b>	X	1	1	<ul style="list-style-type: none"> <li>• 1 food effect study (2731) of 40 mg ODT</li> <li>• Content of high-fat breakfast not specified</li> </ul>
<b>Dissolution:</b>	X			<ul style="list-style-type: none"> <li>• No raw data provided for each dissolution profile (only mean, max and min values were provided)</li> </ul>
<b>(IVIVC):</b>	-	-	-	
<b>Bio-waiver request based on BCS</b>	-	-	-	

BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X	16	-	
Total Number of Studies		6 + dissolution study	5 + dissolution study	
<b>Fiability and QBR comments</b>				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?	X	Comments have been sent to firm (or attachment included), FDA letter date if applicable. Please forward to Sponsor: 1. Please provide the annotated Word file of the proposed labeling 2. Please provide raw data for dissolution profiles for bio-batch listed in Item 4 (cmc) and Item 6 (hpbio), and justification of dissolution method 3. Please specify the content of high-fat food for food-effect study 4. BE study with 20 mg ODT should be conducted		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> <li>• Is the to-be-marketed ODT formulation bioequivalent to the RLD formulation of same strength?</li> <li>• Can bio-waiver been given to TBM ODT of 20 mg strength?</li> <li>• Are different-strengths of the to-be-marketed formulations bioequivalent?</li> <li>• Is there a food effect on the bioavailability of citalopram ODT?</li> <li>• How do the dissolution conditions and specifications support the bioequivalence of different formulations?</li> <li>• What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?</li> <li>• Are the bioanalytical methods adequate and appropriately validated?</li> </ul>		
Other comments or information not included above		Project Manager: Please request DSI inspection of the clinical and the analytical sites - Studies 2730 and 2750		
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 21-679, HFD-850(Electronic Entry or Lee), HFD-120(R. Gujral), HFD-860 (R. Uppoor, A. Rahman, M. Mehta

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Ta-Chen Wu  
2/1/05 12:44:35 PM  
BIOPHARMACEUTICS

Ramana S. Uppoor  
2/1/05 12:52:26 PM  
BIOPHARMACEUTICS

Mehul Mehta  
2/2/05 08:42:39 AM  
BIOPHARMACEUTICS