# NDA Multidisciplinary Review and Evaluation

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| **Application Type** | NDA |
| **Application Number(s)** | 021164 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | December 23, 2022 |
| **Received Date(s)** | December 23, 2022 |
| **PDUFA Goal Date** | September 23, 2023 |
| **Division/Office** | Division of Psychiatry/Office of Neuroscience |
| **Review Completion Date** | September 22, 2023 |
| **Established/Proper Name** | Gepirone ER |
| **(Proposed) Trade Name** | Exxua |
| **Pharmacologic Class** | Antidepressant |
| **Code Name** | N/A |
| **Applicant** | Fabre-Kramer Pharmaceuticals, Inc. |
| **Dosage form** | Tablet |
| **Applicant Proposed Dosing Regimen** | 1) The recommended starting dose is 20 mg administered orally once daily with food at approximately the same time each day; 2) If the 20 mg initial dose is adequately tolerated, an increase to 40 mg given once daily may begin as early as Day 4 of dosing; 3) If the 40 mg dose is well tolerated and additional efficacy is desired, the dose may be increased to 60 mg after one week and to 80 mg after an additional week; 4) Adjust dose by 50% when a moderate CYP3A4 inhibitor is administered. |
| **Applicant Proposed Indication(s)/Population(s)** | Treatment of major depressive disorder in adults |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | 370143000 \| Major depressive disorder (disorder) \| |
| **Recommendation on Regulatory Action** | Approval |

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Abbreviations: DP, Division of Psychiatry; OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

# Additional Reviewers of Application

| | |
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Abbreviations: CSS, Controlled Substance Staff; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DRM, Division of Risk Management; DUOG, Division of Urology, Obstetrics and Gynecology; IRT, Interdisciplinary Review Team for Cardiac Safety Studies; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

## Signatures

Please refer to uploaded memos for each discipline in DARRTS.

# Glossary

| | |
|---|---|
| AE | adverse event |
| ANDA | abbreviated new drug application |
| APA | American Psychiatric Association |
| APTT | activated partial thromboplastin time |
| AR | adverse reaction |
| AUC | area under the concentration-time curve |
| CDER | Center for Drug Evaluation and Research |
| CDRS-R | Children's Depression Rating Scale-Revised |
| CFB | change from baseline |
| CMC | chemistry, manufacturing, and controls |
| CMH | Cochran-Mantel-Haenszel |
| CRF | case report form |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| CTM | clinical trial material |
| DCOA | Division of Clinical Outcome Assessment |
| DP | Division of Psychiatry |
| DPMH | Division of Pediatric and Maternal Health |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DUOG | Division of Urology, Obstetrics and Gynecology |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ER | extended release |
| FDA | Food and Drug Administration |
| FDRR | Formal Dispute Resolution Request |
| FMI | final market image |
| HAMD-17 | 17-item Hamilton Depression Rating Scale |
| IND | Investigational New Drug |
| IR | immediate release |
| ISS | integrated summary of safety |
| ITT | intent-to-treat |
| IVIVC | in vivo correlation studies |
| JAS | juvenile animal study |
| LOCF | last-observation-carried-forward |
| MAOI | monoamine oxidase inhibitor |
| MDD | major depressive disorder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | new drug application |

| | |
|---|---|
| NME | new molecular entity |
| NOAEL | no observed adverse effect level |
| OCP | Office of Clinical Pharmacology |
| ODE-I | Office of Drug Evaluation |
| OL | open-label |
| OLE | open-label extension |
| OND | Office of New Drugs |
| OPQ | Office of Pharmaceutical Quality |
| OSIS | Office of Study Integrity and Surveillance |
| PDAC | Psychopharmacological Drug Advisory Committee |
| PK | pharmacokinetic |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PND | postnatal day |
| PREA | Pediatric Research Equity Act |
| PWR | pediatric written request |
| SAE | serious adverse event |
| SNRI | serotonin norepinephrine reuptake inhibitors |
| SMQ | Standard MedDRA Queries |
| SSRI | serotonin reuptake inhibitors |
| TEAE | treatment emergent adverse event |
| TRD | treatment resistant depression |
| ΔΔQTc | maximum mean increase in QT, placebo-corrected and adjusted for heart rate |

# 1 Executive Summary

## 1.1. Product Introduction

Gepirone extended release (ER) is a 5HT1A receptor agonist intended for the treatment of major depressive disorder (MDD) in adults. Gepirone is a new molecular entity (NME) that was first developed by Mead Johnson and Bristol-Myers Company, later transferred in 1993 to the Applicant, Fabre-Kramer Pharmaceuticals, and further developed by Organon. Gepirone is not currently marketed in any countries. The Applicant originally submitted NDA 021164 on October 1, 1999. FDA subsequently issued a total of three Not Approvable letters based on a lack of substantial evidence of effectiveness—first in response to the original application, and then in response to two subsequent resubmissions. The Applicant later filed a Formal Dispute Resolution Request (FDRR) and, following consideration by then-Office of New Drugs (OND) Director, John Jenkins, MD, and a public advisory committee meeting, Dr. Jenkins granted the dispute appeal on March 16, 2016, in favor of the Applicant. However, Dr. Jenkins noted that the Applicant would need to submit chemistry, manufacturing, and controls (CMC) information and a thorough QT study before the application could be approved. The Deputy Director of the former Office of Drug Evaluation-I (ODE-I) appealed the OND decision to the Center for Drug Evaluation and Research (CDER) Director; the CDER Director upheld the OND decision.

The Applicant resubmitted the NDA on December 23, 2022. The NDA resubmission included the previously requested QT studies and CMC information described in the 2016 Appeal Granted letter, new analyses on longer-term efficacy and sexual dysfunction, new pediatric study data, and a request for pediatric exclusivity. The resubmission did not include the requested Controlled Substance Staff (CSS) data or analyses that were requested during a Type B presubmission planning meeting held on January 30, 2017.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness of gepirone ER in adults was previously determined during a dispute resolution process and was not reassessed as part of the current NDA resubmission. According to the FDRR documentation, the Applicant demonstrated evidence of effectiveness in two studies: Study 134001, “A double-blind, multicenter, randomized, placebo-controlled, efficacy and safety study of Org 33062 ER in subjects with major depressive disorder,” and Study FKGBE007, “A double-blind multicenter, randomized, placebo-controlled efficacy and safety study of Org 33062 ER in subjects with major depressive disorder.” The primary endpoint for both studies was the change from baseline (CFB) to 8 weeks in the 17-item Hamilton Depression Rating Scale (HAMD-17) total score for gepirone ER compared to placebo, administered to subjects with MDD using a flexible-dose titration for gepirone ER 20 mg, 40 mg, 60 mg, and 80 mg. The primary endpoints in both studies were statistically significant. The Applicant’s long-term efficacy study (28709) failed to demonstrate efficacy for maintenance

treatment of MDD. In order to fulfill the terms of a prior Pediatric Written Request (PWR), the Applicant also conducted two pediatric efficacy studies for gepirone ER (Study 134019 and Study 134020), which did not demonstrate efficacy on their primary endpoint, CFB to 9 weeks on the Children's Depression Rating Scale-Revised (CDRS-R).

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Gepirone extended release (ER) is a 5HT1A receptor agonist and NME proposed for the treatment of major depressive disorder (MDD). Although gepirone ER is not associated with an established pharmacologic class, the mechanism of action is similar to buspirone, which is approved for the treatment of generalized anxiety disorder. The Applicant conducted 17 randomized, double-blind phase 2 or 3 controlled studies, of which only two (Study 134001 and Study FK-GBE-007) had statistically significant results on their primary endpoint. During a dispute resolution process initiated by the Applicant, FDA determined that these two positive adequate and well-controlled studies provided substantial evidence of effectiveness.

With this submission, the Applicant also provided a post hoc re-analysis of a prior longer-term study, the results of two pediatric efficacy trials (including both children and adolescents), (b) (4) However, none of this information will be reflected in the approved product labeling.

Our updated examination of gepirone ER's safety data reveals that the drug is associated with high rates of adverse reactions (ARs) such as dizziness, headache, and nausea, and that dosing adjustments are required for patients of geriatric age, receiving a moderate CYP3A4 inhibitors, or with hepatic or renal impairment. Gepirone ER may cause clinically significant QT interval prolongation; the product labeling will include a Warning and Precaution for QT prolongation and, in Dosage and Administration, note prescribers should perform electrocardiogram (ECG) and electrolyte monitoring prior to initiating treatment. Gepirone ER is contraindicated in patients with congenital long QT syndrome, severe hepatic impairment, and patients receiving concomitant strong CYP34A inhibitors or monoamine oxidase inhibitors (MAOIs). These risk considerations can still be adequately conveyed to clinicians and patients in the gepirone ER prescribing information and medication guide. Postmarketing studies will be required to better characterize safety during pregnancy and lactation, and to better assess risks associated with QTc prolongation. In addition, there will be a post-marketing commitment to conduct a randomized withdrawal study.

Given the prior OND-level dispute appeal resolution determination that the gepirone ER application meets the standard for substantial evidence of effectiveness in adults over age 18, and safety concerns that can be sufficiently mitigated through labeling, gepirone ER will be approved for the treatment of MDD, with the indicated population limited to adults.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • MDD is a leading cause of disability and major contributor to the overall global burden of disease. The lifetime prevalence of MDD is estimated at 18 percent. Although the point prevalence of MDD in childhood is rare, by adolescence, the incidence is comparable to that found in adulthood (around 7%). MDD is considered a chronic disorder that can cause long-term and clinically significant distress and impairment in social, occupational, physical, and other important areas of functioning. | MDD is a common psychiatric disorder with symptoms that often begin during youth. Symptoms of MDD can be debilitating and require long-term treatment. |
| Current Treatment Options | • The treatment of MDD involves psychotherapy and, if needed, prescription medication. Drugs used to treat MDD affect brain neurotransmitters, most require daily dosing, and are often used long-term. There are over three dozen drugs with FDA indications to treat MDD in adults from multiple drug classes. Two drugs have indications for the treatment of MDD in children (fluoxetine and escitalopram); off-label use of other medications is common for treating pediatric MDD. Approximately half of patients diagnosed with MDD will not achieve sustained remission from treatment, even after multiple drug trials. | There are numerous treatment options available for MDD. Nonetheless, treatment failure or incomplete treatment of symptoms remains common, and many patients continue to have symptoms despite adequate treatment with FDA approved medication. |
| Benefit | • The Applicant demonstrated efficacy for gepirone ER in two placebo-controlled efficacy trials in adults as follows:<br>1) Study 134001: least-squares mean change from Baseline to Week 8 in HAMD-17 total score (standard error), gepirone ER -9.04 (0.78) compared to placebo -6.75 (0.77), with a placebo-subtracted difference -2.47 (p-Value 0.013); and | Gepirone ER offers another treatment option for adults with MDD. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | 2) Study FK-GBE-007: least-squares mean change from Baseline to Week 8 in HAMD-17 total score (standard error), gepirone ER -10.22 (0.75) compared to placebo -7.96 (0.73), with a placebo-subtracted difference -2.45 (p-Value 0.018).<br>• The Applicant did not demonstrate longer-term efficacy in adults, efficacy in pediatric subjects, or that gepirone ER offers an advantage of less sexual dysfunction effects. | |
| Risk and Risk Management | • In pooled safety data for adults, high rates of ARs were observed with gepirone ER compared to placebo, including dizziness (49%), nausea (35%), and headaches (31%). Other ARs occurring in ≥2% of subjects and greater than the incidence in placebo include: insomnia, feeling sleepy or tired, migraine, diarrhea, dry mouth, abdominal pain, vomiting, increased appetite, dyspepsia, constipation, nasal congestion, hyperhidrosis, palpitations, weight increased, agitation, feeling jittery, heart rate increased, paresthesia, and lethargy. Overall, there are no clinically relevant mean changes in vital signs (weight, blood pressure, heart rate) or laboratory values with gepirone ER compared to placebo, or ARs at a rate of concern for vital signs or laboratory values.<br>• Pooled safety results from pediatric studies were similar to or less than ARs reported in the pooled adult safety data for gepirone ER, with the exception of vomiting (13% in pediatric patients compared to 6.6% in adults).<br>• Gepirone ER is associated with clinically relevant QT interval prolongation, and prescribers should obtain an ECG and, if needed, | Gepirone ER has contraindications, high rates of certain ARs, dosage restrictions, and monitoring requirements that are different than other drugs for MDD (including buspirone) which will be important for clinicians and patients to understand prior to using gepirone. These risks for now can be adequately conveyed in the gepirone ER prescribing information and medication guide and postmarketing requirement (PMR) studies will be used to better characterize safety during pregnancy and lactation, and to better assess extent of and risk associated with QTc prolongation. The gepirone ER prescribing information (PI) will include risks associated with serotonergic antidepressants as a class; a PMR is necessary to understand if the if the mechanism of action associated with increased |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | correct electrolyte abnormalities prior to treatment initiation, and continue to monitor ECGs with dose adjustment and periodically thereafter. Caution should be exercised prior to use of gepirone ER in patients at higher risk for torsade de pointes.<br>• Dosage adjustments are required for geriatric patients, when a moderate CYP3A4 inhibitor is administered, and for hepatic and renal impairment.<br>• Gepirone ER is contraindicated in patients with congenital long QT syndrome due to risk of torsades de pointes.<br>• Gepirone ER is contraindicated in patients receiving concomitant strong CYP34A inhibitors or severe hepatic impairment due to risk associated with elevated levels of gepirone ER. Gepirone ER is contraindicated in individuals taking, or within 14 days of stopping, MAOIs due to risk of hypertensive crisis and serotonin syndrome.<br>• Embryotoxicity: Based on nonclinical studies, gepirone ER may cause fetal harm and is present in rat milk. Additional postmarket studies are necessary to better characterize the risk associated with gepirone ER during pregnancy and in lactating women.<br>• QTc prolongation could not be fully assessed due to limitations in the Applicant's assessment of QTc during their drug development program. Additional postmarket studies are necessary to better characterize risks associated with QT prolongation and gepirone ER.<br>• The Applicant did not conduct or submit the requested abuse liability studies/analyses; however, the controlled substance staff (CSS) reviewer used the available data to determine that gepirone ER does not have abuse potential, similar to most commonly used serotonergic | bleeding risk in SSRIs also extends to gepirone ER or its metabolites. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | antidepressants.<br>• As a serotonergic antidepressant, the gepirone ER product label will include drug class warnings, including: 1) increased risk of suicidal thoughts and behaviors, especially in pediatric and young adult patients; 2) serotonin syndrome; 3) activation of mania/hypomania; and 3) fetal and neonatal adverse reactions based on maternal exposure. | |

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to this Application** (check all that apply)

| | | | | |
|---|---|---|---|---|
| ☐ | **The patient experience data that were submitted as part of the application include:** | | | Section of review where discussed, if applicable |
| | ☐ | Clinical outcome assessment (COA) data, such as | | |
| | | X | Patient reported outcome (PRO) | Section 15.5 |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | X | Clinician reported outcome (ClinRO) | Section 8.1<br>Section 8.2 |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify): | | |

| | | | |
|---|---|---|---|
| ☐ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | |
| | ☐ | Input informed from participation in meetings with patient stakeholders | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | ☐ | Observational survey studies designed to capture patient experience data | |
| | ☐ | Other: (Please specify): | |
| ☐ | **Patient experience data was not submitted as part of this application.** | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

The World Health Organization describes MDD as a leading cause of disability and major contributor to the overall global burden of disease (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). The lifetime prevalence of MDD in developed countries such as the United States and Europe is estimated at 18 percent (Kessler et al. 2011). The majority of patients with MDD have comorbid psychiatric or other medical conditions, further complicating treatment (Kessler et al. 2011).

The phenotype of MDD is heterogeneous, and the etiology involves multiple interacting factors, including biological factors (e.g., genetics, neurobiology), psychological factors (e.g., psychological tendencies and traits), and social factors (e.g., stressful life events, trauma, lack of support). Determination of the diagnosis of MDD is clinical. No reliable laboratory tests or biomarkers are available to aid in the diagnosis of MDD. The most commonly used taxonomy for a clinical diagnosis of MDD is the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association 2013).

Symptoms of MDD often start in youth (Costello et al. 2003; Kessler et al. 2005). Although the point prevalence of MDD in childhood is rare, by adolescence, the incidence is comparable to that found in adulthood; around 5% to 7% (Costello et al. 2003; Kessler et al. 2005). Numerous treatment modalities exist to improve symptoms of MDD (see Table 1). Although treatment to remission is the goal (Rush et al. 2006), approximately half of those with MDD will not achieve sustained remission, even after multiple adequate drug treatment trials (McIntyre et al. 2014).

## 2.2. Analysis of Current Treatment Options

The treatment of MDD involves psychotherapy and, if needed, prescription medication. Drugs used to treat MDD affect brain neurotransmitters, typically require daily administration, and are generally used long-term for this chronic episodic condition.

In adults, treatment options for MDD include serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other antidepressants such as mirtazapine and bupropion. Of these, SSRIs and SNRIs are relatively newer, have a more favorable benefit to risk profile, and are prescribed more frequently than older antidepressant drugs. SSRIs and SNRIs are generally well-tolerated, with common adverse reactions (ARs) of nausea/vomiting, weight gain, diarrhea, sleep disturbances, and sexual dysfunction. Uncommon but potentially serious adverse events associated with SSRIs and SNRIs include serotonin syndrome, increased risk of bleeding, activation of mania or hypomania, discontinuation syndrome, seizures, hyponatremia, and

drug-drug interactions such as with MAOIs. All antidepressant labels include a boxed warning about an increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults.

Given the range of effective options available for the treatment of depression, there are few nonapproved treatments that are widely used for MDD off-label in adults. The lay population occasionally uses over-the-counter herbal remedies such as St. John's Wort. Drugs with approval as adjunctive treatment for MDD include quetiapine XR, aripiprazole, and brexpiprazole, in combination with an antidepressant medication. The FDA approved esketamine (Spravato) and a fixed-combination drug of fluoxetine plus olanzapine (Symbyax) for treatment resistant depression (TRD). Devices used to treat TRD in adults include electroconvulsive therapy and transcranial magnetic stimulation. Drugs with FDA indications for adults with MDD are commonly used off-label in the treatment of pediatric patients with MDD.

**Table 1. Summary of Treatment Armamentarium for MDD**

| **Drug Name (Trade Name, Approval Year)** | **Common Adverse Reactions** | **Serious Adverse Reactions/Cautions** |
|---|---|---|
| *Tricyclic (TCAs) and tetracyclic Antidepressants* | | |
| Amitriptyline (Elavil, 1977), Amoxapine (Asendin,1992), Desipramine (Norpramin 1964), Doxepin (Sinequan 1969), Imipramine (Tofranil 1959), Maprotiline* (Ludiomil 1988), Nortriptyline (Pamelor 1964) Protriptyline (Vivactil 1967), Trimipramine (Surmontil 1979) | Dry mouth, constipation, blurred vision, drowsiness, low blood pressure | Urinary retention, confusion, fainting, seizures, arrhythmias. Use with caution with narrow-angle glaucoma |
| *MAOIs* | | |
| Isocarboxazid (Marplan 1959), Maprotiline (Mylan 1959), Phenelzine (Nardil 1961), Tranylcypromine (Parnate 1961), Selegiline patch (Emsam 2006) | Nausea, restlessness, problems sleeping, dizziness, drowsiness | Headache, stroke, fainting, heart palpitations, blood pressure changes, drug-drug interactions |
| *SSRIs* | | |
| Citalopram (Celexa 1998), Escitalopram (Lexapro 2002)*, Fluoxetine (Prozac 1987)*, Paroxetine (Paxil 1992, Paxil CR 1999, Pexeva 2003), Vortioxetine (Trintellix 2013), Vilazodone (Viibryd 2011), Sertraline (Zoloft 1991) | Nausea, tremor, nervousness, difficulty sleeping, sexual problems, sweating, agitation, fatigue | Seizures, abnormal bleeding or bruising, withdrawal symptoms, and serotonin syndrome. |

| Drug Name (Trade Name, Approval Year) | Common Adverse Reactions | Serious Adverse Reactions/Cautions |
|---|---|---|
| *SNRIs* | | |
| Duloxetine (Cymbalta 2004), Venlafaxine (Effexor 1993, Effexor XR 1997), Levomilnacipran (Fetzima 2013), Desvenlafaxine (Pristiq 2008, Khedezla 2013) | Nausea, vomiting, dry mouth, constipation, fatigue, feeling drowsy, dizziness, sweating, sexual problems | Seizures, abnormal bleeding or bruising, withdrawal symptoms, and serotonin syndrome |
| *Atypical Antidepressants* | | |
| Trazodone (Desyrel 1981) Nefazodone (Serzone 1994) | Dry mouth, dizziness, blurred vision, drowsiness, constipation | Erection, low blood pressure, fainting, confusion, liver failure |
| *Other Antidepressants* | | |
| Mirtazapine (Remeron 1996) | Drowsiness, weight gain, dizziness | Agranulocytosis, elevated cholesterol, liver enzymes increase |
| Bupropion (Wellbutrin 1989, Wellbutrin SR 1996, Wellbutrin XL 2003) | Dizziness, constipation, nausea, vomiting, blurred vision | Seizures, changes in blood pressure |
| Dextromethorphan/buprion (Auvelity, 2022) | Dizziness, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhidrosis | Seizures, changes in blood pressure, activation of mania, psychosis, angle-closure glaucoma, serotonin syndrome, embro-fetal toxicity. |

Source: Clinical Reviewer Generated Table from Drug Prescribing Information
*Has pediatric indication.
Abbreviations: MAOI, monoamine oxidase inhibitors; MDD, major depressive disorder; SNRI, serotonin norepinephrine reuptake inh bitors; SSRI, serotonin reuptake inhibitors; TCA, tricyclic antidepressants

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Gepirone is not yet approved or marketed in the United States or other countries.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Gepirone was originally developed by Mead Johnson and Bristol-Myers Company for the treatment of both anxiety and depression, first as an immediate-release (IR) formulation, and later as an extended-release product. In 1992, Bristol-Myers Company terminated ongoing phase 3 trials due to a business decision and, in 1993, Fabre-Kramer Pharmaceuticals, Inc. (Houston, Texas) acquired the rights to gepirone ER. In May 1998, Organon, Inc. executed an agreement with Fabre-Kramer Pharmaceuticals granting Organon rights to further develop and market gepirone ER (for a review of the gepirone IR and ER IND 033626 regulatory history, refer to FDA NDA clinical reviewers by Earl Hearst, MD, entered into record on February 2, 2002, and

October 24, 2007). See below for the NDA 021164 regulatory history:

- **September 30, 1999**: Organon submitted the original NDA on September 30, 1999. FDA refused to file on November 30, 1999, because the Applicant did not have two positive and well-controlled trials.

- **May 18, 2001**: Organon resubmitted the NDA and included two short-term studies with the ER formulation in subjects with MDD along with three efficacy studies using the IR formulation. FDA issued a Non-Approvable Letter dated March 15, 2002, citing inadequate evidence of effectiveness.

- **December 23, 2003**: Organon amended the NDA with additional clinical data from a long-term relapse prevention study (Study 28709). The interpretation of this study was confounded by issues related to reclassification of relapsed subjects after unblinding and definition of the intent-to-treat (ITT) population. These deficiencies were outlined in a second Non-Approvable Letter issued to Organon on June 23, 2004. On June 24, 2005, ownership of gepirone was transferred from Organon to Fabre-Kramer Pharmaceuticals.

- **October 12, 2005**: Fabre-Kramer met with FDA to discuss the resubmission of the NDA for gepirone ER. The Applicant advised that they would likely file an application based on the results of two positive short-term studies (Studies FK-GBE-007 and 134001). Also, during the October 12, 2005 meeting, FDA indicated that they would consider a claim for a lower risk of sexual dysfunction with gepirone ER. During a May 31, 2006 teleconference, FDA agreed that most of the analyses of routine safety data would focus on gepirone ER data, but for exposure, deaths, serious adverse events (SAEs), discontinuations for AEs, and other AEs of special interest, both ER and IR data would be analyzed. FDA agreed that a proposed analysis for several specific measures of sexual dysfunction showing noninferiority to placebo for gepirone ER and inferiority for active controls may be sufficient to support a claim of lack of sexual dysfunction with gepirone ER. FDA also agreed that the efficacy analysis would focus on 12 adequately-designed ER studies, summary information from gepirone IR studies, and a relapse prevention study (Study 28709), and that the pediatric data could be submitted at a later date.

- **May 3, 2007**: The Applicant resubmitted the NDA and included a new efficacy study FK-GBE-007 (one of the two positive efficacy studies). FDA conducted a full review of the safety data (see review dated October 24, 2007, by Earl Hearst, MD, Medical Officer, which supplemented the previous reviews by Dr. Hearst dated February 20, 2002 and May 12, 2004, and Tarek Hammad, MD, Medical officer, dated February 26, 2002), which did not identify safety concerns for gepirone ER that would preclude approval. Although there were two positive studies (the newly submitted FK-GBE-007, and study 134001, originally submitted as part of the May 18, 2001, NDA resubmission), the application was not approved. The November 2, 2007 Non-Approval Letter described concerns with short and long-term efficacy, unacceptable effect sizes, and concerns about active comparators

demonstrating efficacy over placebo in failed studies when gepirone ER did not.

- **December 10, 2012**: Applicant submitted an amendment based on discussion with FDA during a Type C meeting on November 29, 2011 and requested an informal review of the available efficacy data. FDA responded with an Advice letter on April 18, 2014, stating ongoing concerns about the efficacy of gepirone ER.

- **June 13, 2014**: The Applicant submitted an FDRR, appealing the November 2, 2007, Not Approvable Letter and the April 18, 2014, General Advice Letter in which ODE-I concluded that the Applicant had not demonstrated substantial evidence of effectiveness. Initially, FDA did not accept this request for dispute resolution because it contained a new re-analysis not previously evaluated by FDA. On November 12, 2014, the Applicant requested reconsideration by FDA Chief Counsel; and on January 27, 2015, FDA accepted the Applicant's request for dispute resolution.

- **December 1, 2015**: FDA conducted a Psychopharmacological Drug Advisory Committee (PDAC) meeting to discuss the efficacy and safety of gepirone ER. Of the 13-member committee, 9 members did not agree that the Applicant provided substantial evidence of effectiveness; 9 members did not agree that there was a favorable benefit-risk profile for gepirone ER, even though 11 members agreed that the Applicant adequately characterized safety, with 2 members noting a lack of longer-term study data presented during the advisory committee and limited assessment of suicidal ideation.

- **March 16, 2016**: The FDA OND Director John Jenkins, MD, granted the Applicant's appeal, stating the Applicant met the standard for substantial evidence of effectiveness with two positive and well-controlled studies and that the Applicant should conduct thorough QT studies, develop a plan for linking the to-be-marketed drug product to the clinical trial material used in Studies 007 and 001, and address remaining CMC issues noted in the 2007 Not Approvable Letter.

- **January 30, 2017**: During a Type B Pre-NDA Meeting, FDA provided advice on addressing CMC issues; clinical pharmacology requirements (a bioequivalence study for the new manufacturing site; a pharmacokinetic (PK) bridging between the study drug and the to-be-marketed drug; and comparative dissolution data); CSS requirements for assessing abuse potential; and an agreement that DP would abide by the Appeal Granted letter and would not require additional efficacy data. Regarding safety, FDA agreed there were no new safety concerns, no need for a new safety update, and FDA did not request any modernization of the databases but noted that analysis with Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries may be helpful. FDA confirmed that a thorough QT study would be needed because of problems with data quality in existing studies. FDA provided parameters for resubmitting sexual dysfunction study data based on the Applicant's request, including a recommendation that the data come from positive studies that have assay sensitivity. CSS also outlined numerous requirements related to

abuse potential evaluation. FDA stated they would re-assess the long-term efficacy of gepirone ER as part of the NDA amendment and that the Applicant should submit their pediatric studies to the NDA.

- **March 17, 2020**: During a Type C Meeting, CMC provided feedback about expectations related to in vitro – in vivo correlation studies (IVIVC) and how findings can be used to support the Applicant's biowaiver requests, which should be submitted with the NDA.
- **December 23, 2022**: The Applicant resubmitted the NDA, including three pediatric studies that had not previously been reviewed and a request for pediatric exclusivity; a new dedicated QT study; a new re-analysis of Study 28709; a request for new review of sexual dysfunction (b) (4); and the original Draft Labeling Text, not previously reviewed by FDA.

The pediatric regulatory history is as follows:

- **August 30, 2001**: The Applicant submitted a Proposed Pediatric Study Request under IND 033626.
- **December 12, 2001**: FDA issued a PWR, with a study report timeframe of "within 3 years," noted as December 21, 2004.
- **July 2, 2002**: FDA re-issued the PWR without changes (prompted by the Best Practices for Children Act (BPCA) being signed into law on January 4, 2002).
- **January 21, 2003:** The Applicant agreed to conduct the studies as outlined in the PWR.
- **February 26, 2003:** The Applicant submitted a revised PWR.
- **July 18, 2003:** FDA issued an amended PWR, extending the timeframe by 3 years (to December 21, 2006). Additionally, the Office of Clinical Pharmacology (OCP) team added new requirements: 1) conduct sparse sampling for further confirmatory pharmacokinetic analysis in the clinical safety or efficacy studies in a representative population due to concerns about P450-based racial differences; 2) distribute the ages within the PK study; and 3) compare descriptive PK parameters in the pediatric population to the adult PK data.
- **May 7, 2004:** FDA amended the PWR to specify ethnic and racial category designations as newly required under the BPCA.
- **May 31, 2006:** During a teleconference with the Applicant, FDA agreed to extend the PWR to June 30, 2007, and the Applicant agreed "to provide a formal response extending the deadline for submitting the pediatric data."
- **November 21, 2006:** FDA advised the Applicant to submit a formal request for an extension.

- **December 19, 2006:** The Applicant submitted a request to extend the study report timeframe to August 31, 2007. It appears the Applicant's submission may have been miscoded by the Document Room as general correspondence. By the time the miscoding was corrected, the PWR timeframe had passed; so instead of amending the original PWR, FDA issued a new PWR as described next.

- **April 30, 2007:** FDA issued a new PWR with a new request to include fluoxetine as a control group in the pediatric efficacy and safety studies. FDA noted the new PWR was issued because the previous PWR timeframe had lapsed and stated that the pediatric study reports must be submitted within 3 years of the date of the letter.

- **May 23, 2007:** The Applicant submitted a letter raising objections to the issuance of a new PWR by FDA, citing phone calls and stating they believed they had been granted an extension for the previous PWR. The Applicant stated they already completed their program, and it was unwarranted to issue new study requirements. There does not appear to be a documented response from FDA to the Applicant's letter.

- **May 30, 2008:** The Applicant submitted a pediatric PK study report study FK-GBE-009 under IND 033626.

- **June 26, 2008:** The Applicant submitted the clinical study reports (CSR) for the above pediatric PK studies to IND 133626, with no specific mention of a pediatric exclusivity request. FDA did not review the data at that time and archived the submission as "no action indicated."

- **January 30, 2017:** During a Type B presubmission planning meeting, the Applicant stated that, "the Applicant had reached agreement regarding extending the time to submit the pediatric study results to the IND, but final documentation of this agreement was not completed prior to the issuance of another PWR. The Applicant believes that the pediatric studies completed and submitted to associated IND 033626 are sufficient to comply with the extension agreement and the existing Pediatric Written Request and that the only requirement is to submit these pediatric study reports to the NDA post-approval." FDA did not agree and stated, "The Written Request issued in 2007 has expired and no Written Request is in effect at this time. Furthermore, there are no existing patents or exclusivities for which we could issue a new Written Request." FDA further clarified during the meeting, "The Division will not issue a new Written Request for these completed pediatric studies as they are not in alignment with what the Division would require for this indication. Therefore, the completed studies would not offer a potential for a public health benefit in pediatric patients...FDA will not issue a new PWR..." FDA advised the Applicant to submit the pediatric data with the NDA Amendment.

- **December 23, 2022:** The Applicant submitted the pediatric CSRs as part of the NDA resubmission. The Applicant requested a Pediatric Exclusivity Determination based on the July 18, 2003 WR stating, "On April 30, 2007, FDA issued a new Pediatric Written Request letter but that exceeded FDA's statutory authority by requiring new pediatric studies when FDA had already issued a Written Request for appropriate pediatric studies, and when that prior Written Request—FDA's Amended Pediatric Written Request of July 18, 2003—was still constructively in effect."

# 4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations

On February 9, 2023, the OSIS declined to conduct on-site inspections because the sites were already reviewed within the past year and "OSIS concluded that data from the reviewed studies were reliable."

## 4.2. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 021164 with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Devices and Companion Diagnostic Issues

Not applicable.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

This review examines a resubmission for NDA 021164 for gepirone ER tablets, originally indicated for the treatment of MDD in adult patients 18 years of age and older. All nonclinical data to support the original NDA have been reviewed previously by Linda Fossom, PhD (March 8, 2002), with the exception of a newly submitted juvenile animal study (JAS) which was

completed on August 8, 2005. The previously submitted nonclinical section was found to be approvable, and labeling recommendations were provided by Dr. Fossom.

The newly submitted JAS (Study # OGN/048) has been reviewed with the current resubmission, and the findings will be included in the labeling. The study protocol was reviewed by the Division and the Applicant was given comments and advised to proceed on April 7, 2003.

This JAS is a combined repeat dose, neurobehavioral, and fertility study conducted in juvenile rats treated orally by gavage with 0, 10, 40, and 70 mg/kg of gepirone ER for 28 days from postnatal day 14 to 42. A standard set of toxicology parameters were evaluated including clinical signs, body weight, hematology, clinical chemistry, organ weight, gross pathology, and histopathology. Blood plasma samples were analyzed for pharmacokinetics of gepirone ER and its two major metabolites (3-OH-gepirone and 1- (2-pyrimidinyl)-piperazine) following single-dose gepirone and at the end of the 4-week period of daily dosing. Additional developmentally sensitive measures were evaluated, including a battery of neurobehavioral assessments, extensive brain histopathology, sexual maturation, and reproductive capacity.

Initially the high dose was set to 160 mg/kg. However, severe clinical signs (low body temperature/prone posture for 5-7 hours) were observed after administration of a single dose at 160 mg/kg and also at 100 mg/kg. The animals receiving these higher doses were sacrificed after a single dose and the high dose was set to 70 mg/kg. No mortality was observed during the study period at doses of 70 mg/kg/day and below.

A significant increase in blood glucose and decrease in albumin levels was observed at doses ≥40 mg/kg/day in both male and female animals. These effects were present at the end of the treatment period and persisted following a two-week recovery period (up to 20% compared to control group). While these findings appear to be treatment related, the long-term consequences and relevance to humans are unknown.

The battery of neurobehavioral assessments performed indicate a small but consistent effect of gepirone across multiple tests at doses ≥40 mg/kg/day in both males and females. In particular, treatment at doses ≥40 mg/kg/day increased motor activity along the cage floor (Low beam) and increased the latency to reach the escape platform in the Morris water maze, indicative of impairment to learning and memory. The no observed adverse effect level (NOAEL) for neurobehavioral development in this study was 10 mg/kg/day.

The JAS also identified treatment effects on reproductive capacity. A significant increase was observed in the rate of preimplantation loss on day 14 of gestation in the 70 mg/kg group. Thus, the NOAEL for reproductive capacity in this study was 40 mg/kg/day.

The pharmacokinetic data indicate that plasma concentrations of gepirone and its two major metabolites achieved exposure levels (both $C_{max}$ and the area under the concentration-time curve $[AUC]_{last}$) in both male and female rats greater than those measured in human adults at the maximum recommended daily dose of 80 mg.

## 5.2. Toxicology

### 5.2.1. Juvenile Animal Studies

#### 5.2.1.1. Preliminary Single-dose Study in Juvenile Rats (Study # NL0051657)

**Study Title: An Oral Single Dose Toxicity Study with ORG 33062 in Male and Female Juvenile Sprague-Dawley Rats**

The objective of this non-GLP study was to assess the toxicity of oral (gavage), single-dose administration of gepirone (ORG 33062) in juvenile rats.

Four groups of male and female rats (6/sex/group) were administered gepirone once at doses of 0, 300, 400, and 600 mg/kg. Dosing occurred on postnatal day (PND) 14 in the control group and 300 mg/kg group. Dosing occurred on PND 15 in the 400 mg/kg group and PND 16 in the 600 mg/kg group.

Administration of 600 mg/kg caused mortality or moribundity within minutes in 2/2 males and 2/2 females. The other 4 males and 4 females in the 600 mg/kg group were not dosed for humane reasons. The 300 and 400 mg/kg dose groups showed severe clinical signs including ventral recumbency in all animals (at both doses) lasting from 2.5 hours to greater than 7 hours. Irregular breathing, decreased body temperature, and hypoactivity were observed in multiple males and females in each of these groups. Convulsions were observed in one female in the 300 mg/kg group. Body weights were reduced by 2-10% in all males and females in the 300 and 400 mg/kg groups and relative body weights were decreased compared to controls up to 12 days after dosing.

Based on this preliminary study, the maximum nonlethal oral dose of gepirone in juvenile rats is 400 mg/kg. A maximum tolerated dose was not determined in this study.

#### 5.2.1.2. Pivotal Study in Juvenile Rats (Study # OGN/048)

**Study Title: ORG 33062 Toxicity Study in the Neonatal/Juvenile Rat by Oral (Gavage) Administration**

**Table 2. Study Information for ORG 33062 Toxicity Study in the Neonatal/Juvenile at by Oral (Gavage) Administration**

| Study Features | Details |
|---|---|
| Study number | OGN/048 |
| Study report location | (b) (4) |
| Conducting laboratory and location | (b) (4) |
| Duration | 28-day treatment, 2-week recovery |
| GLP compliance | Yes; lists compliance with UK (1999), OECD (1997), and EC directive (2004). |

| Study Features | Details |
|---|---|
| Drug, lot # | ORG 33062 (gepirone), IPA No. IW007-1 |

Abbreviations: GLP, good laboratory practice; UK, United Kingdom

Key Study Findings

- Clinical Chemistry: A significant increase in blood glucose and decrease in albumin levels was observed at doses ≥40 mg/kg/day in both male and female animals. This effect was observed both during treatment and after the two-week recovery period. The biological relevance of this finding is unknown.

- Neurobehavioral: Increased motor activity and increased latency to reach the escape platform in the Morris water maze at doses ≥40 mg/kg/day in both male and female animals following the 2-week recovery period. The NOAEL was 10 mg/kg/day.

- Reproductive capacity: Increased preimplantation loss occurred at 70 mg/kg/day. The NOAEL was 40 mg/kg/day.

**Table 3. Study Methods for ORG 33062 Toxicity Study in the Neonatal/Juvenile at by Oral (Gavage) Administration**

| Study Methods | Details |
|---|---|
| Doses | 0, 10, 40, 70[1] mg/kg/day |
| Frequency of dosing | Once daily |
| Number/sex/group | 20/sex/group in phase 1, 20/sex/group in phase 2, and 3/sex/group in phase 3. Phase 1 was used for primary toxicology and histology evaluation. Phase 2 was used for assessment of neurobehavior and reproductive capacity. Phase 3 was used to determine toxicokinetics (TK). |
| Dose volume | 10 mL/kg |
| Formulation/vehicle | Gelatin 0.5% w/v/Mannitol 5.0% w/v, water |
| Route of administration | ORAL GAVAGE |
| Species | Rat |
| Strain | Sprague-Dawley |
| Age at start of experiment | Postnatal Day (PND) 14 |
| Period of development studied | PND 14 through 42 of age |
| Comment on study design and conduct | Due to the short half-life (~3h) of the test compound, twice daily dosing would have been preferred. The study does not evaluate bone growth. |
| Parameters and key endpoints evaluated | The study examined a standard battery of toxicology endpoints with the addition of neurobehavioral and reproductive assessments. |

[1] The initial high dose was 160 mg/kg. This was reduced to 100 mg/kg and finally to 70 mg/kg on the first day of the study due to severe clinical signs (low body temperature/prone posture for 5-7 hours) observed at the higher doses.

| Study Methods | Details |
|---|---|
| Dosing solution analysis | Test item analysis for each study phase showed all concentrations to be within 10% of the expected values. |

Design and Procedures

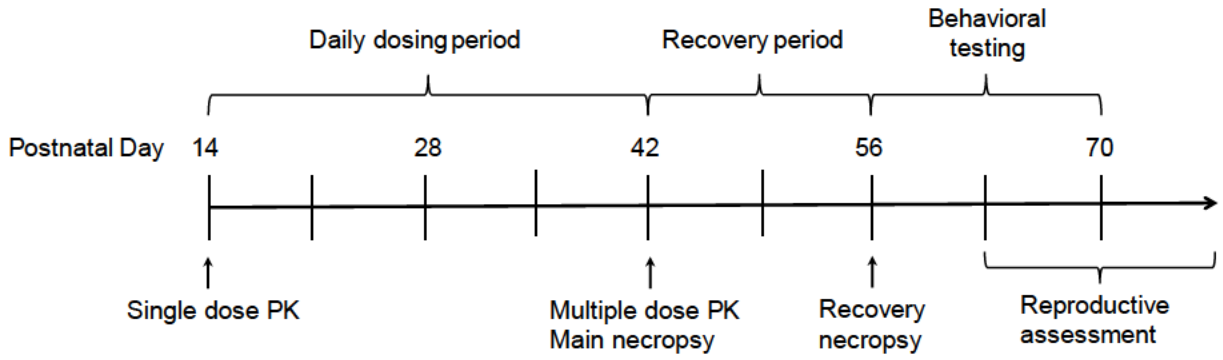
The study consisted of three phases with three separate cohorts assessed for general toxicology, neurobehavioral and reproductive alterations, and toxicokinetic profile, respectively.

Phase 1: N=20 rats/sex/group. There was a 28-day period of daily dosing ranging from PND 14 through 41. Half of the animals (10/sex/group) were terminated on PND 42 while the other half (10/sex/group) were terminated after a 14-day recovery period. Clinical signs, body weight, ophthalmology, hematology, blood chemistry, gross pathology, organ weights and histopathology were assessed during the treatment phase. Blood draws for chemistry and hematology occurred on PND 40 and 54. A subset of 10 male and 10 female animals from each group were selected for blood sampling.

Phase 2: N=20 rats/sex/group. There was a 29-day period of daily dosing ranging from PND 14 through 42, followed by 2-3 weeks of recovery prior to neurobehavioral and reproductive evaluation. Neurobehavioral assessments included motor activity, the Morris water maze, auditory startle habituation, and rotarod performance were only evaluated after the recovery phase. Sexual maturation and reproductive performance were also evaluated in these animals.

Phase 3: N=3 rats/sex/group. Toxicokinetic profiles of gepirone and two major metabolites were determined after a single dose (PND 14) and after 29 days of daily dosing (PND 42).

**Figure 1. Study Timeline**




Source: Created by reviewer
Abbreviations: PK, pharmacokinetic

**Observations and Results**

Mortality

Methods: Each animal was visually checked at least twice per day and physically inspected once per week throughout the study period. During the dosing period, detailed observations were recorded immediately before and after individual dosing, upon completion of dosing all animals, 0.5 to 1 hour after dosing, 2 to 3 hours after dosing, and at the end of the working day.

Results: Initially the high dose was set at 160 mg/kg/day based on a dose range finding study estimating that a single dose up to 400 mg/kg was tolerated in age 14-day rats. However, in that study the animals dosed at 300 mg/kg and 400 mg/kg showed marked decrease in body temperatures and 5 to 7 hours of decreased activity and prone postures.

In this 28-day study, the same clinical signs were observed at 160 mg/kg and 100 mg/kg. All animals were sacrificed due to the severity of the clinical signs after dosing at 160 mg/kg. Following dosing at 100 mg/kg, 5 males and 6 females were sacrificed. The high dose was therefore reduced to 70 mg/kg/day.

There were no treatment related mortalities during the study for animals dosed in the 10 to 70 mg/kg/day range. One animal in the 40 mg/kg group was sacrificed on postnatal day 40 due to a complication (swollen/misshapen eye) following blood sampling from the retro-orbital sinus.

Clinical Signs

Methods: During the dosing period, detailed observations were recorded immediately before and after individual dosing, upon completion of dosing all animals, 0.5 to 1 hour after dosing, 2 to 3 hours after dosing, and at the end of the working day.

Results: At 70 mg/kg/day, half of the animals (21/41 males and 21/41 females) showed reduced activity and 12/41 males and 12/41 females had reduced body temperatures the first day of dosing. However, these effects were not generally observed on subsequent days of dosing. Partially closed eyelids were frequently noted throughout the dosing period and fully closed eyelids were noted at least once for half of the animals. Salivation was noted on one or two occasions for 15/41 males and 19/41 females. Repetitive movements were observed on one or two occasions for 6/41 males and 6/41 females. Urine staining was observed for 16/41 females and 3/41 males on one or two occasions. One female exhibited prostrate posture on day 34 of age (after 20 days of dosing).

At 40 mg/kg, partially closed eyelids were frequently noted, and repetitive movements were observed on one or two occasions for 7/40 males and 9/40 females. Other signs were reduced relative to the 70 mg/kg group and generally occurred more frequently in females. These included underactivity (4/40 males and 6/40 females), salivation (4/40 males and 13/40 females), urine staining (9/40 females, 0/40 males), and fully closed eyelids (6/40 males and

6/40 females). One female in the 40 mg/kg group also exhibited prostrate posture on day 34 of age (after 20 days of dosing).

At 10 mg/kg, half of the animals showed partially closed eyelids, but the other clinical signs were greatly reduced compared to the higher dose groups. Observed signs included reduced body temperature (1/40 males, 0/40 females), fully closed eyelids (2/40 males, 1/40 females), salivation (1/40 males, 2/40 females), and urine staining (0/40 males, 4/40 females).

**Table 4. Clinical Signs**

Males

| Clinical sign | Number of animals showing sign in group: | | | | | |
|---|---|---|---|---|---|---|
| | Group 1: Control 0 | Group 2: 10 mg/kg/day | Group 3: 40 mg/kg/day | Group 4: 70 mg/kg/day | Group 4: 100 mg/kg/day# | Group 4: 160 mg/kg/day# |
| Number of animals dosed | 40 | 40 | 40 | 41 | 13 | 6 |
| Underactivity | | | 4 | 21 | 11 | 6 |
| Reduced body temperature | | 1 | 2 | 12 | 7 | 6 |
| Prostrate posture | | | | | 7 | 5 |
| Abnormal gait | | | | | | 1 |
| Partially closed eyelids | | 21 | 37 | 40 | | |
| Closed eyelids | | 2 | 6 | 21 | | |
| Salivation | | 1 | 4 | 15 | | |
| Repetitive movements | | | 7 | 6 | | |
| Urine staining | | | | 3 | | |

Females

| Clinical sign | Number of animals showing sign in group: | | | | | |
|---|---|---|---|---|---|---|
| | Group 1: Control 0 | Group 2: 10 mg/kg/day | Group 3: 40 mg/kg/day | Group 4: 70 mg/kg/day | Group 4: 100 mg/kg/day# | Group 4: 160 mg/kg/day# |
| Number of animals dosed | 40 | 40 | 40 | 41 | 14 | 6 |
| Underactivity | 1 | | 6 | 21 | 12 | 6 |
| Reduced body temperature | | | | 12 | 7 | 6 |
| Prostrate posture | | | 1 | 1 | 9 | 4 |
| Abnormal gait | | | | | 1 | 3 |
| Partially closed eyelids | | 23 | 39 | 41 | | |
| Closed eyelids | | 1 | 6 | 19 | | |
| Salivation | | 2 | 13 | 19 | | |
| Repetitive movements | | | 9 | 6 | | |
| Urine staining | | 4 | 9 | 16 | | |

# All animals treated at 160 or 100 mg/kg/day were killed after administration of the first dose

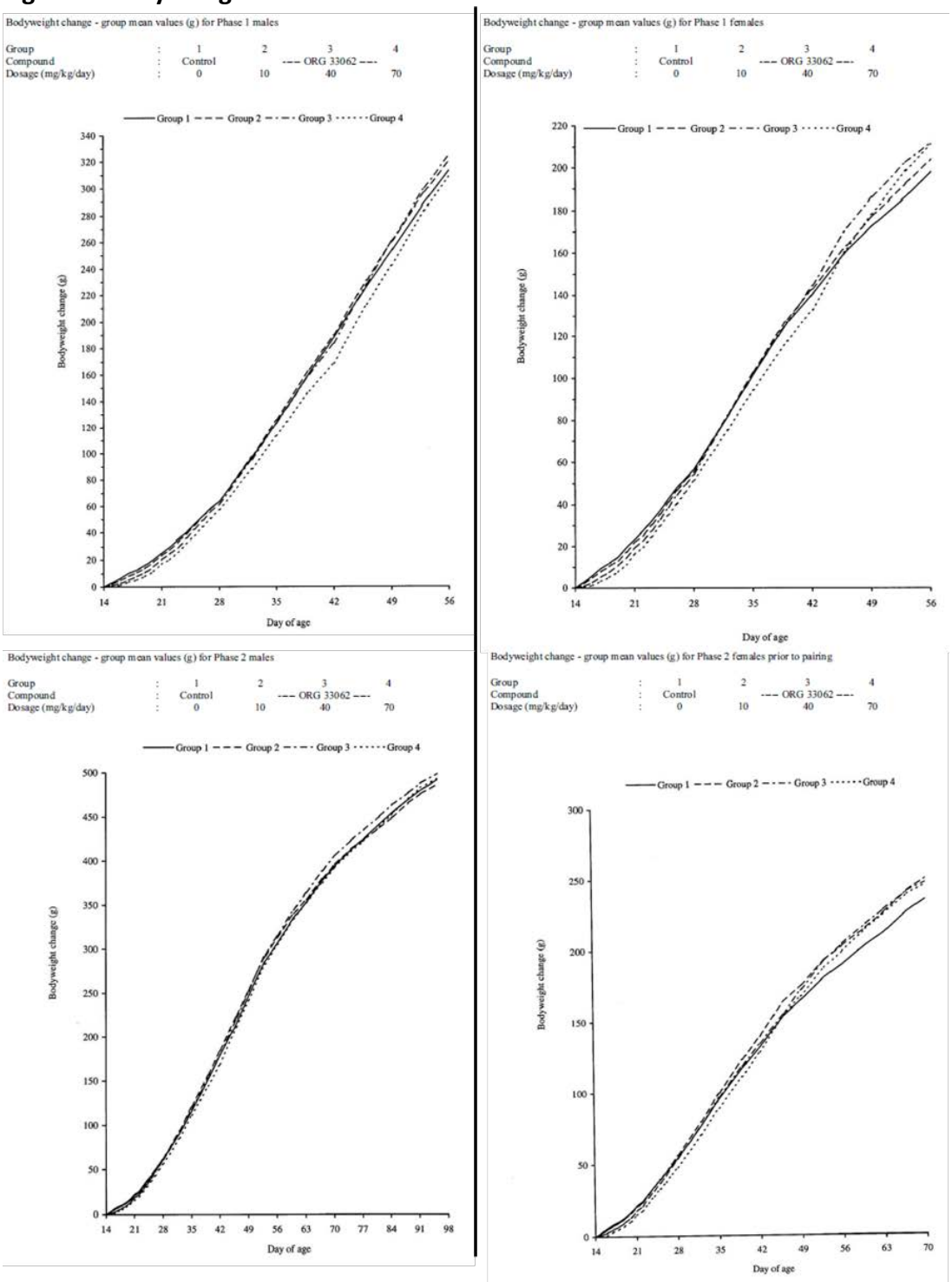
Source: From Applicant study report; pages 68-69

Body Weight

Methods: Animals in phases 1 and 2 were weighed on Day 1, 4, 7, and 11 of age prior to the treatment period. During the first two weeks of treatment, the animals were weighed daily from Day 14 through Day 28 of age and thereafter the animals were weighed twice per week until termination.

Results: Similar body weight dynamics were observed across phase 1 and phase 2 cohorts. In both males and females there was an initial dose-dependent decrease in body weight gain over the first week of treatment. After 7 days of treatment (21 days of age), 70 mg/kg and 40 mg/kg males weighed 13% and 8% less than controls, respectively. Females in the 70 mg/kg and 40 mg/kg groups weighed 12% and 7% less than controls, respectively. Body weights in all dose groups recovered over the ensuing week to approximately match controls for the remainder of the treatment period. Following the recovery period, body weights were slightly higher in all dose group animals compared to controls, except for 70 mg/kg males whose weights were roughly equal to controls.

**Figure 2. Body Weights**




Source: Applicant's study report; pages 58-61
Top = Phase 1; Bottom = Phase 2
Left Column = Males; Right Column = Females.

Feed Consumption

Feed consumption was not reported.

Ophthalmoscopy

No effects of dosing were observed during ophthalmic examinations at the end of the dosing period and at the of the recovery period.

Hematology

Methods: Blood draws from the retro-orbital sinus were performed 2 days prior to the end of the dosing period (Day 40) and again 2 days prior to the end of the recovery period (Day 54). Blood samples (0.3 mL) were collected into tubes containing EDTA anticoagulant for automated hematology analysis. A Technicon H1 hematology analyzer was used to obtain a standard battery of cell counts. Staining and examination via light microscopy were performed to obtain reticulocyte counts and check for abnormal morphology. Additional blood samples (~0.5 mL) were collected into tubes with citrate anticoagulant for examination of prothrombin time and activated prothrombin time.

Results: Significantly shorter activated partial thromboplastin time (APTT) was observed for the 70 mg/kg group females at end of dosing period and for all female dose groups at end of recovery period. For males in the 70 mg/kg group, APTT was shorter (but not statistically significant) at the end of the dosing period but did not differ from the control group at the end of the recovery period. There were no differences in APTT for males in the other dose groups at either time point.

No other treatment effects were apparent at the end of the dosing period. However, several treatment effects were evident only at the end of the recovery period. Following the recovery period, dose-dependent decreases in hematocrit and red blood cell counts were evident for both males and females, reaching statistical significance relative to controls for both sexes in the 70 mg/kg groups. Further, for both the male and female 70 mg/kg groups, hemoglobin and mean cell hemoglobin concentration were significantly reduced relative to controls. For 70 mg/kg group females, numbers of white blood cells, lymphocytes, basophils, and large unstained cells were significantly increased as well. These findings are unusual since there were no differences observed for these measures at the end of the treatment period. The Applicant states, “the clustering of effects on hematocrit, hemoglobin levels, red cell counts and mean cell hemoglobin concentrations among males and females in the 70 mg/kg/day group are suspicious and an effect of treatment cannot be discounted.” The long-term consequences and potential relevance to humans from these findings are unknown.

Clinical Chemistry

Methods: Additional blood draws from the retro-orbital sinus were performed for clinical chemistry analysis two days prior to the end of the dosing period (Day 40) and again two days

prior to the end of the recovery period (Day 54). Blood samples (0.6 mL) were collected in tubes with lithium heparin anticoagulant. These samples were agitated for two minutes and centrifuged at 3,000 rpm for 10 minutes to separate the blood plasma for analysis. A standard set of chemical concentrations was then quantified from the plasma.

Results: Significant, dose-dependent increases in blood glucose (up to 12% compared to control group) were evident in both males and females at the end of the dosing period. Blood glucose levels remained elevated (up to 20% compared to control group) in a dose-dependent manner for both males and females following the recovery period.

Dose-dependent decreases in blood calcium levels were observed in both males and females at the end of the dosing period. The decrease was minor in magnitude (up to 5%) but reached statistical significance in all dose group males and females in the 70 mg/kg. Following the recovery period, no effect on calcium levels was observed in males but a minor decrease (up to 3%) was evident in all dose group females.

A small (3 to 6%), but statistically significant decrease in albumin levels was observed for the 40 mg/kg and 70 mg/kg groups in both males and females at the end of the dosing period. The same effect was also present at the end of the recovery period.

Triglycerides were dose-dependently decreased in both males and females at the end of the dosing period. The decrease was statistically significant for the 40 mg/kg and 70 mg/kg groups with levels decreased by 50% in both male and female groups treated with 70 mg/kg/day. No effect on triglyceride levels was observed following the recovery period.

Cholesterol showed a dose-dependent decrease in males (at all doses) and was statistically significantly reduced (~20%) in both male and female 70 mg/kg groups at the end of the dosing period. No effect on cholesterol levels was observed following the recovery period.

**Table 5. Clinical Chemistry**

| Day 40 | Glucose (mmol/L) | | Albumin (g/L) | | Calcium (mmol/L) | | Triglycerides (mmol/L) | | Cholesterol (mmol/L) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 mg/kg | 8.98 | 9.26 | 32 | 33 | 2.83 | 2.76 | 1.43 | 1.09 | 1.79 | 1.66 |
| 10 mg/kg | 9.91 | 9.74 | 31 | 33 | 2.73 | 2.74 | 1.19 | 0.84 | 1.72 | 1.70 |
| 40 mg/kg | 10.04 | 10.09 | 30 | 32 | 2.69 | 2.70 | 0.98 | 0.79 | 1.57 | 1.66 |
| 70 mg/kg | 9.74 | 10.27 | 31 | 33 | 2.69 | 2.66 | 0.72 | 0.53 | 1.43 | 1.33 |
| Day 54 | Glucose (mmol/L) | | Albumin (g/L) | | Calcium (mmol/L) | | Triglycerides (mmol/L) | | Cholesterol (mmol/L) | |
| Group | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| 0 mg/kg | 8.82 | 9.27 | 34 | 36 | 2.82 | 2.84 | 1.76 | 1.38 | 1.62 | 1.70 |
| 10 mg/kg | 9.35 | 9.83 | 34 | 35 | 2.82 | 2.77 | 2.01 | 1.48 | 1.60 | 1.70 |
| 40 mg/kg | 10.34 | 10.95 | 33 | 34 | 2.81 | 2.75 | 1.87 | 1.23 | 1.69 | 1.68 |
| 70 mg/kg | 10.61 | 10.54 | 32 | 35 | 2.81 | 2.78 | 1.70 | 1.40 | 1.74 | 1.71 |

Source: Subset reconstructed from Applicant tables; pages 97-104

Urinalysis

Urinalysis was not reported.

Sexual Maturation

Methods: Females were examined daily for vaginal opening beginning on Day 28 of age. Males were examined daily for balano-preputial separation beginning on Day 38 of age.

Results: No effects of dosing were observed on the age of female vaginal opening or male preputial separation. On average, completion of vaginal opening was recorded on Day 33 of age, occurring during the treatment period. On average, preputial separation was recorded on Day 45 of age, occurring 3 days after the end of the treatment period.

Mating Performance

Methods: Vaginal smears were taken to determine estrous cycles in all females for at least 15 days prior to pairing. Upon reaching at least 9 weeks of age animals were paired with a partner from the same treatment group. Following pairing, cage trays were checked daily for ejected copulation plugs and daily vaginal smears were used to confirm mating and to detect the presence of sperm and the stage of estrous cycle. Latency to mating (pre-coital interval) was calculated as the number of days between initial the pairing and detection of mating.

Results: No group differences were observed for estrous cycles, sperm counts, latency to mating (pre-coital interval), percentage mating, or conception rate.

There was a small but statistically significant reduction in the number of copulation plugs following mating for the 70 mg/kg group. The relationship of this effect to the test article and potential biological relevance of the effect to humans are unclear.

**Table 6. Mating Performance**

Mating performance and fertility - group values for Phase 2 males and females

| Group | | : | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Compound | | : | Control | | ----- ORG 33062 ----- | |
| Dosage (mg/kg/day) | | : | 0 | 10 | 40 | 70 |

| Group | Number of animals | | Number of copulation plugs at mating 1 | 2 | 3 | 4 - 6 |
|---|---|---|---|---|---|---|
| 1 | 19 | n | 0 | 4 | 4 | 11 |
| | | (%) | | (21) | (21) | (58) |
| 2 | 18 | n | 0 | 4 | 5 | 9 |
| | | (%) | | (22) | (28) | (50) |
| 3 | 19 | n | 2 | 3 | 8 | 6 |
| | | (%) | (11) | (16) | (42) | (32) |
| 4a | 20 | n | 1 | 8 | 6 | 5 |
| | | (%) | (5) | (40) | (30) | (25) |

Historical control data (8 studies)

| | | | | |
|---|---|---|---|---|
| Mean (%) | 8.8 | 15.6 | 23.1 | 52.5 |
| Minimum (%) | 0 | 0 | 5 | 30 |
| Maximum (%) | 20 | 30 | 40 | 70 |

a Distribution of data significant when compared with Group 1: a – $p<0.05$ - analysis performed on mean numbers of copulation plugs at mating

Source: Applicant's study report; page 131

Reproductive Capacity

Methods: Phase 2 females (20/group) were terminated on day 14 of gestation. For each animal, the number of corpora lutea was determined for each ovary and the number of implantation sites, resorption sites (early and late), and embryos (live and dead) were recorded for each uterine horn.

Results: A significant increase in the rate of preimplantation loss (12.9% versus 3.4% in controls) occurred at the 70 mg/kg dose. There was a corresponding reduction in implantations and live embryos at this 70 mg/kg dose. A total of four litters had more than 20% preimplantation loss compared with none in the control group and only 7/19 litters had no loss compared to 13/20 in control group.

A statistically significant increase in preimplantation loss was also observed at 40 mg/kg. However, the number of corpora lutea, implantations, and live embryos were all higher in the 40 mg/kg group than for the control group. Therefore, the Applicant argues that the increased level preimplantation loss does not have biological significance at the 40 mg/kg dose. This reviewer agrees with that interpretation. However, it should be noted that preimplantation loss

increased in a dose-dependent manner with rates higher than the background control range observed for all dose groups.

**Table 7. Reproductive Capacity**

Litter data - group mean values for Phase 2 females on Day 14 of gestation

| | | | | | |
|---|---|---|---|---|---|
| Group | : | 1 | 2 | 3 | 4 |
| Compound | : | Control | | ----- ORG 33062 ----- | |
| Dosage (mg/kg/day) | : | 0 | 10 | 40 | 70 |

| Group | | Corpora lutea | Implantations | Live embryos | Resorptions Early | Resorptions Late | Resorptions Total | Implantation loss (%) Pre- | Implantation loss (%) Post- |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Mean | 17.1 | 16.5 | 15.8 | 0.7 | 0.0 | 0.7 | 3.4 | 4.4 |
| | SD | 1.8 | 1.8 | 2.2 | | | | | |
| | n | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| 2 | Mean | 17.3 | 16.2 | 15.6 | 0.7 | 0.0 | 0.7 | 8.1 | 4.0 |
| | SD | 2.3 | 2.9 | 2.8 | | | | | |
| | n | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| 3 | Mean | 18.6 | 17.0 | 16.3 | 0.7 | 0.0 | 0.7 | 9.1A | 3.9 |
| | SD | 2.2 | 2.3 | 2.2 | | | | | |
| | n | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |
| 4 | Mean | 17.3 | 15.2 | 14.3 | 0.9 | 0.0 | 0.9 | 12.9A | 6.4 |
| | SD | 3.4 | 4.1 | 4.0 | | | | | |
| | n | 19 | 19 | 19 | 19 | 19 | 19 | 19 | 19 |

Significant when compared with Group 1: A-p<0.05

Source: Applicant's study report; page 133
Abbreviations: SD, standard deviation

Central Nervous System/Neurobehavioral Assessment

The neurobehavioral testing battery included assessment of motor activity, learning and memory via the Morris water maze, auditory startle habituation, and rotarod performance after a 14-day recovery period.

Motor Activity

Methods: Animals were placed in specialized cages equipped with infrared beams spanning the area inside the cage. Motor activity was captured by recording the number of beam breaks during the one-hour test period. The beams were located both along the cage floor (low beams) to capture general ambulation, and at an elevated height (high beams) to capture rearing behavior.

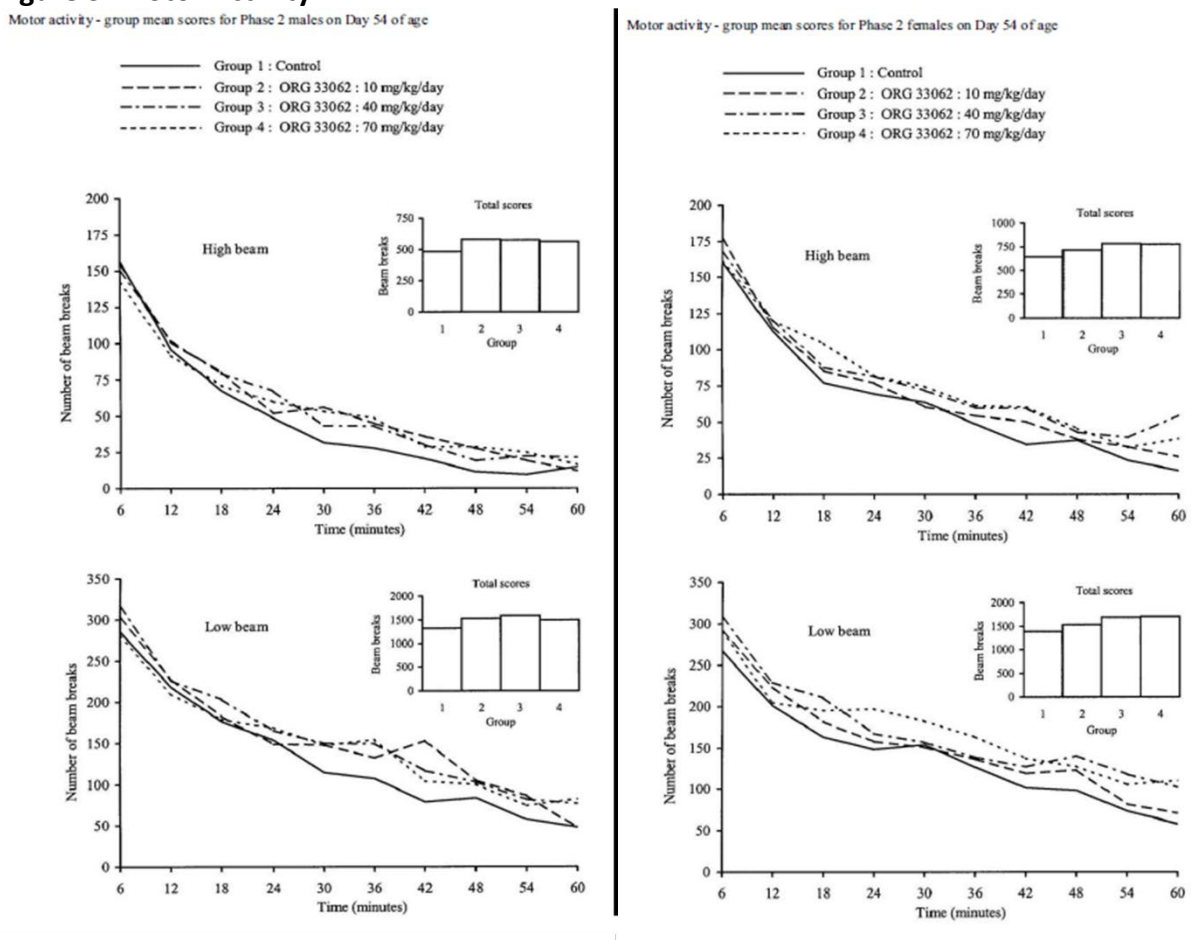
Both male and female animals showed increased motor activity at all doses. Increased motor activity was indicated by beam breaks for both low and high beams. In females, the increased motor activity was clearly dose-dependence for both low and high beam breaks, with the

40 mg/kg and 70 mg/kg dose groups achieving statistical significance for the increase in low beam breaks.

Although none achieved statistical significance, the motor activity was elevated for males in each dose group and the activity levels were approximately equal for each dose. The Applicant argues this does not provide convincing evidence for a treatment effect in males. However, given the clear effect observed in female animals taken together with the greater exposure levels in the females, the evidence indicates a treatment effect on motor activity may be present in the males as well and would have been likely to achieve statistical significance if they achieved higher plasma levels.

The Applicant concludes that the increased motor activity observed in females should be considered adverse at doses ≥40 mg/kg. While this reviewer disagrees that no treatment effect is present in males, overall, the data appears to reasonably support the conclusion that doses ≥40 mg/kg can cause increased motor activity.

**Figure 3. Motor Activity**




Source: Applicant's study report; pages 63-64
Left = males; right = females

Morris Water Maze

Methods: The Morris water maze was used to test learning and memory performance after a two-week recovery period. Each animal underwent 3 trials on each of 4 consecutive days. For each trial, the animals were placed at a random starting location in round pool filled with opaque water. The time (latency) to reach the escape platform and number of separate quadrant entries in route to the platform were recorded.

Results: A dose-dependent treatment effect was evident for both male and female animals. Animals in all groups showed improvements in latency to reach the escape platform (swimming time) and reductions in the number of incorrect sector entries across the 4 days of testing. However, for both males and females, the control group exhibited greater improvement in swimming time across test days than any of the dosed groups.

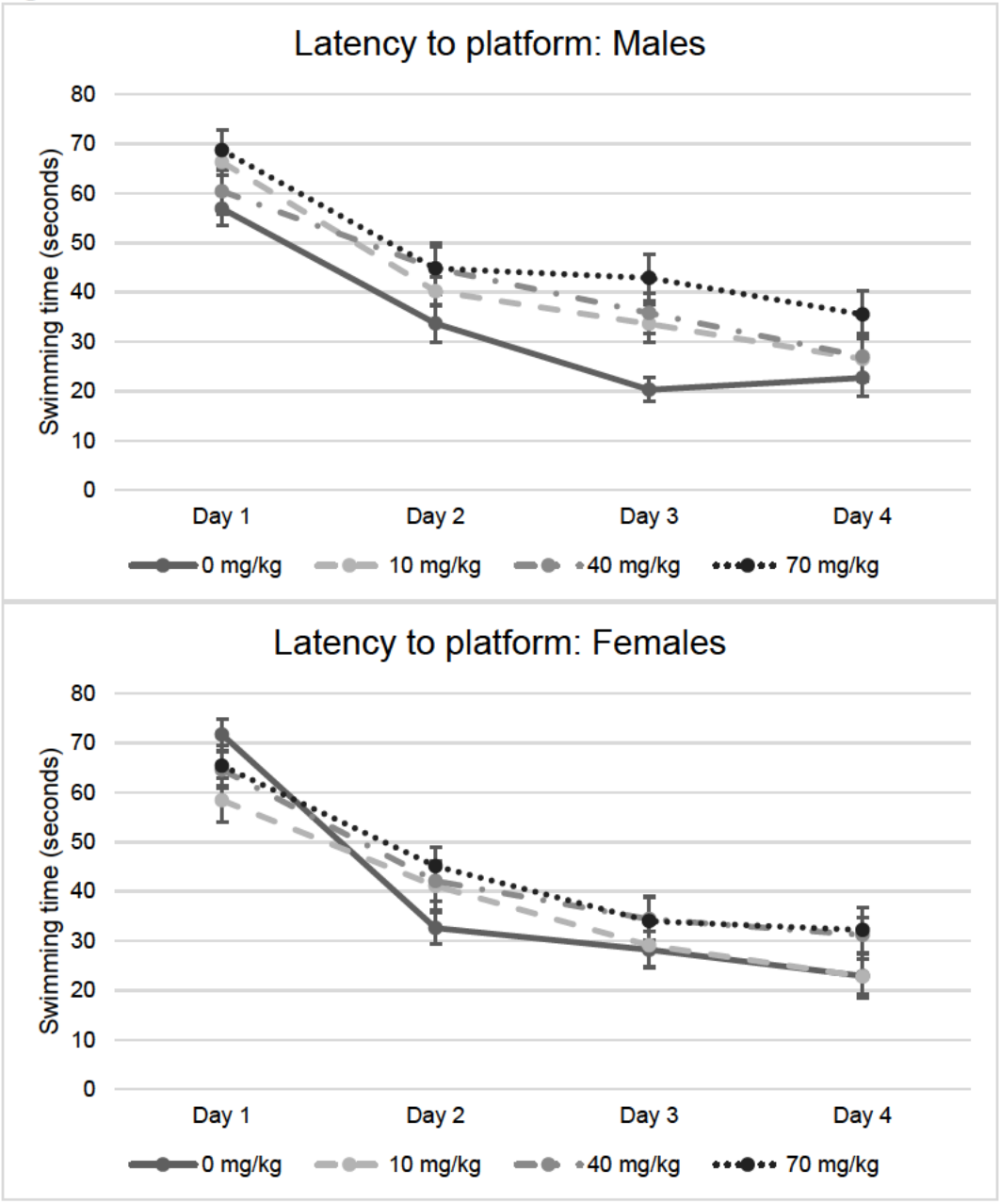
In males, the control group exhibited lower swimming time than any dosed group on each day of treatment, while the 70 mg/kg dose group had the highest swimming time on all four days. On day 3, all dose groups performed significantly worse than controls overall and each of the dose groups displayed reduced day-to-day improvement, compared to day 1, than control animals (see Table 8). These effects displayed clear dose-dependence and were also evident (to a lesser extent) on day 4.

In females, the control animals exhibited the longest swim times on day 1 but showed greater day-to-day improvement than dose group animals. On day 3 and day 4 there was a split in performance with the control and 10 mg/kg groups performing considerably better than the 40 mg/kg and 70 mg/kg groups (although this did not reach statistical significance).

Ideally the Applicant would have recorded swim speeds as slower swim speed can potentially increase latency to reach the escape platform in the absence of any effect on learning or memory. However, given the increases in incorrect sector entries corresponding to the longer swim times for each of the dose groups, taken together with the slight increase in general motor activity observed in the dose group animals, it is reasonable to assume that the observed effects were probably not the result of reduced swim speeds.

The Applicant concludes that the observed impact on learning and memory in the ≥40 mg/kg groups was adverse. This reviewer agrees with that interpretation.

**Figure 4. Morris Water Maze Performance**




Source: Generated from data in Applicant's study report; pages 107-108
Error bars represent standard error of the mean

**Table 8. Morris Water Maze Day-to-Day Improvement**

| Day 3 | Latency reduction | | Sector entry reduction | |
|---|---|---|---|---|
| **Group** | **Male** | **Female** | **Male** | **Female** |
| **0 mg/kg** | 64% | 61% | 57% | 59% |
| **10 mg/kg** | 49% | 50% | 42% | 50% |
| **40 mg/kg** | 41% | 47% | 27% | 42% |
| **70 mg/kg** | 38% | 48% | 34% | 44% |
| **Day 4** | **Latency reduction** | | **Sector entry reduction** | |
| **Group** | **Male** | **Female** | **Male** | **Female** |
| **0 mg/kg** | 60% | 68% | 51% | 66% |
| **10 mg/kg** | 60% | 61% | 55% | 58% |
| **40 mg/kg** | 55% | 52% | 48% | 46% |
| **70 mg/kg** | 48% | 51% | 45% | 42% |

Source**:** Generated from data in Applicant's study report; pages 107-108
Reduction in latency to platform and sector entries on Day 3 and Day 4 compared to Day 1. A higher % reduction indicates greater improvement in performance.

Accelerating Rotarod

Methods: An accelerating rotarod test was performed to assess coordinated motor activity. Animals were placed on the rod, which accelerated linearly over a 5-minute test period from starting at a near standstill up to 40 rotations per minute. The test trial concluded when the animal fell off the rod, stopped walking and clung to the rod, or was still walking on the rod after 300 seconds. Three trials were performed for each animal and the maximum time.

Results: The Applicant concludes that there was not an effect of treatment and offers no further comment on the results. However, the lack of statistically significance may be due to high individual variability masking a modest treatment effect. There is a clear trend towards lower times in the higher dose groups for both males and females. This result should not be considered adverse when examined in isolation but is in line with the other neurobehavioral data which generally indicate an effect of treatment on behavioral development.

**Table 9. Coordinated Motor Activity**

Accelerating rotarod - group mean times (seconds) for Phase 2 males and females on Day 55 of age

| | | | | | |
|---|---|---|---|---|---|
| Group | : | 1 | 2 | 3 | 4 |
| Compound | : | Control | | ----- ORG 33062 ----- | |
| Dosage (mg/kg/day) | : | 0 | 10 | 40 | 70 |

| Group | Number of animals | | Maximum time* Males | Females |
|---|---|---|---|---|
| 1 | 20 | Mean | 123.4 | 196.6 |
| | | SD | 47.2 | 47.1 |
| 2 | 20 | Mean | 114.9 | 191.7 |
| | | SD | 39.1 | 51.6 |
| 3 | 20 | Mean | 94.7 | 189.1 |
| | | SD | 24.1 | 43.4 |
| 4 | 20 | Mean | 110.9 | 184.6 |
| | | SD | 29.1 | 36.3 |

* During three trials (test terminated if 300 seconds achieved)

Source: Applicant's study report; page 109
Abbreviations: SD, standard deviation

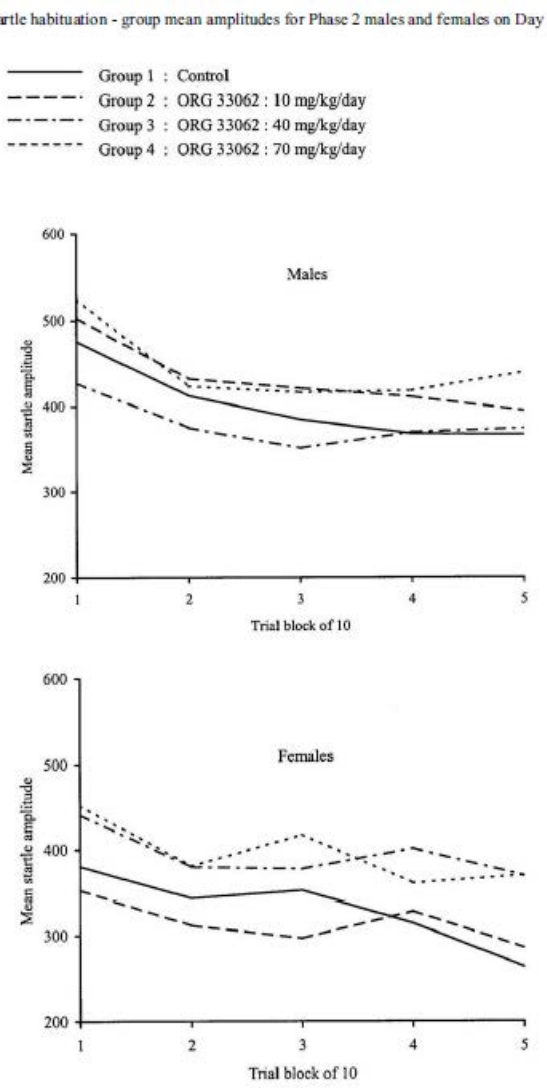
Auditory Startle Habituation

Methods: An assessment of auditory startle response habituation was performed. The animals were acclimatized to background noise at a level of 70 decibels. Subsequently, there were 5 consecutive blocks of 10 trials (50 trials total) with a 12-second interval between each trial. For each trial, a 40-millisecond burst of 105 decibels of white noise served as the startle stimulus. Startle amplitude and latency to peak response were recorded for each trial.

Results: Compared to controls, the latency to peak response took significantly longer for the 70 mg/kg group females during the first 10 trials ($p<0.01$) and when averaged across all 50 trials ($p<0.01$). Mean startle amplitudes were greater for females in the 40 and 70 mg/kg groups during the final 10 trials when compared to control animals ($p<0.05$). While very high individual variability in all groups limits the interpretability of the data, there appears to be a modest, dose-dependent trend towards greater startle amplitudes and reduced habituation.

The Applicant argues that there is not conclusive evidence of a treatment effect on auditory startle response habituation. This conclusion is appropriate when the data is considered in isolation. However, the greater startle amplitudes and trend towards reduced habituation for females in the ≥40 mg/kg groups, provide additional evidence for a treatment effect on neurobehavioral development when taken together with the other neurobehavioral assessments.

**Figure 5. Auditory Startle Amplitude**




Source: Applicant's study report; page 66

Bone Evaluation

Bone evaluation was not performed.

Gross Pathology

On day 42 of age (end of treatment period) 4/20 males in the 70 mg/kg group exhibited swollen spleens. Swelling was not apparent in the spleens of animals in the other dose groups or in the females on day 42 of age and was not apparent for any animals on day 56 of age (following recovery period). No other gross pathology observations were made that appear potentially related to treatment.

Organ Weights

Methods: Organ weights were recorded for 10/20 animals per sex/group at the end of the dosing period (Day 42) and another 10/20 animals per sex/group at the end of the recovery period (Day 56). Weights were obtained for adrenals, brain, epididymis, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, salivary glands, seminal vesicles, spleen, testes, thymus, thyroid, and uterus.

Results: At the end of the recovery period the weight of the thymus was significantly elevated in both absolute weight (~25% higher) and relative to body weight for females in the 70 mg/kg group relative to controls. While the increased thymus weight is not statistically significant for any other dose groups, mean thymus weight did increased in a dose-dependent manner in both males and females at the end of the recovery period. At the end of the dosing period (prior to the recovery period) there was no difference in thymus weight for any dose group for either sex.

At the end of the dosing period the weight of the spleen was significantly elevated in both absolute weight (~20%) and relative to body weight for males in the 70 mg/kg group relative to controls. Following the recovery period this difference was no longer apparent. The weight of the spleen did not differ from controls in any of the other male or female groups at either time point.

At the end of the dosing period the weight of the adrenals was significantly elevated relative to body weight and nonsignificantly elevated in absolute weight (~10%) for males in the 70 mg/kg group relative to controls. Following the recovery period this difference was no longer apparent. The weight of the adrenals did not differ from controls in any of the other male or female groups at either time point.

Histopathology

Methods: A thorough histopathology examination was conducted for 10/20 animals per sex/group at the end of the dosing period (Day 42) and another 10/20 animals per sex/group at the end of the recovery period (Day 56). An appropriate selection of tissue samples was collected, processed, and examined via light microscopy. Tissue samples included 10 coronal brain slices. Special emphasis was placed on the brain samples to assess any potential neural developmental changes.

Results: No significant histopathological findings appear to be related to treatment with gepirone. No findings related to the increased organ weight of the spleen were observed. The most notable findings were observed in the kidneys and lymph nodes.

Kidneys: A malignant nephroblastoma was found in one of the 10 mg/kg females. Tubular cysts in the cortex were a common finding in all dose groups as well as control animals. While the

histopathologist notes that the nephroblastoma is considered rare, neither of these findings were interpreted as treatment related.

Lymph nodes: At the end of the dosing period (Day 42) a greater number of plasmablasts were observed in the mesenteric lymph nodes of dose group animals relative to controls with the highest numbers observed in the 70 mg/kg group. Following the recovery period (Day 56) there was no difference in lymph node plasmablasts between controls and dose group animals.

Brain: A single high dose male was noted as having a minimal focal mononuclear cell aggregation in the perivascular space. There were no other brain findings reported.

Pharmacokinetics/Toxicokinetics

Methods: Toxicokinetic profiles of gepirone and two major metabolites were determined after a single dose (PND 14) and after 29 days of daily dosing (PND 42). On each sampling day, blood draws were performed in at least 3 animals/sex/group at 22, 45, 90, and 180 minutes after dosing.

Exposures were similar in males and females after a single dose, but significantly higher in female rats after multiple doses, consistent with other studies. This effect is thought to be related to the metabolic interaction of gepirone with enzyme CYP3A4.

The two major metabolites of gepirone, 3-OH-gepirone (Org 25907; 3-OH) and 1- (2-pyrimidinyl)-piperazine (Org 33552; 1-PP), were both present at exposure levels comparable to the parent compound. A sex difference was observed between the two metabolites with higher concentrations of Org 25907 observed in females while higher concentrations of Org 33552 were observed in males.

Due to the relatively brief half-life of gepirone in the rat (<3h), a higher dosing frequency would have been preferred. Further, blood samples were only acquired at a maximum of 3h postdose so we do not know if any drug present was present at the end of each 24h period between daily doses. However, the toxicokinetic data shows that higher concentrations and exposures were achieved in these juvenile rats than in adult humans receiving the maximum recommended daily dose of 80 mg. According to a statement from the Applicant, after adjusting for weight, the exposure levels in children and adolescents appear similar to exposures in adults.

**Table 10. Juvenile Rat PK Data**

| kinetic parameters | Sex | 10 mg·kg$^{-1}$ | | 40 mg·kg$^{-1}$ | | 70 mg·kg$^{-1}$ | |
|---|---|---|---|---|---|---|---|
| | | SD | MD | SD | MD | SD | MD |
| $AUC_{(0.37-3)}$ (ng·h·mL$^{-1}$) | M | 355 | 98.5 | 1885 | 582 | 3839 | 1320 |
| | F | 321 | 668 | 2136 | 4070 | 5396 | 6085 |
| $NAUC_{(0.37-3)}$ (ng·h·mL$^{-1}$)/(mg·kg$^{-1}$) | M | 35.5 | 9.85 | 47.1 | 14.5 | 54.8 | 18.9 |
| | F | 32.1 | 66.8 | 53.4 | 102 | 77.1 | 86.9 |
| $C_{max}$ (ng·mL$^{-1}$) | M | 422 | 69.2 | 1053 | 705 | 2130 | 1015 |
| | F | 308 | 573 | 1400 | 2157 | 2777 | 2903 |
| $NC_{max}$ (ng·mL$^{-1}$)/(mg·kg$^{-1}$) | M | 42.2 | 6.92 | 26.3 | 17.6 | 30.4 | 14.5 |
| | F | 30.8 | 57.3 | 35.0 | 53.9 | 39.7 | 41.5 |
| $t_{max}$ (h) | M | 0.75 | 0.37 | 1.5 | 0.37 | 0.75 | 0.75 |
| | F | 0.75 | 0.75 | 0.75 | 0.37 | 1.5 | 0.75 |

Source: Applicant's study report; page 546
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum plasma concentration; F, female; M, male; MD, multiple dose; NAUC, normalized area under the curve; $NC_{max}$, maximum plasma concentration normalized by dose; PK, pharmacokinetic; SD, single dose; $t_{max}$, time to maximum concentration

# 6 Clinical Pharmacology

## 6.1. Executive Summary

This application is a resubmission of NDA 021164 for gepirone ER tablets, originally submitted in 1999 for the treatment of MDD in adults and resubmitted in 2003 and 2007 after nonapproval letters. The clinical pharmacology studies were extensively reviewed before and refer to the clinical pharmacology reviews archived on 2/19/2002, 7/15/2002, 5/5/2003 and 10/1/2007 for additional information. Given that the to-be-marketed formulation is different from the formulation used in the phase 3 clinical studies, the Applicant conducted two relative bioavailability studies and a dose proportionality study and submitted the results in this resubmission. PK studies in pediatric subjects were previously submitted however they have not been reviewed before. The current clinical pharmacology review focused on studies submitted in this resubmission as well as PK studies in pediatric population. The review team relied on the summary comments and conclusions from the previous clinical pharmacology reviews to inform labeling.

Based on the relative bioavailability studies included in this resubmission, the 20 mg final market image (FMI) is equivalent to the 20 mg clinical trial material (CTM). Eighty milligrams (1 x 80 mg) of the FMI formulation is also equivalent to 80 mg (4 x 20 mg) of the CTM. Biowaiver is granted to the 40 mg and 60 mg strengths (Refer to Office of Product Quality-Biopharmaceutics review for additional information.

The PK studies in children and adolescents with MDD suggest that $AUC_{0-24h}$ and $C_{max}$ values were about 21% and 37% higher for gepirone, 57% and 51% higher for the metabolite, 1-PP and

43% and 51% higher for the pharmacologically active metabolite, 3-OH-gepirone, respectively in children 7 -11 years compared to adolescents 12 -17 years. Weight and/or age appeared to correlate to exposures (AUC, $C_{max}$) when estimated via linear regression analysis. The exposures in pediatric patients with MDD are consistent with those observed in adults. Caucasian pediatric patients showed 52% and 66% higher $C_{max}$ and $AUC_{inf}$, respectively than African American pediatric patients.

Gepirone will not be approved for treating MDD in pediatric patients aged 7 -17 years in this review cycle due to lack of efficacy in this population. If gepirone is approved for pediatric patients in future, the dose should be modified based on weight to a matching dose with similar exposures in adults. Dose modification recommendation for African American pediatric patients is not necessary given that patient dosage would generally be titrated to effect. However, African American pediatric patients may need higher doses than their Caucasian counterpart.

For details about efficacy in pediatric patients with MDD, refer to the clinical efficacy Section 8.

OSIS determined that inspections were not needed for both the clinical and analytical sties for the pivotal bioequivalence studies submitted in this resubmission. The reasons by OSIS were that both the clinical and analytical sites were inspected recently for ANDA 217194 and the findings concluded that data from the sites were reliable.

The key findings from previous clinical pharmacology reviews and dosing recommendations are briefly summarized here.

1) In the food effect study, the high fat meal (850 calories) showed approximately 62% increase in peak plasma concentrations ($C_{max}$). A low (about 200 calories) and medium (about 500 calories) fat meal increased $C_{max}$ 27% and 55%, respectively. Total exposure ($AUC_{inf}$) for high, medium and low-fat meal increased by 32%, 18%, and 14%, respectively. Gepirone should be administered with food to improve bioavailability after oral administration. Given that high-, medium-, and low-fat meal all improve bioavailability, patients can take gepirone with any type of food irrespective of fat content to help improve compliance.
2) A strong pharmacokinetic interaction was observed between gepirone and a strong CYP3A4 inhibitor (ketoconazole- 5-fold increase in gepirone concentrations) and a moderate CYP3A4 inhibitor (verapamil – 2.6-fold increase in gepirone concentrations). Strong CYP3A inhibitors are contraindicated with gepirone. A maximum dose of 40 mg is recommended when patients are taking gepirone and a moderate CYP3A inhibitor concomitantly
3) The results of the hepatic impairment study showed that the gepirone exposure was augmented 2-fold in moderate hepatic impaired subjects in conjunction with a 3- and 2-fold reduction in the $C_{max}$ and AUC of the metabolite 1-PP. The pharmacokinetics of gepirone has not been adequately characterized in severe hepatic impairment. The

maximum recommended dose in moderate hepatic impaired patients is 40 mg. Gepirone is contraindicated in patients with severe hepatic impairment.

4) The results of the renal impairment study suggested that the plasma concentrations of gepirone and its major metabolites (1-PP and 3-OH-gepirone) were elevated by approximately 70% in patients with moderate and severe renal impairment. The maximum recommended dose in moderate dose in moderate and severe renal impaired patients is 40 mg

5) The results of a study that evaluated the effect of age indicated that $C_{max}$ and AUC in the elderly (≥65 years) increased by 30% -60% and 50% – 80%, respectively. The maximum recommended dose in geriatric patients is 40 mg.

6) Gepirone exposure decreased up to about 50% in African Americas and Asians compared to Caucasians. No dose adjustment is necessary in African Americans and Asians since patients are dose-titrated to effect

The Office of Clinical Pharmacology reviewed the studies submitted in this application, in addition to the previous reviews, finds that all dosage strengths (20 mg, 40 mg, 60 mg and 80 mg) of the FMI formulation are recommended for approval.

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics and pharmacology information are based on previous clinical pharmacology reviews of the original application in 1999 and subsequent resubmissions. The following table summarizes the pharmacokinetics of gepirone.

**Table 11. Pharmacokinetics of Gepirone**

| Characteristics | Drug Information |
|---|---|
| *Pharmacology Activity* | |
| Mechanism of Action | Selective partial agonist at serotonergic (5-HT1A) receptors |
| Active Moieties | Gepirone |
| QT prolongation | In a thorough QT study, the largest mean increase in baseline- and placebo-corrected QTc interval with administration of 100 mg per day immediate-release formulation of gepirone was 18.4 msec (upper 90% confidence interval [CI] =22.7 ms) on Day 1 and 16.1 msec (upper 90% CI =20.7 ms) on Day 7. The exposure in this study was 2-fold the exposure of the maximum recommended dose. |
| *General Information* | |
| Bioanalysis | Liquid Chromatography-tandem mass spectrometry (LC-MS/MS)<br>Calibration range: 0.1– 25 ng/mL; 0.1 to 10 ng/mL<br><br>Gas Chromatography (GC)/MS<br>Calibration range: 0.1 – 25 ng/mL |

| Characteristics | Drug Information |
|---|---|
| Pharmacokinetics at steady state following the therapeutic dosing regimen | **Table 12. Mean ± SD PK Parameters for Gepirone Young Male Adults (18 -40 years)**<br>**Parameter** / **20 mg** / **40 mg** / **80 mg**<br>$C_{max}$ (ng/mL) / 3.9±1.6 / 9.1±4.9 / 23±15.9<br>$T_{max}$ (hr) / 4.5(1.5-8) / 3.0 (1-7) / 2.5 (1.5-4)<br>AUC(0-T) (hr*ng/mL) / 51.4±23.6 / 108±81.5 / 296±210<br>Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; PK, pharmacokinetic; SD, standard deviation; $T_{max}$, time to maximum plasma concentration<br><br>**Table 13. Young Females (18 – 40 years)**<br>**Parameter** / **20 mg** / **40 mg** / **80 mg**<br>$C_{max}$ (ng/mL) / 4.7±1.8 / 8.8±5.7 / 22.9±11.5<br>$T_{max}$ (hr) / 3(1-4) / 4 (2.5-6) / 2.5 (1-5)<br>AUC(0-T)(hr*ng/mL) / 54.9±22.6 / 105±61.3 / 273±133<br>Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; $T_{max}$, time to maximum plasma concentration |
| Range of Effective doses(s) or exposure | 40 mg – 80 mg |
| Maximally tolerated dose or exposure | 80 mg |
| Dose proportionality | 20 – 80 mg |
| Time to achieve steady state | After 2 days of dosing |
| Bridge between to-be-marketed (TBM) and clinical trial formulations (CTF) | 20 mg FMI is equivalent to 20 mg CTM; 80 mg FMI is equivalent to 80 mg CTM. Waiver is recommended for 40 mg and 60 mg intermediate strengths |
| *Absorption* | |
| Bioavailability | 14 -17% |
| Median (range) $T_{max}$ | 5 (1- 10) hours |
| Food Effect<br>High-Fat meal (822 calories)<br>Medium-Fat meal (549 calories)<br>Low-Fat meal (194 calories) | <br>$C_{max}$ ↑ by 62%, AUC ↑by 32%, $T_{max}$ ↓1 h<br>$C_{max}$ ↑ by 55%, AUC ↑ by 18%, $T_{max}$ ↓2h<br>$C_{max}$ ↑ by 27%, AUC ↑ by 14%, $T_{max}$ ↓2h |
| *Distribution* | |
| Volume of Distribution | 313.3±94.5 L |
| Plasma Protein binding | 72% for gepirone |
| *Elimination* | |
| Metabolism | Following oral administration of gepirone, less than 9% of the radioactivity in plasma was unchanged gepirone. In contrast, intravenous administration of the drug resulted in greater than 50% of unchanged drug in plasma. Thus, gepirone is subjected to first pass metabolism in the liver and/or the gut wall. CYP 3A4 (primary) and CYP 2D6 (minor) enzymes involved in the metabolism of gepirone. Major metabolites: 1-(2-pyrimidinyl) piperazine (1-PP) and 3'OH-gepirone. Other metabolites, mainly 3' 5-dihydroxy-gepiorne present in urine |
| Excretion<br>Half-life<br>Primary excretion pathway (%dose) | <br>$T_{½}$: 4.5 – 12 hours<br>81% administered dose in urine and 13% feces |

| Characteristics | Drug Information |
|---|---|
| *Intrinsic factors and specific populations* | |
| Age | $C_{max}$ ↑ by 30 – 60% in elderly<br>AUC ↑ by 50 -80% in elderly |
| Gender | No significant gender differences observed in PK |
| Race | Up to 50% ↓ in exposure in African Americans and Asians compared to Caucasians |
| Renal Impairment | $C_{max}$ ↑ by 74% in severe<br>AUC ↑ by 65- 71% (moderate and severe) |
| Hepatic Impairment | $C_{max}$ and AUC ↑ 2-fold (moderate)<br>Severe not studied |
| *Drug Interaction* | |
| Strong CYP3A4 inhibitor (Ketoconazole) | AUC ↑ 5-fold gepirone |
| Moderate CYP3A4 inhibitor (Verapamil) | $C_{max}$ and AUC ↑ 2.6-fold gepirone |
| CYP 3A4 strong Inducer (Rifampin) | $C_{max}$ ↓ 20-fold, AUC ↓ 29-fold gepirone |
| CYP2D6 strong inhibitor (Paroxetine) | Not significant effect at 40 mg gepirone dose |

Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; FMI, final market image; PK, pharmacokinetic; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

The recommended starting dosage is 20 mg once daily with food. If the 20 mg is adequately tolerated, an increase to 40 mg once daily may begin as early as day 4 of dosing. If the 40 mg dose is well tolerated and additional efficacy is desired, the dose maybe increased to 60 mg after one week and to 80 mg after an additional week.

**Therapeutic Individualization**

Hepatic Impairment: Gepirone is contraindicated in patients with severe hepatic impairment. The recommended maximum dose for patients with moderate hepatic impairment is 40 mg.

Renal Impairment: The maximum recommended dosage for patients with severe and moderate renal impairment is 40 mg daily.

CYP3A4 Inhibitors and Inducers: Gepirone is contraindicated in patients who are taking strong CYP3A4 inhibitors and inducers.

The maximum recommended dosage for patients taking moderate CYP 3A4 inhibitors is 40 mg daily.

(b) (4)

Geriatric Patients (≥65 years): The maximum recommended daily dosage of gepirone should not exceed 40 mg.

**Outstanding Issues**

The effect of moderate CYP3A inducers has not been studied as was requested in previous review cycles. Therefore, gepirone would be labeled not to be administered concomitantly with strong, moderate or mild inducers.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. Clinical Pharmacology Questions

**Is the PK bridge between the FMI formulation and the CTM formulation adequately demonstrated at 20 mg and 80 mg dosage strengths?**

Yes, the PK bridge between the FMI formulation and the CTM formulation has been adequately demonstrated at 20 mg and 80 mg strengths. In a single dose, randomized, 4-period, crossover replicate design study (Study 2666), both $C_{max}$ and $AUC_{inf}$ of gepirone were comparable between the FMI formulation and the CTM formulation under fasted conditions and met the bioequivalent criteria (80% -125%) based on the parent moiety (gepirone) evaluation. The median $T_{max}$ for the FMI formulation and the CTM formulation was 5.5 hours and 6.5 hours respectively. Given that gepirone is intended for chronic administration, the minimal difference in $T_{max}$ between the formulations are considered clinically not significant. Overall, the Applicant demonstrated that 20 mg gepirone FMI formulation was equivalent to 20 mg gepirone CTM formulation based on the parent moiety (gepirone) evaluation. In another study (Study 2667), the Applicant demonstrated that 1 x 80 mg FMI formulation is equivalent to 4 x 20 mg CTM formulation based on the parent moiety (gepirone) evaluation. The following tables provide the results of the pharmacokinetic analyses. Refer to the Appendices for details of the studies.

**Table 14. Statistical Analysis of Gepirone 20 mg Final Marketing Image Formulation Compared to 20 mg Phase 3 Clinical Trial Formulation (Study 2666)**

**Average Bioequivalence Analysis Results for Plasma Gepirone**

STUDY 2666 FAST (20DEC2021 - 09:16)
Average Bioequivalence Analysis Results for Plasma Gepirone
TREATMENT B vs TREATMENT A

| Parameter ($N_B/N_A$) | Geometric Means Arithmetic Means (CV %) TRT B | TRT A | Ratio of Geometric Means (%) | 90% Confidence Interval (%) | 95% Upper Confidence Bound | Analysis | Intra-Subject CV (%) TRT B | TRT A |
|---|---|---|---|---|---|---|---|---|
| AUCt (pg.h/mL) (62 /64 ) | 31050.25 36835.88(61.52 ) | 33878.65 39886.09(61.42 ) | 91.65 | 81.54, 103.02 | N/A | Unscaled | 36.14 | 29.12 |
| AUCinf (pg.h/mL) (49 /55 ) | 33607.99 41890.12(60.32 ) | 35141.74 42826.77(60.09 ) | 95.64 | 82.79, 110.48 | N/A | Unscaled | 40.49 | 28.62 |
| Cmax (pg/mL) (62 /65 ) | 2207.80 2572.27 (52.14 ) | 2393.68 2756.70 (54.91 ) | 94.01 | N/A | -0.045 | Reference-scaled | 21.74 | 31.82 |
| Tmax* (h) (62 /65 ) | 5.50 (2.00 - 16.00 ) | 6.50 (2.00 - 16.00 ) | | | | | | |
| Lambda# (1/h) (49 /55 ) | 0.1354 (46.94 ) | 0.1389 (42.11 ) | | | | | | |
| T1/2# (h) (49 /55 ) | 7.58 (101.23 ) | 6.14 (49.69 ) | | | | | | |
| AUCt/AUCinf# (49 /55 ) | 0.9523 (8.98 ) | 0.9693 (5.84 ) | | | | | | |

Note: $N_B/N_A$ are the number of observations for Treatment B and A, respectively
*: Presented as median and range #: Presented as arithmetic mean (CV%) only
Treatment A(Reference): Gepirone HCl, 20mg ER Tablets; Batch/Lot No: 98-013T; (b) (4)
Treatment B (Test): Gepirone HCl, 20mg ER Tablets; Batch/Lot No: 8L015; (Mission Pharmacal (USA))

Source: Study 2666 page 92
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

**Table 15. Statistical Analysis of Gepirone 80 mg (1 x 80 mg) FMI Formulation Compared to 80 mg (4 x 20 mg) Phase 3 Clinical Trial Formulation (Study 2667)**

| Pharmacokinetic Parameter | Test/Reference Ratio of Geometric Means (90% Confidence Interval) (%) | Intra-Subject CV for Test (%) | Intra-Subject CV for Reference (%) |
|---|---|---|---|
| $AUC_t$ | 96.57 (84.67 – 110.13) | 44.60 | 26.75 |
| $AUC_{inf}$ | 96.15 (84.12 – 109.90) | 45.00 | 26.68 |
| $C_{max}$ | 111.60 (102.88 – 121.05) | 21.11 | 15.86 |

Source: Study 2667 page 70
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; FMI, final market image

**Did the FMI formulation exert dose proportional PK characteristics?**

In study FK-GBE-011, the pharmacokinetics of gepirone 20 mg and 80 mg FMI formulation were evaluated in healthy subjects. The results suggest that the pharmacokinetics of the gepirone

20 mg FMI formulation was dose proportional to 80 mg FMI formulation based on $AUC_{inf}$. However, less than dose proportional increase in $C_{max}$ was observed between 20 mg and 80 mg.

**Table 16. Statistical Assessment of Dose Proportionality for Gepirone 20 mg and 80 mg FMI Formulation**

| Dose-Normalized Pharmacokinetic Parameter (units) | Treatment | Geometric LS Means (n) | Comparison | Ratio of Geometric LS Means | 90% CI |
|---|---|---|---|---|---|
| $AUC_{0-inf}$/Dose (h*ng/mL/mg) | A | 1.66 (36) | A/B | 0.90 | (0.78, 1.03) |
| | B | 1.85 (37) | | | |
| $AUC_{0-36}$/Dose (h*ng/mL/mg) | A | 1.61 (40) | A/B | 0.88 | (0.78, 0.99) |
| | B | 1.83 (40) | | | |
| $AUC_{0-t}$/Dose (h*ng/mL/mg) | A | 1.60 (40) | A/B | 0.88 | (0.78, 0.99) |
| | B | 1.83 (40) | | | |
| $C_{max}$/Dose (ng/mL/mg) | A | 0.12 (40) | A/B | 0.74 | (0.66, 0.82) |
| | B | 0.16 (40) | | | |

Abbreviations: CI, confidence interval; LS, least squares; n, number of subjects.

Note: An analysis of variance (ANOVA) model was fitted to the ln-transformed dose-normalized AUCs and $C_{max}$ data, with treatment as a fixed effect.

Treatment A: Single dose of 20 mg Gepirone ER Mission under fasted conditions.

Treatment B: Single dose of 80 mg Gepirone ER Mission under fasted conditions.

Source: Study FK-GBE-011 page 60
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; FMI, final market image; LS, least squares

**Is the PK of gepirone similar between adults with MDD and pediatric patients with MDD?**

In a study 28721, steady-state pharmacokinetics of gepirone was evaluated in children 7 to 11 years and adolescents 12 to 17 years with MDD. The average $AUC_{0-24}$ and $C_{max}$ values were 21% and 37% higher, for gepirone, 57% and 51% higher for 1-PP and 43% and 51% higher for the pharmacologically active metabolite, 3-OH-gepirone, respectively for children 7 – 11 years compared to adolescents 12 -17 years. For details about the effectiveness of gepirone in pediatric patients with MDD, refer to Section 8 in this review for the efficacy evaluation.

In a cross-study comparison of the pharmacokinetics of gepirone and its metabolites between pediatric patients 7 – 17 years from study 28721 and young adults 18 – 45 years from studies, 28703 and 28706, the mean results of the PK parameters in children and adolescents were comparable to those for young male adults, 18 - 45 years. Based on the previous clinical pharmacology review (archived on 2/19/2002), the pharmacokinetics of gepirone were comparable between male and female adults. Therefore, use of young male adults for the purpose of pharmacokinetic comparison to children and adolescents appear reasonable.

**Table 17. Summary of Mean (SD) Pharmacokinetic Parameters for Three Multiple Dose Studies Comparing Pediatric Patients (7-17 years) to Young Adults (18-45 Years)**

| Study | Dose | Population | Analyte | $C_{max}$ (ng/ml) | $AUC_{0-24}$(ng.h/ml) | $t_{1/2}$(h) |
|---|---|---|---|---|---|---|
| 28703 | 2x20 mg | Young, male adults | Gepirone | 9.7 (5,5) | 124 (69) | 8.0 (6.8) |
| | | | 1-PP | 9.3 (4.2) | 134 (76) | 8.1 (3.1) |
| | | | 3'OH-gepirone | 28.2 (6.5) | 460 (119) | 12.3 (6.0)) |
| 28706 | 2x20 mg | Young, male adults | Gepirone | 12.7 (4.7) | 173 (80) | 7.4 (3.4) |
| | | | 1-PP | 6.9 (2.6) | 101 (49) | 7.1 (2.0) |
| | | | 3'OH-gepirone | 25.4 (4.8) | 402 (110) | 12.1 (4.7) |
| 28721 | 2x20 mg | Male/female children and adolescents | Gepirone | 9.3 (4.3) | 119 (45) | 10.5 (7.2) |
| | | | 1-PP | 8.7 (5.2) | 125 (78) | 10.5 (4.2) |
| | | | 3'OH-gepirone | 31.5 (12.1) | 456 (154) | 13.4 (5.1)) |
| 28721 | 2 x 20 mg | Male/female children | Gepirone | 10.7 (5.5) | 130.6 (52.5) | 13.8 (9.2) |
| | | | 1-PP | 10.7 (6.7) | 150.4 (105.5) | 10.9 (5.6) |
| | | | 3'OH-gepirone | 37.1 (14.1) | 516.4 (191.5) | 14.2 (5.9) |
| 28721 | 2 x 20 mg | Male/female adolescents | Gepirone | 7.8 (2.4) | 107.8 (37.6) | 7.3 (2.0) |
| | | | 1-PP | 6.8 (2.2) | 99.9 (29.7) | 10.1 (2.5) |
| | | | 3'OH-gepirone | 26.0 (6.9) | 395.5 (83.5) | 12.6 (4.5) |

Source: Study 28721 page 62
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; SD, standard deviation; $T_{1/2}$, half-life

**Is the PK of gepirone similar between Caucasian and African-American pediatric patients with MDD?**

In a pediatric study FK-GBE-009**,** Caucasian pediatric patients showed 52% and 66% higher $C_{max}$ and $AUC_{inf}$, respectively than African American pediatric patients. However, $C_{max}$ and AUC of the metabolites (3-OH-gepirone and 1-PP) were similar. Based on the previous clinical pharmacology review (archived on 2/19/2002), the AUC of gepirone in adults was 1.5- to 2-fold higher in Caucasian compared to African Americans. The mean values of gepirone were not significantly different between females and males. Refer to the Appendices for details of study FK-GBE-009.

**Table 18. Summary of Pharmacokinetic Parameters for Gepirone, 1-PP, and 3-OH-Gepirone by Race for Pediatric Patients**

| Parameter[1] | | | Gepirone Metabolite | | | |
|---|---|---|---|---|---|---|
| | N | Gepirone | N | 1-PP | N | 3'-OH-gepirone |
| **African-American** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 4.36 ± 1.92 | 12 | 8.30 ± 3.97 | 12 | 29.1 ± 12.9 |
| $T_{max}$ (h) | 12 | 3.95 [1.9-11.9] | 12 | 4.93 [3.0-5.0] | 12 | 4.95 [3.0-12.0] |
| $AUC_{0\text{-tlast}}$ (h*ng/mL) | 12 | 60.6 ± 32.1 | 12 | 159 ± 83.2 | 12 | 610 ± 248 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 6 | 49.4 ± 20.2 | 10 | 177 ± 81.1 | 6 | 606 ± 217 |
| $\lambda z$ ($h^{-1}$) | 6 | 0.1262 ± 0.0550 | 10 | 0.0944 ± 0.0336 | 6 | 0.0428 ± 0.0123 |
| $t_{1/2}$ (h) | 6 | 7.03 ± 4.84 | 10 | 8.18 ± 2.70 | 6 | 17.4 ± 5.19 |
| CL/F (mL/min) | 6 | 15,389 ± 5,867 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 6 | 10,616 ± 10,647 | -- | --[2] | -- | --[2] |
| **Caucasian** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 9.03 ± 4.66 | 12 | 10.2 ± 4.42 | 12 | 28.3 ± 10.3 |
| $T_{max}$ (h) | 12 | 3.93 [0.9-7.9] | 12 | 5.01 [3.0-12.0] | 12 | 5.95 [3.0-12.0] |
| $AUC_{0\text{-tlast}}$ (h*ng/mL) | 12 | 128 ± 76.2 | 12 | 173 ± 108 | 12 | 610 ± 285 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 7 | 145 ± 80.5 | 11 | 178 ± 113 | 12 | 613 ± 285 |
| $\lambda z$ ($h^{-1}$) | 7 | 0.1478 ± 0.0751 | 11 | 0.1507 ± 0.0487 | 12 | 0.0822 ± 0.0177 |
| $t_{1/2}$ (h) | 7 | 5.79 ± 2.66 | 11 | 5.04 ± 1.58 | 12 | 8.78 ± 1.79 |
| CL/F (mL/min) | 7 | 7,271 ± 7,088 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 7 | 3,553 ± 2,895 | -- | --[2] | -- | --[2] |

Source: Study FK-GBE-009 page 49
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

See Table 19 below for a list of all of the Applicant's clinical trials considered during the review of this resubmission; see previous clinical reviews for additional clinical study details (Hearst review 2002; Hearst review 2007).

**Table 19. List Clinical Studies of Gepirone in Adult and Pediatric Patients With Depression**

| Study No. | Duration | Control Drug | Gepirone Dose | Population |
|---|---|---|---|---|
| FK-GBE-010 | 7 days | Placebo, 400 mg moxifloxacin on day 7 | 100 mg gepirone IR | Healthy Adults (18 to 50) |
| FK-GBE-011 | Single Dose | N/A | 20 mg, 80 mg | Healthy Adults (18 to 50) |
| FK-GBE-012<br>Study 2666 | Single Dose | N/A | 20 mg | Healthy Adults (18 to 55) |
| FK-GBE-014<br>Study 2667 | Single Dose | N/A | 20 mg, 80 mg | Healthy Adults (18 to 55) |
| FK-GBE-009 | Single Dose | N/A | 40 mg | Pediatric ((6 to 18) |
| Study No. 28721 | 7 days | N/A | 20 mg day 1<br>40 mg daily 2-5 days | Pediatric (7 to 17) |
| *Phase 2/3 placebo-controlled clinical studies of gepirone ER in adults and pediatric patients with depression* | | | | |
| 134001*<br>NCT US0001104 | Acute (8 weeks) | Placebo | 20-80 mg | Adult (18 to 69) |
| FK-GBE-007*<br>No NCT issued | Acute (8 weeks) | Placebo | 40-80 mg | Adult (18 to 64) |
| 134002 | Acute (8 weeks) | Placebo | 20-80 mg | Adult (18 to 69) |
| 134023 | Acute (9 weeks) | Placebo | 20-80 mg | Adult/Elderly (18 to 70) |
| FK-GBE-008 | Acute (8 weeks) | Placebo | 40-80 mg | Adult/Elderly (18 to 65) |
| CN105-057 | Acute (8-week titration) | Placebo | 2-40 mg | Adult/Elderly (18 to 79) |
| CN105-078 | Acute (6-week titration)<br>Extension (20 weeks) | Placebo | 10-100 mg | Adult/Elderly (17 to 77) |

| Study No. | Duration | Control Drug | Gepirone Dose | Population |
|---|---|---|---|---|
| CN105-083 | Acute (6-week titration)<br>Extension (20 weeks) | Placebo | 10-100 mg | Adult/Elderly (15 to 78) |
| 134004 | Acute (8 weeks) | Placebo, Fluoxetine | 20-80 mg | Adult (18 to 65) |
| 134502 | Extension (44 weeks) for patients completing 134004 | Placebo, Fluoxetine | 20-80 mg | Adult (18 to 65) |
| 134006 | Acute (8 weeks) | Placebo, Paroxetine | 20-80 mg | Adult (18 to 64) |
| 134503 | Extension (16 weeks) for patients completing 134006 | Placebo, Paroxetine | 40-80 mg | Adult (18 to 64) |
| 134017 | Acute (8 weeks) | Placebo, Fluoxetine | 20-80 mg | Adult (18 to 64) |
| 134506 | Extension (16 weeks) for patients completing 134017 | Placebo, Fluoxetine | 20-80 mg | Adult (18 to 64) |
| CN105-052 | Acute (8-week titration)<br>Extension (42 weeks) | Placebo, Fluoxetine | 20-60 mg | Adult (19 to 63) |
| CN105-053 | Acute (8-week titration)<br>Extension (44 weeks) | Placebo, Imipramine | 10-60 mg | Adult (19 to 74) |
| CN105-064 | Acute (8-week titration)<br>Extension (44 weeks) | Placebo, Imipramine | 5-40 mg | Adult/Elderly (20 to 78) |
| 134019 | Acute (8 week) | Placebo; fixed dose study | 20-80 mg | Pediatric (7 to 17) |
| 134020 | Acute (8 weeks) | Placebo, gepirone | 20-80 mg | Pediatric (7 to 17) |
| *Open-label extension studies* | | | | |
| 28709<br>NL0050245 | Open-label extension | Gepirone, no control | 20 mg-80 mg | Adult (18 to 79) |
| 134507 | Open-label extension | Gepirone, no control | 20 mg-80 mg | Pediatric (7 to 17) |

Source: Applicant generated table based on Applicant submissions
*Primary efficacy trials considered during the dispute resolution process and used as the basis for pooled safety in adults.
Abbreviations: ER, extended release; IR, immediate release

## 7.2. Review Strategy

This statistical and clinical review is for the NDA 021164 resubmission for gepirone ER tablets submitted to FDA on December 23, 2022. As described in Section 3.1., regulatory history, the Applicant originally submitted NDA 021164 on October 1, 1999, followed by resubmissions and amendment submissions in 2001, 2003, and 2007. On March 16, 2016, FDA determined that gepirone ER meets substantial evidence of effectiveness for the treatment of MDD in adult patients 18 years of age and older based on efficacy studies 134001 and FK-GBE-007, as decided by the dispute resolution process. The December 23, 2022, resubmission is considered a response to the November 2, 2007, Not Approvable Letter.

The Applicant's December 23, 2022, resubmission includes the following, for review, in alignment with the deficiencies and agreement described by FDA in the March 16, 2016, Appeal Granted letter and during the January 30, 2017, Type B pre-NDA meeting:

- Draft Label Text (FDA did not address the Applicant's Draft Labeling Text during previous review cycles);
- Previously requested QT studies;
- Pediatric short-term efficacy studies and long-term safety study to meet PREA requirements and the 2003 version of the PWR (as described above, the Applicant first submitted the pediatric studies to the IND 033626 during 2008, but these studies were not reviewed by FDA);
- Post hoc re-analysis of long-term Study 28709 (b) (4) and
- Post hoc re-analysis of sexual dysfunction findings for review (b) (4)

Note: The Applicant did not submit any newly conducted adult safety, efficacy study data, or summaries of safety or efficacy. The Applicant also did not include the abuse liability data or analyses requested by CSS or revise their databases using Standard MedDRA Queries as requested by FDA during the January 30, 2017, Type B Meeting.

The following statistical and clinical review focuses on the above-noted newly submitted information. FDA used numerous information requests (documented in DARRTs) to allow FDA to review the safety data of gepirone ER, including resubmitting results using Standard MedDRA Queries, refining pooling strategies to minimize bias, and providing additional data and analyses to allow assessment of safety concerns (including abuse liability), as described in Section 8.3.

For the current review cycle, we did not re-adjudicate previous FDA efficacy findings for the short-term treatment of MDD in adults, and we generally accepted the prior safety findings from previous reviews, with some updates that will be noted in our review as warranted. See Section 8 for reference to previously conducted FDA safety and efficacy reviews.

# 8 Statistical and Clinical Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy – Adults

The efficacy and safety studies for adults were included in the following previous and current NDA submissions for gepirone ER:

- SDN 3: received May 18, 2001 (including the positive study 134001)
- SDN 32: received December 23, 2003 (including the long-term efficacy study 28709)
- SDN 48: received May 1, 2007 (including the positive study FK-GBE-007)
- SDN 57: received December 7, 2012 (including the long-term efficacy study 28709)
- SDN 71: current submission (including the long-term efficacy study 28709)

FDA determined that substantial evidence of effectiveness of gepirone ER was met based on results from two short-term flexible-dose efficacy studies, 134001 and FK-GBE-007, as part of a dispute resolution. For additional details, please refer to the "Appeal Granted" letter authored by John K. Jenkins, MD, then-director of OND, signed into record on March 16, 2016, and clinical and statistical reviews for each of the above submissions of the statistical evidence leading to determination of substantial evidence of effectiveness. See below for a brief overview of statistical findings for studies 134001 and FK-GBE-007 and a new review of additional information provided in the current 2022 submission for the long-term efficacy study 28709.

Briefly, the effectiveness of gepirone ER in adults was established in two 8-week randomized, double-blind, placebo-controlled, flexible-dose studies in adults (age 18 to 69 years) meeting DSM IV criteria for MDD.

In Study 134001, subjects received gepirone ER 20 mg to 80 mg once daily (n=102) or placebo (n=106). After an initial dosage of 20 mg daily, the dosage was titrated to 40 mg daily on Day 4 of treatment. The dosage could then be increased to 60 mg daily after 7 days, and to 80 mg daily after 14 days. The final mean dosage of gepirone ER was 70.3±14.86 mg once daily, and for 66% of patients the final prescribed dosage was 80 mg once daily.

In Study FK-GBE-007, patients received gepirone ER 20 mg to 80 mg daily (n=124) or placebo (n=124). After an initial dosage of 20 mg daily, the dosage was titrated to 40 mg daily on Days 4 to 7 of treatment. The dosage could then be increased to 60 mg daily on Days 8 to 14, and to 80 mg daily after 14 days. The final mean dosage was 70.6±14.83 mg once daily, and for 66% of patients the final prescribed dosage was 80 mg once daily.

In both studies, gepirone ER was statistically superior to placebo as measured by improvement on the HAMD-17 total score at Week 8 (Table 20).

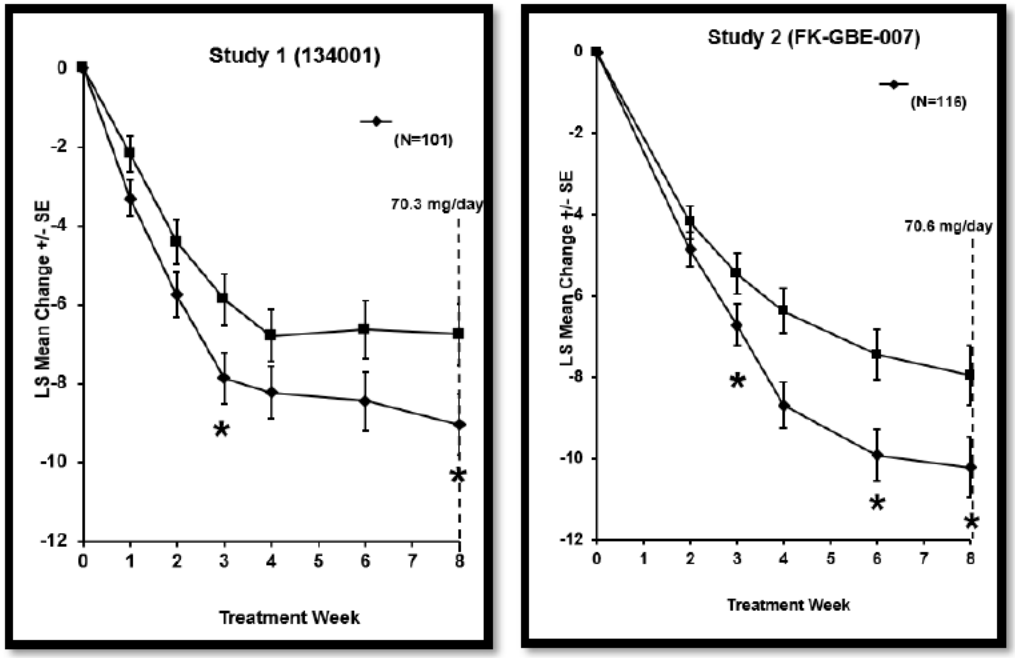
**Table 20. Primary Efficacy Results for Change from Baseline in HAMD-17 Total Score at Week 8 in Adult Patients With MDD (Study 1 and Study 2)**

| Study Number | Treatment Group | Mean Baseline Score (SD) | Week 8/ET LS Mean CFB (SE) | Placebo-Subtracted Difference (95% CI)* | p-Value |
|---|---|---|---|---|---|
| 134001 | Gepirone ER (N=101) | 22.7 (2.45) | -9.04 (0.78) | -2.47 (-4.41, -0.53) | 0.013 |
| | Placebo (N=103) | 22.8 (2.51) | -6.75 (0.77) | | |
| FK-GBE-007 | Gepirone ER (N=116) | 23.9 (2.69) | -10.22 (0.75) | -2.45 (-4.47, -0.43) | 0.018 |
| | Placebo (N=122) | 24.2 (2.93) | -7.96 (0.73) | | |

Source: CSR 134001 Table 12, Appendix F8.6.1.1-2, CSR FKGBE007 Table 15 and ISE Tables 3.1 and 3.2.
*Difference in baseline-adjusted means from ANCOVA.
Abbreviations: CFB, change from baseline; CI, confidence interval; ER, extended release; HAMD-17, 17-item Hamilton Depression Rating Scale; LS, least-squares; MDD, major depressive disorder; N, sample size; SD, standard deviation; SE, standard error

See Figure 6 for the Applicant's change from baseline in HAMD-17 total score by week 8 compared to placebo for studies 134001 and FK-GBE-007. The figure appears to suggest a downward trend from Baseline to Week 8, noting that only the 8-week values represent the prespecified endpoint and that the other values in this figure are exploratory and cannot be considered for statistical significance and may not be clinically meaningful.

**Figure 6. Change From Baseline in HAMD-17 Total Score by Treatment Week**




Source: Applicant generated figure (b) (4) submitted December 23, 2023.
Abbreviations: HAMD-17, 17-item Hamilton Depression Rating Scale; LS, least squares; SE, standard error

All secondary endpoints for these studies were not prespecified or controlled for Type I error, so they are all considered exploratory, and the results are not considered eligible for labeling

claims. See below for the review of additional efficacy re-analyses submitted with the current resubmission for the long-term efficacy study, Study 28709.

### 8.1.1. Long-Term Study 28709

Title: A Multicenter, Placebo-Controlled Study of Relapse Prevention During Long-Term Treatment with gepirone ER in Outpatients with Recurrent Major Depressive Disorder.

#### 8.1.1.1. Trial Design

This is a European, multicenter, placebo-controlled trial in outpatients with MDD. The trial, conducted by Organon Oss, started with an open-label phase of 8 to 12 weeks, which was followed by a double-blind continuation phase of 40 to 44 weeks.

All subjects were to undergo a single-blind, placebo wash-out period of 3 to 14 days, starting with signing the Informed Consent form. At the end of the screening period, baseline assessments were to be performed. Subjects, who met the baseline selection criteria, were eligible for enrollment in the open-label (OL) acute treatment phase of the trial. During the OL phase (8 or 12 weeks), all subjects were to be treated with gepirone ER. The aim of the OL phase was to select subjects responding (the Applicant used the term "remission") to gepirone ER (HAMD-17 total score ≤8, at week 8 or week 12). Responder subjects were to be randomized to placebo or gepirone ER for 40 to 44 weeks of double-blind continuation treatment. If the subject failed to respond after 12 weeks of treatment with an adequate dose of gepirone, the subject was to be withdrawn from the trial and the investigator was to consider an alternative treatment.

During the open label phase, subjects' dosages were titrated up to 40 mg of gepirone ER by day 4 and were then titrated within a range of 40 to 80 mg/day for the remainder of that phase. The double-blind phase involved the random assignment of responding subjects (1:1) to either gepirone ER (at their last dose during the open label phase) or placebo. Subjects were then observed for relapse over the next 40 to 44 weeks.

#### 8.1.1.2. Study Endpoints

The primary efficacy endpoint was relapse at the end of the continuation phase. However, we noted that the Applicant failed to define relapse explicitly or consistently. See Table 21 for different definitions of relapse across the protocol and the CSR.

**Table 21. Inconsistent Definitions of Relapse Found Across the Protocol and the Clinical Study Report**

| Location of Appearance | Relapse Definition |
|---|---|
| Protocol synopsis (Page 5)<br>Protocol definition Section (Page 12) | Relapse will be defined to have occurred in any of the following cases:<br>Discontinuation due to lack of efficacy<br>HAMD-17 score ≥16 |

| Location of Appearance | Relapse Definition |
|---|---|
| Protocol Section 5.3 (Page 28) | Relapse is defined as having a HAMD-17 score ≥16 or discontinuation due to lack of efficacy. In addition to these hard criteria, the investigator must have the opinion that the subject meets the criteria for major depressive episode. |
| Clinical study report synopsis (Page III) | For the primary analysis, relapse was defined by: (recalculated) HAMD-17 total score ≥16, or discontinuation due to 'Relapse criteria fulfilled' on the EOT form. |
| Clinical study report Section 4.1 Clinical trial design (Page 17) | Relapse was defined as having a HAMD-17 total score ≥16 OR discontinuation due to lack of efficacy. In addition to these criteria, the investigator had to have had the opinion that the subject met the DSM-IV criteria for major depressive episode. Investigators were to record the clinical judgement that a subject was discontinuing due to lack of efficacy according to these criteria by checking the item "Relapse Criteria Fulfilled" on the EOT CRF. |

Source: Clinical study report of protocol 28709 under NDA resubmission (SDN 32) received 23 December 2003, located here: \\fdswa150\NONECTD\N21164\N_000\2003-12-23\clinstat\28709-2003.pdf. The original protocol (dated June 1999) is included in report Appendix D.
Abbreviations: CRF. Case report form; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EOT, end of trial; HAMD-17, 17-item Hamilton Depression Rating Scale

The Applicant has noted the inconsistency of relapse definition. The CSR Section 7.13.1 noted that "The protocol did not specifically instruct investigators to tick the end of trial case report form (CRF) 'Relapse Criteria Fulfilled' item when they discontinued a subject who had relapsed for lack of efficacy. This, however, was the intention of the protocol, the statistical analysis plan, and the CRF design." In the current NDA submission (SDN 71), the report for Reconsideration of Data stated "However, the precise intended operational definition of a relapse was not perfectly clear and may have led to some confusion."

A secondary efficacy endpoint is the time-to-first-relapse.

#### 8.1.1.3. Statistical Analysis Plan

The relapse rates during the continuation phase were compared between treatment groups, using the Cochran-Mantel-Haenszel (CMH) test, controlling for centers. Furthermore, the secondary endpoint – time-to-first-relapse, was expressed as the number of days from the start of the continuation phase to the first occurrence of relapse. The time to relapse was considered as survival time, for which right censoring could occur due to premature discontinuation or completion before a relapse occurred. Treatment groups were compared using the Log-rank test. The primary efficacy analysis set for efficacy analyses consisted of all randomized patients who received at least one dose of assigned treatment and who had at least one post baseline efficacy evaluation.

#### 8.1.1.4. Study Results

The long-term efficacy study 28709 was included in the first NDA resubmission received (December 23, 2003, SDN 32). It was subsequently included in the NDA Amendment (December 7, 2012, SDN 57). Refer to the reviews of these submissions for additional details.

**The 2003 NDA Submission**

The long-term efficacy study 28709 was first included in the NDA resubmission (SDN 32) received December 23, 2003. According to the Applicant's CSR, the result of the primary analysis (CMH test adjusting for centers) was statistically significant, but the analysis result of the secondary endpoint, time-to-first-relapse, was not.

Based on the FDA statistical reviewer Ms. Roswitha Kelly's findings, the study failed to demonstrate efficacy. She pointed out that the CMH test as performed by the Applicant excluded centers that had either only one treatment arm or that had no relapses. As a consequence, 32 ITT subjects were not part of the sponsor's primary analysis.

Prior to unblinding the data, the Applicant identified five gepirone ER subjects who appeared to have met relapse criteria given that they appeared to have been discontinued due to worsening of depression but had not been designated as such on the case report form (CRF: Note: discontinuation due to lack of efficacy was one of two criteria for relapse). In fact, there is an internal company memo indicating that these subjects would be redefined as having relapsed, and they were so redefined (CSR Section 7.13.1). Subsequent to unblinding and analysis, the Applicant found that these subjects' HAMD-17 total scores had not met the ≥16 criterion, but it was too late to query investigators, given that they had also been unblinded. Nevertheless, the Applicant then decided to exclude these subjects as relapsers, on the grounds that the redefinition had not been done for formal amendment, and it had not been possible to query investigators.

Extracted below is a list of concerns from Ms. Kelly's review:

> The sponsor's primary statistical analysis did not use all ITT patients. When using all ITT patients, the comparison of relapse rates between gepirone-treated patients and placebo-treated patients did not reach statistical significance. This finding held for the Cochran-Mantel-Haenszel test when adjusting for Center or for Country.
>
> Five patients may have relapsed but were not treated as such in the sponsor's primary analysis. These patients all received gepirone and their reclassification reduces treatment differences to statistical nonsignificance.
>
> One important secondary endpoint is time to first relapse. The log-rank test did not reach statistical significance for the original data, when stratified by center or by country, nor when the five patients in question were considered to have relapsed (Roswitha Kelly, FDA Statistical Reviewer).

Table 22 is a summary of Ms. Kelly's findings from the primary efficacy analysis.

**Table 22. Efficacy Analysis Results of Primary Endpoint (Study 28709, Submitted Dec. 23, 2003)**

| Analysis Methods | Gepirone ER | Placebo | CMH p-Value |
|---|---|---|---|
| Applicant's analysis | 29/126 (23.0%) | 43/124 (34.7%) | 0.0244 |
| Reviewer's analyses: | | | |
| Grouping small centers[(1)] | 29/126 (23.0%) | 43/124 (34.7%) | 0.0971 |
| Grouping centers into countries | 29/126 (23.0%) | 43/124 (34.7%) | 0.0805 |
| Grouping small centers[(1)] and reclassifying five subjects as relapses | 34/126 (27.0%) | 43/124 (34.7%) | 0.3302 |
| Grouping by country and reclassifying five subjects as relapses | 34/126 (27.0%) | 43/124 (34.7%) | 0.3145 |

Source: Table 6 of FDA statistical review by Ms. Roswitha Kelly for the NDA resubmitted on Dec. 23, 2003 (SDN 32).
Grouping centers with at least two empty cells (single treatment assignment or single relapse status) with centers, which have four or less subjects, into one fictitious center. In total, 39 subjects from 12 centers were grouped. In the absence of a prespecified method for pooling centers, HFD-120's practice during the review time is to combine centers with less than five subjects.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ER, extended release

**The 2012 NDA Submission**

On December 7, 2012, the Applicant submitted an NDA 021164 Amendment in Response to Information Request[2] (SDN 57). This Amendment included Applicant's re-evaluation of this study, in which the Applicant listed factors indicating poor design and conduct of the trial.

- Investigators did not fully understand the protocol or the primary endpoint, as evidenced by a significant number of protocol violations.
- A high proportion of subjects received central nervous system drugs during the double-blind period, which can influence HAMD-17 ratings.
- Response criteria to qualify for randomization were not clearly defined and confirmed during the open-label period.
- Post hoc analyses restricted to qualified, protocol-compliant subjects show positive results for gepirone ER.
- Post hoc analyses do not prove that this study shows efficacy for gepirone ER. However, they do show had the study were done properly, the results would have been positive for gepirone ER.

[2] \\cdsesub4\NONECTD\NDA021164\5196098

The statistical reviewer of the NDA Amendment,[3] Dr. Yeh-Fong Chen, noted the following in Applicant's analyses:

(1) There were five subjects who had relapsed but their relapse events were not counted;

(2) The data of approximately 30 subjects (depending on the type of analyses, the numbers varied a bit) from the centers which had only a single treatment arm or had no relapse were removed from the CMH analysis with centers as strata;

(3) In the sponsor's re-analyses, subjects who were incorrectly identified as true drug responders were not removed from the analysis, but they were treated as nonrelapsers.

After adding back relapses and subjects described in (1) and (2) above, Dr. Chen's analyses yielded very different results with all p-values much larger than 0.05 (Table 23). It is also noted that these post hoc analyses were performed on selected analysis sets, which were likely to violate the randomization principle, an important assumption for a valid statistical analysis. Dr. Chen's findings were conveyed to the Applicant through a General Advice Letter[4] dated April 18, 2014.

**Table 23. Efficacy Reanalysis Results of Primary Endpoint (Study 28709, SDN 57 Submitted 7 Dec 2012)**

| | Applicant's Analysis Results | | | FDA Analysis Results | | |
|---|---|---|---|---|---|---|
| Analysis Populations | Gepirone ER | Placebo | CMH p-Value | Gepirone ER | Placebo | CMH p-Value |
| Original ITT | 29/126 (0.23) | 43/124 (0.35) | 0.024 | 34/126 (0.27) | 43/124(0.35) | 0.36[d] |
| Per protocol | 25/104 (0.24) | 41/106 (0.39) | 0.023 | 25/104 (0.24) | 40/106(0.37) | 0.11 |
| Redefined Nonresponders[a] | 22/126 (0.18) | 40/124 (0.32) | 0.007 | 26/118 (0.22) | 40/121(0.33) | 0.17 |
| Redefined Nonresponders[b] | 22/126 (0.18) | 42/124 (0.34) | 0.003 | 26/118 (0.22) | 42/123(0.34) | 0.11 |
| Redefined Nonresponders[c] | 25/126 (0.20) | 42/124 (0.34) | 0.013 | 29/121 (0.24) | 42/123(0.34) | 0.25 |

Source: Table 8 of FDA statistical review by Dr. Yeh-Fong Chen of the NDA Amendment submitted on 7 Dec 2012 (SDN 57).
[a] Excludes relapses on 1st visit after randomization, i.e., 11 subjects were removed.
[b] Excludes relapses on 1st visit after randomization if response was confirmed prior to randomization, i.e., nine subjects were removed.
[c] Includes subjects with 50% drop in HAMD-17 prior to randomization as responders, i.e., six subjects were removed from the analysis.
[d] Grouping centers with at least two empty cells (single treatment assignment or single relapse status) into one fictitious center. In total, 32 subjects from 10 centers are grouped.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ER, extended release; HAMD-17, 17-item Hamilton Depression Rating Scale; ITT, intent-to-treat

[3]Reference ID: 3381114

[4]Reference ID: 3491931

**The 2022 NDA Submission**

On December 28, 2016, the Applicant submitted a Type B meeting package (SDN 67/eCTD Seq 0001) to support a face-to-face meeting on January 30, 2017, in which the Applicant presented a re-assessment of long-term efficacy data in Study 28709 for FDA's reconsideration. The Division did not decline to review the post hoc re-assessment of long-term efficacy data as a part of the NDA resubmission, but warned that post hoc analyses pose significant problems that would need to be addressed and that we would require a very convincing justification for us to accept the results of the post hoc analyses.

On December 23, 2022, the Applicant resubmitted the NDA (SDN 71/eCTD Seq 0005) and requested that the FDA reconsider Study 28709. The Applicant listed four main issues:

(1) Choice of statistical method for analyzing data on the primary endpoint

(2) Treatment of three subjects who apparently met relapse criteria but were not discontinued

(3) Treatment of five arguable relapses that were not counted as such

(4) Treatment of subjects who may not have been true remissions at entry.

Below is a summary of their arguments, proposed changes, and associated results.

**Choice of Statistical Method for Analyzing Data on the Primary Endpoint**

The prespecified primary analysis to compare the relapse rates at endpoint was the CMH test adjusting for centers. In this resubmission, the Applicant considered that this method had many disadvantages in this study and there was no empirical evidence to justify the need to adjust for site effect variability. The Applicant re-analyzed data using the Fisher Exact Test in place of the prespecified CMH test. Their re-analysis leads to the following results:

Gepirone ER: 29/126 (23%)

Placebo: 43/124 (35%)

The p-value comparing these rates is 0.051.

***Statistical Reviewer Comment***

*Each analysis has its advantages and disadvantages. Center is often included as a factor in statistical analysis to increase study power when heterogeneity is expected among centers. In the two positive studies that the Applicant and FDA agreed on (FKGBE007 and 134001), the primary efficacy analysis ANOVA also included center as a factor in addition to treatment group. We do not consider the change of primary analysis in a post hoc manner to be acceptable.*

**Continued Patients Who Apparently Satisfied Relapse Criteria but Were Not Discontinued**

Subjects were expected to discontinue from the study after relapse (HAMD-17 total score of 16 or more). However, the Applicant pointed out that seven subjects remained in the study after meeting the relapse criteria (refer to the Applicant's Briefing Document submitted December 28, 2016 (SDN 67)). Four of seven subjects were ultimately counted as relapsers. However, three of them (one in the gepirone ER group with ID (b) (6), and the other two in the placebo group with IDs (b) (6) and (b) (6)) who remained in the study were not counted as relapses. After adding in the three inappropriately omitted relapses, the Applicant's results are:

Gepirone ER: 30/126 (24%)

Placebo: 45/124 (36%)

The p-value for the Fisher Exact Test comparing these rates is 0.038.

The Applicant noted that in the secondary endpoint analysis comparing time-to-first-relapse, the three relapses were correctly included, and the corresponding Log-rank test produces a p-value of 0.057.

***Statistical Reviewer Comment***

*We would agree that these three subjects should be treated as relapse because they had HAMD-17≥16 at an earlier assessment visit, and that their time-to-relapse should be the time to their "first relapse." However, correcting for these three subjects does not influence the analysis results if using the prespecified primary analysis method – CMH. (Refer to rows D1 to E2 in Table 24).*

**Treatment of Five Arguable Relapses That Were Not Counted as Such**

The Applicant pointed out that there were eight subjects who chose to discontinue from the trial for "Reason not mentioned above, please specify" and specified "worsening depression" as the primary reason. Three of these had endpoint HAMD-17 scores ≥16. However, five others ((b) (6)) were not counted as relapses. Four of these had final HAMD-17 scores that were less than 16, and one had no available score. The Applicant did not count these five subjects as relapsers in the primary analysis while FDA's analyses did.

As noted earlier, there is an internal company memo[5] by the former Applicant (Organon OSS) indicating that these five subjects would be redefined as having relapsed, although they were eventually excluded from relapsers in the primary analysis after data unblinding. Furthermore, in the 2016 Type B meeting package (SDN 67), the current Applicant (Fabre-Kramer) agreed

[5] Refer to CSR Section 7.13: \\fdswa150\NONECTD\N21164\N_000\2003-12-23\clinstat\28709-2003.pdf

that these five subjects appeared to meet the alternate criterion of discontinuation for lack of efficacy because relapse was clearly evident based on other clinical evidence (p53). However, the document of Reconsideration of Data in the current 2022 NDA resubmission turns over this decision, stating that:

> The fallacy is the assumption that any mention of worsening depression must be tantamount to the investigator's opinion that a relapse (i.e., an episode of major depression) had occurred. As explained in Section 2 above, such an opinion, in the case of a discontinuation, had to be certified explicitly by checking the specific item on the End of Trial case report form.
>
> Prior to unblinding, Organon informally authorized a post hoc modification to expand the relapse definition. Overlooked, however, was the possibility that "worsening depression" could be responsible for the subject's withdrawal, yet not be severe enough to constitute a return of major depression (Reconsideration of Data, 2022 NDA resubmission).

***Statistical Reviewer Comment***

- *For the NDA resubmission received December 2003 (SDN 32), FDA issued a Response Letter (dated June 23, 2004) with the following comments on this issue:*

  > *We consider it inappropriate, after looking at the results of the analysis, to decide not to include these patients as relapsers, when they had already been quite reasonably reclassified as relapsers by you prior to unblinding the data. It seems obvious, on face, that these 5 patients who were discontinued for worsening depression should be counted as relapsers, given that their discontinuations were for 'worsening of depression', whether or not there was an opportunity to query the investigators to try to verify this result. Thus, we believe the appropriate analysis is the one that includes these 5 patients as having relapsed (FDA Response Letter, June 23, 2004).*

- *The statistical reviewer notes that the list of discontinuation reasons in the end of trial CRF does not contain "lack of efficacy," so investigators may only be able to tick other reasons if a subject is indeed discontinued due to lack of efficacy.*
- *We do not consider the presented arguments justifiable for revoking these five subjects from relapsers, particularly after unblinding the treatment code.*

**Treatment of Subjects Who May Not Have Been True Remissions at Entry**

The Applicant pointed out that among those who had relapses, 18 subjects (12 on gepirone ER and six on placebo) experienced an apparent relapse at their first visit after randomization, and all these first visits occurred within the first 30 days after randomization. The Applicant commented that requiring only a single HAMD-17 score ≤8 was a relatively weak criterion for entering the randomized withdrawal phase and asserted that the unexpectedly large number of individuals who reverted to having a HAMD-17 score ≥16 by day 30 was potentially attributable to "false" remissions. In addition, the Applicant found the remission rate in the OL phase for this study was around 60%, much higher than those in the two pivotal gepirone ER HC1 ER

studies (both were under 40%). The Applicant considered that the findings in remission rates supported their assertion for why many patients met the relapse criteria at the first visits after randomization. Hence, the Applicant proposed to exclude these 18 subjects, leading to the following results:

Gepirone ER: 20/114 (18%)

Placebo: 39/118 (33%)

The p-value for the Fisher Exact Test comparing these rates is 0.010.

***Statistical Reviewer Comment***

- *We disagree with the exclusion of these 18 subjects from the analysis population. The Applicant's findings and arguments are post hoc with no convincing evidence regarding whether these subjects are true remitters or not. In addition, Applicant noted in the previous meeting package, "The existence of such measurement error did not invalidate the study, because it affected both treatment groups randomly. However, this additional 'noise' did, to some unknown degree, reduce the statistical power of the study." If measurement error is suspected, the validation should have been conducted in a prespecified manner instead of a post hoc manner.*
- *It is of great concern that the Applicant kept changing remission criteria in a post hoc manner. In its 2012 submission (SDN 57), the Applicant used different criteria to redefine remission (a 50% drop in baseline HAMD-17 total score) and concluded that eight subjects should thus be excluded from the analysis population. After excluding these eight subjects, the Applicant re-analyzed data and obtained a p-value of 0.013. However, the FDA statistical reviewer noted an error in the Applicant's analysis. In the 2022 NDA resubmission, the Applicant came up with a different approach to remove subjects who may not be true remitters. From the statistical perspective, such data-fishing is not acceptable.*

***Statistical Reviewer Summary***

Table 24 below summarizes FDA re-analysis results using the prespecified CMH test including all ITT patients, where rows A through C2 are identical to the results produced by the former statistical reviewer Ms. Roswitha Kelly (Table 22). D1 and D2 are the results after adding the three relapsers who remained in the study but were not counted as relapses (refer to item [2] above), in addition to adding the five subjects who should be counted as such (refer to item [3] above). E1 and E2 are the results after adding the three relapsers who remained in the study but were not counted as relapses (refer to item [2] above), but not adding the five subjects who should be counted as such (refer to item [3] above).

**Table 24. Efficacy Reanalysis Results of Primary Endpoint (Study 28709, SDN 71 Submitted on 23 Dec 2022)**

| | Analysis Methods | Gepirone ER | Placebo | CMH Test p-Value |
|---|---|---|---|---|
| A | Applicant's analysis (original) | 29/126 (23.0%) | 43/124 (34.7%) | 0.0244 |
| B1 | Grouping small centers[a] | 29/126 (23.0%) | 43/124 (34.7%) | 0.0971 |
| B2 | Grouping centers into countries | 29/126 (23.0%) | 43/124 (34.7%) | 0.0805 |
| C1 | Grouping small centers[a] and reclassifying five subjects as relapses | 34/126 (27.0%) | 43/124 (34.7%) | 0.3302 |
| C2 | Grouping by country and reclassifying five subjects as relapses | 34/126 (27.0%) | 43/124 (34.7%) | 0.3145 |
| D1 | Grouping small centers[a] and reclassifying five subjects as relapses and adjusting for three subjects who should be discontinued after relapse | 35/126 (27.8%) | 45/124 (36.3%) | 0.3231 |
| D2 | Grouping by country and reclassifying five subjects as relapses and adjusting for three subjects who should be discontinued after relapse | 35/126 (27.8%) | 45/124 (36.3%) | 0.2537 |
| E1 | Grouping small centers[a] and adjusting for three subjects who should be discontinued after relapse | 30/126 (23.8%) | 45/124 (36.3%) | 0.0845 |
| E2 | Grouping by country and adjusting for three subjects who should be discontinued after relapse | 30/126 (23.8%) | 45/124 (36.3%) | 0.0604 |

Source: FDA statistical reviewer Dr. Yiming Chen
[a] grouping centers with at least two empty cells (single treatment assignment or single relapse status) with centers, which have four or less patients, into one fictitious center. In total, 39 subjects from 12 centers are grouped.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ER, extended release

In summary, the Applicant's arguments for salvaging this trial are not acceptable except the argument of adding in three subjects (IDs (b) (6)) who were relapsers, but not counted as such in the primary analysis. These three subjects had HAMD-17≥16 at an earlier assessment visit but still remained in the study. We would agree that they should be counted as relapsers. However, correcting for these three subjects does not influence the analysis results if using the prespecified primary analysis method – CMH test (Refer to rows D1 to E2 in Table 24). The Applicant's other arguments are not acceptable for reasons summarized below:

- In general, the definition of response (or remission) during the open-label period to select responders (or remitters) to enter the randomized withdrawal phase is not unique. It is the Applicant's responsibility to ensure reasonable and clear definition, and to reach agreement with FDA during the protocol development stage. Any change in a post hoc manner undermines the study integrity and poses challenges in interpreting the treatment effect.
- Likewise, the analysis method is not unique, so it is critical to prespecify a reasonable analysis. Any change in a post hoc manner is difficult to defend and is likely to inflate the overall Type I error rate.
- It is of concern that the Applicant made attempts to re-analyze data post hoc from different aspects to salvage this trial. The chance of a false positive conclusion increases with more analyses conducted without a multiplicity adjustment. Furthermore, if the

data are convincing and robust, the conclusion should remain the same with minor changes in methods (such as statistical analysis, relapse definition).

**Efficacy Results – Secondary and Other Relevant Endpoints**

Time-to-first-relapse was a secondary endpoint. The FDA's re-analyses (Table 25) did not yield statistically significant results.

**Table 25. Efficacy Reanalysis Results of Time to First Relapse (SDN 71, Submitted 23 Dec 2022)**

| | Analysis Methods | Gepirone ER | Placebo | Log-rank p-Value |
|---|---|---|---|---|
| A | Applicant's analysis (clinical trial report) | 29/126 (23.0%) | 43/124 (34.7%) | 0.065 |
| C1 | Reclassifying five subjects as relapses[a] | 34/126 (27.0%) | 43/124 (34.7%) | 0.240 |
| D1 | Reclassifying five subjects as relapses[a] and adjusting for three subjects who should be discontinued after relapse | 35/126 (27.8%) | 45/124 (36.3%) | 0.202 |
| E1 | Adjusting for three subjects who should be discontinued after relapse | 30/126 (23.8%) | 45/124 (36.3%) | 0.057 |

Source: FDA statistical reviewer Dr. Yiming Chen
[a] The time-to-first-relapse for these five subjects were calculated as days from the randomization to treatment discontinuation.
Abbreviations: ER, extended release

### 8.1.2. Assessment of Efficacy Across Trials: Adults

The Applicant conducted 17 phase 2 and 3 efficacy trials, and the efficacy of gepirone ER was determined as part of the aforementioned dispute resolution process based on two positive short-term efficacy studies 134001 and FK-GBE-007. FDA did not re-evaluate efficacy across trials during the current review cycle.

### 8.1.3. Integrated Assessment of Effectiveness: Adults

Gepirone ER meets the statutory evidentiary standard for effectiveness for the treatment of MDD in adults, as determined by our aforementioned dispute resolution process. The change from baseline to 8 weeks on the HAMD-17 total score statistically significantly separates from placebo by week 8, and the change in total score is in the clinically meaningful range, according to Rush and colleagues (Rush et al. 2021).

Although FDA determined that efficacy is demonstrated in the two short-term studies 134001 and FK-GBE-007, we do not agree that efficacy is demonstrated in the long-term efficacy study 28709. It appears that the Applicant designed Study 28709 insufficiently to yield interpretable evidence, with an ambiguous definition of relapse. The Applicant's attempt to salvage this trial by changing the criteria for determining the relapsers or entry criteria to the randomized withdrawal phase in a post hoc manner is not acceptable for consideration as substantial evidence of long-term or maintenance effectiveness.

## 8.2. Review of Relevant Individual Trials Used to Support Efficacy – Pediatrics

The Applicant included pediatric efficacy and safety studies under the current NDA resubmission (SDN 71) in response to prior PREA commitments and a PWR. The Applicant's current submission included two short-term safety and efficacy studies 134019 and 134020, and one open-label extension safety study 134507.

See below for the review of the Applicant's two short-term pediatric efficacy studies, Study 134019 and 134020.

### 8.2.1. Pediatric Studies 134019 and 134020

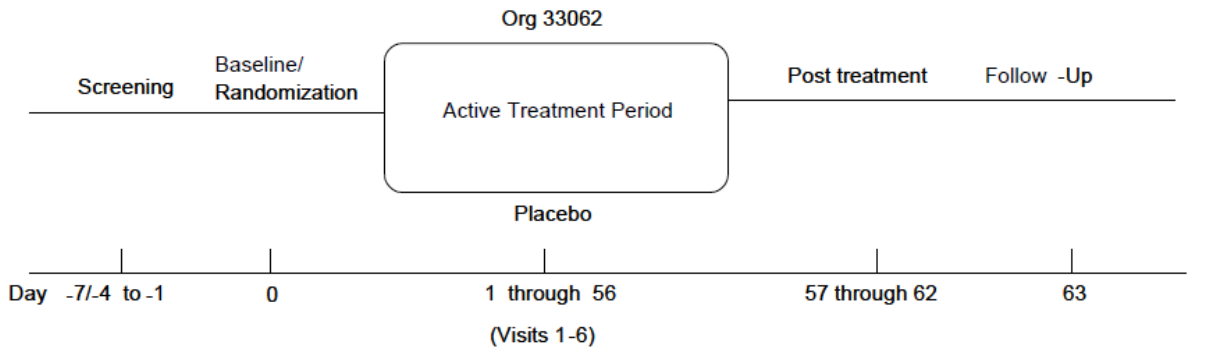
#### 8.2.1.1. Trial Design

Study 134019 is a multicenter, randomized, double-blind, placebo-controlled, fixed-dose, safety and efficacy trial of gepirone ER in outpatient children and adolescents (ages of at least 7 and less than 18 years old) with MDD. In this study, all subjects began with a screening visit approximately 14 days (Day -14) prior to Baseline, followed by a second screening visit 7 days later (Day -7) for completion of the Inclusion/Exclusion Checklist. Subjects who met screening criteria began a 1-week single-blind placebo run-in period on Day -6. After completion of the second screening week and after meeting the Selection Checklist Criteria, subjects were randomized 1:1:1:1 to one of three active treatment groups or placebo (Day 1) for 8 weeks of treatment.

The randomization was stratified by age group (ages 7 to 11 and ages 12 to 17). Besides placebo, the trial also contained three active treatment arms: 40, 60, and 80 mg gepirone ER once daily. See Figure 7 for the Applicant's study design for Study 134019 (there is no study design figure for Study 134020).

For Study 134019, all randomized subjects started on an initial dose of 20 mg gepirone ER once daily. Subjects randomized to the 40-mg group were titrated up to 40 mg by Day 4 and were to remain at 40 mg until Day 56. Subjects randomized to the 60-mg group were titrated to 40 mg by Day 4, 60 mg by Day 8 and were to remain at 60 mg until Day 56. Subjects randomized to the 80-mg group were titrated to 40 mg by Day 4, 60 mg by Day 8, 80 mg by Day 15, and were to remain at 80 mg until Day 56.

**Figure 7. Applicant's Study Design for Study 134019**




Source: Applicant's Clinical Study Report for Study 134019: Figure 9.1.

Study 134020 targeted a similar population. Differing from Study 134019, Study 134020 allowed flexible dosing (40 to 80 mg) based on tolerability. Eligible subjects were randomized 1:1 to either active treatment or placebo, stratified by age group (ages 7 to 11 and ages 12 to 17). The active treatment group received a starting dose of 20 mg of gepirone per day. The dose had to be increased to 40 mg per day on Day 4, and investigators had the option to increase the dose further to 60 mg per day at Week 2 or 80 mg per day at Week 3. If, after the initial 3 days of dosing, the subject appeared to require a slower titration, the investigator could use an alternative titration schedule.

#### 8.2.1.2. Study Endpoints

The primary efficacy variable for both studies was the change from Baseline in Children's Depression Rating Scale-Revised (CDRS-R) total raw score. The primary timepoint for treatment comparisons was the Endpoint assessment (the last assessment performed in the in-treatment period, which was defined as the period from first up to and including last Investigational Product administration (plus the allowed time frame for efficacy and safety data).

Secondary endpoints of both studies included:

1) Clinical Global Impressions, Responders-the proportion of subjects who responded in each treatment group, where responder is defined as a subject with a Global Impression of Change rating of 1 or 2 ("very much or much improved")
2) Hamilton Rating Scale for Depression, 17 item (HAMD-17)
3) Hamilton Rating Scale for Depression, 25 item (HAMD-25)

4) Children's Global Assessment Score, level of general functioning during the current episode, worst level of general functioning during the current episode, and the highest level of general functioning within the past year. The general level of functioning since Baseline was determined at Visit 4. The general level of functioning since the last postbaseline assessment of the general level of functioning was determined at Visit 6. At each visit, scores for each parameter were given in 10 categories (level 1:1-10, level 2: 11-20, level 3: 21-30, level 10: 91-100).
5) DSM-IV MDD Atypical Features
6) Kiddie-SADS PL, Depressive Disorders Section

#### 8.2.1.3. Statistical Analysis Plan

The primary efficacy analysis population was the ITT population which consisted of all randomized subjects who received at least one dose of trial medication and had at least one postbaseline efficacy measurement. Both studies employed an ANCOVA model, which included treatment group, center, and treatment group by center as effect terms, and the baseline CDRS-R total score as a covariate to analyze the primary endpoint. Sites with a total enrollment less than or equal to five subjects with zero subjects enrolled in at least one treatment group were pooled into a single site. If the test for treatment group by center interaction was not significant at the 0.10 level, the treatment group by center interaction term was dropped from the model, and the inference would be made from the reduced model. In case of a significant interaction ($p \leq 0.10$), the kind of interaction was discussed and further explored to evaluate whether it was still justified to present an overall estimate of the treatment effect. For all time points, the last-observation-carried-forward (LOCF) approach was used to impute missing data in primary analysis. Subgroup analyses based on age group (ages 7 to 11, and ages 12 to 17) were also conducted.

For Study 134019, a two-sided Dunnett's multiple comparison procedure was used to compare each of the three doses of gepirone ER to placebo, to correct for multiplicity.

***Statistical Reviewer Comment***

*We do not agree to the approach of model selection by first testing the treatment group by center interaction and then dropping the interaction term if it is not statistically significant, because this approach may inflate the overall Type I error if the same data set is used for model selection and then the statistical inference. In principle, the interaction term of treatment group by center should not be included in the primary analysis because we do not expect the treatment effect to differ from one center to another. In addition, the single-value imputation approach has become a great concern in recent years because it tends to underestimate the variability, although it was a common approach decades ago. However, these concerns are moot in these two studies because the primary analysis results are not statistically significant anyway (see Table 33 and Table 34 under Study Results Section).*

**Compliance With Good Clinical Practices**

The Applicant noted that they complied with Good Clinical Practices and filed an approval from an internal review board prior to beginning the clinical trials.

**Financial Disclosure**

The submitted financial certification that there were no financial disclosures to make for any of the investigators for any of the clinical studies described in this NDA submission (pediatric studies and clinical efficacy studies).

**Patient Disposition**

See Table 26 and Table 27 for subject disposition by study, including the total number of subjects in the ITT analysis. Note that the Applicant refers to gepirone ER as "Org 33062 ER" in some tables.

**Table 26. Subject Disposition for Study 134019**

| | Number (%, where applicable) of Subjects | | |
|---|---|---|---|
| Disposition | Org 33062 ER | Placebo | Overall |
| **All Subjects** | | | |
| Total number of subjects randomized (AST) | 321 | 108 | 429 |
| Total number of subjects treated (ITT) | 310 | 105 | 415 |
| Total number of subjects completed | 252 (81.3%) | 81 (77.1%) | 333 (80.2%) |
| Total number of subjects who discontinued | 58 (18.7%) | 24 (22.9%) | 82 (19.8%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 8 ( 2.6%) | 6 ( 5.7%) | 14 ( 3.4%) |
| AE or SAE | 21 (6.8%) | 1 ( 1.0%) | 22 ( 5.3%) |
| Other | 29 (9.4%) | 17 (16.2%) | 46 (11.1%) |
| **Subjects Ages 7-11** | | | |
| Total number of subjects randomized (AST) | 162 | 52 | 214 |
| Total number of subjects treated (ITT) | 156 | 50 | 206 |
| Total number of subjects completed | 119 (76.3%) | 47 (94.0%) | 166 (80.5%) |
| Total number of subjects who discontinued | 35 (22.4%) | 8 (16.0%) | 43 (20.9%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 5 ( 3.2%) | 2 ( 4.0%) | 7 ( 3.4%) |
| AE or SAE | 6 ( 3.8%) | 1 ( 2.0%) | 7 ( 3.4%) |
| Other | 24 (15.4%) | 5 (10.0%) | 29 (14.1%) |
| **Subjects Ages 12-17** | | | |
| Total number of subjects randomized (AST) | 159 | 56 | 215 |
| Total number of subjects treated (ITT) | 154 | 55 | 209 |
| Completed Treatment | 124 (80.5%) | 43 (78.2%) | 167 (79.9%) |
| Total number of subjects who discontinued | 30 (19.5%) | 12 (21.8%) | 42 (20.1%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 3 ( 1.9%) | 4 ( 7.3%) | 5 ( 2.4%) |
| AE or SAE | 15 (9.7%) | 0 | 15 (7.2%) |
| Other | 12 (7.8%) | 8 (14.5%) | 20 (9.6%) |

Source: Applicant's Clinical Study Report for Study 134019: Table 10.4
Abbreviations: AE, adverse event; AST, All subjects treated; ER, extended release; ITT, intent-to-treat; SAE, serious adverse event

**Table 27. Subject Disposition for Study 134020**

| Disposition | Number (%, where applicable) of Subjects | | |
|---|---|---|---|
| | Org 33062-ER | Placebo | Overall |
| **All Subjects** | | | |
| Total number of subjects randomized (AST) | 105 | 98 | 203 |
| Total number of subjects treated (ITT) | 103 | 98 | 201 |
| Total number of subjects completed | 76 (73.8%) | 88 (89.8%) | 164 (81.6%) |
| Total number of subjects who discontinued | 27 (26.2%) | 10 (10.2%) | 37 (18.4%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 5 ( 4.8%) | 1 (1.0%) | 6 ( 3.0%) |
| AE or SAE | 7 ( 4.9%) | 1 (1.0%) | 8 ( 4.0%) |
| Other | 15 (14.6%) | 8 (8.2%) | 23 (11.4%) |
| **Subjects Ages 7-11** | | | |
| Total number of subjects randomized (AST) | 50 | 51 | 101 |
| Total number of subjects treated (ITT) | 50 | 51 | 101 |
| Total number of subjects completed | 38 (76.0%) | 45 (88.2%) | 83 (82.2%) |
| Total number of subjects who discontinued | 12 (24.0%) | 6 (11.8%) | 18 (17.8%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 0 | 1 (2.0%) | 1 (1.0%) |
| AE or SAE | 5 (10.0%) | 1 (2.0%) | 6 ( 5.9%) |
| Other | 7 (14.0%) | 4 (7.8%) | 11 (10.9%) |
| **Subjects Ages 12-17** | | | |
| Total number of subjects randomized (AST) | 55 | 47 | 102 |
| Total number of subjects treated (ITT) | 53 | 47 | 100 |
| Completed Treatment | 38 (71.7%) | 43 (91.5%) | 81 (81.0%) |
| Total number of subjects who discontinued | 15 (28.3%) | 4 ( 8.5%) | 42 (19.0%) |
| Lack of efficacy: subject/investigator initiated discontinuation | 5 (9.4%) | 0 | 5 (5.0%) |
| AE or SAE | 2 (3.8%) | 0 | 2 (2.0%) |
| Other | 12 (7.8%) | 8 (14.5%) | 20 (9.6%) |

Source: Applicant's Clinical Study Report for Study 134020: Table 10.3
Abbreviations: AE, adverse event; AST, All subjects treated; ER, extended release; ITT, intent-to-treat; SAE, serious adverse event

***Clinical Reviewer Comment***

*See "Dropouts and/or Discontinuations Due to Adverse Effects" below for a discussion about dropouts.*

**Protocol Violations/Deviations**

In Study 134019, the Applicant noted two protocol violations, one in gepirone ER 40-mg group and one in the 60-mg group. These were not specified, but one was noted as, "non-compliance with [sic] w," with no additional information provided. The Applicant did not describe protocol violations in Study 134020.

***Clinical Reviewer Comment***

*We note that the small number of protocol violations did not likely contribute to the failure of the studies or bias the safety results in a meaningful way and, therefore, we did not pursue additional details.*

**Table of Demographic Characteristics**

See Table 28 and Table 29 for the Applicant's demographic characteristics by study for the ITT population for pediatric subjects. The Applicant recorded the demographics during screening. Summary statistics for continuous variables included N (number of nonmissing observations), mean, standard deviation, minimum, median, and maximum. For categorical variables, the Applicant presented frequency counts and percentages, with demographics and baseline characteristics summarized by treatment group. These studies were conducted prior to FDA requirements for recording ethnicity and expanded racial subgroups. See also Table 30 for the demographics for the pediatric open-label extension (OLE), Study 134507, which included subjects from the pediatric efficacy studies. Study 134507 was not considered for efficacy and is presented below for comparison to the parent studies 134019 and 134020. When applicable, the Applicant based the baseline values for Study 134507 on the subject's original enrollment in the parent efficacy study.

**Table 28. Demographic Characteristics for Study 134019**

| | | Org 33062 ER 40 mg (N=109) | Org 33062 ER 60 mg (N=106) | Org 33062 ER 80 mg (N=106) | Placebo (N=108) | Total (N=429) |
|---|---|---|---|---|---|---|
| Age (yrs) | n | 105 | 102 | 106 | 105 | 418 |
| | Mean | 12.0 | 11.8 | 11.8 | 12.1 | 11.9 |
| | SD | 3.00 | 2.78 | 2.81 | 2.74 | 2.83 |
| | Median | 11.0 | 12.0 | 11.0 | 12.0 | 11.5 |
| | Min | 7 | 7 | 7 | 7 | 7 |
| | Max | 17 | 17 | 17 | 17 | 17 |
| Age group | n | 105 | 102 | 106 | 105 | 418 |
| | Ages 7-11 | 55 (52%) | 50 (49%) | 54 (51%) | 50 (48%) | 209 (50%) |
| | Ages 12-17 | 50 (48%) | 52 (51%) | 52 (49%) | 55 (52%) | 209 (50%) |
| Sex | n | 105 | 102 | 106 | 105 | 418 |
| | Female | 48 (46%) | 50 (49%) | 60 (57%) | 65 (62%) | 223 (53%) |
| | Male | 57 (54%) | 52 (51%) | 46 (43%) | 40 (38%) | 195 (47%) |
| Race | n | 105 | 102 | 106 | 105 | 418 |
| | Caucasian | 82 (78%) | 77 (75%) | 75 (71%) | 75 (71%) | 309 (74%) |
| | Black | 11 (11%) | 11 (11%) | 13 (12%) | 16 (14%) | 51 (12%) |
| | Asian | 0 | 1 (<1%) | 1 (<1%) | 1 (<1%) | 3 (<1%) |
| | Other | 12 (11%) | 13 (13%) | 17 (16%) | 13 (12%) | 55 (13%) |
| Height (cm) | n | 105 | 102 | 106 | 105 | 418 |
| | Mean | 150.5 | 151.52 | 150.0 | 150.6 | 150.7 |
| | SD | 15.38 | 14.60 | 16.01 | 14.03 | 14.99 |
| | Median | 151.0 | 152.0 | 151.5 | 152.0 | 152.0 |
| | Min | 117 | 122 | 121 | 115 | 115 |
| | Max | 185 | 181 | 188 | 180 | 188 |
| Weight (kg) | n | 105 | 102 | 106 | 105 | 418 |
| | Mean | 53.7 | 56.9 | 53.5 | 55.9 | 55.0 |
| | SD | 20.67 | 21.58 | 21.75 | 23.91 | 21.97 |
| | Median | 51.2 | 52.5 | 50.5 | 52.4 | 51.8 |
| | Min | 21 | 23 | 21 | 23 | 21 |
| | Max | 121 | 124 | 135 | 146 | 146 |

Source: Applicant's Clinical Study Report for Study 134019: Table 10.2A
Abbreviations: ER, extended release; SD, standard deviation

**Table 29. Demographic Characteristics for Study 134020**

| | | Org 33062-ER (N = 105) | Placebo (N = 98) | Total (N = 203) |
|---|---|---|---|---|
| Age (yrs) | n | 105 | 98 | 203 |
| | Mean | 12.0 | 11.6 | 11.9 |
| | SD | 2.84 | 2.89 | 2.86 |
| | Median | 12.0 | 11.0 | 12.0 |
| | Min | 7 | 7 | 7 |
| | Max | 17 | 17 | 17 |
| Age group | n | 105 | 98 | 203 |
| | Ages 7-11 | 50 (48%) | 51(52%) | 101(50%) |
| | Ages 12-17 | 55 (52%) | 47(58%) | 102 (50%) |
| Sex | n | 105 | 105 | 203 |
| | Female | 62 (59%) | 46 (47%) | 108 (53%) |
| | Male | 43 (41%) | 52 (53%) | 95 (47%) |
| Race | n | 105 | 98 | 203 |
| | Caucasian | 77 (73%) | 66 (67%) | 143 (70%) |
| | Black | 21 (20%) | 21 (21%) | 42 (21%) |
| | Asian | 2 ( 2%) | 1 ( 1%) | 3 ( 1%) |
| | Other | 5 ( 5%) | 1 (10%) | 7 ( 7%) |
| Height (cm) | n | 105 | 98 | 203 |
| | Mean | 151.8 | 149.4 | 150.7 |
| | SD | 15.26 | 14.74 | 15.02 |
| | Median | 152 | 150.5 | 151.0 |
| | Min | 119 | 112 | 112 |
| | Max | 185 | 182 | 185 |
| Weight (kg) | n | 105 | 98 | 203 |
| | Mean | 54 | 50.49 | 52.4 |
| | SD | 21.53 | 19.37 | 20.55 |
| | Median | 51.5 | 46.6 | 49.5 |
| | Min | 23 | 17 | 17 |
| | Max | 117 | 109 | 117 |

Source: Applicant's Clinical Study Report for Study 134020: Table 10.2A
Abbreviations: ER, extended release; SD, standard deviation

**Table 30. Demographics for Study 134507**

| | | Gepirone ER (N=276) | Placebo (N=140) | Total (N=416) |
|---|---|---|---|---|
| Age[1] (yrs) | n | 276 | 140 | 416 |
| | Mean | 11.8 | 11.7 | 11.8 |
| | SD | 2.81 | 2.84 | 2.82 |
| | Median | 11.0 | 11.0 | 11.0 |
| | Min. | 7 | 7 | 7 |
| | Max. | 17 | 17 | 17 |
| Age Group | n | 276 | 140 | 416 |
| | Ages 7-11 | 141 (51%) | 72 (51%) | 213 (51%) |
| | Ages 12-17 | 135 (49%) | 68 (49%) | 203 (49%) |
| Sex | n | 276 | 140 | 416 |
| | Female | 137 (50%) | 73 (52%) | 210 (50%) |
| | Male | 139 (50%) | 67 (48%) | 206 (50%) |
| Race | n | 276 | 140 | 416 |
| | Caucasian | 199 (72%) | 104 (74%) | 303 (73%) |
| | Black | 40 (14%) | 23 (16%) | 63 (15%) |
| | Asian | 1 (<1%) | 0 | 1 (<1%) |
| | Other | 36 (13%) | 13 (9%) | 49 (12%) |
| Height (cm) | n | 276 | 140 | 416 |
| | Mean | 151.2 | 149.2 | 150.5 |
| | SD | 15.06 | 14.27 | 14.81 |
| | Median | 151.0 | 151.0 | 151.0 |
| | Min. | 117 | 112 | 112 |
| | Max. | 185 | 176 | 185 |
| Weight (kg) | n | 276 | 140 | 416 |
| | Mean | 55.0 | 51.2 | 53.7 |

Source: Applicant's Study 134507 CSR Table DT1
Abbreviations: ER, extended release; SD, standard deviation

**Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)**

The Applicant did not provide a summary of other baseline characteristics for their pediatric studies.

***Clinical Reviewer Comment***

*The demographics for the primary efficacy studies are generally similar and met FDA expectations in 2002, when the trials started.*

*Contrary to the May 4, 2004 PWR Amendment, the Applicant did not collect ethnicity data and only specifically reported on Caucasian, Black, and Asian races. We note the Applicant only enrolled 6 Asian subjects. The lack of ethnic and racial data and diversity in the study limits our ability to conduct subgroup analyses and to generalize the findings across race and ethnicities. However, the clinical review team accepted the Applicant's approach, given that the Applicant started their clinical trials in 2002, well before the PWR amendment.*

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

In pediatric trials Study 134019, the mean (standard deviation) daily dose of gepirone ER was 38.1 (3.2), 53.5 (7.5), and 66.7 (15.1) mg/day in the 40, 60, 80 mg group, respectively, which is consistent with some noncompliance in the study. In 134020, the mean (standard deviation) daily dose of gepirone ER was 59.1 (13.6) mg/day, which is lower than the mean daily dose in adult studies.

In both pediatric studies, the Applicant calculated overall compliance (in percentage) as 100 times the number of tablets taken divided by the number of tablets that should have been taken. Missing values were recorded as being compliant. See Table 31 and Table 32 for the Applicant's reported overall percent compliance to study medication in the ITT for studies 134019 and 134020.

**Table 31. Overall Compliance for Study 134019**

| | | Org 33062 ER 40 mg | Org 33062 ER 60 mg | Org 33062 ER 80 mg | Placebo |
|---|---|---|---|---|---|
| | n | 105 | 102 | 106 | 105 |
| Overall percent compliance | Mean | 102.8 | 103.5 | 99.8 | 103.6 |
| | SD | 31.2 | 35.1 | 24.7 | 35.3 |
| | Median | 98.1 | 99.8 | 96.8 | 99.5 |
| | Min | 28.2 | 56.5 | 71.4 | 73.3 |
| | Max | 339.1 | 322.0 | 275.8 | 375.0 |

Source: Applicant's Clinical Study Report for Study 134019: Table 10.3.2.1
Abbreviations: ER, extended release; SD, standard deviation

**Table 32. Overall Compliance for Study 134020**

| Parameter | n | Org 33062-ER | Placebo |
|---|---|---|---|
| | | 103 | 98 |
| Overall percent compliance | Mean | 97.5 | 97.4 |
| | SD | 11.8 | 8.2 |
| | Median | 99.5 | 98.3 |
| | Min | 66.7 | 71.9 |
| | Max | 175.0 | 141.0 |

Source: Applicant's Clinical Study Report for Study 134020: Table
Abbreviations: ER, extended release; SD, standard deviation

In the pediatric OLE Study 134507, the overall compliance of gepirone ER was 96% (mean, SD =21%); median 96%; minimum 29% and maximum 243%, with similar results for the placebo group, 96% (mean, SD =28%); median 96%; minimum 13% and maximum 294%.

***Clinical Reviewer Comment***

*The Applicant did not describe any efforts to monitor for or encourage compliance beyond pill counts. We note the maximum percent of compliance far exceeded 100, which should not be possible given the calculation used to determine compliance and is inconsistent with the lower-than-expected mean daily dosing for the fixed-dose study 134019. The Applicant did not explain why their maximum percentage exceeds 100 or discuss compliance results in the CSRs.*

*We note that the Applicant recorded missing values as compliant and speculate that the data were entered wrong or there were extra pill counts (i.e., subjects brought their bottles in at a later time, and those counts were recorded, in addition to the 100% for the previous "missing" visit). In the absence of meaningful data, we cannot comment on compliance in the pediatric studies, which limits our ability to understand efficacy (and safety) results. We note that the Applicant did not report compliance over 100% for the adult studies, further suggesting these results are in error.*

#### 8.2.1.4. Study Results

**Efficacy Results – Primary Endpoint**

For studies 134019 and 134020, the Applicant used the ANCOVA model that included factors for treatment and center, baseline as a covariate. According to the Applicant, the LS mean change from baseline to week 8 was not statistically significantly greater in any of the gepirone ER treatment arms compared to placebo. The Applicant noted that there were no statistically significant results for gepirone ER compared to placebo at any evaluation point or for either age group (ages 7 to 11 and 12 to 17).

For both studies, the Applicant included in the CSR appendices two sets of efficacy results, provided by Organon and (b) (4) respectively, although each CSR Section 9.9.2 seems to suggest that the (b) (4) statistical analyses provided data for the age 15 to 17 group only. Table 33 and Table 34 summarize the results from Organon and (b) (4) respectively. Although there are differences in numerical results between the two sets, overall the conclusions are the same that there were no statistically significant differences between any of the gepirone ER treatment groups and placebo in both studies. It is also noted that in both studies, the numerical results were even *in favor of placebo* for each gepirone ER treatment group, whether based on Organon's or (b) (4) results, but the results for the gepirone ER 80-mg fixed-dose arm alone were trending numerically similar to those for the placebo group (although still worse than placebo).

**Table 33. Organon's Primary Efficacy Results for Change From Baseline in CDRS-R Total Raw Score at Endpoint (Pediatric Studies 134019 and 134020)**

| Study Number | Treatment Group | Mean Baseline Score (SD) | Endpoint LS Mean CFB (SE) | p-Value* |
|---|---|---|---|---|
| 134019 | Gepirone ER 40 mg (N=102) | 58.8 (9.95) | -19.49 (1.222) | 0.398 |
| | Gepirone ER 60 mg (N=102) | 60.0 (9.03) | -18.19 (1.223) | 0.091 |
| | Gepirone ER 80 mg (N=106) | 60.1 (8.37) | -21.32 (1.193) | 0.987 |
| | Placebo (N=105) | 60.4 (9.61) | -21.77 (1.192) | |
| 134020 | Gepirone ER 40 to 80 mg (N=103) | 56.1 (7.94) | -17.22 (1.261) | 0.067 |
| | Placebo (N=97) | 56.4 (7.73) | -20.45 (1.298) | |

Source: 134019 CSR Tables 11.2.1A and 11.2.2A; 134020 CSR Tables 6.1.1 and 6.2.1.
Statistical model was based on reduced ANCOVA model (treatment and site as factors, baseline as a covariate).
* p-values were two-sided. For Study 134019, the p-values were based on the Dunnett's test to adjust for multiplicity.
Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CFB, change from baseline; CI, confidence interval; ER, extended release; LS, least squares; N, number of patients in the primary efficacy analysis set; SD, standard deviation; SE, standard error

**Table 34. (b) (4) Primary Efficacy Results for Change From Baseline in CDRS-R Total Raw Score at Endpoint (Pediatric Studies 134019 and 134020)**

| Study Number | Treatment Group | Mean Baseline Score (SD) | Endpoint LS Mean CFB (SE) | Placebo-Subtracted Difference (95% CI) | p-Value* |
|---|---|---|---|---|---|
| 134019 | Gepirone ER 40 mg (N=105) | 58.7 (9.84) | -18.6 (1.18) | +2.5 (-1.5, 6.4) | 0.315 |
| | Gepirone ER 60 mg (N=102) | 60.0 (9.03) | -17.8 (1.19) | +3.3 (-0.7, 7.2) | 0.127 |
| | Gepirone ER 80 mg (N=106) | 60.1 (8.37) | -20.7 (1.17) | +0.3 (-3.6, 4.2) | 0.995 |
| | Placebo (N=105) | 60.4 (9.61) | -21.0 (1.17) | | |
| 134020 | Gepirone ER 40-80 mg (N=103) | 56.1 (7.94) | -16.2 (1.18) | +3.1 (-0.3, 6.4) | 0.070 |
| | Placebo (N=98) | 56.4 (7.72) | -19.3 (1.21) | | |

Source: 134019 CSR Tables ET1 and ET7; 134020 CSR Tables ET1 and ET7.
Statistical model was based on reduced ANCOVA model (treatment and site as factors, baseline as a covariate).
* p-values were two-sided. For Study 134019, the p-values were based on the Dunnett's test to adjust for multiplicity.
Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CFB, change from baseline; CI, confidence interval; ER, extended release; LS, least squares; N, number of patients in the primary efficacy analysis set; SD, standard deviation; SE, standard error

Exploratory subgroup analysis results generally did not suggest efficacy in any of the gepirone ER treatment groups in either age cohort for both studies (Table 35 and Table 36). Although in Study 134019, the estimated treatment effect (relative to placebo) for gepirone ER 60 mg in the 7 to 11 years cohort appeared relatively large with a 95% confidence interval barely exceeding zero. The results are considered exploratory because these studies were not designed to detect a treatment difference within each age cohort and there was no multiple testing procedure prespecified to control the study-wise Type I error, including testing across age cohorts.

**Table 35. Organon's Subgroup Analysis Results by Age Group for Change From Baseline in CDRS-R Total Raw Score at Endpoint (Pediatric Studies 134019 and 134020)**

| Study Number | Age Group | Treatment Group | Mean Baseline Score (SD) | Endpoint LS Mean CFB (SE) |
|---|---|---|---|---|
| 134019 | 7 to 11 years | Gepirone ER 40 mg (N=52) | 58.3 (9.12) | -20.07 (1.797) |
| | | Gepirone ER 60 mg (N=50) | 60.2 (8.89) | -16.84 (1.830) |
| | | Gepirone ER 80 mg (N=54) | 59.1 (8.96) | -23.17 (1.701) |
| | | Placebo (N=50) | 59.7 (9.20) | -22.42 (1.775) |
| | 12 to 17 years | Gepirone ER 40 mg (N=50) | 59.4 (10.80) | -19.43 (1.791) |
| | | Gepirone ER 60 mg (N=52) | 59.8 (9.25) | -19.87 (1.744) |
| | | Gepirone ER 80 mg (N=52) | 61.2 (7.65) | -19.67 (1.760) |
| | | Placebo (N=55) | 61.1 (10.01) | -21.38 (1.691) |
| 134020 | 7 to 11 years | Gepirone ER 40 to 80 mg (N=50) | 53.7 (7.11) | -17.16 (1.790) |
| | | Placebo (N=51) | 55.2 (8.14) | -20.80 (1.794) |
| | 12 to 17 years | Gepirone ER 40 to 80 mg (N=53) | 58.4 (8.05) | -18.08 (1.992) |
| | | Placebo (N=46) | 57.7 (7.12) | -20.83 (2.104) |

Source: Study 134019 CSR Table 11.2.1B, 11.2.2B, 11.2.1C, and 11.2.2C; Study 134020 CSR Tables 6.1.1 and 6.2.1.
Statistical model was based on reduced ANCOVA model (treatment and site as factors, baseline as a covariate).
Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CFB, change from baseline; CI, confidence interval; ER, extended release; LS, least squares; N, number of patients in the primary efficacy analysis set; SD, standard deviation; SE, standard error

**Table 36. [redacted](b) (4) Subgroup Analysis by Age Group for Primary Efficacy Results for Change From Baseline in CDRS-R Total Raw Score at Endpoint (Pediatric Studies 134019 and 134020)**

| Study Number | Age Group | Treatment Group | Mean Baseline Score (SD) | Endpoint LS Mean CFB (SE) | Placebo-Subtracted Difference (95% CI*) |
|---|---|---|---|---|---|
| 134019 | 7 to 11 years | Gepirone ER 40 mg (N=55) | 58.0 (8.94) | -18.6 (1.64) | +3.9 (-1.7, 9.6) |
| | | Gepirone ER 60 mg (N=50) | 60.2 (8.89) | -16.3 (1.72) | +6.2 (0.4, 11.9) |
| | | Gepirone ER 80 mg (N=54) | 59.1 (8.96) | -23.4 (1.65) | -0.9 (-6.6, 4.7) |
| | | Placebo (N=50) | 59.7 (9.20) | -22.5 (1.71) | |
| | 12 to 17 years | Gepirone ER 40 mg (N=50) | 59.5 (10.79) | -18.7 (1.73) | +1.1 (-4.5, 6.8) |
| | | Gepirone ER 60 mg (N=52) | 59.8 (9.25) | -19.0 (1.68) | +0.8 (-4.8, 6.4) |
| | | Gepirone ER 80 mg (N=52) | 61.2 (7.65) | -17.8 (1.68) | +2.0 (-3.5, 7.6) |
| | | Placebo (N=55) | 61.1 (10.01) | -19.8 (1.63) | |
| 134020 | 2 to 11 years | Gepirone ER 40 to 80 mg (N=50) | 53.7 (7.11) | -16.0 (1.71) | +4.0 (-0.8, 8.8) |
| | | Placebo (N=51) | 55.2 (8.14) | -19.9 (1.69) | |
| | 12 to 17 years | Gepirone ER 40 to 80 mg (N=53) | 58.4 (8.05) | -16.6 (1.62) | +1.7 (-3.0, 6.5) |
| | | Placebo (N=47) | 57.8 (7.08) | -18.3 (1.73) | |

Source: 134019 CSR Tables ET2, ET3, ET8, and ET9; 134020 CSR Tables ET2, ET3, ET8, and ET9.
Statistical model was based on reduced ANCOVA model (treatment and site as factors, baseline as a covariate).
*The 95% confidence intervals for the Placebo-subtracted Difference in study 134019 were adjusted for multiple comparisons using the Dunnett method within each age cohort.
Abbreviations: CDRS-R, Children's Depression Rating Scale-Revised; CFB, change from baseline; CI, confidence interval; ER, extended release; LS, least squares; N, number of patients in the primary efficacy analysis set; SD, standard deviation; SE, standard error

### 8.2.2. Assessment of Efficacy Across Trials and Integrated Assessment of Effectiveness: Pediatric

The Applicant submitted two adequate and well-controlled 8-week efficacy trials (one fixed-dose, one flexible-dose) that were based on the July 18, 2003, PWR issued by FDA. Both pediatric efficacy studies 134019 and 134020 failed to demonstrate efficacy on their primary endpoint. In each study, most of the numerical results even trended in favor of placebo for each gepirone treatment group.

There is no basis for further consideration of pediatric efficacy for gepirone ER.

## 8.3. Review of Safety – Adult and Pediatric Studies

### 8.3.1. Safety Review Approach

As described above in Section 3.1 and Section 7.2, FDA reviewed the safety of gepirone ER for adults with MDD during the Applicant's previous NDA submissions and during the PDAC conducted on December 1, 2015; these reviews concluded that the safety of gepirone ER is generally acceptable in adults. Therefore, the current clinical safety review mainly focuses on the Applicant's Draft Labeling Text, and newer data and analyses submitted by the Applicant with this NDA resubmission (e.g., results from a new dedicated QT study, new pediatric safety data, and re-analysis of sexual dysfunction data), and new information requests from FDA to the Applicant[6] to address some issues with the Applicant's presentation and analysis of safety data via older standards (e.g., for abuse lability, adverse reaction tables, sexual dysfunction, safety monitoring results such as electrocardiograms (ECGs)/QT interval, and height and weight in pediatric subjects).

See below for the new (i.e., not previously discussed) safety reviews/concerns identified during this review:

- QTc prolongation (requiring ECG and electrolyte correction in all patients prior to dosing, and additional ECG monitoring with dosage adjustments and periodically during treatment);
- New contraindications related to QTc prolongation (congenital long QT syndrome, severe hepatic impairment, or concomitant strong CYP34A inhibitors or current/recent MAOI use);
- Embryotoxicity based on nonclinical studies; presence of gepirone ER in rat milk;
- Class risks associated with serotonergic antidepressants (e.g., suicidal thoughts and behaviors, serotonin syndrome, mania/hypomania; use in pregnancy and risk to fetus/neonate);
- Dosage adjustments (for geriatric patients, when a moderate CYP3A4 inhibitor is administered, and for hepatic and renal impairment);
- Review of abuse liability potential, concluding that gepirone ER does not have a potential for abuse; and,
- Pediatric safety: adverse reactions were generally similar to or less frequent than those reported in adult studies, with the exception of higher incidence of vomiting in pediatric subjects compared to adults.

[6] Information request exchanges are available in FDA's DARRTs

For the adult safety findings, we present results of the Applicant's new safety data and re-analyses. Regarding previously adjudicated safety results, we highlight key findings from past FDA safety reviews (e.g., by FDA Medical Officers Dr. Earl Hearst in 2002, 2004, and 2007 and Dr. Tarek Hammad in 2002), and as warranted, supplemented with re-analyses from information requests, and data from the Applicant's 2007 integrated summary of safety (ISS).

Given that most of the adult safety data were previously adjudicated by FDA, we present the new pediatric safety findings alongside the adult data, to allow for direct comparison of adult and pediatric safety findings (March 2019).

### 8.3.2. Review of the Safety Database

**Overall Exposure**

According to the Applicant's 2007 ISS and the review of safety by Dr. Earl Hearst (page 30), a total of 8407 adult subjects were enrolled in the Applicant's phase 2 and 3 studies, including uncontrolled trials, active control trials, and trials conducted in the pursuit of other indications (i.e., not MDD subjects). Most subjects received gepirone ER (N=3117, 37.1%); 21% (N=1859) received gepirone IR, and 30% received placebo (N=2483). An additional 14% were treated with an active control antidepressant (fluoxetine 8.3%; paroxetine 3.3%, and imipramine 2.9%) and 2% received benzodiazepines. In total, 1976 unique subjects with MDD received gepirone ER in phase 2 and 3 studies. These data include 303 subjects with MDD receiving gepirone ER who completed the 52 long-term efficacy study (Study 28709).

In the pediatric MDD studies, 426 pediatric subjects with MDD (ages 7 to 17) received gepirone ER during placebo-controlled trials and 206 pediatric subjects with MDD received placebo. This includes 102 pediatric MDD subjects who completed the long-term open label extension study (134507). See Table 19 in Section 7.1 for a list of clinical studies considered during this review cycle.

**Safety Population**

The Applicant conducted their safety analyses using all subjects who received any treatment. The Applicant did not include AEs occurring after more than 7 days off study drug unless the AEs were classified as serious (SAEs).

***Clinical Reviewer Comment***

*We agree with previous FDA reviewers that the number of and duration of exposures are adequate for reviewing the safety of gepirone ER and that the safety population is acceptable.*

**Adult Safety Pooling Strategy**

The Applicant's originally submitted adverse reaction table for adults was derived from a pool of 17 studies of different designs, duration, and gepirone doses, and only presented results for a 40-mg modal dose using nonstandardized terms (there is no documentation discussing FDA agreement on this strategy). Our clinical data scientists were unable to verify the quality of the data. Using information requests and reference to FDA guidance to base the AR table on the best available data (January 2006), FDA worked with the Applicant to create acceptable AR tables that reduce bias by using Standard MedDRA Queries (SMQs) and pooled data from studies with assay sensitivity only.

In response to FDA's information request to use a different pooling strategy that reduces bias, the Applicant advocated their preference for a safety pool that combines all 14 of the short-term efficacy trials, whereas FDA contends that the safety pool should be limited to studies with assay sensitivity (i.e., studies with assay sensitivity yield best available data when data quality cannot be confirmed). It is important to note that only 2 of the 14 studies in the Applicant's phase 2/3 safety pool were positive for efficacy for gepirone ER, and data quality concerns continue to exist for the failed studies.

See Table 37 for a comparison of AEs for the pool of 14 short-term efficacy studies chosen by the Applicant compared to the pool of only the two positive efficacy studies (which have assay sensitivity).

**Table 37. Comparing Adverse Reactions in Two Safety Pools**

| Preferred Term | Gepirone ER [1] 14 RCTs (20 mg to 80 mg) (N=1383) n (%) | Gepirone ER [2] Positive Efficacy Studies Only (20 mg to 80 mg) (N=226) n (%) |
|---|---|---|
| Dizziness[a] | 489 (35%) | 110 (49%) |
| Headache[b] | 404 (29%) | 71 (31%) |
| Nausea | 398 (29%) | 80 (35%) |
| Insomnia[c] | 224 (16%) | 31 (14%) |
| Feeling sleepy or tired[d] | 200 (15%) | 35 (15.5%) |
| Dry mouth | 105 (7.6%) | 22 (9.7%) |
| Abdominal pain[e] | 87 (6.3%) | 16 (7.1%) |
| Dyspepsia | 69 (5.0%) | 14 (6.2%) |
| Paresthesia | 58 (4.2%) | 9 (4.0%) |
| Palpitation | 47(3.4%) | N/A |
| Tremor | 41 (3.0%) | N/A |
| Weight increased | 36 (2.6%) | N/A |
| Agitation | 32 (2.3%) | 6 (2.7%) |
| Vision blurred | 30 (2.2%) | N/A |
| Sinusitis[f] | 33 (2.4%) | N/A |

| Preferred Term | Gepirone ER [1] 14 RCTs (20 mg to 80 mg) (N=1383) n (%) | Gepirone ER [2] Positive Efficacy Studies Only (20 mg to 80 mg) (N=226) n (%) |
|---|---|---|
| Lethargy | N/A | 5 (2.2%) |

Source: Clinical Reviewer Created Table based on Applicant Responses to FDA Information Requests submitted June 15, 2023.
[1] Phase 2/3 placebo-controlled depression trials include 134001, 134002, 134004, 134006, 134017, 134023, CN105-052, CN105-053, CN105-057, CN105-064, CN105-078, CN105-083, FK-GBE-007, and FK-GBE-008.
[2] Only the positive efficacy trials: 134001 and FK-GBE-007
[a] DIZZINESS includes LIGHTHEADEDNESS, DIZZINESS, DIZZINESS POSTURAL.
[b] HEADACHE includes CLUSTER HEADACHE, HEADACHE, SINUS HEADACHE, TENSION HEADACHE[c] INSOMNIA includes INITIAL INSOMNIA, INSOMNIA, MIDDLE INSOMNIA, TERMINAL INSOMNIA.
[d] FEELING SLEEPY OR TIRED includes FATIGUE, SEDATION, SOMNOLENCE.
[e] ABDOMINAL PAIN includes ABDOMINAL DISCOMFORT, ABDOMINAL PAIN, ABDOMINAL PAIN LOWER, ABDOMINAL PAIN UPPER.
[f] SINUSITIS includes ACUTE SINUSITIS, ALLERGIC SINUSITIS, CHRONIC SINUSITIS, SINUSITIS.
Abbreviations: ER, extended release; N, number of patients in treatment arm; n, number of patients with adverse event.; N/A, <2% for that database and not included in the table; RCT, randomized controlled trial

***Clinical Reviewer Comment***

*The Applicant wishes to include a large safety database that includes studies with no assay sensitivity and includes over 1000 extra gepirone ER subjects from failed trials, including multiple trials with different designs and potential data quality concerns. In comparing the two different pools (the Applicant's preferred pool of 14 clinical trials and FDA's preferred pool of two trials with assay sensitivity), we note that the overall AE percentages in each column are similar, which is noteworthy in its consistency given the very different denominators (N). Importantly, the only AEs excluded in FDA's preferred smaller pool are palpitations, tremor, weight increased, and vision blurred; these are relatively low in incidence considering the large N of 1383. Additionally, the omitted AEs are not affiliated with any of the gepirone ER warnings, precautions, or contraindications, and likely are events that only appeared in the larger-than-usual safety database and can be included in the prescribing information under "Other Adverse Reactions."*

*Therefore, although this comparison table adds no meaningful interpretation to our review of safety because of data quality concerns in the randomized controlled trials without assay sensitivity, by comparing both safety databases, we were able to confirm in general that limiting the prescribing information AR table to only studies with assay sensitivity is both appropriate and informative, and any missing ARs can be included in the "Other Adverse Reactions" section of the label.*

**Pediatric Pooling Strategy**

The Applicant originally submitted a safety pool that combined the short- and long-term studies, used a modal dose of 40 mg for present ARs, and did not use SMQs/preferred terms. Using information requests and reference to FDA guidance to base the AR table on the best available data (January 2006), FDA worked with the Applicant to create acceptable AR tables

that reduce bias by using SMQs and only pooling data from the short-term efficacy studies. The Applicant agreed with this change.

Below, Table 38 specifies the safety population by safety pool in adults and pediatric subjects. We note the number of subjects in the "Adult Safety Pool," which was used to create the adverse reaction table described in this document (b) (4). When relevant, we also referred to data from the "Applicant's 2007 ISS Pool" because this pool is the basis of FDA's 2007 comprehensive safety review for gepirone ER, conducted by Dr. Earl Hearst.

**Table 38. Safety Population of Gepirone ER in Adults and Pediatric Subjects**

| Trials | Gepirone ER 20 mg to 80 mg (n) | Placebo (n) |
|---|---|---|
| Adult safety pool (studies FK-GBE-007 and 134001 only) | 226 | 230 |
| Pediatric pooled safety data (studies 134019 and 134507) | 426 | 206 |
| Adult safety pool, all short-term studies only [a] | 1383 | 1275 |
| Applicant's 2007 ISS pool [b] (all subjects receiving gepirone ER) | 3117 | 1439 [c] |

Source: Clinical Reviewer generated table based on the Applicant's 2007 ISS (pages 93 and 119) and Applicant's response to information submitted to FDA on June 15, 2023.
N is the sum of all available numbers in each column
[a] This pool is based on FDA request to only include short-term, 6 to 9 weeks in length, phase 2 or 3 controlled depression trials (34001, 134002, 134004, 134006, 134017, 134023, CN105-052, CN105-053, CN105-057, CN105-064, CN105-078, CN105-083, FK-GBE-007, and FK-GBE-008).
[b] Applicant's 2007 ISS Pool includes 25 phase 2 and 3 clinical trials and doses above and below the to-be-marketed doses.
[c] Includes fluoxetine (N=630); paroxetine (N=276); and Imipramine (N=74) and is the basis for the 2007 ISS.
Abbreviations: ER, extended release; ISS, integrated summary of safety

**Longer-Term Studies**

- **Pediatric Study 134507:** Open-label extension study in pediatric subjects ages 7 to 17 with MDD; efficacy results are reviewed in Section 8.1, and the safety findings are incorporated below, where relevant.
- **Adults**: The Applicant did not submit new adult safety data or resubmit the safety data analysis for Study 28709; FDA confirmed that the Applicant did not need to submit new safety data during the January 30, 2017, Type B Pre-NDA meeting (see Section 3.1) because all of these data were reviewed during previous submissions. Therefore, we did not re-adjudicate the Study 28709 safety results during this submission, but include long-term safety data information below, where appropriate.

**Adequacy of the Safety Database**

The Applicant's safety database includes an adequately large number of subjects exposed to the range of to-be-marketed doses. Applicant conducted a fixed-dose study in pediatric subjects, allowing for evaluation of dose response. Although a fixed-dose study in adults would have been helpful for evaluation of dose response, the very large safety database was usable for evaluating dose-response trends. The Applicant's studies are of adequate length to assess short- and long-term safety in a wide range of patients that generally represent the U.S. target population, with the exception of limitations in ethnic and cultural diversity as noted above,

which is unfortunately common with older clinical trials (see Clinical Reviewer Comment below for discussion).

**Issues Regarding Data Integrity and Submission Quality**

The Applicant conducted their clinical trials in the 1990's and early 2000's, with the latest study completed in 2005. Although the Applicant's approaches were viewed as appropriate for that era, FDA has changed its expectations for clinical trial design, statistical analysis, safety monitoring, and technical data standards. Our clinical data scientists were not able to conduct a quality review of the Applicant's databases because the databases were not in the required format for FDA review. The data presentation in the CSRs does not meet our current expectations, and much of the data are presented as raw output tables (e.g., the Applicant's 2007 ISS was over 30,000 pages long).

Nonetheless, we feel we were able to conduct a thorough and adequate review of safety during previous review cycles and during the current review cycle (see Clinical Reviewer Comment below for discussion).

### 8.3.3. Adequacy of Applicant's Clinical Safety Assessments

As noted above, FDA previously determined that the Applicant's clinical safety assessments were acceptable based on the standards at the time of review, and FDA did not require any additional clinical assessments during the January 30, 2017 Type B Pre-NDA meeting (other than for abuse liability; see Section 8.3.9 for details). However, there are numerous safety monitoring deficits that would not currently be acceptable, such as not defining orthostatic hypotension in all studies; not prospectively measuring suicidal ideation or behavior or using validated measures to assess suicidal ideation or behavior (e.g., prospective monitoring for the emergence of suicidal ideation using Columbia Classification Algorithm for Suicide Assessment criteria or C-SSRS); not conducting abuse liability studies; not regularly obtaining ECGs during the clinical studies; not obtaining temperature in all clinical studies; lack of use of stadiometers for measuring height in pediatric subjects (this requirement was specified in the PWR); not monitoring for serotonin syndrome; using nonstandard parameters for normal laboratory and vital sign values in adults and pediatric subjects, leading to unusual shift tables that are difficult to interpret).

***Clinical Reviewer Comment***

*Regarding the submission quality and adequacy of the Applicant's database/clinical safety assessments, we acknowledge that the Applicant's studies were not designed to assess safety to current expectations. However, the Applicant's approach was considered acceptable in the era in which the studies were conducted, and FDA did not set forth new clinical requirements during the dispute resolution or the January 30, 2017, Type B Pre-NDA meeting (the safety limitations*

*are described in the transcript of the Advisory Committee meeting and the meeting minutes for the Type B meeting).*

*Importantly, we feel that the safety database is very large, includes dozens of phase 2/3 clinical trials, includes doses above the to-be-marketed dose, and a wide range of ages and comorbidities. Therefore, when considered in total, the data pools and assessments provide a comprehensive review of the safety of gepirone, and limitations in assessment are mostly overcome by the large adverse event database and range of assessment techniques.*

*Therefore, FDA considers the Applicant's safety assessments to be acceptable for the purposes of adequately describing risks in the gepirone prescribing information for adults and describing differences in safety for pediatric subjects, in the context of negative pediatric efficacy findings, and we were able to fill gaps using information requests, labeling (see Section 10), and postmarketing requirement (PMRs) (see Section 12).*

*The Applicant did not submit the requested CSS studies, but as described in Sections 8.3.9, the CSS review team was able to make a determination regarding abuse potential by using information requests to the Applicant and has no further requests for information or PMRs.*

**Categorization of Adverse Events**

In the adult and pediatric studies that are the focus of this safety review (short term adult studies FK-GBE-007 and 134001, short term pediatric studies 134019 and 134020, and longer-term studies 28709 and 134507), the Applicant defined an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which did not necessarily have a causal relationship with this treatment. The Applicant inquired about AEs at each visit, and all responses were recorded in the AE form, with notations of start and stop date, maximum intensity, actions taken, and a specified procedure for reporting SAEs (defined as death, life threatening, hospitalization, significant disability, or a birth defect) within 24 hours and completing a prespecified SAE form. The Applicant predefined an acceptable range for vitals and laboratory values, and recorded outliers as AEs.

**Routine Clinical Tests**

In the short-term adult studies (FK-GBE-007 and 134001), short term pediatric studies (134019 and 134520), and longer-term adult (28709) and pediatric long-term OLE (134507) studies, the Applicant used the same general approach for obtaining vital signs, obtaining physical exams and ECGs, and conducting laboratory assessments:

- The Applicant measured blood pressure (including orthostatic blood pressure), heart rate, and body weight and recorded abnormal values of "clinical significance" as adverse events. See Table 39 for the Applicant's definition of orthostatic blood pressure as defined in pediatric studies (the Applicant did not include a specific definition in the adult efficacy studies).

- Heart rate shifts defined as change from baseline +/- ≥15 bpm
- The Applicant conducted full physical examinations, including neurological exams, at screening/baseline and at the end of study/end of treatment visit and recorded abnormal findings as AEs.
- The Applicant conducted a 12-lead ECG at screening/baseline and end of treatment/study visit and recorded clinically significant changes (they did not obtain on-treatment ECGs).
- The Applicant measured hematology, blood chemistry (included liver transaminases and total bilirubin), and urinalysis at screening/baseline, and throughout the studies. The Applicant identified out-of-range results as "significant abnormal laboratory values" using the standard laboratory values. The Applicant classified all laboratory measurements as follows. The Applicant created categories to track shifts, as follows:
  - Category A: value ≤ lower safety range;
  - Category B: value > lower safety range and value < lower normal range;
  - Category C: value ≥ lower normal range and value ≤ upper normal range;
  - Category D: value > upper normal range and value < upper safety range;
  - Category E: value ≥ upper safety range.

The Applicant did not identify or monitor for AEs of special interest and did not conduct any special testing or monitoring to track a specific safety concern.

**Table 39. Applicant's Criteria for Orthostatic Hypotension in Pediatric Studies (Only)**

| Orthostatic Hypotension Criteria: |
|---|
| [1] Systolic BP (Standing 1 min) – Systolic BP (Supine 5 min) ≤ -20 mm Hg |
| [2] Systolic BP (Standing 3 min) – Systolic BP (Supine 5 min) ≤ -20 mm Hg |
| [3] Systolic BP satisfying condition [1] and [2] |
| [4] Systolic BP satisfying condition [1] or [2] |

Source: CSR 134019 Table 9.9.12; CSR 134020 Table 9.9.12
Abbreviations: BP, blood pressure

See Table 40 below for a list of the clinical laboratory tests collected by the Applicant.

**Table 40. Example of Clinical Laboratory Tests Obtained in Applicant's Clinical Efficacy Trials**

| | |
|---|---|
| Hematology: | Blood Chemistry: |
| Hemoglobin | Sodium |
| Hematocrit | Potassium |
| Red blood cell (RBC) count | Calcium |
| RBC morphology | Chloride |
| White blood cell (WBC) count | Blood urea nitrogen (BUN) |
| WBC differential | Albumin |
| Platelet count | Creatinine |
| | Glucose |
| Urinalysis: | Cholesterol |
| Glucose | Triglycerides |
| pH | Alkaline phosphatase |
| Protein | Total bilirubin |
| Ketones | Alanine aminotransferase (ALT) (SGPT) |
| WBC | Aspartate aminotransferase (AST) (SGOT) |
| RBC | Gamma-glutamyl transpeptidase (GGT) |
| Microscopic examination | Lactate dehydrogenase (LDH) |
| | Total protein |
| Urine Drug Screen (Screening only) [a]: | Globulin |
| Cocaine | |
| Amphetamines | Urine Pregnancy Test: |
| Barbiturates | At the discretion of the investigator |
| Benzodiazepines | |
| Opiates | Serum Pregnancy Test: |
| Ethanol | At the time of laboratory sampling |

[a] Additional urine drug screens were performed at any time during the study at the discretion of the investigator.

Source: Applicant's CSR for Study 134019, 134020, for example.

***Clinical Reviewer Comment***

*The Applicant's approach to safety was based on generally accepted practices at the time of the studies (over 20 years ago) and, therefore, limits our ability to assess certain risks based on current standards. For example, the Applicant did not use a validated measure for baseline or prospective assessment of suicidal ideation and behavior, which limits our ability to assess risk for emergent suicidal ideation. The Applicant only collected total bilirubin, which limits our ability to determine the cause of an elevated value. The Applicant's shift table approach was unusual and difficult to interpret. The Applicant did not routinely assess ECGs (e.g., there is no "on treatment" ECG) so it is difficult to assess the level of risk associated with ECG changes or prolonged QTc interval. These limitations notwithstanding, the Applicant did record AEs based on predetermined abnormal clinical values, contributing to a very large safety database that was reviewed by FDA over multiple review cycles. Additionally, the dispute resolution and Advisory Committee considered the safety results and, as noted above, the safety databases as*

*acceptable for FDA to adequately describe and mitigate potential risks in the prescribing information and PMRs.*

### 8.3.4. Safety Results

**Deaths**

According to the 2007 safety review by Hearst (page 21-23) and the Applicant's 2007 ISS, there were 9 deaths in adult subjects who participated in phase 2/3 studies; 4 of these deaths were in subjects receiving gepirone ER. The Applicant did not attribute these deaths to the study drug. FDA reviewed the narratives for these deaths during past review cycles (see Hearst 2002 and 2007 FDA review) and determined that the deaths were not related to the study drug. See Table 41 below for details.

**Table 41. Deaths by Treatment Arm**

| Treatment Arm | Subject ID | Study | Cause, Per Applicant Description |
|---|---|---|---|
| placebo | (b) (6) | Study 134004; | Suicide by gunshot, prior to randomization, during placebo wash-out period |
| placebo | | CN105-031; Short-term study | Myocardial infarction; 62-year-old with past history of cardiovascular disease |
| paroxetine | | 28715, Short-term study | Heart arrest; 86-year-old male; after 42 days of dosing |
| fluoxetine | | CN105-052; Longer-term study | Metastatic cancer; 45-year-old, 109 days after last dose. |
| Gepirone ER | | 134501; Short-term study | Suicide; 45-year-old, death by hanging after 20 days exposure to gepirone ER; history of "multiple" past suicide attempts. |
| Gepirone ER | | 28715; Longer-term study | Coronary heart disease; 83-year-old male after 191 days of dosing and during tapering off; past history of coronary artery disease. |
| Gepirone ER | | C-1762; Longer-term study | Suicide; 50-year-old male, overdose of alcohol and other drugs after 184 days on gepirone ER; past history of suicide attempt. |
| Gepirone ER | | 715-0201 | Pulmonary embolus; 79-year-old male; 30 days after last dose of gepirone ER |
| Gepirone IR | | 03A7A-002 | Aortic dissection 40 days after last dose after 35 days of gepirone IR- 8-year history of treated hypertension |

Source: Clinical reviewer-created table based on FDA 2007 safety review by Hearst (page 21-23) with supplemental and "cause of death" information from Section 10.1 of the Applicant's Integrated Summary of Safety, dated March 23, 2007.
Abbreviations: ER, extended release; ID, identifier; IR, immediate release

In total, there were 4 deaths in subjects treated with gepirone ER. Two subjects died from suicide, both with a history of previous suicide attempts; 1 subject died from coronary artery disease; and 1 subject died from pulmonary embolism. There was no information to link these

deaths to long QTc or abnormal cardiac rhythm. There were no deaths reported in the long-term study, Study 28709. There were no deaths in the pediatric short- or long-term studies.

To better understand if any of the deaths were due to QT interval prolongation, FDA submitted an information request to the Applicant asking them to evaluate the QTc at baseline and around the time of death for the above subjects who died. We reviewed the Applicant's response and compared the dates of deaths with the most recent ECG-recorded QTc interval values. None of the QTc values were over 450, and there were no subjects with an increase in QTc value from baseline to the last recorded ECG; therefore, there is no clear indication of QT interval prolongation for these cases. Of note, the Applicant did not have any ECGs from within a few days of the date of death (most were from months before) so we cannot completely rule out any associations with QT prolongation, although suspicion is low. We feel any remaining concerns about this issue can still be addressed through labeling (see Section 10) and a PMR (see Section 12).

***Clinical Reviewer Comment***

*There were no deaths in pediatric studies and 4 deaths across all adult studies in the gepirone ER arm; two due to suicide. Dr. Hearst (2002 and 2007 FDA NDA clinical reviews) did not think these deaths were due to the study drug, and the above Table 41 suggests an equal number of deaths in the gepirone ER group compared to other arms combined (placebo and active comparator), with similar causes of death among the two groups. Although this number of deaths is notable for an NDA, the Applicant conducted numerous trial and reports that over 6011 total subjects participated in the adult trials (noted as more by the FDA reviewer). Several trials were longer-term and/or elderly subjects and subjects with related pretrial comorbidities. Therefore, the number of deaths during the drug development program may be due to chance. The causes of death do not appear to be directly linked to gepirone ER or IR. There is not enough information to link gepirone to completed suicide based on these data, and the Applicant describes that the subjects who died by suicide had a past history of suicide attempt, which puts patients at higher risk of future death by suicide.*

Given the known risks of suicidal ideation and behavior with antidepressant drugs, the prescribing information will include the current standardized boxed warning that describes risk of suicidal thoughts and behaviors in some subjects who take antidepressant medications. Additionally, we will require a PMR to further evaluate the risks of prolonged QTc.

**Serious Adverse Events**

According to the 2007 FDA safety review (page 23), across the groups of phase 2/3 studies, the incidence of SAEs in the gepirone ER and IR combined (2% to 3%) group was higher than the incidence in the placebo (0.9% to 1%) and imipramine (0.8%) groups, and lower than the incidence in the fluoxetine (3%) and paroxetine (5%) groups. The most commonly reported SAEs in gepirone ER and IR combined group subjects that were reported more frequently than in placebo subjects were depression (approximately 0.2%), suicidal ideation (approximately

0.2%), suicide attempt (approximately 0.2%), pneumonia (approximately 0.2%), and pregnancy (approximately 0.3%). FDA reviewer Dr. Hearst reviewed the narratives for the SAEs and noted no new safety concerns or clear link to gepirone. See the Applicant's Table 42, which includes all SAEs in the program occurring in 2 or more subjects. Of note, there were 5 SAEs in the longer-term adult study, Study 28709; one SAE was in the gepirone group (depression) and the rest were placebo.

**Table 42. Serious Adverse Reactions in All Gepirone Trials (Occurring in 2 or More Subjects)**

| Preferred Term | Gepirone | | | Placebo | Antidepressants | | |
|---|---|---|---|---|---|---|---|
| | ER (N=3117) | IR (N=1859) | ER+IR (N=4976) | (N=2483) | Fluoxetine (N=700) | Paroxetine (N=276) | Imipramine (N=240) |
| **Subjects with at Least 1 SAE** | **77 (2.5%)** | **45 (2.4%)** | **122 (2.5%)** | **29 (1.2%)** | **22 (3.1%)** | **14 (5.1%)** | **2 (0.8%)** |
| **Psychiatric Disorders** | **27 (0.9%)** | **16 (0.9%)** | **43 (0.9%)** | **6 (0.2%)** | **6 (0.9%)** | **6 (2.2%)** | **0** |
| Depression | 8 (0.3%) | 3 (0.2%) | 11 (0.2%) | 1 (0.0%) | 3 (0.4%) | 1 (0.4%) | 0 |
| Major Depression | 6 (0.2%) | 0 | 6 (0.1%) | 2 (0.1%) | 2 (0.3%) | 1 (0.4%) | 0 |
| Suicidal Ideation | 6 (0.2%) | 2 (0.1%) | 8 (0.2%) | 2 (0.1%) | 0 | 0 | 0 |
| Psychiatric Symptoms | 0 | 7 (0.4%) | 7 (0.1%) | 1 (0.0%) | 0 | 0 | 0 |
| Suicide Attempt | 4 (0.1%) | 1 (0.1%) | 5 (0.1%) | 0 | 0 | 2 (0.7%) | 0 |
| Panic Attack | 2 (0.1%) | 0 | 2 (0.0%) | 1 (0.0%) | 1 (0.1%) | 0 | 0 |
| Completed Suicide | 2 (0.1%) | 0 | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Infections and Infestations** | **8 (0.3%)** | **1(0.1%)** | **9 (0.2%)** | **7 (0.3%)** | **3 (0.4%)** | **3 (1.1%)** | **0** |
| Appendicitis | 1 (0.0%) | 0 | 1(0.0%) | 2 (0.1%) | 0 | 0 | 0 |
| Pneumonia | 2 (0.1%) | 0 | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Pregnancy, Puerperium, and Perinatal Conditions** | **10 (0.3%)** | **4 (0.2%)** | **14 (0.3%)** | **1 (0.0%)** | **5 (0.7%)** | **0** | **0** |
| Pregnancy | 10 (0.3%) | 3 (0.2%) | 13 (0.3%) | 1 (0.0%) | 5 (0.7%) | 0 | 0 |
| **Injury, Poisoning & Procedural Complications** | **6 (0.2%)** | **4 (0.2%)** | **10 (0.2%)** | **3 (0.1%)** | **4 (0.6%)** | **0** | **2 (0.8%)** |
| Road Traffic Accident | 1 (0.0%) | 3 (0.2%) | 4 (0.1%) | 2 (0.1%) | 1 (0.1%) | 0 | 2 (0.8%) |
| Overdose | 1 (0.0%) | 1 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Nervous System Disorders** | 8 (0.3%) | 5 (0.3%) | 13 (0.3%) | 2 (0.1%) | 0 | 1 (0.4%) | 0 |
| Convulsion | 2 (0.1%) | 1 (0.1%) | 3 (0.1%) | 1 (0.0%) | 0 | 0 | 0 |
| Loss of Consciousness | 3 (0.1%) | 1 (0.1%) | 4 (0.1%) | 0 | 0 | 0 | 0 |
| **Cardiac Disorders** | 5 (0.2%) | 1 (0.1%) | 6 (0.1%) | 1 (0.0%) | 2 (0.3%) | 2 (0.7%) | 0 |
| Angina Pectoris | 1 (0.0%) | 1 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| Coronary Artery Disease | 2 (0.1%) | 0 | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Reproductive System and Breast Disorders** | **4 (0.1%)** | **3 (0.2%)** | **7 (0.1%)** | **1 (0.0%)** | **0** | **3 (1.1%)** | **0** |
| Benign Prostatic Hyperplasia | 0 | 0 | 0 | 0 | 0 | 2 (0.7%) | 0 |
| Breast Mass | 0 | 2 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Renal and Urinary Disorders** | **5 (0.2%)** | **2 (0.1%)** | **7 (0.1%)** | **0** | **0** | **1 (0.4%)** | **0** |
| Nephrolithiasis | 3 (0.1%) | 1 (0.1%) | 4 (0.1%) | 0 | 0 | 0 | 0 |
| **Respiratory, Thoracic and Mediastinal Disorders** | **1 (0.0%)** | **0** | **1 (0.0%)** | **3 (0.1%)** | **2 (0.3%)** | **2 (0.7%)** | **0** |
| Asthma | 0 | 0 | 0 | 2 (0.1%) | 0 | 1 (0.4%) | 0 |
| **General Disorders and Administrative Site Conditions** | **1 (0.0%)** | **2 (0.1%)** | **3 (0.1%)** | **2 (0.1%)** | **2 (0.3%)** | **0** | **0** |
| Hernia | 0 | 2 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| **Hepatobiliary Disorders** | **2 (0.1%)** | **1 (0.1%)** | **3 (0.1%)** | **1 (0.0%)** | **1 (0.1%)** | **1 (0.4%)** | **0** |
| Cholelithiasis | 2 (0.1%) | 0 | 2 (0.0%) | 0 | 1 (0.1%) | 1 (0.4%) | 0 |
| **Investigations** | 3 (0.1%) | 2 (0.1%) | 5 (0.1%) | 0 | 0 | 0 | 0 |
| ALT Increased | 1 (0.0%) | 1 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| AST Increased | 1 (0.0%) | 1 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |
| WBC Count Decreased | 1 (0.0%) | 1 (0.1%) | 2 (0.0%) | 0 | 0 | 0 | 0 |

Source: Table 67 of the 2007 Integrated Summary of Safety
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ER, extended release; IR, immediate release; SAE, serious adverse event; WBC, white blood cell

In pediatric studies, there were no SAEs in the shorter-term trial. In the longer-term trial, Study 134507, there were 10 SAEs; of the eight in the gepirone group, seven were related to worsening depression and one was gastrointestinal infection.

***Clinical Reviewer Comment***

*SAEs were relatively rare in both adult and pediatric studies compared to the number of subjects and duration of the studies. SAEs were more common with gepirone IR and ER than placebo but less common than active comparators, although we do not have proper data to draw conclusions about relative safety because these were failed efficacy studies. We again see suicidal ideation and suicide attempt, which can occur with antidepressants, and there is a boxed warning for this issue in antidepressant medication prescribing information. Suicidal ideation and behavior may also be due to lack of efficacy and worsening depression, which occurred in some subjects receiving gepirone IR and ER.*

**Disposition and Dropouts and/or Discontinuations Due to Adverse Effects**

- **Adults**: According to the 2007 Hearst FDA safety review (page 24), in phase 2/3 adult studies, incidence of AEs leading to discontinuation in the gepirone groups were consistently higher than the incidence in the placebo. According to the Applicant, discontinuations due to AEs occurred in 10% of gepirone ER subjects in Study 134001 and 4% of gepirone ER subjects in Study FKG-BE-007 compared to 3% and 2% in placebo, respectively. AEs associated with discontinuation for gepirone ER included tachycardia, vomiting, stupor, nervousness, and agitation, compared to eosinophilia, flu syndrome, and depression in the placebo group. The Applicant notes the dropout rate was highest during the first 3 weeks of treatment, and more than half of the dropout subjects did so by treatment Week 5 (out of 9 recorded weeks).

  In the longer-term adult Study 28709, only eight discontinued due to an AE; three were in the gepirone ER arm, and the AEs reported for the gepirone ER dropouts due to AEs were one each for depression, anxiety, and pregnancy.

- **Pediatrics**: For Study 134019: Across all ages, more subjects discontinued in the placebo group treatment group, with lack of efficacy and AEs being common reasons for discontinuation. Notably, younger children (age 7 to 11) on study drug were more likely to discontinue due to AEs compared to children receiving placebo (of the same age), which may be related to the higher rates of vomiting seen in younger children (see below for discussion and Table 26 for data).

  For Study 134020: In the study drug group, 26% of subjects discontinued compared to 10% on placebo; reasons listed include 5% for lack of efficacy, 5% due to an AE, and 15% other for gepirone ER, compared to 1%, 1%, and 8% for placebo, respectively (see Table 27 for data). Comparing reasons for dropout by age, lack of efficacy was the most common reason for subjects in the older group (age 12 to 17) and AEs/other were the most common reasons for ages 7 to 11. The most common AEs related to discontinuation in pediatric patients were dizziness, nausea, and insomnia.

  The discontinuation rate was high for the pediatric open-label extension trial, Study

134507: for the gepirone ER group, 34% completed compared to 40% of the placebo group. The primary reasons for discontinuation, as recorded by the Applicant, were adverse events (8% for gepirone ER and 10% for placebo) and lack of efficacy (9% for gepirone ER and 11% for placebo). We reviewed the Applicant's data reports for "other," and these were not subcategorized into different groups. The Applicant submitted brief individual narratives for each of the discontinuations due to AEs, which included a broad range of ARs (headaches, nausea, dizziness, vomiting, insomnia, fever, foot pain, abdominal pain, urinary tract infection).

In pediatric subjects, there were two reports of discontinuation due to worsening depression and suicidal ideation; and one report each of worsening depression and aggression; irritability; hallucinations; and "suicidal gesture" (no additional details given regarding the suicidal-related ARs or hallucinations).

***Clinical Reviewer Comment***

*Overall, the rate of dropouts due to AE for gepirone ER was higher than placebo for both adult and pediatric groups. The dropout rates in short-term studies were relatively low given the incidence of AEs, suggesting that subjects were willing to stay on the study drug even while experiencing AEs. The Applicant notes the dropout rate was highest during the first 3 weeks of treatment; possibly suggesting that subjects who couldn't tolerate gepirone ER dropped out early or that some subjects were able to acclimate to AEs over time; both of these possible reasons for early dropouts are commonly reported with serotonergic antidepressant drugs.*

**Treatment Emergent Adverse Events and Adverse Reactions**

**Adults**: See Section 8.3.1 and 8.3.2 for an explanation for the pooling strategy used to create the AR table. We also asked the Applicant to group similar terms. See Table 43 below for the resultant AR table using the pooled safety data from the Applicant's primary efficacy trials, FK-GBE-007 and 134001 and SMQs by system organ class.

**Table 43. Adverse Reactions Reported in >=2% Gepirone ER-treated Subjects and Greater Than in Placebo-Treated Patients in Short-Term (8 Weeks) Clinical Efficacy Trials (FK-GBE-007 and 134001)**

| System Organ Class<br>Preferred Term | Gepirone ER (20 mg to 80 mg) (N=226) n (%) | Placebo (N=230) n (%) |
|---|---|---|
| Nervous system disorders | | |
| Dizziness [a] | 110 (49%) | 24 (10%) |
| Headache [b] | 71 (31%) | 46 (20%) |
| Paraesthesia | 9 (4.0%) | 2 (0.9%) |

| System Organ Class<br>Preferred Term | Gepirone ER (20 mg to 80 mg) (N=226) n (%) | Placebo (N=230) n (%) |
|---|---|---|
| Gastrointestinal disorders | | |
| Nausea | 80 (35%) | 31 (14%) |
| Dry mouth | 19 (8.4%) | 11 (4.8%) |
| Abdominal pain [c] | 16 (7.1%) | 6 (2.6%) |
| Vomiting | 15 (6.6%) | 10 (4.3%) |
| Dyspepsia | 14 (6.2%) | 5 (2.2%) |
| Psychiatric disorders | | |
| Insomnia [d] | 31 (14%) | 11 (4.8%) |
| Agitation | 6 (2.7%) | 1 (0.4%) |
| General disorders and administration site conditions | | |
| Feeling jittery | 6 (2.7%) | 0 |
| Respiratory, thoracic and mediastinal disorders | | |
| Nasal congestion | 10 (4.4%) | 4 (1.7%) |
| Skin and subcutaneous tissue disorders | | |
| Hyperhidrosis | 8 (3.5%) | 1 (0.4%) |
| Metabolism and nutrition disorders | | |
| Increased appetite | 12 (5.3%) | 7 (3.0%) |
| Cardiac disorders | | |
| Palpitations | 9 (4.0%) | 1 (0.4%) |

Source: Applicant generated table based on pooled data from efficacy trials, submitted to FDA on June 15, 2023. based on FDA information request
[a] DIZZINESS includes LIGHTHEADEDNESS, DIZZINESS, DIZZINESS POSTURAL.
[b] HEADACHE includes HEADACHE, SINUS HEADACHE, TENSION HEADACHE.
[c] ABDOMINAL PAIN includes ABDOMINAL DISCOMFORT, ABDOMINAL PAIN, ABDOMINAL PAIN UPPER.
[d] INSOMNIA includes INITIAL INSOMNIA, INSOMNIA, MIDDLE INSOMNIA, TERMINAL INSOMNIA.
Abbreviations: ER, extended release; N, number of patients in treatment arm; n, number of patients with adverse event.

FDA examined the results of the Applicant's originally submitted pools and the above pools to limit bias and determined that the results were relatively similar and that the nonbiased pools accurately reflect the safety findings for gepirone ER.

**Dose Response**

Both adult studies were flexible dose, and there was no meaningful way to examine dose response based on these two efficacy trials; FDA's previous safety reviews do not assess dose response. However, the 2007 ISS provides an analysis of dose-response relationships in the phase 2/3 all studies pool. According to the Applicant, dizziness was the only individual AE that showed a clear and clinically meaningful dose-response after examining their database based on "modal" categories based on final dose. The Applicant also noted smaller dose responses for the AEs of nausea, paraesthesia, increased weight, and feeling jittery, and states that these were smaller effects.

**Pediatric Subjects**

As mentioned above, for the pediatric data, the Applicant originally pooled short- and long-term studies and presented incidence of AEs by modal doses. Therefore, FDA submitted

information requests to the Applicant to pool only the pediatric efficacy studies, which were of similar design and length, to include the range of doses used in the study, and to group like terms.

In an analysis of pooled data from both pediatric efficacy studies, the most commonly reported AEs (occurring in greater than 10% of subjects and more than placebo) were headache (27% for gepirone versus 20% placebo); dizziness (24% for gepirone versus 3.9% placebo); nausea (24% for gepirone versus 13% placebo); vomiting (13% for gepirone versus 5% placebo); and somnolence/ fatigue/tired (12% for gepirone versus 3.4% placebo). The only fixed-dose trial was pediatric Study 134019. According to the Applicant's AR table, there was an apparent dose response for headache (40 mg =24%; 60 mg =27%; 80 mg =35%; placebo =19%), nausea (40 mg =20%; 60 mg =25%; 80 mg =31%; placebo =15%), and vomiting (40 mg =7%; 60 mg =28%; 80 mg =20%; placebo =5%, discussed below in more detail (Source Table 12.5A, Study 134019 CSR). See Table 44 for details.

**Table 44. Adverse Reactions Reported in >=2% Gepirone-Treated Patients and Greater Than in Placebo-Treated Patients in Short-term Pediatric Clinical Efficacy Trials (134019 and 134020)**

| System Organ Class<br>Preferred Term | Gepirone ER<br>(20 mg to 80 mg)<br>(N=426)<br>n (%) | Placebo<br>(N=206)<br>n (%) |
|---|---|---|
| Nervous system disorders | | |
| Headache [a] | 116 (27.2%) | 41 (19.9%) |
| Dizziness [b] | 104 (24.4%) | 8 (3.9%) |
| Feeling sleepy or tired [c] | 53 (12.4%) | 7 (3.4%) |
| Gastrointestinal disorders | | |
| Nausea | 101 (23.7%) | 27 (13.1%) |
| Vomiting | 56 (13.1%) | 11 (5.3%) |
| Abdominal pain [d] | 55 (12.9%) | 26 (12.6%) |
| Diarrhea | 13 (3.1%) | 6 (2.9%) |
| Dry mouth | 10 (2.3%) | 4 (1.9%) |
| Infections and infestations | | |
| Influenza | 15 (3.5%) | 5 (2.4%) |
| Psychiatric disorders | | |
| Insomnia [e] | 33 (7.7%) | 7 (3.4%) |
| Respiratory, thoracic and mediastinal disorders | | |
| Nasal congestion | 9 (2.1%) | 2 (1.0%) |
| General disorders and administration site conditions | | |
| Pyrexia | 16 (3.8%) | 6 (2.9%) |

| System Organ Class<br>Preferred Term | Gepirone ER (20 mg to 80 mg) (N=426) n (%) | Placebo (N=206) n (%) |
|---|---|---|
| Metabolism and nutrition disorders | | |
| Decreased appetite | 10 (2.3%) | 3 (1.5%) |

Source: Applicant generated table based on pooled data from efficacy trials, submitted to FDA on June 15, 2023, based on FDA information request.
Treatment-emergent adverse events are defined as adverse events that started after the first dose of study medication.
[a] HEADACHE includes HEADACHE, SINUS HEADACHE, TENSION HEADACHE.
[b] DIZZINESS includes LIGHTHEADEDNESS, DIZZINESS, DIZZINESS POSTURAL.
[c] FEELING SLEEPY OR TIRED includes FATIGUE, SEDATION, SOMNOLENCE.
[d] ABDOMINAL PAIN includes ABDOMINAL DISCOMFORT, ABDOMINAL PAIN, ABDOMINAL PAIN LOWER, ABDOMINAL PAIN UPPER.
[e] INSOMNIA includes INITIAL INSOMNIA, INSOMNIA, MIDDLE INSOMNIA, TERMINAL INSOMNIA.
Abbreviations: ER, extended release; N, number of patients in treatment arm; n, number of patients with adverse event

***Clinical Reviewer Comment***

*Gepirone ER is associated with high rates of AEs that may not be tolerable for all adult patients (dizziness, headache, nausea). Gepirone ER is not indicated for pediatric patients, but pediatric AEs were generally similar to or less than AEs reported in the pooled adult safety data for gepirone, with the exception of vomiting which was worse (13% in pediatric patients compared to 6.6% in adults).*

*Based on our review of the submitted materials, most AEs of vomiting in pediatric subjects occurred in Study 134019, which was the only fixed-dose study submitted with this NDA (pediatric study 134020 and the adult efficacy studies allowed for titration and dose reduction based on tolerability); it is possible that the lack of flexible dosing contributed to the pediatric vomiting signal. However, in Study 134019, the incidence of vomiting was higher in children compared to adolescents, and there was an apparent dose-response: gepirone ER 40 mg/day: children 9% versus adolescents 6%; gepirone ER 60 mg/day: children 27% versus adolescents 9%; and gepirone ER 80 mg/day children 28% versus adolescents 12%). These findings are consistent with clinical experience and literature reports suggesting that gastrointestinal ARs are more common in children compared to adolescents (e.g., a literature review by (Safer and Zito 2006), described that vomiting was 2- to 3-fold more prevalent in children than in adolescents for SSRIs). We also note the relatively higher rate of nausea for adults (35% gepirone versus 14% placebo) compared to pediatric (24% gepirone versus 14% placebo) subjects.*

Therefore, the increased incidence of vomiting in pooled pediatric studies is likely due to increased sensitivity of younger subjects to serotonergic drugs combined with study design differences that exposed children to higher doses of gepirone without the option of reducing based on tolerance, in the context of a study drug with high rates of gastrointestinal ARs.

**Laboratory Findings**

According to FDA's 2007 safety review for adults by Hearst, there were during no clinically meaningful changes from baseline for laboratory values and gepirone ER in adults. The Applicant's 2007 ISS and the February 26, 2002, FDA review by Tarek Hammad, MD, medical officer, reached the same conclusion. However, Dr. Hammad notes that increase in "total bilirubin (>=1.5 ULN equivalent to 1.5 mg/dL) occurred with an incidence of approximately 1.4% (25/1849) in the combined gepirone IR & ER formulation group compared to an incidence of 0.5% (6/1176) in the placebo group (risk =2.65, 1.41-4.97, with no difference in risk between the two gepirone formulations [risk =0.98]." Dr. Hammad stated that he reviewed these bilirubin changes by subject, and they were not in conjunction with elevations in liver transaminase or dose-response. During both the 2002 and 2007 review cycles, FDA evaluated the outliers on a case-by-case basis and determined that there were no elevated transaminases, and therefore there was no clear relationship between gepirone ER and elevated bilirubin or other laboratory values. This conclusion is confirmed based on information requests regarding liver transaminase results presented by Dr. Hearst in the May 12, 2004 supplemental safety review.

In the primary efficacy study FKG-BE-007, there were no reports of an elevation in total bilirubin for gepirone ER (compared to 2 with placebo); and in the primary efficacy study 134001, no subjects had a clinically abnormal bilirubin.

The Applicant did not report any clinically meaningful value changes in mean laboratory values for pediatric subjects from baseline to Visit 6. I reviewed the end of treatment bilirubin values and did not observe clinically meaningful outliers among the report tables that were not also present at baseline. In the fixed-dose pediatric study 134019, the mean bilirubin was lower at Visit 6 than at baseline for gepirone 80 mg and had almost no change for the other doses or for placebo. There were no clinically meaningful outliers for liver transaminases in pediatric studies.

***Clinical Reviewer Comment***

*The bilirubin results are not seen as clinically significant for the following reasons: the Applicant did not obtain indirect and direct bilirubin levels that would further allow for evaluation of etiology, including benign elevations. Importantly, the results are from a large pool that includes gepirone IR and supratherapeutic doses. I read through the documentation noted that the only 7 subjects receiving gepirone ER had elevated bilirubin across <u>all</u> studies and that liver transaminases were reported as normal for all of those subjects, which is not suggestive of drug-induced liver disease.*

**Vital Signs**

Temperature

The Applicant did not report safety signals related to temperature for adults (the Applicant did not describe measuring temperature for pediatric subjects).

Blood Pressure/Heart Rate

In the May 12, 2004, FDA review for adults, Dr. Hearst noted the blood pressure results and described "no consistent decreases in blood pressure" and "no clinically meaningful differences among the treatment groups in the percentage of subjects with orthostatic change in systolic blood pressure." The only statistically significant finding in the phase 2/3 trials was a greater risk of orthostatic change in systolic blood pressure for the gepirone IR >40 mg group compared to the placebo group, but there were no mean differences among the groups when all doses were considered. According to FDA's 2007 safety review for adults, there no clinically significant changes from baseline compared to placebo for body temperature, pulse, or systolic or diastolic blood pressure for short-term and long-term extension trials of gepirone ER. Additionally, there were during no clinically significant changes from baseline seen in comparison to placebo for body temperature, pulse, or systolic or diastolic blood pressure for short-term and long-term extension trials of gepirone ER in adults. Dr. Hearst noted no meaningful differences between gepirone ER and placebo regarding orthostatic hypotension in FDA's May 12, 2004, supplemental safety review.

In the pediatric pooled data, four subjects had elevated heart rate, defined as greater or equal to 30 beat per minute increase change from baseline during treatment period. The maximum range for all subjects was within normal limits (close to 100 beats per minute). In the longer-term study 134507, 5 subjects (2%) in the gepirone ER met criteria for an AE of elevated heart rate (compared to 2 in placebo); however, none met the threshold for greater than or equal to 30 beats per minute increase from baseline. I reviewed the maximum range values and noted that the maximum ranges were similar for placebo and gepirone ER throughout the study.

For blood pressure, the mean changes were all within normal limits, and the ranges did not include maximum values that different from placebo or that were concerningly high (the largest "maximum" value for blood pressure during any pediatric study visit for any dose for gepirone ER was 146 and for placebo was 149 for systolic blood pressure, seen in the fixed dose study 134019). In the long-term study 134507, there was one AE of blood pressure increase.

***Clinical Reviewer Comment***

*Dr. Hearst's safety review in adults noted that gepirone ER does not appear to significantly affect vital signs or physical exam findings in adults.*

*Similarly, based on our review of pediatric data, we did not find clinically significant changes in*

*vital signs or physical exam findings in adults or pediatric subjects, when compared to placebo.*

Adult Weight

According to the Applicant's 2007 ISS, in pooled data from 8-week controlled trials of adults in phase 2/3 studies, the percentage of subjects with clinically significant weight gain (defined as ≥7% of baseline body weight) was greater for patients treated with gepirone ER (4% to 6%) compared with placebo-treated patients (3%). The mean increase in body weight from baseline in patients treated with gepirone was 0.52 kg relative to placebo (0.06-0.07 kg). See Table 45 for additional parameters.

These data included doses *above* the to-be-marketed dose. Dr. Hearst's previous FDA safety reviews noted no meaningful differences between gepirone ER and placebo regarding weight, and described that most of the weight gain was in the first week of treatment. Per Dr. Hearst's special review of weight reported in FDA's May 12, 2004, supplemental safety review: "The small magnitude of the mean weight increase observed during Org 33062 treatment and the fact that the increase in weight was apparent from week one of treatment with no further increase in time, indicates that the clinical relevance of this effect, if any, is very small" and that the small weight gain described by some subjects appeared to be dose-related.

When examining shifts by body mass index category, gepirone ER appears to be associated with some minor shifts to heavier weight, including those at ideal weight at baseline. Shifts in body mass index toward lower weight were similar for gepirone ER compared to placebo.

**Table 45. Weight-Related Parameters for Adult Placebo Controlled Gepirone ER Studies in MDD**

| Weight-Related Parameters | Gepirone ER N=1300 (n=%) | Placebo N=1275 (n=%) |
|---|---|---|
| AE of weight increased | 2.4 | 1.4 |
| % shift with weight gain | | |
| From ideal at baseline to overweight BMI at Week 8 | 3.3 | 1.6 |
| From overweight at baseline to obese at Week 8 | 1.7 | 1.1 |
| From underweight at baseline to ideal at Week 8 | 0.4 | - |

Source: Clinical Reviewer Generated Table created by combining data from the 2007 Applicant's ISS output
These studies include doses above the to-be-marketed dose of gepirone ER.
Abbreviations: AE, adverse event; BMI, body mass index; ER, extended release; MDD, major depressive disorder

When looking at 134001 and FKB-BE-007 only, 3% of gepirone ER subjects experienced ≥7% of baseline increased (compared to 1% with placebo). In Study FKG-BE-007, the mean change in weight from baseline to Week 6 was +0.5 kg, with a range of -7 to +8 kg, compared to placebo (0.2 kg, -7 to +4 kg)). For Study 134001, the mean change in weight was +0.7 kg (compared to 0.1 for placebo), with a range of -7 to +10 kg for gepirone ER (compared to -7 to +6 kg). In the longer-term study 28709, 3.6% of the subjects a clinically significant increase and in 1.7% a clinically significant decrease was found in body weight during the open-label stage, but there was no placebo group for comparison.

Pediatric Weight

The Applicant did not describe meaningful changes to height or weight in their pediatric CSRs. To verify, FDA requested additional information about pediatric height and weight changes. According to the Applicant's submission dated June 20, 2023, height was measured weekly for the short-term studies and monthly for the extension study, Study 134507. The Applicant chose to present these data as a pool of 8-week controlled pediatric studies (134019 and 134020) with the long-term extension study (134507). According to the Applicant, in the pooled pediatric studies, the average change in weight after 8 weeks of double-blind treatment was +1.00 kilogram (kg) on gepirone ER versus +1.13 kg on placebo.

Over the same period of time, an increase in body weight of 7% or more was observed in fewer patients who received gepirone ER compared to placebo-treated patients. After 36 weeks on gepirone ER, the average weight gain was 2.64 kg (relative to Baseline 1) and 2.23 kg (relative to Baseline 2), but these results have no placebo comparison. The percentage of patients showing an increase in weight of 7% or more during the 36-week span of treatment with gepirone ER was 11.6% (relative to Baseline 1, the beginning of the randomized controlled trial) and 9.7% (relative to Baseline 2, the beginning of the OLE), with again no placebo comparison available. See Table 46 and Table 47 below for pediatric weight-related parameters.

**Table 46. Weight-Related Parameters for Pediatric Gepirone ER Studies in MDD**

| Weight-Related Parameters | Gepirone ER N=426 (n=%) | Placebo N=206 (n=%) |
|---|---|---|
| % shift with weight gain from baseline to Week 8 | | |
| Decrease from Baseline >=7% | 0 | 0 |
| Increase from Baseline >=7% | 1.4 | 2.4 |
| % shift with weight gain from baseline to Week 36 in the OLE | | |
| Decrease from baseline >=7% | 0.4 | - |
| Increase from RCT baseline >=7% | 11.6 | - |
| Increase from OLE baseline 2 >=7% | 9.7 | - |

Source: Clinical Reviewer Generated Table created from Applicant's June 20, 2023, response to FDA information requests
Abbreviations: ER, extended release; MDD, major depressive disorder; OLE, open-label extension; RCT, randomized control trial

Pediatric Height

The Applicant describes that they examined height using "height velocity," described as annualized rate of change from baseline in height during the gepirone ER treatment period. See Table 47 for the Applicant's mean changes in weight and height. In the longer-term studies, 33% of subjects had an annualized height velocity (cm/year) of 6 or greater, and another 10% had an annualized height velocity (cm/year) of between 4 and 6.

**Table 47. Change in Body Weight and Height (Pooled Pediatric Studies)**

| Parameter | | Gepirone (N=578) | Placebo (N=206) |
|---|---|---|---|
| *Body Weight (kg)* | | | |
| Baseline | Mean | 54.52 | 53.25 |
| | SD | 21.414 | 21.937 |
| | n | 426 | 206 |
| Week 8/Endpoint | Mean Change | +1.00 | +1.13 |
| | SD | 2.547 | 1.746 |
| | n | 376 | 180 |
| Week 36/Endpoint | Mean Change | +2.64 | |
| | SD | 5.099 | |
| | n | 338 | |
| *Height (cm)* | | | |
| Baseline | Mean | 151.00 | 149.91 |
| | SD | 15.279 | 14.453 |
| | n | 426 | 206 |
| Week 8/Endpoint | Mean Change | +0.79 | +0.78 |
| | SD | 2.087 | 2.794 |
| | n | 374 | 179 |
| Week 36/Endpoint | Mean Change | +2.79 | |
| | SD | 4.165 | |
| | n | 334 | |

Source: Applicant table submitted to FDA on June 20, 2023, based on an information request.
Abbreviations: SD, standard deviation

***Clinical Reviewer Comment***

*Dr. Hearst's safety review in adults noted that gepirone ER does not appear to significantly affect weight or height in adults. Compared to placebo, there appears to be some weight gain (and for a few, weight loss) associated with gepirone ER in the larger pooled database; however, the databases include doses over the to-be-marketed doses of gepirone ER, and the Applicant described weight gain as having a dose-response. The predefined threshold for incidence of significant weight change (+/- 7% or greater) was not common enough to include on the adverse reaction table. For pediatric short-term studies, weight changes do not appear to be a concern; the mean increases in weight were small and similar to placebo. Shifts towards significant weight gain were small (around 1%) for the short-term studies. The longer-term OLE had a higher percentage of increases in weight, but there was no placebo group. We know most of the subjects were younger (i.e., had not completed puberty) and, therefore, would be expected to gain weight over the long duration of the OLE. This possibility is supported by the height velocity data: 43% of subjects had 4 or higher cm/year annualized height velocity, and weight gain would occur with height growth. However, it cannot be fully ruled out that gepirone ER causes meaningful weight gain in some pediatric subjects.*

ECGs

According to the Applicant, in adult and pediatric subjects, there were no mean differences with regard to QTc, QT interval, PR interval, QRS interval, or shifts in rate for gepirone ER

compared to placebo during the drug's clinical efficacy trials. However, FDA identified QTc prolongation issues of note in the more recent dedicated QT study submitted with this NDA (see the next section). Additionally, based on our review, the Applicant only obtained ECGs at screening/baseline and end-of-treatment (not "on" study drug); therefore, it is unclear if gepirone may have effects on the ECG while on study drug.

**QT**

The Applicant submitted QT data and these data were reviewed by FDA's QT-IRT team. Please refer to their reviews for more details. Per the QT-IRT team: "In a thorough QT study, the largest mean increase in baseline- and placebo-corrected QTc interval (referred to as the "ΔΔQTc") with administration of 100 mg per day immediate-release formulation of gepirone was 18.4 msec (upper 90% CI =22.7 ms) on Day 1 and 16.1 msec (upper 90% CI =20.7 ms) on Day 7. The exposure in this study was 2-fold the exposure of the maximum recommended dose."

FDA disagreed with the Applicant's approach of using linear and nonlinear ($E_{max}$) model to predict QTc prolongation based on data from the Thorough QT study. The study showed different relationship between gepirone plasma concentration and ΔΔQTc (maximum mean increase in QT, placebo-corrected and adjusted for heart rate) on Day 1 (nonlinear) and Day 7 (linear). It is unclear which one is the true relationship. FDA therefore described the maximum observed QTc effect in label.

FDA and the Applicant agree that in the thorough QT study, there were no subjects who experienced QTcF values of >480 msec or ΔQTcF >60 msec. However, this study was only conducted in healthy subjects and there were concerns about the design and inconsistent findings.

The Applicant confirmed that they only assessed ECGs during the screening and end-of-treatment in their program and therefore, there are no "on-treatment" ECGs in subjects to gather data.

The QT-IRT reviewers examined AEs that may be related to QT. There were no AEs from the narrow SMQ of torsade de pointes/QT prolongation (MedDRA v25.1) in the gepirone ER group according to the Applicant's analysis. There were no clear AEs related to serious abnormal heart rhythm or deaths due to prolonged QTc.

Broad SMQ of torsade de pointes/QT prolongation (see Table 48) showed that more subjects in the gepirone ER group had syncope and loss of consciousness than placebo. Dizziness-related AEs have been known to occur during treatment with antidepressant drugs and are not specific indicators of other medical conditions.

**Table 48. Adverse Events Based on Broad SMQ of Torsade de Pointes/QT Prolongation for Gepirone ER**

| | Gepirone N=1868 n(%) | Placebo N=1275 n(%) | Absolute Risk Difference (95.0% CI) |
|---|---|---|---|
| **AE Grouping Related to AESI** | 10 (0.5%) | 2 (0.2%) | 0.4 (-0.0, 0.8) |
| SYNCOPE | 6 (0.3%) | 1 (0.1%) | 0.2 (-0.1, 0.5) |
| LOSS OF CONSCIOUSNESS | 4 (0.2%) | 1 (0.1%) | 0.1 (-0.1, 0.4) |
| **Serious** | 3 (0.2%) | 0 (0.0%) | 0.2 (-0.0, 0.3) |
| **Resulting in discontinuation** | 2 (0.1%) | 0 (0.0%) | 0.1 (-0.0, 0.3) |
| **Maximum severity** | | | |
| Mild | 0 (0.0%) | 0 (0.0%) | 0.0 (0.0, 0.0) |
| Moderate | 4 (0.2%) | 0 (0.0%) | 0.2 (0.0, 0.4) |
| Severe | 5 (0.3%) | 2 (0.2%) | 0.1 (-0.2, 0.4) |
| Unknown | 0 (0.0%) | 0 (0.0%) | 0.0 (0.0, 0.0) |

Source: QT reviewer generated table from ISS database
Abbreviations: AESI, adverse event of special interest; CI, confidence interval; ER, extended release; SMQ, Standard MedDRA Queries

FDA requested QTc data for all subject deaths and SAEs that may be cardiac related and did not find any conclusive data to support that any deaths or SAEs were related to QT prolongation.

***Clinical Reviewer Comment***

*The ΔΔQTc (maximum mean increase in QT, placebo-corrected and adjusted for heart rate) for gepirone ER is high (18.4 mg) and the confidence interval is very wide (22.7 ms), which indicates a less precise estimate, and we have uncertainty about the Applicant's Thorough QT results, as described above. By comparison, several of the most commonly prescribed antidepressants (Luo et al. 2020) have a warning and precaution in their prescribing information for QT interval prolongation (e.g., sertraline ΔΔQTc =10 ms and postmarking incidences of torsades de pointes; citalopram (ΔΔQTc =8.5 ms); fluoxetine (based on postmarketing incidences of torsades de pointes). Venlafaxine and escitalopram are not associated with a meaningful QT prolongation effect, according to their respective prescribing information content. None of these common MDD treatments prolong the QT interval to the same extent as gepirone ER (ΔΔQTc =18.4 ms). Notably, citalopram 60 mg (ΔΔQTc at 60 mg =18.5 ms) was removed as a marketed dose based on an August 24, 2011 FDA Drug Safety Communication, requiring a reduction in the maximum allowable daily dose from 60 mg to 40 mg due to concerns about QT interval prolongation at the 60 mg dose.*

*The concerns about QT interval prolongation for gepirone ER can be conveyed in the prescribing information, via warnings and precautions, contraindications, and dosage and administration requirements related to QT interval prolongation (See Section 10). Concerns about the Applicant's Thorough QT study will be addressed by a PMR (see Section 12).*

*We reviewed the QT guidance and discussed the results with the QT team and the review team during multiple label meetings conducted in August and September 2023 and decided that the Thorough QT study design left enough uncertainty that our teams still recommend that all subjects should receive an ECG and, if needed, electrolyte correction prior to initiating treatment, and repeat ECGs during dose titration, and throughout treatment. To minimize risk, we added contraindications for individuals with congenital long QT syndrome, concomitant use of a strong CYP3A4 inhibitor, and severe hepatic impairment. We further recommend that gepirone ER should not be escalated if the QTc is greater than 450 mg. Additionally, the dose of gepirone ER should be reduced with CYP3A inhibitors. All of these concerns can be adequately conveyed in the prescribing information for gepirone ER (see Section 10). Concerns about the Applicant's Thorough QT study will be addressed by a PMR (see Section 12).*

*The review team determined that there was not adequate information to support a boxed warning for QTc prolongation based on FDA guidance (October 2011). We note that most drugs with similar QTc prolongation do not receive boxed warnings, although there are exceptions (e.g., toremifene (with a mean QTc prolongation of 7 ms at 20 mg and 26 ms for 80 mg) and bedaquiline (largest mean increase in QTcF during the 24 weeks of treatment was 15.7 ms). Therefore, we feel that the existing data do not yet meet the FDA guidance criteria for a boxed warning and instead will explain the requirements for dosing and initiate PMRs to further investigate risks associated with gepirone ER and QT prolongation.*

**Suicidal Ideation and Behavior**

The Applicant excluded subjects who were deemed at risk for suicide attempt (based on baseline structured interview). The Applicant did not assess for the emergence of suicidal ideation or behavior prospectively in any adult or pediatric study (which was not uncommon during the time of the initial studies). However, the review team undertook extensive review of related AEs, in both the 2004 and 2007 Hearst reviews, concluding that there is no additional risk to describe beyond the standard antidepressant boxed warning.

As noted above, the 2007 Hearst review confirms two completed suicides in gepirone ER group, and one in a placebo wash-out subject. Overall, in the studies included the entire program, there were 13 suicide attempts (including intentional overdoses and suicidal gestures; 7 gepirone ER subjects, 2 gepirone IR subjects, 1 imipramine subject, 2 paroxetine subjects, and 1 placebo run-in subject). Dr. Hearst describes that suicide-related AEs possibly occurred more commonly in the gepirone ER group (2.8%) and ranged from 1.8% (placebo) to 2.7% (imipramine) in the remaining treatment groups.

FDA statistical reviewer Fanhui Wong conducted an analysis of possible suicidal-related AEs in phase 2/3 subjects with data for review, with 1723 subjects receiving gepirone ER, 1393 subjects receiving gepirone IR, 2292 receiving placebo, 457 receiving fluoxetine, 142 receiving paroxetine, and 220 receiving imipramine. Based on severity rating categories used at the time, Drs. Hearst and Wong concluded that gepirone "does not seem to have increased the suicidal behavior and suicide attempt for gepirone ER compared to placebo. In fact, there were 3

patients with suicidal behavior (who had a total of 3 suicidal behaviors) and 2 suicide attempts in a total of 1723 gepirone ER patients compared to none in a total of 2292 placebo patients. They do not seem to give statistically significant results. The Fisher's exact test gives p-values of 0.08 for the differences of suicide behavior between gepirone ER and placebo and a p-value of 0.12 for suicide attempts." (Although we note this study was not prespecified to determine statistical significance for suicidal ideation and behavior events.) In our own assessment, we did not find a clear relationship between suicide and gepirone. Refer to Dr. Hearst's 2007 review for additional details.

In pediatric short-term studies, one subject had an AE of suicidal ideation and three subjects in the longer-term study had suicidal ideation, compared to no subjects on placebo. The Applicant provided the following case narratives for Study 134507:

- Subject (b) (6) a 12-year-old Black female was randomized to Org 33062 in study 134019 and continued into the extension. She took her first dose in the extension on (b) (6) The subject experienced the following adverse events: increased major depression and suicidal ideation (b) (6) to (b) (6). The subject discontinued the study on (b) (6). She was hospitalized for major depression with suicidal ideation and was treated with Seroquel 50 mg twice daily. The investigator rated the adverse events as severe and unlikely to be drug related.
- Subject (b) (6) a 13-year-old Caucasian female was randomized to Org 33062 in study 134019 and continued into the extension. She took the first dose of medication in the extension on (b) (6). The subject experienced the following adverse event: suicidal gesture (b) (6). The medication was stopped on (b) (6) by the mother. The subject discontinued the study on (b) (6). The investigator rated the suicidal gesture as moderate and not drug related.
- Subject (b) (6) an 8-year-old Asian male was randomized to Org 33062 in study 134019 and continued into the extension. He took the first dose of medication on the extension on (b) (6). The subject experienced the following adverse events: increased depression and suicidal ideation/ suicidal threats (b) (6) to (b) (6). The subject became more depressed and threatened to cut his wrists with a knife. He did not harm himself but he was admitted to a psychiatric inpatient hospital. The subject discontinued the study on (b) (6). He was subsequently treated with Prozac. The investigator rated the increased depression and suicidal ideation/threats as moderate and not drug related.

***Clinical Reviewer Comment***

*The Applicant reported two deaths due to suicide in the gepirone ER group of 1723 adult subjects compared to one in the placebo wash-out group. Although deaths in clinical trials are always concerning, these represent 0.1% of subjects exposed to gepirone ER, and the subjects reportedly had a history of previous suicidal ideation (and of course major depression). There*

*were no deaths in the pediatric studies, but there were AEs of suicidal ideation and one AE of suicidal gesture/attempt in the gepirone ER group, compared to none in the placebo group. These AEs appear to be paired with AEs of worsening depression which all happened during the extension study phase (i.e., all had been on drug for weeks before their AE occurrence). Given the failed efficacy of gepirone ER in pediatric studies, and in other adult studies reviewed during previous submissions, some subjects may have encountered lack of efficacy and worsening depression, which in a clinical setting, would usually result in medication change or additional treatment. Additionally, antidepressants are associated with suicidal thoughts and behaviors in young adults and children, and the boxed warning to explain will be in the gepirone ER label.*

**Immunogenicity**

There was no pattern to suggest concerns with immunogenicity with gepirone when compared to placebo in adults (incidence of rash or allergic reaction was higher in placebo compared to gepirone)

In the longer-term pediatric study, one subject in the gepirone group reported rash and one reported "swelling face" compared to one subject with eczema and one subject with pruritis in the placebo group.

These findings are not adequate to suggest gepirone is associated with immunogenicity. This conclusion is consistent with a more extensive review conducted by Dr. Hearst in the 2004 FDA supplemental review.

### 8.3.5. Analysis of Submission-Specific Safety Issues

**Applicant's Request for FDA Review of Sexual Dysfunction** (b) (4)

The Division consulted the Division of Urology, Obstetrics and Gynecology (DUOG) to assess (b) (4) gepirone ER has fewer AEs related to sexual dysfunction in males and females compared to SSRIs in patients with MDD. According to the DUOG review team, the Applicant collected AEs and semistructured interviews and self-report questionnaires related to sexual function. DUOG requested information from the Applicant and conducted an extensive review, (b) (4) The Division of Clinical Outcome Assessment (DCOA) also participated in the review and concurred with DUOG's assessment, noting that there is insufficient information to fully review the Applicant's selected instruments

(b) (4)

The Applicant did not identify any other submission-specific safety issues requiring additional study or review.

FDA did not find sufficient information to inform whether gepirone ER has bleeding risk similar to SSRIs. Therefore, FDA will include a PMR to assess bleeding risk for gepirone ER. See Section 12 for details.

### 8.3.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

See comments above regarding assessment of sexual dysfunction. Otherwise, the Applicant did not use clinical outcome assessments to evaluate tolerability or special aspects of safety.

### 8.3.7. Safety Analyses by Demographic Subgroups

The Applicant did not conduct subgroup safety analyses by race or gender. Primary datasets were also unavailable or not properly formatted to conduct additional independent analyses.

**Geriatric Subjects**

The Applicant reports that they excluded elderly patients in most of their placebo-controlled studies of gepirone. This report describes that, of the 4092 patients in placebo-controlled clinical studies, 1.4% were 65 years of age or over. According to the Applicant, there were no overall differences in safety or effectiveness observed between younger and older subjects. The Applicant conducted a randomized, double-blind trial comparing gepirone (40-80 mg/day, n=137) and paroxetine (20-60 mg/day, n=134) in patients 65 years of age or older (mean age 72.7 years) with MDD. There was no placebo group, so it is unclear how meaningful or interpretable it is to compare gepirone with a drug that has common and similar AEs.

Importantly, the clinical pharmacology reviewer notes the dosing recommendation in the elderly should be reduced to a maximum of 40 mg, based on 50 to 80% increase in plasma concentrations in the elderly. As such, the prescribing information will include a special section on dosing and geriatric subjects.

**Pediatric Subjects**

As noted above, younger subjects experience more AEs of vomiting compared to older pediatric subjects and adults. Gepirone ER is not indicated in pediatric patients due to lack of efficacy in controlled trials.

### 8.3.8. Specific Safety Studies/Clinical Trials

The Applicant did not submit new clinical safety studies for review, and previous reviews did not indicate any relevant specific safety studies that could be used to further inform the prescribing information or benefit-risk of gepirone ER. We note that OCP review determined that reduced doses are needed for individuals with renal or hepatic impairment. Individuals with severe hepatic impairment should not take gepirone ER as there is no safe dose for this population.

### 8.3.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Not applicable.

**Human Reproduction and Pregnancy**

Subject matter experts from DPMH reviewed the effect of gepirone ER on fertility, embryofetal toxicity, and lactation.

Fertility

Gepirone was not mutagenic or genotoxic. Fertility studies in male and female rats revealed no evidence of impaired fertility in males and females at doses up to 24.5 mg/kg/day (approximately three times the MRHD on a mg/m2 basis). Higher doses (>58.1 mg/kg/day) were associated with a higher incidence of stillborns, lower implantation and survival indices, and reduced fetal weight and crown-rump distances, and these were associated with maternal findings (reduced weight gain and food intake).

Embryofetal Risk

Based on animal reproduction studies, gepirone has been shown to have adverse effects on embryo/fetal and postnatal development. There are also known risks from other serotonergic drugs, e.g., “third trimester use may increase the risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability) in the neonate.”

Lactation

There are no data on the presence of gepirone in human milk, the effects on the breastfed infant, or the effects on milk production. Gepirone is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are reports of breastfed infants exposed to other serotonergic antidepressants experiencing irritability, restlessness, excessive somnolence, decreased feeding, and weight loss.

Based on the information above, DPMH recommended changes to the Applicant's proposed prescribing information. In addition, there will be postmarketing requirements related to pregnancy and lactation (see Section 12).

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Overdose

According to the Applicant, in clinical studies, cases of acute ingestions up to 454 mg (cases include ER and IR formulations), alone or in combination with other drugs, were reported with none being fatal. Signs and symptoms reported in association with overdose included vomiting, altered level of consciousness and a 60-second convulsion, and transient incomplete bundle branch block. This information was also reviewed by the CSS.

Abuse Liability

During the current NDA review cycle, CSS conducted a review of the abuse-related data. The following information is based on the CSS review team review documents; please refer to their review for complete details.

During the January 30, 2017, Type B Pre-NDA meeting, subject matter experts from CSS provided the Applicant with a link to FDA's guidance for industry, *Assessment of Abuse Potential of Drugs* (January 2017), and informed the Applicant that gepirone ER would need to be evaluated for its abuse potential and a proposal for scheduling will be required at the time of the NDA submission. However, the Applicant did not submit any of the requested information in their NDA resubmission, so CSS worked with the Applicant to receive the available data via information requests.

CSS reviewed the data from the information requests, nonclinical, and clinical abuse-related data submitted in NDA 021164 for gepirone. There were no reports of misuse, abuse, or diversion of gepirone in clinical trials.

The Applicant did not test physical dependence liability of gepirone in humans. However, AEs related to a withdrawal syndrome were assessed in several studies. In this regard, two subjects reported the preferred term Drug Withdrawal Syndrome. CSS reports this is not significant compared to the 4976 people who received drug. The Applicant conducted studies 03A7A-002 and 28709 to assess relapse of the disease state after gepirone treatment and also contained a discontinuation arm to assess withdrawal syndrome. Subjects received either gepirone IR (Study 03A7A-002) or ER (28709) for a 6- to 12- week period and were assessed for 7 days after drug discontinuation. Although, CSS typically recommends 14 days or longer, there were no clear indications of reported AEs that are indicative of a drug withdrawal syndrome reported in these studies. Overall, we conclude that there is no evidence that gepirone produces physical dependence leading to a distinct withdrawal syndrome.

Based on nonclinical and clinical study data, CSS concludes that the drug does not have abuse potential and should not be controlled under the Controlled Substances Act. This conclusion is based on the following:

- Gepirone is a new molecular entity whose primary mechanism of action is as a moderate affinity agonist of the 5-$HT_{1A}$ receptor. Receptor binding studies indicated that gepirone did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.
- Gepirone is metabolized into one major circulating metabolite 1-pyrimidinylpiperazine (1-PP). The Applicant did not conduct receptor binding studies on this metabolite.
- Gepirone did not produce reinforcing effects in an IV self-administration study using rhesus macaques
- In drug discrimination studies, rats did not generalize to the discriminative effects of amphetamine and partially generalized to LSD
- An analysis of central nervous system-mediated AEs that can be indicative of abuse liability was conducted on the clinical studies provided by the Applicant. This analysis indicated that the most prevalent AEs were dizziness and nausea. There were no concerning reports of AEs that suggest that gepirone has a potential for abuse.

Additionally, CSS recommends that FDA (b) (4)

### 8.3.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

Gepirone has not been marketed yet in any country, and there is no postmarket experience at this time.

**Expectations on Safety in the Postmarket Setting**

The safety of gepirone ER is fairly well-characterized based on the numerous clinical trials conducted by the Applicant, which were reviewed by FDA during multiple NDA submissions and resubmissions. Nonetheless, postmarketing surveillance is important for all new molecular entities, and for drugs with safety monitoring requirements as described in the gepirone ER prescribing information. In the postmarket setting, the Applicant will submit safety reports and periodic adverse event reports that will allow FDA to monitor for patterns of concerns. The public can use the FDA Adverse Event Reporting System to submit any unexpected ARs, and FDA can review the results as necessary.

Based on the aforementioned review concerns, it will be necessary to obtain postmarketing safety data to better understand the effects of gepirone on pregnancy and lactation, for

example, through a pregnancy registration program. See Section 12 for a description of the PMR.

### 8.3.11. Integrated Assessment of Safety

Gepirone ER is a serotonergic agonist with selective activity at the 5HT1A receptor that is not part of an established pharmacologic class but is similar in action to buspirone. Unlike buspirone, gepirone ER is associated with several safety signals that require special monitoring and consideration prior to prescribing gepirone ER.

Gepirone ER has potentially concerning QTc prolongation, requiring ECG and electrolyte correction prior to treatment, and ongoing ECG monitoring with dose changes and throughout treatment. Long QT can result in death and, therefore, individuals with long QT syndrome, concomitant use of a strong CYP3A4 inhibitor, and severe hepatic impairment should not use gepirone ER because these risk factors can further prolong the QT interval. Furthermore, the dose of gepirone ER should not be escalated if the QTc is greater than 450 mg, and individuals taking concomitant CYP3A inhibitors should reduce their dose.

Geriatric patients and individuals with hepatic or renal impairment will need to use lower doses of gepirone due to clearance issues with the drug and/or its metabolite. Individuals with severe hepatic failure should not take gepirone ER as there is no safe dose for this population.

Although there are no fertility concerns with gepirone ER, the drug may cause fetal harm and enters breast milk in nonclinical studies; caution should be used when considering this drug during pregnancy or in lactating women.

Very common adverse events, occurring in over 30% of subjects, include dizziness, headaches, and nausea. Vomiting, insomnia, and agitation can also occur. The high rate of dizziness (49%) means that subjects should take caution to reduce falls or accidents.

Gepirone ER is a serotonergic drug and, therefore, is assumed to have class-related risks such as suicidal thoughts and behaviors, and subjects taking gepirone ER have died from suicide. Individuals taking gepirone ER are at risk for serotonin syndrome and activation of mania and should avoid taking other drugs that may interact with gepirone ER, including MAO-Is.

The AE profile for gepirone ER was relatively similar across studies and in adult and pediatric subjects. Pediatric subjects had higher rates of vomiting compared to adults, which was highest in younger children, possibly due to increased sensitivity to serotonergic drugs. In any case, gepirone ER should not be used in pediatric subjects because the drug has not demonstrated efficacy in that population.

PMRs are necessary to better characterize safety during pregnancy and lactation, to better assess QTc prolongation, and to assess long-term efficacy.

## 8.4. Statistical Issues

For the long-term efficacy study, the primary analysis for the primary efficacy endpoint (proportion of patients who had relapsed) is the CMH test adjusting for centers. However, some centers were too small. Without appropriate pooling of centers, centers that had either only one treatment arm or that had no relapses were excluded from analysis. In this study, a total of 32 ITT patients were not part of the Applicant's primary analysis. These patients needed to be grouped into one center to become part of the analysis.

For the two pediatric studies, the treatment group by center interaction term was initially included in the primary statistical model. If the interaction term was insignificant, it would then be removed from the model. This approach may inflate the overall Type I error because the same data set is used for model selection and then the statistical inference. In principle, the interaction term of treatment group by center should not be included in the primary analysis because we do not expect the treatment effect to differ from one center to another. In addition, the Applicant used the LOCF (last-observation-carried-forward) approach to impute missing data. Single-value imputation approaches, such as LOCF, has become a great concern in recent years because it tends to under-estimate the variability although it was a common approach decades ago. However, these concerns are moot in these two studies because the primary analysis results were not statistically significant. It is also noted that the results in CSR were based on reduced model (that is, without the treatment group by center interaction term).

## 8.5. Conclusions and Recommendations

Substantial evidence of effectiveness of gepirone ER in adults was previously determined during a dispute resolution process based on results of two positive efficacy studies. The Applicant's resubmission of Study 28709, examining long-term efficacy, upon current review has not demonstrated sufficient evidence for maintenance treatment of MDD. Based on current labeling practice, the Indications and Usage statement will simply state that gepirone ER is approved for the treatment of MDD in adults, only the data from the positive acute treatment studies will be included in Section 14 of labeling. The Applicant also conducted two pediatric efficacy studies which both did not demonstrate statistical significance on their primary endpoint. An additional re-analysis of sexual dysfunction data also did not provide sufficient evidence (b) (4)

Gepirone has contraindications, high rates of ARs, dosage restrictions, and monitoring requirements that are different from other drugs indicated for MDD and will be important for clinicians and patients to understand prior to using gepirone. These risks can be adequately conveyed in the gepirone ER prescribing information and medication guide. Postmarketing requirements will be used to better understand risks and address potential safety issues for the use of gepirone ER during pregnancy and lactation and to better assess the QTc prolongation.

Gepirone ER will be approved based on OND's administrative determination of efficacy in adults and an adequate safety profile where the risks can be mitigated with labeling; the drug offers an additional treatment option for patients with MDD.

# 9 Advisory Committee Meeting and Other External Consultations

FDA conducted a PDAC meeting on December 1, 2015, to discuss the efficacy and safety of gepirone ER. See Regulatory history and prior records of the meeting for additional details. FDA did not request advisory meetings or external consultants for the current NDA resubmission but reviewed relevant areas of the transcript and slides from the December 1, 2015, meeting as part of the current review process.

# 10 Labeling Recommendations

## 10.1. Prescription Drug Labeling

FDA sent proposed Draft Label Text revisions to the Applicant on August 15, 2023, which included addition a boxed warning for QT prolongation; deletion of (b) (4); addition of a warning for dizziness, removal of (b) (4); revision of the adverse reaction table to include (b) (4) addition of applicable class language related to serotonergic antidepressants, including embryofetal toxicity and drug-drug interactions; updated contraindications and warnings and precautions; and updated remaining sections based on FDA review. The Applicant submitted responses and the Agency engaged in negotiation. During negotiation, the Agency agreed that the safety signal for QT prolongation did not meet criteria for a boxed warning but would be included in Section 5 of the label as a warning. The primary points of disagreement between the Applicant and the Agency were related to the Applicant's proposed (b) (4), the Agency's proposed language related to QT prolongation, and the selection of studies used to support data in section 6.

See Table 49 for a summary of FDA's changes to the Applicant's Draft Label Text.

**Table 49. Submitted Prescribing Information and Updates/Approved Labeling**

| Section | FDA Proposed Changes to Applicant's Draft Label Text |
|---|---|
| Boxed Warning | None |
| 1. Indications and Usage | No Change |

| Section | FDA Proposed Changes to Applicant's Draft Label Text |
|---|---|
| 2. Dosage and Administration | • Require ECG monitoring and correction of electrolytes prior to dosing for all subjects; perform ECG during titration and periodically during treatment.<br>• Reduce maximum daily dose in geriatric patients and patients with hepatic or renal impairment.<br>• Added dose modifications for known drug-drug interactions. |
| 3. Dosage Forms and Strengths | Updated with additional color and shape information. |
| 4. Contraindications | • Added contraindications related to:<br>– Prolonged QTc interval > 450 msec at baseline<br>– Patients with congenital long QT syndrome.<br>– Concomitant use of strong CYP3A4 inhibitors.<br>– Severe hepatic impairment.<br>– Use with an MAOI or within 14 days of stopping treatment with gepirone ER |
| 5. Warnings and Precautions | Revised addition by Applicant of SI/B, QT interval prolongation, and activation of mania/hypomania. Deleted (b) (4) Added serotonin syndrome. |
| 6. Adverse Reactions | • Updated to present safety data from the two positive efficacy studies (with assay sensitivity), to avoid bias based on pooling of different study durations, populations, doses, and other design differences.<br>• Expanded section on "other" adverse reactions observed<br>• Deleted (b) (4) |
| 7. Drug Interactions | Updated based on reviews |
| 8. Use in Specific Populations | Updated pregnancy, lactation, reproductive, pediatric, geriatric, renal impairment, and hepatic impairment sections to reflect FDA findings during review. |
| 9. Drug Abuse and Dependence | Deleted |
| 10. Overdosage | Updated based on CSS feedback and current labeling practice |
| 11. Description | Updated based on FDA guidance |
| 12. Clinical Pharmacology | Update QT information and pharmacokinetics based on FDA findings during review. |
| 13. Nonclinical Toxicology | Updated, including for known reproductive and embryofetal toxicology for serotonergic drugs, as warranted. |
| 14. Clinical Studies | Updated presentation to align with FDA guidance; updated primary efficacy results to delete (b) (4) and remove (b) (4). |
| 16. How Supplied/ Storage and Handling | No significant changes |
| 17. Patient Counseling | Updated to reflect changes made in other sections |
| 18. Medication Guide | Updated to reflect changes made in other sections |

Source: Applicant's submitted Draft Label Text and related revisions

# 11 Risk Evaluation and Mitigation Strategies

There are no safety issues that necessitate a risk evaluation and mitigation strategy. All safety

issues can be managed via routine labeling.

# 12 Postmarketing Requirements and Commitment

Based on the review of safety for gepirone ER, FDA is issuing PMRs to better characterize safety during pregnancy and lactation, to better assess QTc prolongation and to conduct an adequate maintenance of efficacy study. See below for a brief description of each PMR/postmarketing commitment (PMC) associated with this NDA (see other documentation for full description).

**PMR/PMC Descriptions**

1) **PMR 4485-1**: Collect data from a prospective pregnancy exposure registry, preferably a disease-based multiproduct registry, using a cohort analysis that compares the maternal, fetal, and infant outcomes of women with MDD exposed to Exxua (gepirone) during pregnancy with an unexposed comparator population(s) in a timely manner. Align the study protocol with protocol(s) outside the US to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes described in the protocol will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

   **Rationale**: Nonclinical reproduction studies indicate adverse findings at clinically relevant exposures, which include stillbirths, increased offspring mortality, and persistent growth retardation. The currently available human data from 20 gepirone-exposed pregnancies are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The goal of the prospective pregnancy registry is to evaluate the safety of gepirone in women exposed during pregnancy, including assessing risks of pregnancy complications, and adverse effects on the developing fetus and neonate. The registry is expected to identify unexpected serious adverse reactions or an imbalance of AEs in pregnant subjects exposed to gepirone compared to a control population.

2) **PMR 4485-2**: Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age births and preterm births in women exposed to Exxua (gepirone) during pregnancy compared to an unexposed control population.

**Rationale**: The goal of this study is to evaluate the long-term safety of Exxua (gepirone) in women exposed during pregnancy, including assessing risks of pregnancy complications, and adverse effects on the developing fetus and neonate. Data are needed on the safe use of Exxua during pregnancy as the currently limited available human data are insufficient to inform the safety of Exxua during pregnancy. This retrospective cohort study is expected to identify unexpected serious adverse reactions or an imbalance of AEs in pregnant subjects exposed to gepirone compared to a control population.

The proposed study is an observational study to collect additional data and compare the risks of major congenital malformations, spontaneous abortions, stillbirths, small for gestational age births and preterm births in women with vs without gepirone exposure during pregnancy.

3) **PMR 4485-3**: Perform a lactation study (milk only) in lactating women who have received Exxua (gepirone) to assess concentrations of gepirone in breastmilk using a validated assay and to assess the effects on the breastfed infant.

   **Rationale**: There are no data on the presence of gepirone in human milk, the effects on the breastfed infant, or the effects on milk production. Gepirone is present in rat milk and is likely present in human milk, but it is not known to what extent gepirone transfers into human milk. The lack of clinical data during lactation precludes a clear determination of the risk of gepirone to a breastfed infant. There are reports of breastfed infants exposed to other serotonergic antidepressants experiencing irritability, restlessness, excessive somnolence, decreased feeding, and weight loss. Therefore, this lactation study is needed to provide data on the amount of gepirone in human milk and any reported effects on the breastfed infant.

4) **PMR 4485-4**: Conduct a multiple dose thorough QT/QTc study in healthy subjects to assess the effects of gepirone ER and its major metabolites on the QTc interval using 12-lead digital ECG recordings. The study should include a positive control, a placebo control, the highest recommended dose (72.6 mg once daily) and a supratherapeutic dose which covers the high clinical exposure scenario. The primary analysis should be by-time as described in the ICH E14 guideline. The sample size of the study should have at least as much power as one based on excluding a 10-msec mean increase from placebo in baseline-adjusted QTc interval.

   **Rationale**: The original thorough QT study for gepirone indicated a clear QTc prolongation effect but the study used exposure-response as the primary analysis model showed discrepant exposure response relationships on day 1 and day 7 which is not consistent with a predominant hERG channel blocker. The FDA Interdisciplinary Review Team for Cardiac Safety Studies has recommended that the study should be repeated using an analysis by dosage.

5) **PMC 4485-5:** Conduct a controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of gepirone ER in the treatment of adults with major depressive disorder (MDD). The population should include significant U.S. representation and include underrepresented racial and ethnic minorities. This trial must include a placebo group and must utilize a double-blind, randomized-withdrawal design following an adequate period of stabilization with open-label treatment of gepirone ER. This trial design must incorporate long-term safety assessments (including pre-, post-, and on-treatment electrocardiograms).

   Because the short-term trials used to support efficacy were not fixed-dose, it is important to establish the dose-response for maintenance. Therefore, following open-label stabilization, this trial should randomize subjects to fixed doses of the to-be-marketed doses of gepirone ER (and placebo) during the maintenance phase.

   The goals of this study are to:
   1. Evaluate the longer-term efficacy of gepirone ER
   2. Characterize the dose-response relationship for gepirone ER in a longer-term efficacy study
   3. Determine if higher dose (i.e., 60 or 80 mg/day) gepirone ER is necessary for maintenance treatment

   **Rationale**: For the indication of MDD, a maintenance study is typically conducted as a PMC and is not required prior to approval. The Applicant conducted a maintenance study in 2002, but it was not adequately designed to assess long-term efficacy.

# 13 Division Director (Clinical) Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

# 14 Office Director (or Designated Signatory Authority) Comments

The content of this Unireview reflects the issues discussed in the marketing application assessment and regulatory decisions and actions taken. My feedback and edits have been incorporated above. I agree with the findings as documented by the primary review team.

# 15 Appendices

## 15.1. References

**Literature**

American Psychiatric Association, 2013, Diagnostic and statistical manual of mental disorders (5th ed.),

Costello, EJ, S Mustillo, A Erkanli, G Keeler, and A Angold, 2003, Prevalence and development of psychiatric disorders in childhood and adolescence, Arch Gen Psychiatry, 60(8):837-844.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018, Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet, 392(10159):1789-1858.

Kessler, RC, P Berglund, O Demler, R Jin, KR Merikangas, and EE Walters, 2005, Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication, Arch Gen Psychiatry, 62(6):593-602.

Kessler, RC, J Ormel, M Petukhova, KA McLaughlin, JG Green, LJ Russo, DJ Stein, AM Zaslavsky, S Aguilar-Gaxiola, J Alonso, L Andrade, C Benjet, G de Girolamo, R de Graaf, K Demyttenaere, J Fayyad, JM Haro, C Hu, A Karam, S Lee, JP Lepine, H Matchsinger, C Mihaescu-Pintia, J Posada-Villa, R Sagar, and TB Ustun, 2011, Development of lifetime comorbidity in the World Health Organization world mental health surveys, Arch Gen Psychiatry, 68(1):90-100.

Luo, Y, Y Kataoka, EG Ostinelli, A Cipriani, and TA Furukawa, 2020, National Prescription Patterns of Antidepressants in the Treatment of Adults With Major Depression in the US Between 1996 and 2015: A Population Representative Survey Based Analysis, Front Psychiatry, 11:35.

McIntyre, RS, MJ Filteau, L Martin, S Patry, A Carvalho, DS Cha, M Barakat, and M Miguelez, 2014, Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach, J Affect Disord, 156:1-7.

Rush, AJ, HC Kraemer, HA Sackeim, M Fava, MH Trivedi, E Frank, PT Ninan, ME Thase, AJ Gelenberg, DJ Kupfer, DA Regier, JF Rosenbaum, O Ray, AF Schatzberg, and AT Force, 2006, Report by the ACNP Task Force on response and remission in major depressive disorder, Neuropsychopharmacology, 31(9):1841-1853.

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Safer, DJ and JM Zito, 2006, Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents, J Child Adolesc Psychopharmacol, 16(1-2):159-169.

**Guidance for Industry**

Guidance for Industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006)

Guidance for Industry *Assessment of Abuse Potential of Drugs* (January 2017)

Gudiance for Industry *Major Depressive Disorder: Developing Drugs for Treatment* (June 2018)

Guidance for Industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice* (March 2019)

**Uncategorized References**

Gudiance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011)

## 15.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number):**

**Adult Efficacy Studies:** 134001 and PKGBE007 (previously reviewed; see reviews by Earl Hearst, MD in 2007, Section 4.6 for FKGBE007 and in Section V.E. (page 22) for 134001)

**Pediatric Studies:** 134019 and 134020 (information below)

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 86 | | |
| Number of investigators who are Applicant employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Applicant of covered study: _____ | | |
| N/A<br>Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant)<br>N/A |
| N/A<br>Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 15.3. Nonclinical Pharmacology/Toxicology

All nonclinical data reviewed for this submission is included in Section 5. No additional nonclinical data is included in this section.

## 15.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

**Study No 2666**

Title

A phase 1, open-label, single-dose, randomized, 4-period crossover replicate design study to assess the bioequivalence of two gepirone 20 mg ER tablet formulations (Phase 3 Clinical Trial [P3CT] Formulation [(b) (4) 20 mg ER Formulation] and FMI formulation [Mission 20 mg ER Formulation]) following oral administration in healthy male subjects

Objectives

1) To evaluate the bioequivalence of gepirone HCl, 20mg ER Tablets (P3CT) and gepirone HCl, 20mg ER Tablets (FMI) in healthy subjects under fasted conditions.
2) To characterize the PK profile of gepirone following single dose administration as gepirone HCl, 20mg ER Tablets (P3CT) and gepirone HCl, 20mg ER Tablets (FMI) formulations in healthy subjects.
3) To assess the safety and tolerability of gepirone following single dose administration in healthy subjects.

Design

Single-dose, randomized, open-label, 4-period, 2-sequence, 4-treatment, full replicate crossover study in 36 healthy male subjects between 18 to 55 years old. Subjects were randomly assigned to one to two dosing sequences: A-B-A-B and B-A-B-A. A total of 18 subjects were planned to receive each treatment sequence. The washout period of minimum 3 days. Consumption of grapefruit-containing foods and beverages or other CYP3A4 inhibitors or inducers for 72 hours prior to screening and during the entire study was prohibited. Subjects with significant organ impairment, including renal and hepatic, were excluded from the study. The concentration of gepirone was measured from the plasma samples collected over a 72-hour interval after dosing in each study period by a validated LC/MS/MS analytical assay method.

Subjects were dosed according to randomization schedule with one of the following treatments.

Each subject was scheduled to receive a total of four treatments by the end of the study.

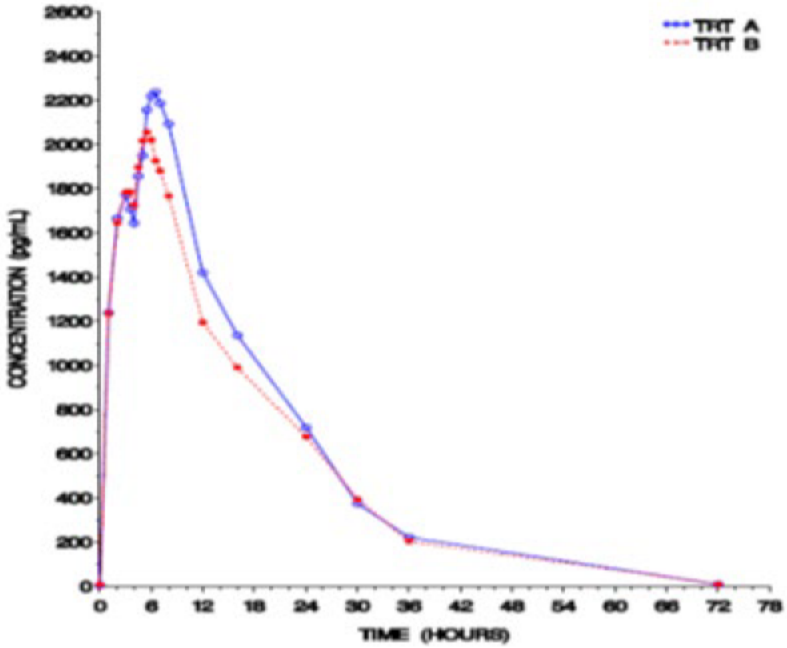
**Table 50. Treatments Administered in Study 2666**

| | |
|---|---|
| Treatment A: | 1 × 20mg Gepirone HCl, ER Tablets ([redacted (b) (4)]) |
| Treatment B: | 1 × 20mg Gepirone HCl, ER Tablets (Mission Pharmacal (USA)) |

Abbreviations: ER, extended release; HCl, hydrochloride

Results

**Figure 8. Average Plasma Concentration-Time Profiles of Gepirone Following Administration of P3CT Formulation (Reference) and FMI Formulation (Test) in Healthy Adults**




Source: Study 2666 page 94
TRT A: 20 mg gepirone HCl, ER Tablets [redacted (b) (4)], P3CT- Reference)
TRT B: 20 mg gepirone HCl ER Tablets (Mission Pharmacal, USA- FMI-Test)
Abbreviations: ER, extended release; HCl, hydrochloride; TRT, treatment

A reference scale was prespecified as the method to be used in determination of bioequivalence. This is acceptable since it was prespecified

The within subject standard deviations of the reference product (SWR) values for the ln transformed $AUC_t$ and $AUC_{inf}$ parameters were 0.2853 and 0.2806, respectively, which were less than 0.294 and hence the unscaled bioequivalence was used for BE determination. The SWR value for the ln transformed $C_{max}$ was 0.3106, which was greater than 0.294 and the reference scaled bioequivalence was used for the BE determination.

## Table 51. Average Bioequivalence Analysis for Gepirone

**Average Bioequivalence Analysis Results for Plasma Gepirone**

STUDY 2666 FAST (20DEC2021 - 09:16)
Average Bioequivalence Analysis Results for Plasma Gepirone
TREATMENT B vs TREATMENT A

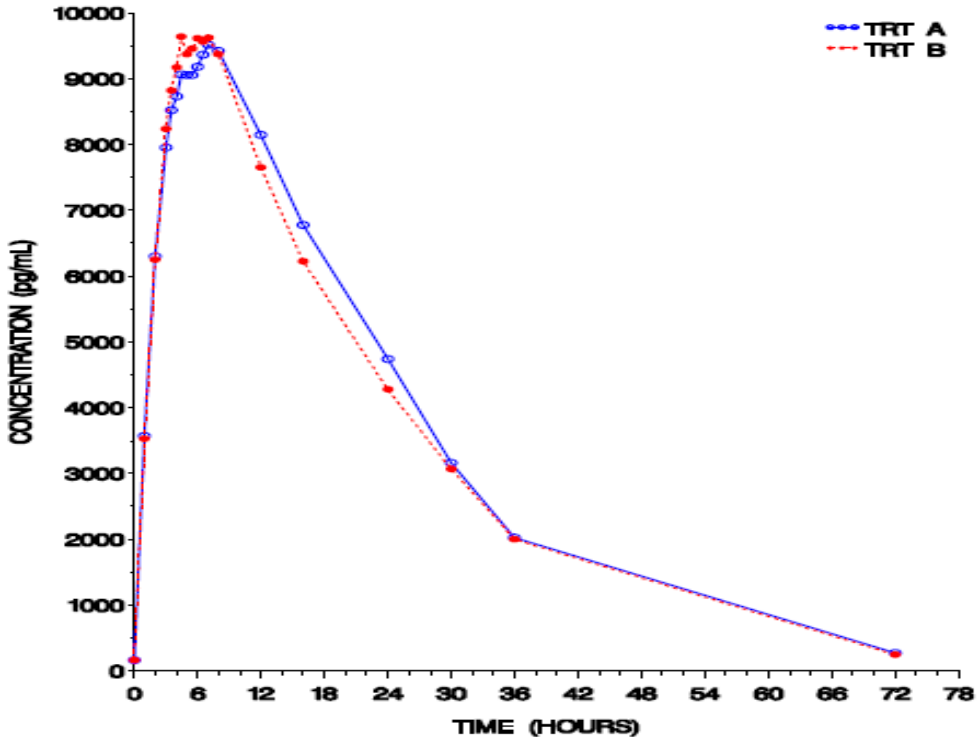
| Parameter ($N_B/N_A$) | Geometric Means Arithmetic Means (CV %) TRT B | TRT A | Ratio of Geometric Means (%) | 90% Confidence Interval (%) | 95% Upper Confidence Bound | Analysis | Intra-Subject CV (%) TRT B | TRT A |
|---|---|---|---|---|---|---|---|---|
| AUCt (pg.h/mL) (62 /64 ) | 31050.25 36835.88(61.52 ) | 33878.65 39886.09(61.42 ) | 91.65 | 81.54, 103.02 | N/A | Unscaled | 36.14 | 29.12 |
| AUCinf (pg.h/mL) (49 /55 ) | 33607.99 41890.12(60.32 ) | 35141.74 42826.77(60.09 ) | 95.64 | 82.79, 110.48 | N/A | Unscaled | 40.49 | 28.62 |
| Cmax (pg/mL) (62 /65 ) | 2207.80 2572.27 (52.14 ) | 2393.68 2756.70 (54.91 ) | 94.01 | N/A | -0.045 | Reference-scaled | 21.74 | 31.82 |
| Tmax* (h) (62 /65 ) | 5.50 (2.00 - 16.00 ) | 6.50 (2.00 - 16.00 ) | | | | | | |
| Lambda# (1/h) (49 /55 ) | 0.1354 (46.94 ) | 0.1389 (42.11 ) | | | | | | |
| T1/2# (h) (49 /55 ) | 7.58 (101.23 ) | 6.14 (49.69 ) | | | | | | |
| AUCt/AUCinf# (49 /55 ) | 0.9523 (8.98 ) | 0.9693 (5.84 ) | | | | | | |

Note: $N_B/N_A$ are the number of observations for Treatment B and A, respectively
*: Presented as median and range #: Presented as arithmetic mean (CV%) only

Treatment A(Reference): Gepirone HCl, 20mg ER Tablets; Batch/Lot No: 98-013T; (b) (4)
Treatment B (Test): Gepirone HCl, 20mg ER Tablets; Batch/Lot No: 8L015; (Mission Pharmacal (USA))

Source: Study 2666 page 92
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; HCl, hydrochloride; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

**Figure 9. Average Concentration-Time Profile for the Active Metabolite, 3-OH-Gepirone**




Source: Study 2666 page 96
TRT A: 20 mg gepirone HCl, ER Tablets (b) (4), P3CT- Reference)
TRT B: 20 mg gepirone HCl ER Tablets (Mission Pharmacal, USA- FMI-Test)
Abbreviations: ER, extended release; HCl, hydrochloride; TRT, treatment

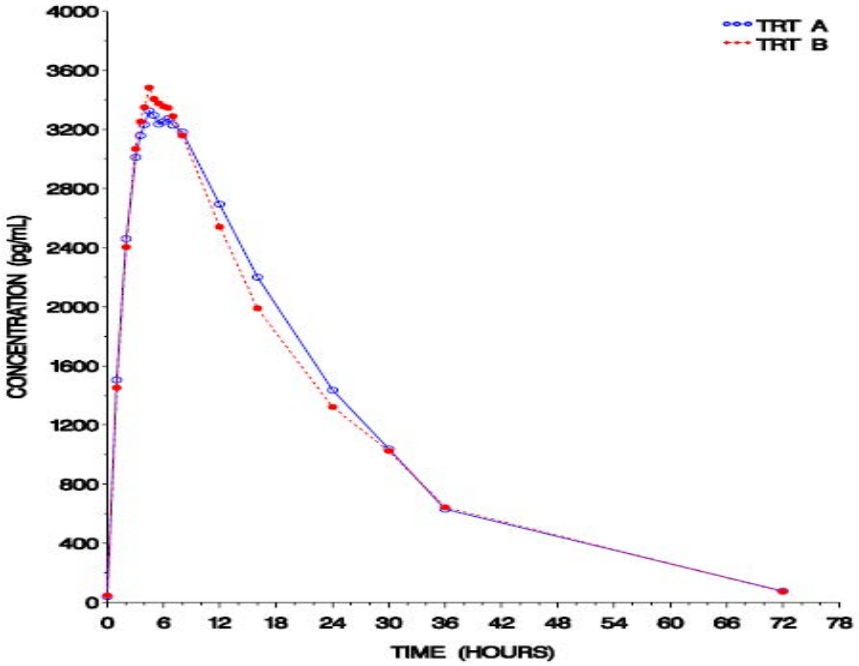
**Table 52. Descriptive Statistics of Pharmacokinetic Parameters for Plasma 3-OH-Gepirone**

| Parameter (unit) | Test (Treatment B) | | | Reference (Treatment A) | | |
|---|---|---|---|---|---|---|
| | N | Calculated mean ± SD | CV% | N | Calculated mean ± SD | CV% |
| $C_{max}$ (pg/mL) | 58 | 10363.51 ± 2432.46 | 22.81 | 63 | 10226.09 ± 2123.89 | 20.77 |
| $T_{max}$* (h) | 58 | 6.25 (3.50 – 30.00) | - | 63 | 6.50 (3.50 – 16.00) | - |
| $AUC_t$ (pg.h/mL) | 58 | 240514.79 ± 72757.61 | 32.42 | 62 | 242075.85 ± 73289.45 | 30.28 |
| $AUC_{Inf}$ (pg.h/mL) | 54 | 248723.08 ± 72354.56 | 29.09 | 62 | 256259.40 ± 75406.53 | 29.43 |
| $T_{1/2}$ (h) | 54 | 11.89 ± 2.90 | 24.41 | 62 | 11.99 ± 3.26 | 27.16 |
| Lambda (1/h) | 54 | 0.0620 ± 0.0164 | 26.46 | 62 | 0.0620 ± 0.0169 | 27.28 |

*Reported as median and range
N: number of observations

Source: Study 2666 page 66
TRT A: 20 mg gepirone HCl, ER Tablets (b) (4), P3CT- Reference)
TRT B: 20 mg gepirone HCl ER Tablets (Mission Pharmacal, USA- FMI-Test)
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; HCl, hydrochloride; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

**Figure 10. Average Concentration-Time Profile for the Metabolite, 1-PP**




Source: Study 2666 page 98
TRT A: 20 mg gepirone HCl, ER Tablets (b) (4), P3CT- Reference)
TRT B: 20 mg gepirone HCl ER Tablets (Mission Pharmacal, USA- FMI-Test)
Abbreviations: ER, extended release; HCl, hydrochloride; TRT, treatment

**Table 53. Descriptive Statistics of Pharmacokinetic Parameters for 1-PP**

| **Parameter** (unit) | **Test (Treatment B)** | | | **Reference (Treatment A)** | | |
|---|---|---|---|---|---|---|
| | N | Calculated mean ±SD | CV% | N | Calculated mean ± SD | CV% |
| $C_{max}$ (pg/mL) | 58 | 3656.05 ± 1245.15 | 34.06 | 61 | 3570.09 ± 1066.10 | 29.86 |
| $T_{max}$ * (h) | 58 | 4.50 (2.00 – 8.00) | - | 61 | 5.00 (2.00 – 16.00) | - |
| $AUC_t$ (pg.h/mL) | 58 | 78299.98 ± 38719.33 | 49.45 | 60 | 78832.00 ± 33574.08 | 42.59 |
| $AUC_{inf}$ (pg.h/mL) | 54 | 85278.89 ± 41666.52 | 48.86 | 58 | 85548.89 ± 34812.40 | 40.69 |
| $T_{1/2}$ (h) | 54 | 10.87 ± 4.71 | 43.39 | 58 | 10.36 ± 3.65 | 35.20 |
| Lambda (1/h) | 54 | 0.0749 ± 0.0303 | 40.42 | 58 | 0.0761 ± 0.0285 | 37.48 |
| *Reported as median and range<br>N: number of observations | | | | | | |

Source: Study 2666 page 66
TRT A: 20 mg gepirone HCl, ER Tablets (b) (4), P3CT- Reference)
TRT B: 20 mg gepirone HCl ER Tablets (Mission Pharmacal, USA- FMI-Test)
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; HCl, hydrochloride; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

## Adverse Events

The Applicant reported that there were 6 AEs involving 2 subjects in this study. All AEs were treatment emergent adverse events (TEAEs). No serious AEs or death were reported during the conduct of this study. None of the subjects discontinued from the study due to AEs. The most

frequent adverse events reported were abdominal pain, nausea, vomiting, toothache and decreased appetite.

Conclusion

Using the unscaled average bioequivalence procedure for BE analysis of $AUC_t$ and $AUC_{inf}$ for gepirone, results showed that the test/reference ratio of geometric means were 91.65% and 95.64% for $AUC_t$ and $AUC_{inf}$, respectively. The corresponding 90% confidence intervals for $AUC_t$ and $AUC_{inf}$ were entirely contained within 80.00%-125.00%. Using the reference scaled approach, the upper bound of the 95% confidence interval was less than the acceptance limit, therefore the two products are bioequivalent with respect to $C_{max}$ as well.

The final market image formulation was found to be equivalent to the clinical trial formulation using the scaled bioequivalence for $C_{max}$ and unscaled for AUC. The sponsor reported no serious adverse events during the conduct of the study.

***Reviewer Comment***

*The reviewer concurs with the Applicant's conclusion that the FMI 20 mg formulation is equivalent to the phase 3 clinical trial formulation (P3 CT).*

**Study Number 2667**

Title

A phase 1, open-label, single-dose, randomized, 4-period crossover replicate design study to assess the bioequivalence of gepirone 4 x 20 mg ER tablets (Phase 3 Clinical Trial [P3CT] Formulation [(b) (4) 20 mg ER Formulation]) and 1 x 80 mg ER tablet formulation FMI Formulation [Mission 80 mg ER Formulation]) following oral administration in healthy male subjects

Objectives

1) To evaluate the bioequivalence of 4 x gepirone HCl, 20mg ER Tablets (P3CT) and 1 x gepirone HCl 80mg ER Tablets (FMI) in healthy subjects under fasted conditions.
2) To characterize the PK profile of gepirone following single dose administration as 4 x gepirone HCl, 20mg ER Tablets (P3CT) and 1 x gepirone HCl 80mg ER Tablets (FMI) formulations in healthy subjects
3) To assess the safety and tolerability of gepirone following single dose administration in healthy subjects.

Design

Phase 1, single-dose, randomized, open-label, 4-period, 2-sequence, 4-treatment, full replicate crossover study designed to evaluate the bioequivalence of gepirone from 4 x gepirone HCl, 20mg ER Tablets (P3CT) and 1 x gepirone HCl 80 mg ER Tablets (FMI) administered to healthy male subjects. Subjects were randomly assigned to one of the two dosing sequences. The study consisted of four study periods. Each study period included a single-dose drug administration of either the Test product or the Reference product. There was a washout period of minimum 3 days between each drug administration. The concentration of gepirone was measured from the plasma samples collected over a 72-hour interval after dosing in each study period using a validated LC/MS/MS. Subjects were dosed according to randomization schedule with one of the following treatments. Each subject was scheduled to receive a total of four treatments by the end of the study.

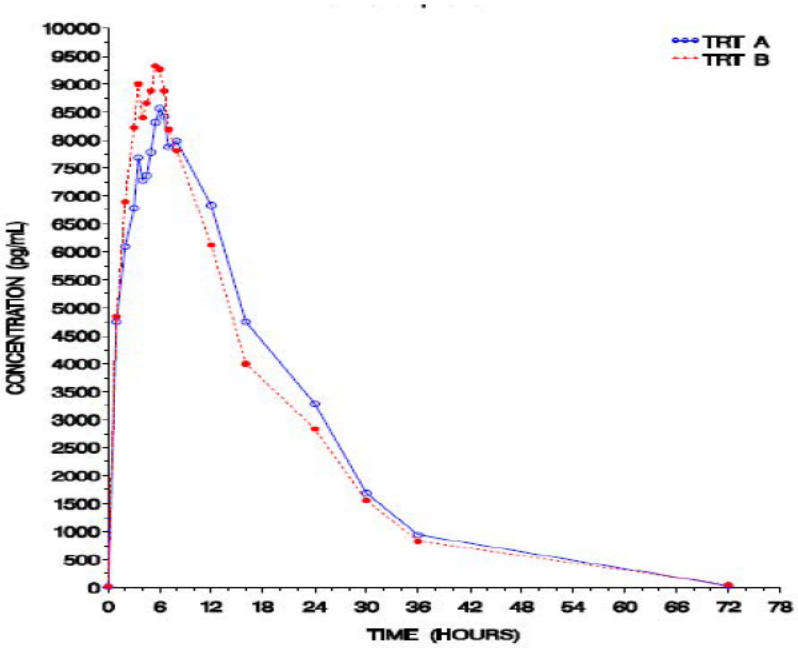
**Table 54. Treatments Administered in Study 2667**

| | |
|---|---|
| Treatment A: | 4 × 20mg Gepirone HCl, ER Tablets ((b) (4)) |
| Treatment B: | 1 × 80mg Gepirone HCl, ER Tablets (Mission Pharmacal (USA)) |

Source: Study 2667 page 23
Abbreviations: ER, extended release; HCl, hydrochloride

Results

**Figure 11. Mean Plasma Concentration Time Profile for Gepirone**



Source: Study 2667 page 86
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: ER, extended release; TRT, treatment

**Table 55. Descriptive Statistics of Pharmacokinetic Parameters for Plasma Gepirone**

| Parameter (unit) | Test (Treatment B) | | | Reference (Treatment A) | | |
|---|---|---|---|---|---|---|
| | N | Calculated mean ± SD | CV% | N | Calculated mean ± SD | CV% |
| $C_{max}$ (pg/mL) | 64 | 11464.76 ± 5663.28 | 49.40 | 59 | 10463.05 ± 5022.56 | 48.00 |
| $T_{max}$* (h) | 64 | 4.75 (2.00 – 12.00) | - | 59 | 6.00 (1.00 - 12.12) | - |
| $AUC_t$ (pg.h/mL) | 64 | 165096.14 ± 107697.25 | 65.23 | 59 | 175382.76 ± 111832.88 | 63.77 |
| $AUC_{inf}$ (pg.h/mL) | 58 | 174305.64 ± 111509.68 | 63.97 | 58 | 179688.26 ± 113194.12 | 62.99 |
| $T_{1/2}$ (h) | 58 | 6.39 ± 4.01 | 62.79 | 58 | 5.93 ± 2.78 | 46.88 |
| Lambda (1/h) | 58 | 0.1378 ± 0.0591 | 42.86 | 58 | 0.1439 ± 0.0648 | 45.02 |
| *Reported as median and range<br>N: number of observations | | | | | | |

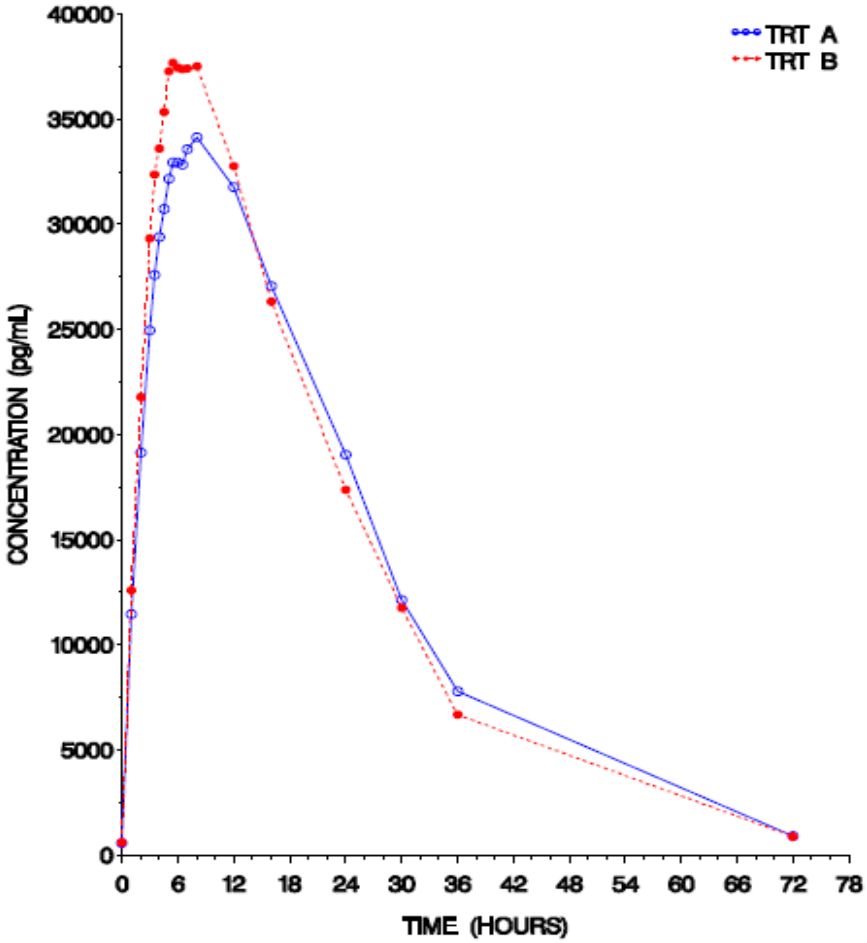
Source: Study 2667 page 59
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

**Table 56. Bioequivalence Analysis Results for Gepirone**

| Pharmacokinetic Parameter | Test/Reference Ratio of Geometric Means (90% Confidence Interval) (%) | Intra-Subject CV for Test (%) | Intra-Subject CV for Reference (%) |
|---|---|---|---|
| $AUC_t$ | 96.57 (84.67 – 110.13) | 44.60 | 26.75 |
| $AUC_{inf}$ | 96.15 (84.12 – 109.90) | 45.00 | 26.68 |
| $C_{max}$ | 111.60 (102.88 – 121.05) | 21.11 | 15.86 |

Source: Study 2667 page 70
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation

**Figure 12. Mean Plasma Concentration-Time Profile for the Active Metabolite, 3-Hydroxy Gepirone**



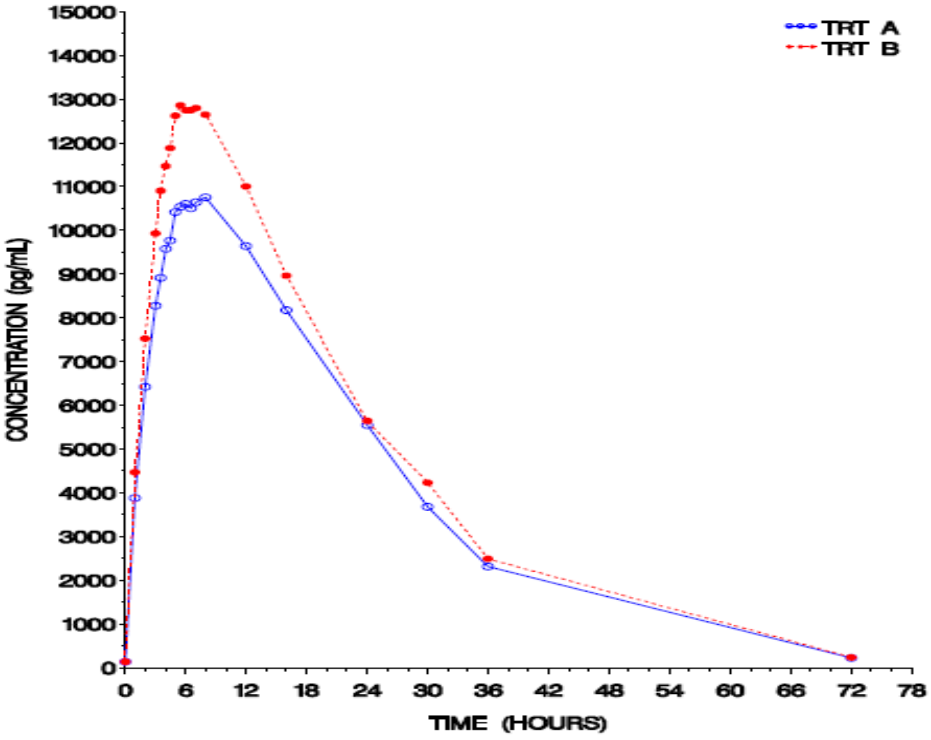

Source: Study 2667 page 88
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: ER, extended release; HCl, hydrochloride; TRT, treatment

**Table 57. Descriptive Statistics of Pharmacokinetic Parameters for Plasma 3-Hydroxy Gepirone**

| Parameter (unit) | Test (Treatment B) | | | Reference (Treatment A) | | |
|---|---|---|---|---|---|---|
| | N | Calculated mean ± SD | CV% | N | Calculated mean ± SD | CV% |
| $AUC_t$ (pg.h/mL) | 58 | 931966.93 ± 274812.20 | 29.49 | 53 | 945721.95 ± 277306.39 | 29.32 |
| $AUC_{inf}$ (pg.h/mL) | 57 | 947750.16 ± 284458.72 | 30.01 | 53 | 961099.89 ± 283858.81 | 29.53 |
| $T_{1/2}$ (h) | 57 | 11.85 ± 3.36 | 28.35 | 53 | 11.08 ± 2.49 | 22.48 |
| Lambda (1/h) | 57 | 0.0631 ± 0.0185 | 29.28 | 53 | 0.0666 ± 0.0210 | 31.58 |
| *Reported as median and range<br>N: number of observations | | | | | | |

Source: Study 2667 page 59
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: AUC, area under the concentration-time curve; CV, coefficient of variation; ER, extended release; SD, standard deviation; $T_{1/2}$, half-life; TRT, treatment

**Figure 13. Mean Plasma Concentration Time Profile for the Metabolite, 1-PP**




Source: Study 2667 page 90
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: ER, extended release; TRT, treatment

**Table 58. Descriptive Statistics of Pharmacokinetic Parameters for 1-PP**

| Parameter (unit) | Test (Treatment B) | | | Reference (Treatment A) | | |
|---|---|---|---|---|---|---|
| | N | Calculated mean ±SD | CV% | N | Calculated mean ± SD | CV% |
| $C_{max}$ (pg/mL) | 60 | 14087.88 ± 5743.53 | 40.77 | 54 | 11835.88 ± 4966.37 | 41.96 |
| $T_{max}$ *(h) | 60 | 6.00 (3.00 - 16.05) | - | 54 | 6.00 (2.00 – 16.00) | - |
| $AUC_t$ (pg.h/mL) | 60 | 317581.62 ± 217299.20 | 68.42 | 54 | 286966.44 ± 191330.87 | 66.67 |
| $AUC_{inf}$ (pg.h/mL) | 60 | 323689.50 ± 221715.15 | 68.50 | 54 | 291416.98 ± 197636.36 | 67.82 |
| $T_{1/2}$ (h) | 60 | 9.56 ± 2.86 | 29.92 | 54 | 9.13 ± 2.56 | 28.03 |
| Lambda (1/h) | 60 | 0.0794 ± 0.0261 | 32.94 | 54 | 0.0839 ± 0.0321 | 38.26 |
| *Reported as median and range<br>N: number of observations | | | | | | |

Source: Study 2667 page 59
Trt A: 4 x 20 mg gepirone ER Tab
Trt B: 1 x 80 mg gepirone ER Tab
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration; TRT, treatment

Conclusion

The 90% confidence interval was contained within the regulatory criteria for bioequivalence, therefore exposures ($C_{max}$ and AUC) after administration of 4 x 20 mg

Gepirone ER clinical trial material versus 1 x 80 mg gepirone ER final market image tablets are equivalent.

The Applicant reported that no SAE or death occurred during the conduct of the study. According to the Applicant, the most frequently reported AEs (>2 subjects) were headache, dizziness, vomiting, nausea, diarrhea, and abdominal pain.

***Reviewer Comments***

*The reviewer agrees with the Applicant's conclusion that the FMI 80 mg formulation is equivalent to the phase 3 clinical trial formulation (P3 CT)*

**Study Number 28721**

Title

Open-label, multiple oral dose study to assess the steady-state pharmacokinetics of Org 33062 ER in children and adolescents with major depressive disorder

Objectives

To determine the steady-state pharmacokinetic characteristics of Org 33062 (gepirone) and its main metabolites 1-PP and 3'-OH-gepirone after multiple dose oral administration of Org 33062

ER in both male and female children and adolescents with major depressive disorder. The subjects were diagnosed according to DSM-IV, with a primary diagnosis of major depressive disorder (nonpsychotic, chronic or recurrent).

Design

An open label, multiple oral dose design was used. Twelve children (3 male and 3 female, aged between 7 and 11 years) and adolescents (3 male and 3 female, aged between 12 and 17 years) were enrolled and completed the study. Org 33062 was administered as a single dose of 20 mg Org 33062 ER on day 1 and multiple doses of 40 mg (2 x 20 mg Org 33062 ER) each day on days 2-5. Based on tolerability data after the first patients were dosed, the multiple dose regimen could be decreased to 20 mg.

Blood samples for determining the pharmacokinetics of gepirone and its main metabolites 1-PP and 3'-OH-gepirone were collected at regular intervals for 48 hours after dosing on day 5 as well as prior to dosing on day 1 and 4. Urine for the determination of the creatinine clearance and the determination of gepirone and the metabolites 1-PP and 3'-OH-gepirone were collected for 24 hours after dosing on day 5. Concentrations were determined using a validated LC/MS/MS analytical method.

Concomitant use of any other psychotropic drug was not allowed during the course of the subject's participation in this study, nor were any compounds known to inhibit or stimulate CYP2D6 or CYP3A4 iso-enzymes allowed during the study period.

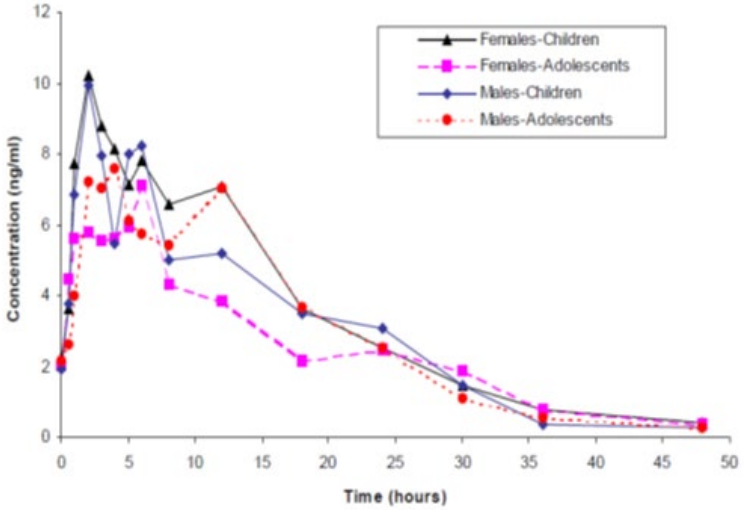
Results

**Table 59. Descriptive Statistics of Quantitative Demographic Parameters by Age Group and Gender**

| Variable | Statistic | Female children | Female adolescents | Male children | Male adolescents | Overall |
|---|---|---|---|---|---|---|
| Age (years) | N | 3 | 3 | 3 | 3 | 12 |
| | Mean | 9.7 | 13.0 | 9.7 | 13.7 | 11.5 |
| | SD | 1.2 | 1.7 | 1.5 | 0.6 | 2.2 |
| | Median | 9.0 | 12.0 | 10.0 | 14.0 | 11.5 |
| | Min | 9 | 12 | 8 | 13 | 8 |
| | Max | 11 | 15 | 11 | 14 | 15 |
| Weight (kg) | N | 3 | 3 | 3 | 3 | 12 |
| | Mean | 36.90 | 43.87 | 31.90 | 75.30 | 46.99 |
| | SD | 12.51 | 4.69 | 8.88 | 20.07 | 20.76 |
| | Median | 41.70 | 45.40 | 35.40 | 79.40 | 43.55 |
| | Min | 22.7 | 38.6 | 21.8 | 53.5 | 21.8 |
| | Max | 46.3 | 47.6 | 38.5 | 93.0 | 93.0 |
| Height (cm) | N | 3 | 3 | 3 | 3 | 12 |
| | Mean | 139.0 | 158.3 | 134.7 | 160.0 | 148.0 |
| | SD | 3.5 | 5.7 | 11.1 | 21.8 | 16.0 |
| | Median | 137.0 | 160.0 | 136.0 | 170.0 | 144.0 |
| | Min | 137 | 152 | 123 | 135 | 123 |
| | Max | 143 | 163 | 145 | 175 | 175 |
| BMI (kg/m^2) | N | 3 | 3 | 3 | 3 | 12 |
| | Mean | 18.98 | 17.45 | 17.29 | 29.07 | 20.70 |
| | SD | 5.97 | 0.65 | 2.53 | 1.47 | 5.84 |
| | Median | 22.22 | 17.73 | 18.31 | 29.36 | 18.73 |
| | Min | 12.1 | 16.7 | 14.4 | 27.5 | 12.1 |
| | Max | 22.6 | 17.9 | 19.1 | 30.4 | 30.4 |

Source: Study 28721 page 80
Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; SD, standard deviation

**Figure 14. Mean Concentration-Time Profiles for Gepirone**




Source: Study 28721 page 54

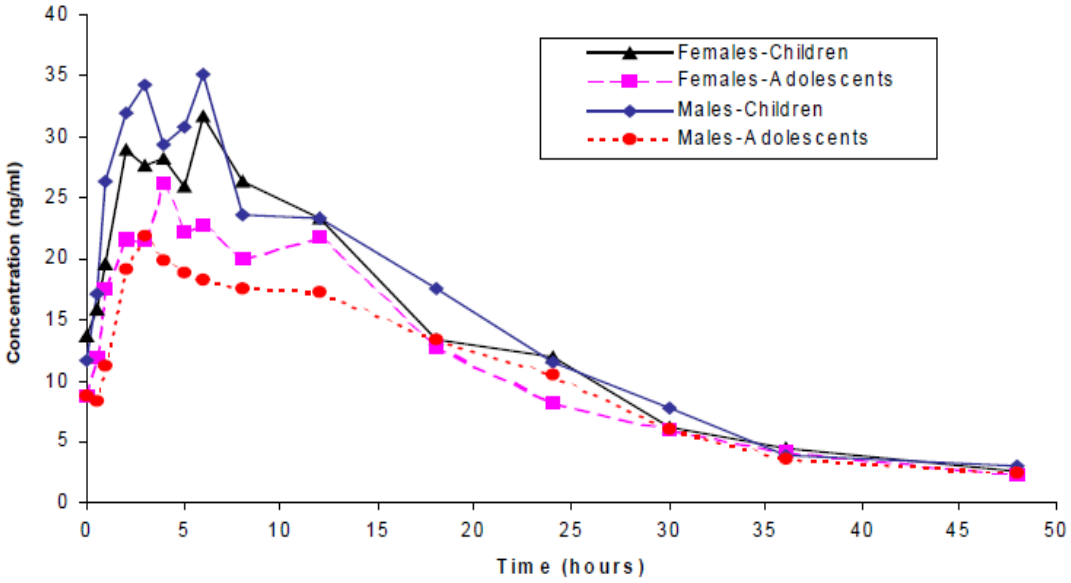
**Table 60. Means and Ranges of PK Parameters for Gepirone**

| PK Parameter | Female children (n=3) | Female adolescents (n=3) | Male children (n=3) | Male adolescents (n=3) | Overall (n=12) |
|---|---|---|---|---|---|
| $AUC_{0-24}$* (ng.h/ml) | 135.3 (98.5-161.2) | 91.6 (73.6-115.2) | 106.9 (53.7-201.0) | 114.2 (65.5-154.6) | 110.9 (53.7-201.0) |
| $C_{max}$* (ng/ml) | 10.4 (9.6-11.7) | 6.8 (4.1-9.5) | 9.1 (5.3-20.8) | 8.2 (5.7-10.0) | 8.5 (4.1-20.8) |
| $t_{max}$** (h) | 2.0 (2.0-6.0) | 6.0 (3.0-6.0) | 3.0 (2.0-4.0) | 4.0 (3.0-12.0) | 3.5 (2.0-12.0) |
| $t_{1/2}$* (h) | 14.7 (5.0-27.4) | 7.0 (5.2-8.7) | 8.9 (6.8-12.5) | 7.2 (5.5-10.5) | 9.0 (5.0-27.4) |
| wn-$CL_{app}$* (L/h/kg) | 7.6 (5.4-10.3) | 9.1 (6.9-10.4) | 11.0 (8.3-17.6) | 4.3 (2.5-7.0) | 7.6 (2.5-17.6) |
| wn-$V_{z,app}$* (L/kg) | 161 (39-405) | 91 (75-130) | 141 (82-318) | 45 (23-106) | 98 (23-405) |
| $CL_R$* (ml/min) | 24.1 (13.7-43.5) | 11.8 (9.4-14.9) | 6.5 (1.9-15.1) | 14.8 (8.4-30.1) | 12.8 (1.9-43.5) |

*geometric means, otherwise arithmetic means ** medians

Source: Study 28721 page 57
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Figure 15. Mean Concentration-Time Profiles for 3-OH-Gepirone**




Source: Study 28721 page 55

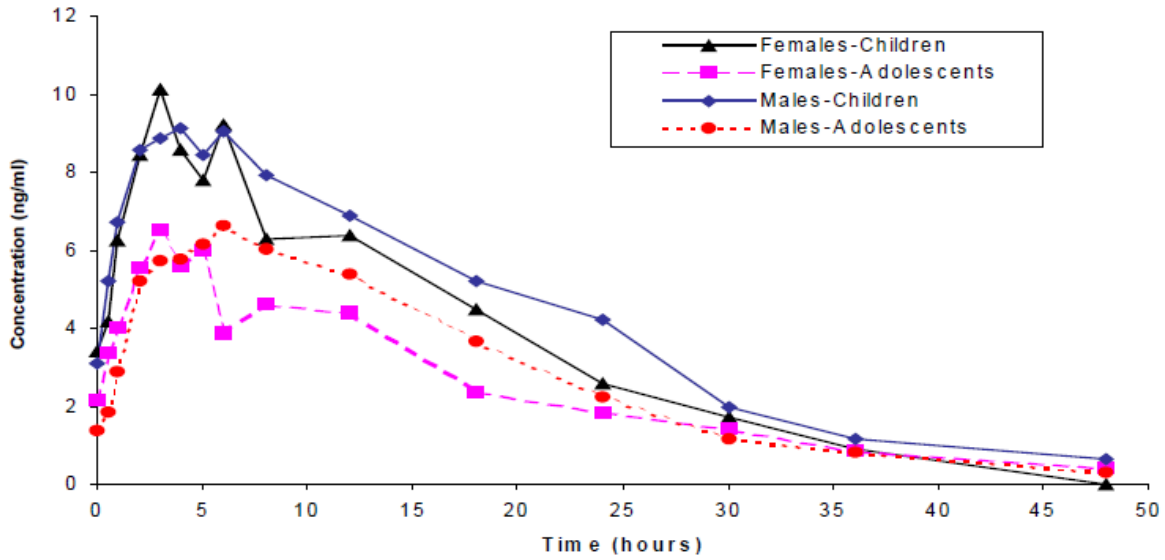
**Table 61. Means and Ranges of PK Parameters for 3-OH-Gepirone**

| PK Parameter | Female children (n=3) | Female adolescents (n=3) | Male children (n=3) | Male adolescents (n=3) | Overall (n=12) |
|---|---|---|---|---|---|
| $AUC_{0-24}$* (ng.h/ml) | 463 (330-768) | 408 (307-529) | 517 (414-750) | 370 (317-437) | 435 (307-768) |
| $C_{max}$* (ng/ml) | 30.6 (18.5-47.1) | 28.0 (18.8-36.3) | 39.6 (29.8-58.9) | 22.8 (20.2-24.9) | 29.7 (18.5-58.9) |
| $t_{max}$** (h) | 6.0 (3.0-24.0) | 4.0 (2.0-5.0) | 6.0 (3.0-6.0) | 4.0 (3.0-4.0) | 4.0 (2.0-24.0) |
| $t_{1/2}$* (h) | 16.1 (9.8-24.7) | 12.1 (7.4-19.2) | 11.1 (9.2-13.4) | 11.7 (7.7-15.1) | 12.6 (7.4-24.7) |
| wn-$CL_{app}$* (L/h/kg) | 2.2 (2.0-2.6) | 2.0 (1.8-2.5) | 2.3 (2.1-2.5) | 1.3 (1.1-2.1) | 1.9 (1.1-2.6) |
| wn-$V_{z,app}$* (L/kg) | 51.8 (37.2-71.3) | 35.7 (18.9-52.9) | 36.2 (32.8-41.0) | 22.7 (20.9-23.9) | 35.1 (18.9-71.3) |
| $CL_R$* (ml/min) | 8.8 (0.7-42.8) | 9.4 (2.8-33.8) | 12.6 (3.4-25.9) | 17.3 (2.8-61.7) | 11.6 (0.7-61.7) |

*geometric means, otherwise arithmetic means **medians

Source: Study 28721 page 58
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Figure 16. Mean Concentration-Time Profiles for 1-PP**




Source: Study 28721 page 55

**Table 62. Means and Ranges of PK Parameters for 1-PP**

| PK Parameter | Female children (n=3) | Female adolescents (n=3) | Male children (n=3) | Male adolescents (n=3) | Overall (n=12) |
|---|---|---|---|---|---|
| $AUC_{0-24}$* (ng.h/ml) | 101.3 (45.8-305.3) | 83.9 (64.2-139.6) | 145.4 (97.3-256.9) | 109.6 (101.3-115.5) | 107.9 (45.8-305.3) |
| $C_{max}$* (ng/ml) | 9.2 (4.8-22.3) | 6.3 (4.7-10.3) | 9.3 (6.6-15.0) | 6.7 (5.8-8.6) | 7.7 (4.7-22.3) |
| $t_{max}$** (h) | 3.0 (3.0-6.0) | 3.0 (3.0-6.0) | 3.0 (2.0-6.0) | 5.0 (4.0-6.0) | 3.5 (2.0-6.0) |
| $t_{1/2}$* (h) | 9.2 (5.1-13.7) | 9.7 (6.7-13.3) | 10.0 (4.3-19.5) | 9.9 (7.8-12.1) | 9.7 (4.3-19.5) |
| wn-$CL_{app}$* (L/h/kg) | 10.2 (5.2-17.1) | 9.9 (5.7-14.7) | 8.1 (6.5-9.7) | 4.5 (3.9-5.9) | 7.8 (3.9-17.1) |
| wn-$V_{z,app}$* (L/kg) | 135 (87-273) | 139 (84-222) | 116 (52-272) | 65 (58-71) | 109 (52-273) |
| $CL_R$* (ml/min) | 76.4[1)] (66.1-88.3) | 66.9 (44.2-83.0) | 58.7 (48.0-85.5) | 103.71 (92.5-114.9) | 74.5 (44.2-114.9) |

*geometric means, otherwise arithmetic means ** medians

Source: Study 28721 page 57

Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

The following table gives a comparative overview of the results in this study compared to data generated from other adult studies.

**Table 63. Summary of Mean (SD) PK Parameters for Gepirone, 1-PP and 3-OH-Gepirone in Three Multiple-Dose Studies in Children, Adolescents and Young Adults**

| Study | Dose | Population | Analyte | $C_{max}$ (ng/ml) | $AUC_{0-24}$(ng.h/ml) | $t_{1/2}$(h) |
|---|---|---|---|---|---|---|
| 28703 | 2x20 mg | Young, male adults | Gepirone | 9.7 (5,5) | 124 (69) | 8.0 (6.8) |
| | | | 1-PP | 9.3 (4.2) | 134 (76) | 8.1 (3.1) |
| | | | 3'OH-gepirone | 28.2 (6.5) | 460 (119) | 12.3 (6.0)) |
| 28706 | 2x20 mg | Young, male adults | Gepirone | 12.7 (4.7) | 173 (80) | 7.4 (3.4) |
| | | | 1-PP | 6.9 (2.6) | 101 (49) | 7.1 (2.0) |
| | | | 3'OH-gepirone | 25.4 (4.8) | 402 (110) | 12.1 (4.7) |
| 28721 | 2x20 mg | Male/female children and adolescents | Gepirone | 9.3 (4.3) | 119 (45) | 10.5 (7.2) |
| | | | 1-PP | 8.7 (5.2) | 125 (78) | 10.5 (4.2) |
| | | | 3'OH-gepirone | 31.5 (12.1) | 456 (154) | 13.4 (5.1)) |
| 28721 | 2 x 20 mg | Male/female children | Gepirone | 10.7 (5.5) | 130.6 (52.5) | 13.8 (9.2) |
| | | | 1-PP | 10.7 (6.7) | 150.4 (105.5) | 10.9 (5.6) |
| | | | 3'OH-gepirone | 37.1 (14.1) | 516.4 (191.5) | 14.2 (5.9) |
| 28721 | 2 x 20 mg | Male/female adolescents | Gepirone | 7.8 (2.4) | 107.8 (37.6) | 7.3 (2.0) |
| | | | 1-PP | 6.8 (2.2) | 99.9 (29.7) | 10.1 (2.5) |
| | | | 3'OH-gepirone | 26.0 (6.9) | 395.5 (83.5) | 12.6 (4.5) |

Source: Study 28721 page 63
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life

When male and female children were combined and male and female adolescents were combined, the average $AUC_{0-24}$ and $C_{max}$ values for gepirone were 21% and 37%, respectively higher for children compared to adolescents. The average $AUC_{0-24}$ and $C_{max}$ values for 1-PP were 57% and 51%, respectively higher for children compared to adolescents. The average $AUC_{0-24}$ and $C_{max}$ values for 3-OH-gepirone were 43% and 51%, respectively higher for children compared to adolescents. This may result from the lower body weight for children. Based on exploratory linear regression analyses, body weight (and age since they are found to be correlated) could be explanatory factor for observed differences in $C_{max}$ and AUC parameters for gepirone and its two metabolites. Furthermore, the exposures observed in children and adolescents are comparable to those observed in adults from previous studies.

No subjects had SAEs and there were no deaths in this trial. The overall highest incidence of AEs by body system and preferred term occurred for the central and peripheral nervous system disorders (dizziness and headache) in 4 (33.3%) subjects and gastro-intestinal system disorders (abdominal pain, dry mouth, nausea) in 4 (33.3%) subjects, followed by psychiatric disorders (somnolence) in 2 (16.7%) subjects and body as a whole – general disorders (chest pain) in 1 (8.3%) subject.

Overall, slightly higher plasma concentrations of gepirone and its metabolites were seen in children: this difference was largely accounted for by body weight (or alternatively age, owing to their strong correlation).

Conclusion

The results from children and adolescents were consistent with that from young adults from previous studies. Body weight (or age which is highly correlated to body weight) appeared to be the most important explanatory variable.

***Reviewer Comment***

*The reviewer agrees with the Applicant's conclusions. It should be noted that Caucasians were not enrolled in this study. The number of subjects for each group was relatively small so the results must be interpreted with caution.*

**Study FK-GBE-009**

Title

Open-Label, Multi-Center, Single Oral Dose Study to Assess the Pharmacokinetics of gepirone Extended-Release Tablets in Caucasian and African-American Children and Adolescents with Major Depressive Disorder

Objectives

To determine the PK characteristics of gepirone and its main metabolites 1-(2-pyrimidinyl) piperazine (1-PP) and 3'-OH-gepirone after single oral dose administration of gepirone extended-release (ER) tablets in both male and female children and adolescents with MDD; and to determine whether the pharmacokinetics of gepirone are different in Caucasian children and adolescents compared to African-American children and adolescents

Design

Open-label, single-center, single oral dose study of gepirone ER 40 mg. Twenty-six (26) subjects were enrolled: 13 Caucasian and 13 African-American. Thirteen (13) subjects (7 male and 6 female) were children, and the remaining 13 subjects (6 male and 7 female) were adolescents. Twenty-four (24) subjects were analyzed for PK parameters: 3 subjects per each age group, race, and gender. On study day 1, each subject was given one dose of 40 mg gepirone as 2 ER tablets, containing 20 mg gepirone each, after a fasting period of at least 4 hours. Blood samples were collected by catheter for determination of concentrations of gepirone and its metabolites 1-PP and 3'-OH-gepirone within 1 hour predose and again at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36, 48, 60, and 72 hours postdose.

Subjects were contacted by telephone 2 weeks after discharge to collect AE and concomitant medication information

Results

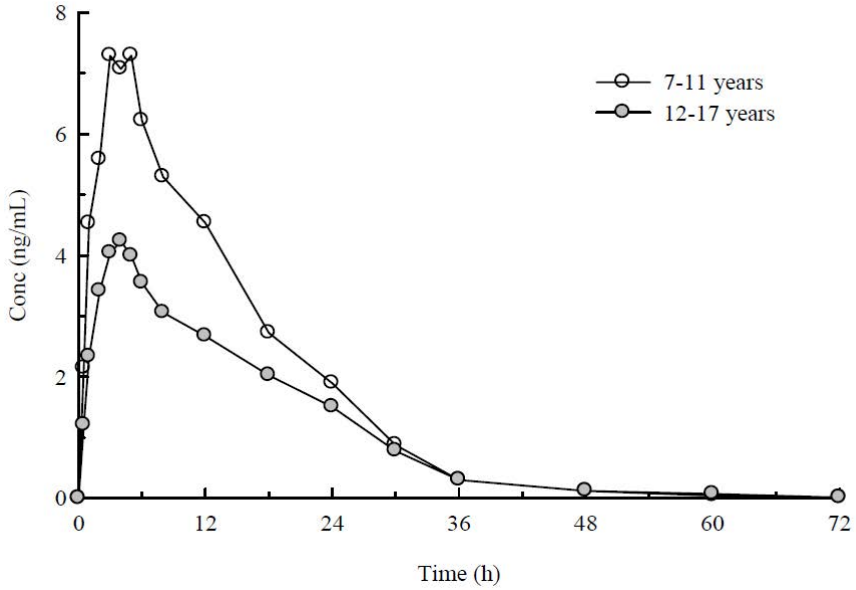
**Table 64. Demographic and Baseline Characteristics of All Treated Subjects**

| | Number (%) of Subjects[1] | | | |
|---|---|---|---|---|
| | Female | | Male | |
| | Caucasian | African-American | Caucasian | African-American |
| **Age Group 6-12 Years:** | | | | |
| **Age (years; N%)** | 3 (100%) | 3 (100%) | 4 (100%) | 3 (100%) |
| Mean ± SD | 9.3 ± 0.6 | 9.3 ± 2.5 | 9.3 ± 2.1 | 9.7 ± 1.5 |
| Median | 9.0 | 9.0 | 9.5 | 10.0 |
| Min, Max | 9.0, 10.0 | 7.0, 12.0 | 7.0, 11.0 | 8.0, 11.0 |
| **Height (inches; N%)** | 3 (100%) | 3 (100%) | 4 (100%) | 3 (100%) |
| Mean ± SD | 52.0 ± 2.2 | 55.3 ± 5.1 | 54.1 ± 3.8 | 55.7 ± 8.0 |
| Median | 51.0 | 54.0 | 55.0 | 55.0 |
| Min, Max | 50.5, 54.5 | 51.0, 61.0 | 49.0, 57.5 | 48.0, 64.0 |
| **Weight (lbs; N%)** | 3 (100%) | 3 (100%) | 4 (100%) | 3 (100%) |
| Mean ± SD | 76.7 ± 21.6 | 78.5 ± 19.5 | 81.0 ± 19.2 | 84.8 ± 29.3 |
| Median | 72.5 | 68.5 | 86.3 | 84.0 |
| Min, Max | 57.5, 100.0 | 66.0, 101.0 | 53.5, 98.0 | 56.0, 114.5 |
| **Clinically Significant Medical Histories (N%):** | 3 (100%) | 3 (100%) | 4 (100%) | 3 (100%) |
| **Subjects with at least one Prior Medication[2] (N%):** | 2 (66.7%) | 3 (100%) | 4 (100%) | 2 (66.7%) |
| **Age Group 13-18 Years:** | | | | |
| **Age (years; N%)** | 3 (100%) | 4 (100%) | 3 (100%) | 3 (100%) |
| Mean ± SD | 14.3 ± 1.2 | 15.3 ± 1.7 | 14.3 ± 2.3 | 14.0 ± 1.0 |
| Median | 15.0 | 15.5 | 13.0 | 14.0 |
| Min, Max | 13.0, 15.0 | 13.0, 17.0 | 13.0, 17.0 | 13.0, 15.0 |
| **Height (inches; N%)** | 3 (100%) | 4 (100%) | 3 (100%) | 3 (100%) |
| Mean ± SD | 64.2 ± 1.6 | 63.8 ± 1.9 | 64.8 ± 7.8 | 67.5 ± 6.1 |
| Median | 63.5 | 64.5 | 64.0 | 66.5 |
| Min, Max | 63.0, 66.0 | 61.0, 65.0 | 57.5, 73.0 | 62.0, 74.0 |
| **Weight (lbs; N%)** | 3 (100%) | 4 (100%) | 3 (100%) | 3 (100%) |
| Mean ± SD | 112.0 ± 13.2 | 132.9 ± 37.6 | 182.0 ± 94.9 | 161.3 ± 65.9 |
| Median | 117.0 | 122.5 | 188.5 | 134.0 |
| Min, Max | 97.0, 122.0 | 100.5, 186.0 | 84.0, 273.5 | 113.5, 236.5 |
| **Clinically Significant Medical Histories (N%):** | 3 (100%) | 4 (100%) | 3 (100%) | 3 (100%) |
| **Subjects with at least one Prior Medication[2] (N%):** | 3 (100%) | 3 (75%) | 3 (100%) | 3 (100%) |

[1] All Subject Treated included subjects who were enrolled in the study and received study drug.
[2] Prior Medication: Medication stop date is before dosing date.
Source: Table 14.1.3, Table 14.1.4, and Table 14.1.5

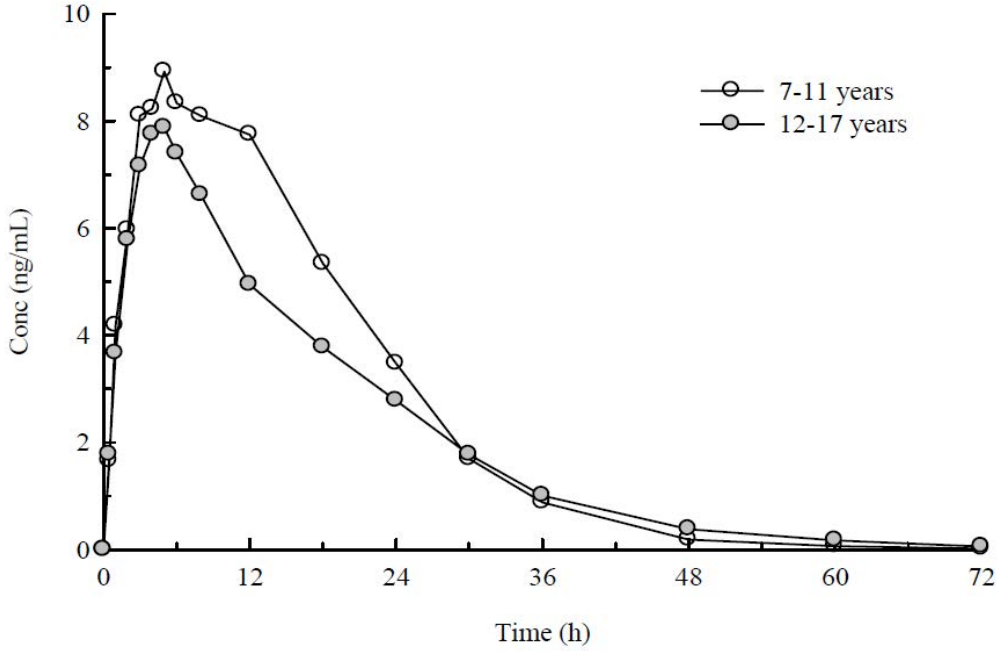
Source: Study FK-GBE-009 page 40
Abbreviations: SD, standard deviation

**Figure 17. Mean Plasma Concentrations of Gepirone by Age Group**



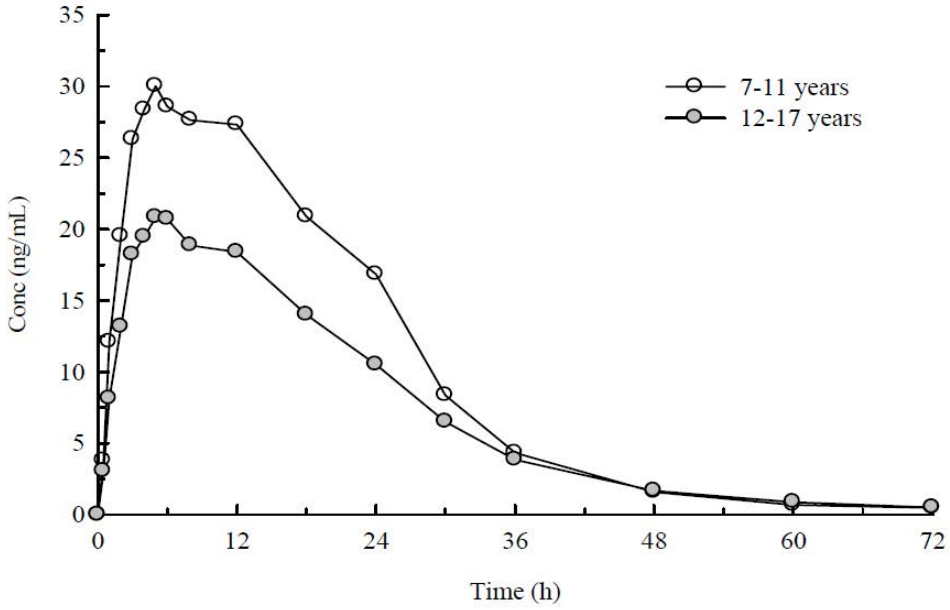

Source: Study FK-GBE-009 page 74
Abbreviations: Conc, concentration

**Figure 18. Mean Plasma Concentrations of 1-PP by Age Group**




Source: Study FK-GBE-009 page 75
Abbreviations: Conc, concentration

**Figure 19. Mean Plasma Concentrations of 3-OH-Gepirone by Age Group**




Source FK-GBE-009 page 76
Abbreviations: Conc, concentration

**Table 65. Summary of Pharmacokinetic Parameters for Gepirone, 1-PP, and 3'-OH-Gepirone: All Subjects Combined**

| Parameter[1] | | | Gepirone Metabolite | | | |
|---|---|---|---|---|---|---|
| | N | Gepirone | N | 1-PP | N | 3'-OH-gepirone |
| $C_{max}$ (ng/mL) | 24 | 6.70 ± 4.23 | 24 | 9.23 ± 4.22 | 24 | 28.7 ± 11.4 |
| $T_{max}$ (h) | 24 | 3.93 [0.9-11.9] | 24 | 4.93 [3.0-12.0] | 24 | 5.92 [3.0-12.0] |
| $AUC_{0\text{-tlast}}$ (h*ng/mL) | 24 | 94.3 ± 66.7 | 24 | 166 ± 94.4 | 24 | 610 ± 261 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 13 | 101 ± 76.6 | 21 | 178 ± 96.9 | 18 | 611 ± 258 |
| $\lambda z$ ($h^{-1}$) | 13 | 0.1378 ± 0.0649 | 21 | 0.1239 ± 0.0502 | 18 | 0.0690 ± 0.0247 |
| $t_{1/2}$ (h) | 13 | 6.36 ± 3.70 | 21 | 6.53 ± 2.67 | 18 | 11.7 ± 5.24 |
| CL/F (mL/min) | 13 | 11,017 ± 7,563 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 13 | 6,813 ± 8,053 | -- | --[2] | -- | --[2] |

N = number of subjects with mean plasma concentrations greater than the lower limits of quantitation.
[1] Mean ± standard deviation except for $T_{max}$ for which the median [Range] was reported.
[2] Parameter not applicable.

Source: Study FK-GBE-009 page 43
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Table 66. Summary of Pharmacokinetic Parameters for Gepirone, 1-PP, and 3'-OH-Gepirone by Age Group**

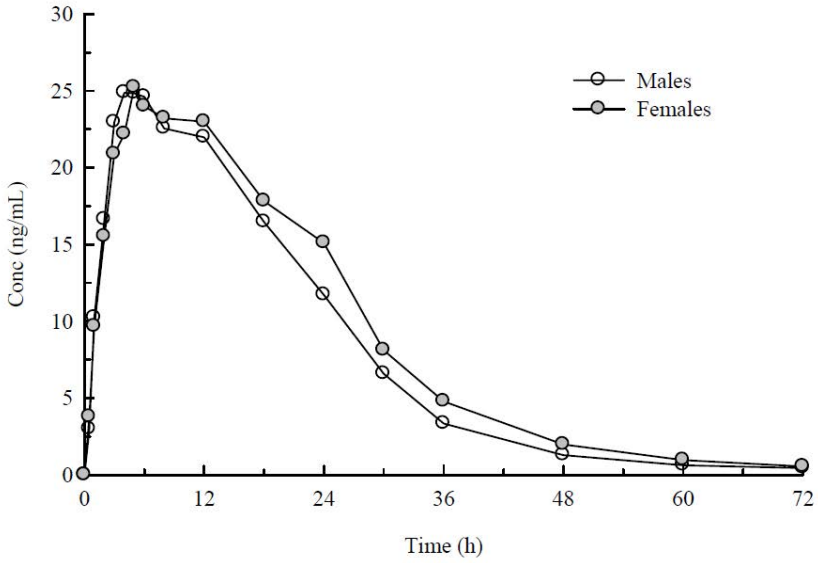
| Parameter[1] | | | Gepirone Metabolite | | | |
|---|---|---|---|---|---|---|
| | N | Gepirone | N | 1-PP | N | 3'-OH-gepirone |
| **Children (7-11 yrs)** | | | | | | |
| $C_{max}$ (ng/mL) | 11 | 8.56 ± 4.59 | 11 | 10.3 ± 5.22 | 11 | 35.7 ± 11.4 |
| $T_{max}$ (h) | 11 | 3.93 [2.0-7.9] | 11 | 4.95 [3.0-12.0] | 11 | 4.95 [3.9-12.0] |
| $AUC_{0\text{-}tlast}$ (h*ng/mL) | 11 | 116 ± 73.5 | 11 | 182 ± 114 | 11 | 723 ± 297 |
| $AUC_{0\text{-}inf}$ (h*ng/mL) | 4 | 137 ± 98.8 | 9 | 205 ± 115 | 7 | 726 ± 306 |
| $\lambda z$ ($h^{-1}$) | 4 | 0.1662 ± 0.0740 | 9 | 0.1388 ± 0.0648 | 7 | 0.0862 ± 0.0207 |
| $t_{1/2}$ (h) | 4 | 4.88 ± 2.15 | 9 | 6.18 ± 3.10 | 7 | 8.46 ± 2.10 |
| CL/F (mL/min) | 4 | 7,190 ± 4,916 | -- | --[1] | -- | --[1] |
| Vz/F (L) | 4 | 3,309 ± 2,985 | -- | --[1] | -- | --[1] |
| **Adolescents (12-17 yrs)** | | | | | | |
| $C_{max}$ (ng/mL) | 13 | 5.12 ± 3.29 | 13 | 8.34 ± 3.09 | 13 | 22.8 ± 7.7 |
| $T_{max}$ (h) | 13 | 3.93 [0.9-11.9] | 13 | 4.92 [3.0-5.9] | 13 | 5.97 [3.0-12.0] |
| $AUC_{0\text{-}tlast}$ (h*ng/mL) | 13 | 75.9 ± 56.8 | 13 | 153 ± 76.5 | 13 | 513 ± 188 |
| $AUC_{0\text{-}inf}$ (h*ng/mL) | 9 | 84.6 ± 64.6 | 12 | 157 ± 79.7 | 11 | 538 ± 204 |
| $\lambda z$ ($h^{-1}$) | 9 | 0.1252 ± 0.0606 | 12 | 0.1127 ± 0.0349 | 11 | 0.0581 ± 0.0210 |
| $t_{1/2}$ (h) | 9 | 7.02 ± 4.15 | 12 | 6.79 ± 2.40 | 11 | 13.7 ± 5.69 |
| CL/F (mL/min) | 9 | 12,719 ± 8,134 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 9 | 8,370 ± 9,224 | -- | --[2] | -- | --[2] |
| ***P* value**[3] | | | | | | |
| $C_{max}$[4] | | 0.0262 | | 0.4826 | | 0.0064 |
| $AUC_{0\text{-}tlast}$[4] | | 0.1163 | | 0.8133 | | 0.1585 |
| $AUC_{0\text{-}inf}$[4] | | 0.2574 | | 0.4641 | | 0.3206 |
| $t_{1/2}$ | | 0.3584 | | 0.6169 | | 0.0343 |

N = number of subjects with mean plasma concentrations greater than the lower limits of quantitation.
1 Mean ± standard deviation except for $T_{max}$ for which the median [Range] was reported.
2 Parameter not applicable.
3 *P* value from a one-way analysis of variance with age as the variable.
4 Natural-log transformed before analysis.

Source: Study KF-GBE-009 page 45
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

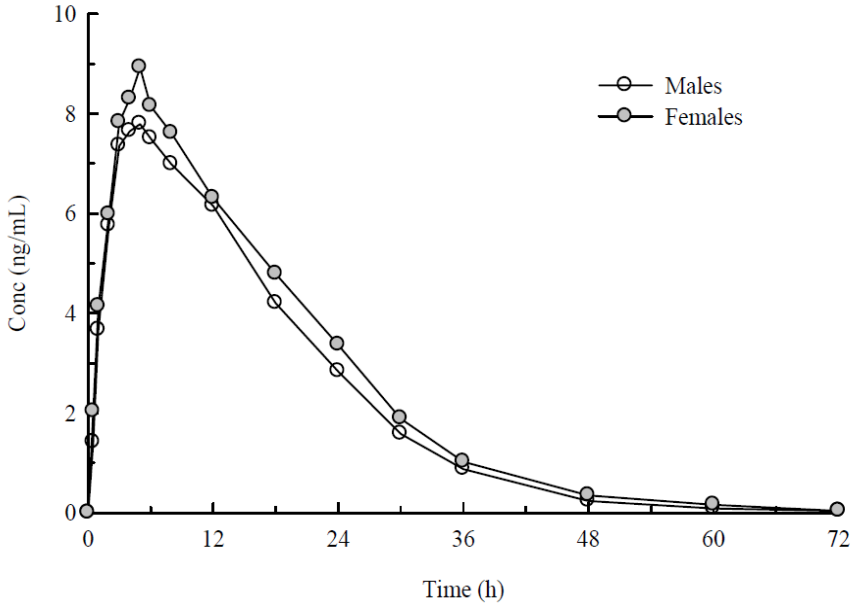
The mean values of gepirone and both 1-PP and 3'-OH-gepirone for $C_{max}$ and AUC were higher in children than in adolescents, but not all differences were statistically significant.

**Figure 20. Mean Plasma Concentrations of 3'-OH-Gepirone by Gender**



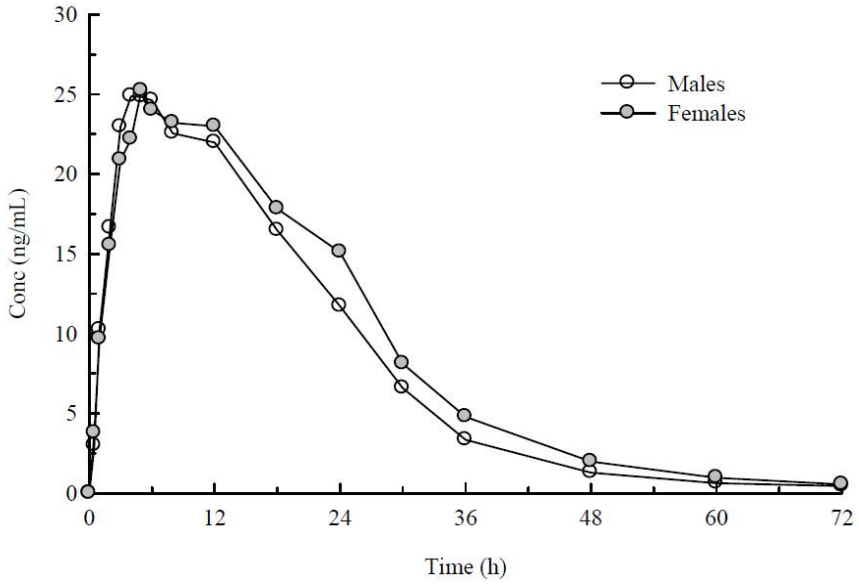

Source: Study FK-GBE-009 page 84
Abbreviations: Conc, concentration

**Figure 21. Mean Plasma Concentrations of 1-PP by Gender**




Source: Study FK-GBE-009 page 83
Abbreviations: Conc, concentration

**Figure 22. Mean Plasma Concentrations of 3-OH-Gepirone by Gender**




Source: Study FK-GBE-009 page 84
Abbreviations: Conc, concentration

**Table 67. Summary of Pharmacokinetic Parameters for Gepirone, 1-PP, and 3'-OH-Gepirone by Gender**

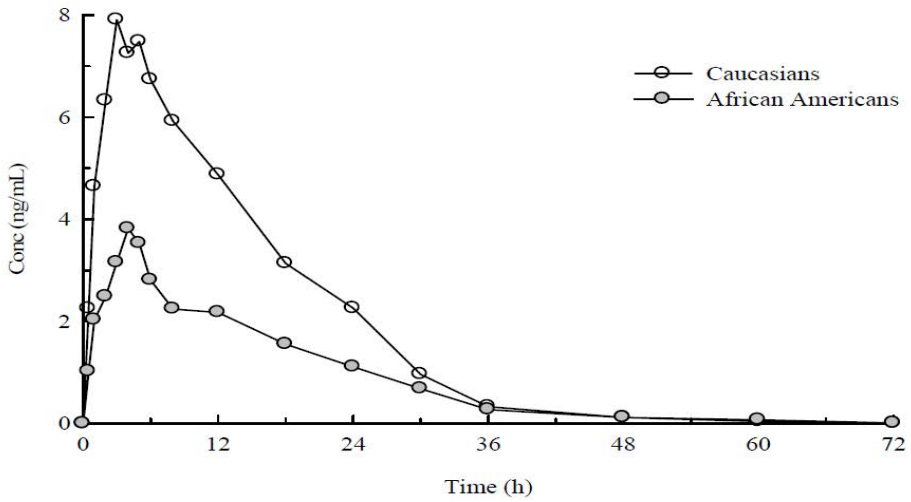
| Parameter[1] | N | Gepirone | Gepirone Metabolite N | 1-PP | N | 3'-OH-gepirone |
|---|---|---|---|---|---|---|
| **Females** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 7.51 ± 4.60 | 12 | 9.57 ± 3.34 | 12 | 29.0 ± 8.84 |
| $T_{max}$ (h) | 12 | 3.98 [1.9-7.9] | 12 | 4.94 [3.0-12.0] | 12 | 5.97 [3.0-12.0] |
| $AUC_{0\text{-last}}$ (h*ng/mL) | 12 | 108 ± 69.3 | 12 | 176 ± 78.6 | 12 | 642 ± 202 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 7 | 122 ± 81.9 | 11 | 183 ± 81.3 | 9 | 693 ± 206 |
| λz ($h^{-1}$) | 7 | 0.1251 ± 0.0585 | 11 | 0.1135 ± 0.0430 | 9 | 0.0641 ± 0.0199 |
| $t_{1/2}$ (h) | 7 | 6.37 ± 2.24 | 11 | 6.98 ± 2.66 | 9 | 12.4 ± 5.93 |
| CL/F (mL/min) | 7 | 8,755 ± 7,144 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 7 | 4,641 ± 3,152 | -- | --[2] | -- | --[2] |
| **Males** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 5.88 ± 3.84 | 12 | 8.88 ± 5.07 | 12 | 28.4 ± 13.9 |
| $T_{max}$ (h) | 12 | 2.99 [0.9-11.9] | 12 | 4.42 [3.0-12.0] | 12 | 4.48 [3.0-12.0] |
| $AUC_{0\text{-last}}$ (h*ng/mL) | 12 | 80.7 ± 64.1 | 12 | 156 ± 110 | 12 | 577 ± 316 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 6 | 76.2 ± 68.5 | 10 | 172 ± 116 | 9 | 529 ± 289 |
| λz ($h^{-1}$) | 6 | 0.1526 ± 0.0742 | 10 | 0.1353 ± 0.0573 | 9 | 0.0739 ± 0.0291 |
| $t_{1/2}$ (h) | 6 | 6.35 ± 5.18 | 10 | 6.04 ± 2.72 | 9 | 10.9 ± 4.70 |
| CL/F (mL/min) | 6 | 13,656 ± 7,779 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 6 | 9,347 ± 11,376 | -- | --[2] | -- | --[2] |
| ***P* value**[3] | | | | | | |
| $C_{max}$[4] | | 0.2974 | | 0.4179 | | 0.5622 |
| $AUC_{0\text{-last}}$[4] | | 0.2218 | | 0.2712 | | 0.2724 |
| $AUC_{0\text{-inf}}$[4] | | 0.2456 | | 0.4546 | | 0.1099 |
| $t_{1/2}$ | | 0.9950 | | 0.4370 | | 0.5740 |

N = number of subjects with mean plasma concentrations greater than the lower limits of quantitation.
[1] Mean ± standard deviation except for $T_{max}$ for which the median [Range] was reported.
[2] Parameter not applicable.
[3] *P* value from a one-way analysis of variance with gender as the variable.
[4] Natural-log transformed before analysis.

Source: FK-GBE-009 page 47
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

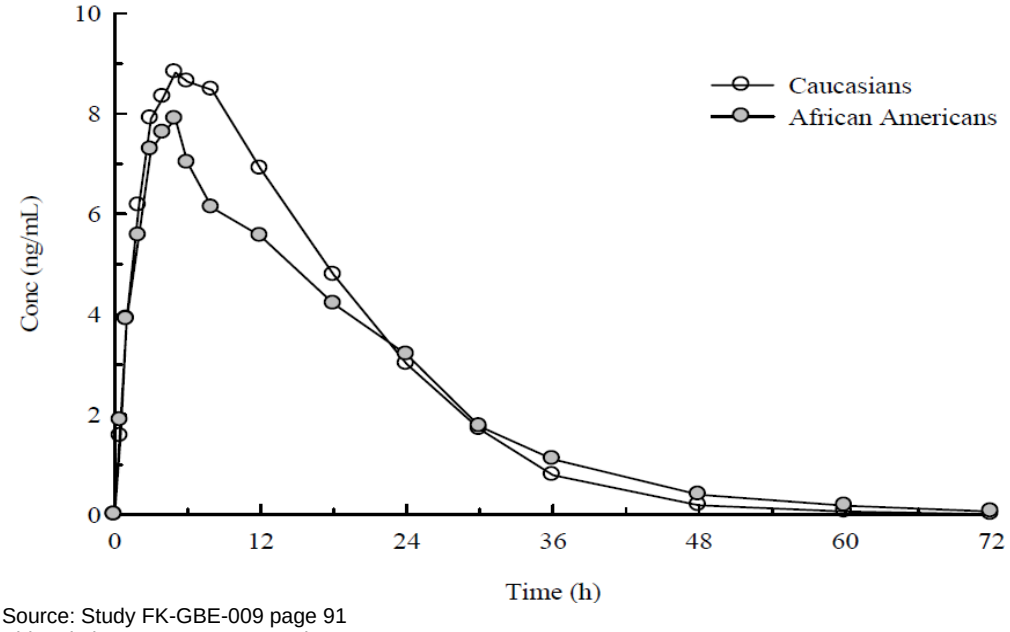
The mean values of gepirone for $C_{max}$ and AUC were higher for female subjects than for male subjects, and while the mean values of 1-PP and 3'-OH-gepirone for $C_{max}$ and AUC were comparable between female and male subjects, values were still slightly higher in female subjects.

**Figure 23. Mean Plasma Concentrations of Gepirone by Race**



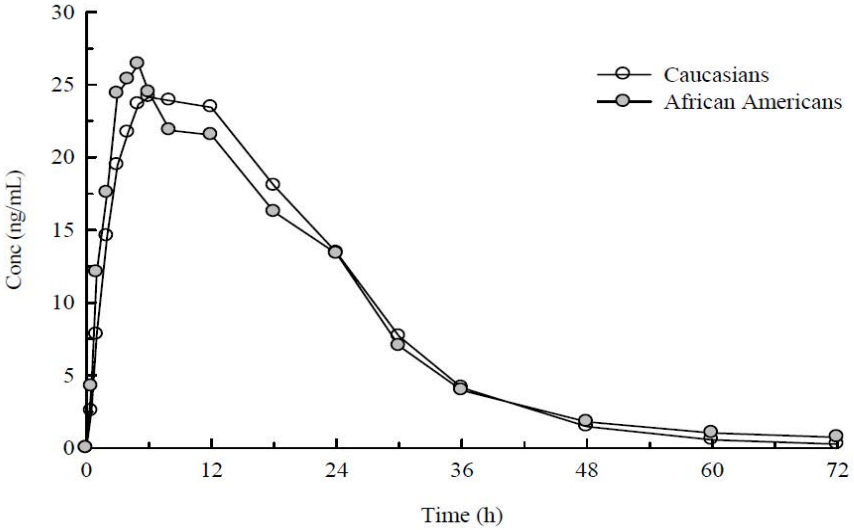

Source: Study FK-GBE-009 page 90
Abbreviations: Conc, concentration

**Figure 24. Mean Plasma Concentrations of 1-PP by Race**




Source: Study FK-GBE-009 page 91
Abbreviations: Conc, concentration

**Figure 25. Mean Plasma Concentrations of 3-OH-Gepirone by Race**




Source: Study FK-GBE-009 page 92
Abbreviations: Conc, concentration

**Table 68. Summary of Pharmacokinetic Parameters for Gepirone, 1-PP, and 3'-OH-Gepirone by Race**

| Parameter[1] | | | Gepirone Metabolite | | | |
|---|---|---|---|---|---|---|
| | N | Gepirone | N | 1-PP | N | 3'-OH-gepirone |
| **African-American** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 4.36 ± 1.92 | 12 | 8.30 ± 3.97 | 12 | 29.1 ± 12.9 |
| $T_{max}$ (h) | 12 | 3.95 [1.9-11.9] | 12 | 4.93 [3.0-5.0] | 12 | 4.95 [3.0-12.0] |
| $AUC_{0\text{-last}}$ (h*ng/mL) | 12 | 60.6 ± 32.1 | 12 | 159 ± 83.2 | 12 | 610 ± 248 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 6 | 49.4 ± 20.2 | 10 | 177 ± 81.1 | 6 | 606 ± 217 |
| λz ($h^{-1}$) | 6 | 0.1262 ± 0.0550 | 10 | 0.0944 ± 0.0336 | 6 | 0.0428 ± 0.0123 |
| $t_{1/2}$ (h) | 6 | 7.03 ± 4.84 | 10 | 8.18 ± 2.70 | 6 | 17.4 ± 5.19 |
| CL/F (mL/min) | 6 | 15,389 ± 5,867 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 6 | 10,616 ± 10,647 | -- | --[2] | -- | --[2] |
| **Caucasian** | | | | | | |
| $C_{max}$ (ng/mL) | 12 | 9.03 ± 4.66 | 12 | 10.2 ± 4.42 | 12 | 28.3 ± 10.3 |
| $T_{max}$ (h) | 12 | 3.93 [0.9-7.9] | 12 | 5.01 [3.0-12.0] | 12 | 5.95 [3.0-12.0] |
| $AUC_{0\text{-last}}$ (h*ng/mL) | 12 | 128 ± 76.2 | 12 | 173 ± 108 | 12 | 610 ± 285 |
| $AUC_{0\text{-inf}}$ (h*ng/mL) | 7 | 145 ± 80.5 | 11 | 178 ± 113 | 12 | 613 ± 285 |
| λz ($h^{-1}$) | 7 | 0.1478 ± 0.0751 | 11 | 0.1507 ± 0.0487 | 12 | 0.0822 ± 0.0177 |
| $t_{1/2}$ (h) | 7 | 5.79 ± 2.66 | 11 | 5.04 ± 1.58 | 12 | 8.78 ± 1.79 |
| CL/F (mL/min) | 7 | 7,271 ± 7,088 | -- | --[2] | -- | --[2] |
| Vz/F (L) | 7 | 3,553 ± 2,895 | -- | --[2] | -- | --[2] |
| ***P* value**[3] | | | | | | |
| $C_{max}$[4] | | 0.0044 | | 0.2154 | | 0.9608 |
| $AUC_{0\text{-last}}$[4] | | 0.0211 | | 0.9166 | | 0.8156 |
| $AUC_{0\text{-inf}}$[4] | | 0.0155 | | 0.6853 | | 0.8272 |
| $t_{1/2}$ | | 0.5678 | | 0.0038 | | 0.0001 |

N = number of subjects with mean plasma concentrations greater than the lower limits of quantitation.
1 Mean ± standard deviation except for $T_{max}$ for which the median [Range] was reported.
2 Parameter not applicable.
3 *P* value from a one-way analysis of variance with race as the variable.
4 Natural-log transformed before analysis.

Source: Study FK-GBE-009 page 49
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

The mean values of gepirone for $C_{max}$ and AUC were about 52% and 66% higher, respectively higher in Caucasian than in African-American subjects.

Conclusions

With regard to the effect of age on the PK parameters of gepirone and its two metabolites, $C_{max}$ in children were statistically significantly different and larger than values found in adolescents. This effect carried over to the metabolite 3'-OH-gepirone, but not to 1-PP. The effect was likely due to the disparity in body weight between children (~33 kg) and adolescents (~63 kg), so that the fixed 40 mg dose represented an effective 2-fold higher dose in children compared to adolescents.

The mean values of gepirone were not statistically significantly different between females and males. Similarly, there were no differences in the plasma concentrations of the metabolites between the 2 genders.

The $C_{max}$ of gepirone for Caucasian subjects was about twice that of African-Americans; this difference was statistically significant. However, the effect was not seen in either of the metabolites.

Overall, the sponsor reported that gepirone ER tablets were well-tolerated in both African-American and Caucasian subjects. There were no deaths or SAEs in this study, and no subjects discontinued treatment due to a TEAE. Moderate TEAEs experienced by the group of children included vertigo, abdominal pain upper, nausea, vomiting, dizziness, and somnolence. The adolescent group experienced mild TEAEs only during the study, which included vertigo, nausea, vomiting, hepatic enzyme increased, dizziness, headache, somnolence, and metrorrhagia. All TEAEs resolved without sequelae by the end of the study. The reviewer concurs with the conclusions by the sponsor.

***Reviewer Comment***

*The reviewer concours with the conclusions that Caucasian had a higher exposure than African American children of the same age group. Dose adjustment may be needed if gepirone is approved in children. Based on the original clinical pharmacology review, archived in DARRTS on 2/19/2022, the exposure in adult Caucasian was 50% to 100% higher than in adult African American patients.*

**Study FK-GBE-011**

Title

Pharmacokinetic Study of 20 mg and 80 mg gepirone ER Tablets (Mission)

Objectives

Primary:

- PK of 20 mg gepirone ER (Mission) in normal healthy subjects under fasted conditions
- To evaluate the PK of 80 mg gepirone ER Mission in normal healthy subjects under fasted conditions

Secondary:

- To assess the dose proportionality of 20 mg gepirone ER Mission relative to 80 mg gepirone ER (Mission)
- To monitor safety and tolerability of gepirone ER Mission in healthy subjects.

Design

Phase 1, single center, randomized, open-label, 2 period crossover study. All subjects were randomly assigned in 1:1 ratio to receive the following treatments. There was 7-day washout period between treatments.

Treatment A: gepirone 20 mg ER Mission

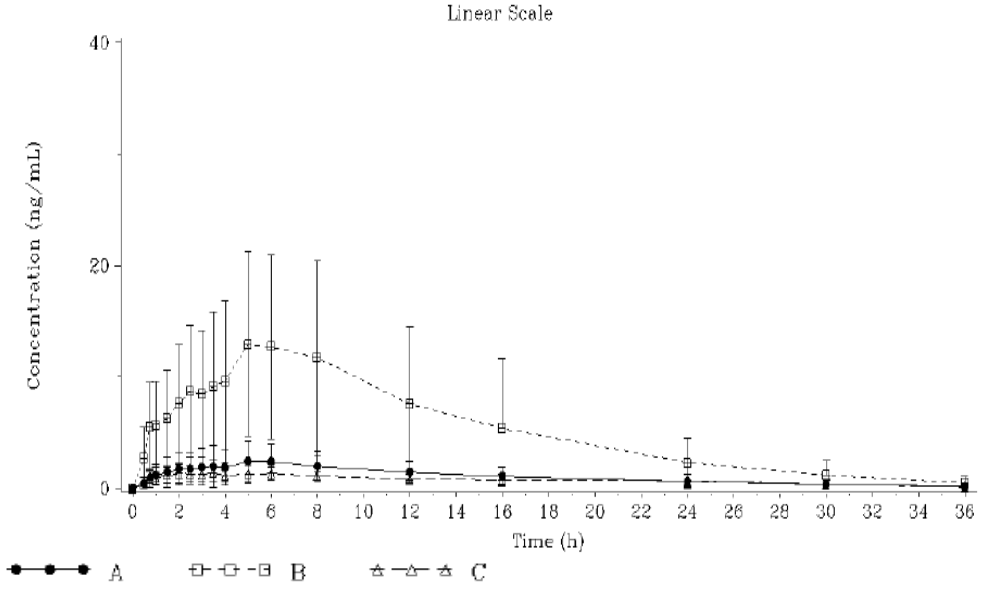
Treatment B: gepirone 80 mg ER Mission

Blood samples for PK analysis were collected predose (0 hour), and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, and 36 hours after dosing on Day 1 of each period.

Results

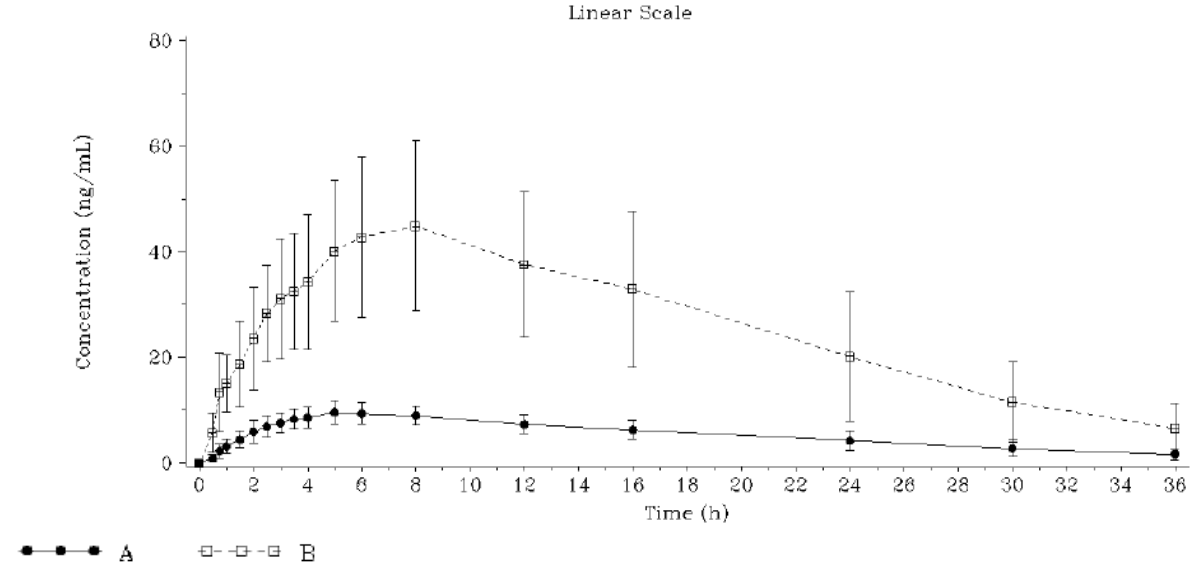
The mean plasma concentration time profile after administration of the 20 mg and 80 mg gepirone is provided in the following figure.

**Figure 26. Mean ± SD Plasma Concentration Time Profile of Gepirone**



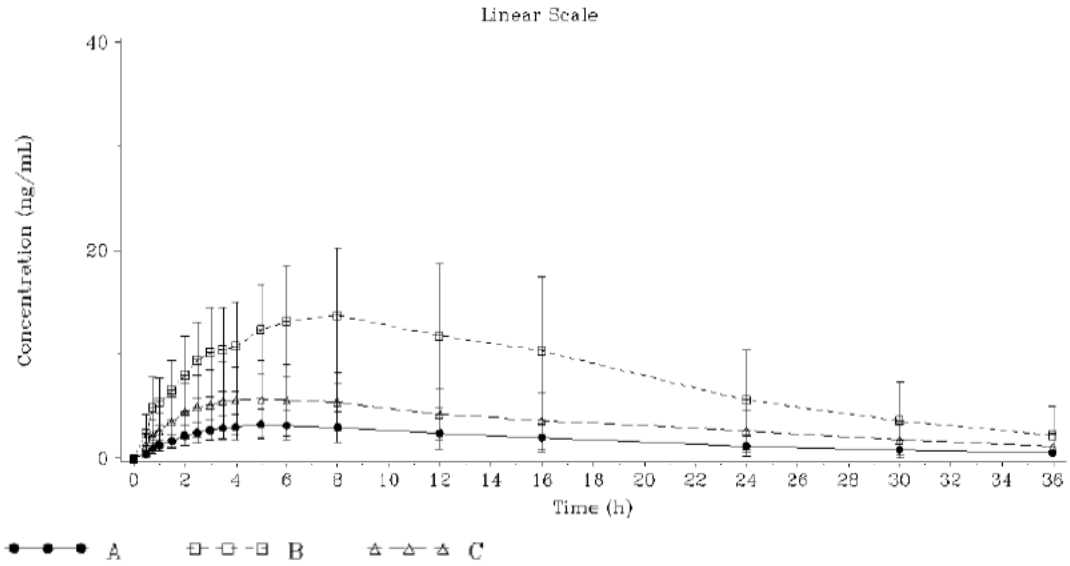

Source: Study FK-GBE-011 page 50
Treatment A: gepirone 20 mg ER (Mission)
Treatment B: gepirone 80 mg ER (Mission)
Treatment C: gepirone 20 mg ER (b) (4) historical data)
Abbreviations: ER, extended release; SD, standard deviation

**Figure 27. Mean ± SD Plasma Concentration Time Profile of 3-OH Gepirone**




Source: Study FK-GBE-011 page 51
Treatment A: gepirone 20 mg ER (Mission)
Treatment B: gepirone 80 mg ER (Mission)
Abbreviations: ER, extended release; SD, standard deviation

**Figure 28. Mean ± SD Plasma Concentration Time Profile of 1-PP**




Source: Study FK-GBE-011 page 52
Treatment A: gepirone 20 mg ER (Mission)
Treatment B: gepirone 80 mg ER (Mission)
Treatment C: gepirone 20 mg ER (b) (4) historical data)
Abbreviations: ER, extended release; SD, standard deviation

**Table 69. Mean (CV) Plasma Pharmacokinetic Parameters of Gepirone**

| Parameter (unit) | Treatment A N=40 | Treatment B N=40 | Treatment C N=35 |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 2.78 (70.0) | 15.4 (63.3) | 1.96 (43.7) |
| $T_{max}$ (h)* | 6.00 (0.75, 12.00) | 5.58 (2.00, 16.00) | 3.50 (1.00, 12.00) |
| $AUC_{0-t}$ (h*ng/mL) | 39.0 (67.0) | 185 (73.2) | 26.8 (51.4) |
| $AUC_{0-36}$ (h*ng/mL) | 39.1 (66.8) | 185 (73.2) | 27.4 (49.9)[e] |
| $AUC_{0-inf}$ (h*ng/mL) | 41.2 (72.8)[c] | 191 (74.5)[f] | 27.2 (48.6)[a] |
| $t_{1/2}$ (h) | 5.93 (70.2)[f] | 4.93 (44.9)[f] | 7.14 (75.2)[b] |
| CL/F (L/h) | 745 (82.4)[f] | 697 (78.7)[f] | 962 (70.5)[b] |
| $V_z$/F (L) | 5770 (84.5)[f] | 4610 (94.3)[f] | 8750 (67.2)[b] |

Abbreviations: CV, coefficient of variation; h, hours.
Treatment A: Single dose of 20 mg Gepirone ER Mission under fasted conditions.
Treatment B: Single dose of 80 mg Gepirone ER Mission under fasted conditions.
Treatment C: Single dose of 20 mg Gepirone ER (b) (4) under fasted conditions (FK-GBE-001 study).
* For $T_{max}$, the median (minimum, maximum) values are presented.
[a] n = 23; [b] n = 25; [c] n = 33; [d] n = 35; [e] n = 36; [f] n = 37.

Source: Study FK-GBE-011 page 53
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Table 70. Mean (CV) Plasma Pharmacokinetic Parameters of 3-OH-Gepirone**

| Parameter (unit) | Treatment A N=40 | Treatment B N=40 |
|---|---|---|
| $C_{max}$ (ng/mL) | 10.1 (19.7) | 51.2 (34.2) |
| $T_{max}$ (h)* | 5.00 (3.62, 12.00) | 8.00 (2.50, 24.00) |
| $AUC_{0-t}$ (h*ng/mL) | 195 (25.0) | 922 (33.3) |
| $AUC_{0-36}$ (h*ng/mL) | 195 (25.0) | 922 (33.3) |
| $AUC_{0-inf}$ (h*ng/mL) | 208 (27.2)[a] | 968 (34.1)[b] |
| $t_{1/2}$ (h) | 9.04 (37.7)[d] | 7.77 (42.3)[c] |

Abbreviations: CV, coefficient of variation; h, hours.
Treatment A: Single dose of 20 mg Gepirone ER Mission under fasted conditions.
Treatment B: Single dose of 80 mg Gepirone ER Mission under fasted conditions.
* For Tmax, the median (minimum, maximum) values are presented.
[a] n = 34; [b] n = 35; [c] n = 38; [d] n = 39.

Source: Study FK-GBE-011 page 54
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Table 71. Mean (CV) Plasma Pharmacokinetic Parameters of 1-PP**

| | | | |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 3.45 (41.8) | 16.3 (41.9) | 7.24 (56.6) |
| $T_{max}$ (h)* | 5.00 (2.50, 12.00) | 7.00 (2.50, 16.08) | 4.00 (1.00, 16.00) |
| $AUC_{0-t}$ (h*ng/mL) | 63.3 (58.2) | 285 (55.6) | 120 (59.0) |
| $AUC_{0-36}$ (h*ng/mL) | 63.3 (58.2) | 285 (55.6) | 121 (55.7)[c] |
| $AUC_{0-inf}$ (h*ng/mL) | 59.9 (48.6)[e] | 276 (53.6)[d] | 120 (55.2)[b] |
| $t_{1/2}$ (h) | 9.50 (8.63) | 7.65 (44.6)[f] | 9.71 (33.8)[a] |

Abbreviations: CV, coefficient of variation; h, hours.
Treatment A: Single dose of 20 mg Gepirone ER Mission under fasted conditions.
Treatment B: Single dose of 80 mg Gepirone ER Mission under fasted conditions.
Treatment C: Single dose of 20 mg Gepirone ER (b) (4) under fasted conditions (FK-GBE-001 study).
* For $T_{max}$, the median (minimum, maximum) values are presented.
[a] n = 20; [b] n = 22; [c] n = 30; [d] n = 34; [e] n = 35; [f] n = 37.

Source: Study FK-GBE-011 page 55
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; $T_{1/2}$, half-life; $T_{max}$, time to maximum plasma concentration

**Table 72. Statistical Assessment for Dose Proportionality for Gepirone ER (Mission)**

| Dose-Normalized Pharmacokinetic Parameter (units) | Treatment | Geometric LS Means (n) | Comparison | Ratio of Geometric LS Means | 90% CI |
|---|---|---|---|---|---|
| $AUC_{0-inf}$/Dose (h*ng/mL/mg) | A | 1.66 (36) | A/B | 0.90 | (0.78, 1.03) |
| | B | 1.85 (37) | | | |
| $AUC_{0-36}$/Dose (h*ng/mL/mg) | A | 1.61 (40) | A/B | 0.88 | (0.78, 0.99) |
| | B | 1.83 (40) | | | |
| $AUC_{0-t}$/Dose (h*ng/mL/mg) | A | 1.60 (40) | A/B | 0.88 | (0.78, 0.99) |
| | B | 1.83 (40) | | | |
| $C_{max}$/Dose (ng/mL/mg) | A | 0.12 (40) | A/B | 0.74 | (0.66, 0.82) |
| | B | 0.16 (40) | | | |

Abbreviations: CI, confidence interval; LS, least squares; n, number of subjects.
Note: An analysis of variance (ANOVA) model was fitted to the ln-transformed dose-normalized AUCs and $C_{max}$ data, with treatment as a fixed effect.
Treatment A: Single dose of 20 mg Gepirone ER Mission under fasted conditions.
Treatment B: Single dose of 80 mg Gepirone ER Mission under fasted conditions.

Source: Study FK-GBE-011 page 60
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; $C_{max}$, maximum observed plasma concentration; CV, coefficient of variation; ER, extended release; LS, least squares;

The Applicant reported that more subjects experienced at least 1 TEAEs after receiving 80 mg gepirone ER (68.3%) (Mission) compared with 20 mg gepirone ER (Mission) (17.5%). The Applicant reported that the most frequently adverse events were nausea, dizziness, somnolence, vomiting, headache and feeling hot. The Applicant reports the majority were determined to be mild.

This was a phase 1, single-center, randomized, open-label, 2-period crossover study to assess the pharmacokinetics and dose proportionality in healthy volunteers, following single doses of 20 mg and 80 mg of gepirone ER (Mission). Overall peak and total plasma exposure of gepirone was higher following administration of a single dose of 20 mg gepirone ER (Mission tablet) compared to the historical data from a single dose of 20 mg gepirone ER tablet by Teva. Given this was a cross-study comparison, the Applicant acknowledged that the PK bridging between 20 mg gepirone ER (Mission tablet) and 20 mg gepirone ER ( (b) (4) tablet, a phase 3 clinical trial formulation) was not reliable. Subsequently, the Applicant conducted two dedicated PK bridging studies (Studies 2666 and 2667) to support the bridge between the FMI formulation and the phase 3 clinical trial formulation at 20 mg and 80 mg strengths.

No formal statistical criteria was prespecified to conclude dose proportionality. Based on the PK assessment, $AUC_{inf}$ was found to be dose proportional between 20 mg and 80 mg. However, the peak exposure was less than dose proportional when the 20 mg was compared to the 80 mg ER formulation (Mission).

***Reviewer Comment***

*When gepirone 20 mg ER compared to 80 mg ER, a dose proportional increase in total plasma exposure ($AUC_{inf}$) and less than dose proportional increase in peak plasma exposures ($C_{max}$) of gepirone were observed.*

Bioanalytical Methods

**Table 73. Method Validation Summary**

| Validation Test | Method AP21-025 Result |
|---|---|
| Analytical Methodology | Supported liquid-liquid extraction with LC-MS/MS detection on a QTRAP 5500 mass spectrometer. |
| Analytes | Gepirone, 3-Hydroxy Gepirone and 2-(1-Piperazinyl)pyrimidine |
| Internal Standards | Gepirone-d8, 3-Hydroxygepirone-d8 and 2-(1-Piperazinyl)pyrimidine-d8 |
| Biological Matrix | Human plasma (K2EDTA) |
| Regression Model | Gepirone: Quadratic, 1/x<br>3-Hydroxy Gepirone: Quadratic, 1/x<br>2-(1-Piperazinyl)pyrimidine: Quadratic, 1/x2 |
| Calibration Range | 20.00 to 20,000.00 pg/mL |
| Calibration Standard | Concentrations:<br>20.00, 40.00, 200.00, 500.00, 1000.00, 2400.00, 4000.00, 12,000.00, 18,000.00, and 20,000.00 pg/mL |
| Quality Control Sample Concentrations | Concentrations:<br>20.00, 60.00, 800.00, 10,000.00, 15,000.00, and 20,000.00 pg/mL |
| Dilution Integrity | DQC/2: 40,000.00 pg/mL with 10-fold dilution<br>DQC/10: 200,000.00 pg/mL with 10-fold dilution |
| Dilution Linearity | ULOQ/2 and ULOQ/10: 20,000.00 pg/mL with 10-fold dilution |
| Recovery | Gepirone: 81.6%<br>3-Hydroxy Gepirone: 79.2%<br>2-(1-Piperazinyl)pyrimidine: 71.2%<br>Gepirone-d8: 92.8%<br>3-Hydroxy Gepirone-d8: 93.7%<br>2-(1-Piperazinyl)pyrimidine-d8: 71.4% |
| System Robustness | Long batch containing 192 samples |
| Bench-Top Stability | 26 hours at 5°C ± 3°C (LQC, HQC, DQC) |
| Freeze-Thaw Stability | 3 F/T cycles, frozen at -70°C ± 10°C, thawed at 5°C ± 3°C (LQC, HQC, DQC) |
| Long-Term Stability in Matrix | 129 days at -70°C ± 10°C (LQC, HQC, DQC) |
| Autosampler Stability | 95 hours at 5°C ± 3°C (LQC, HQC) |
| Processed Sample Stability | 2 hours at room temperature followed by 94 hours at 5°C ± 3°C (LQC, HQC) |
| Whole Blood Stability | 2 hours at 5°C ± 3°C (LQC and HQC) |
| Analyte Stock Solution Stability | 6 hours at room temperature followed by 146 days at 5°C ± 3°C |
| Analyte Mixed Stock Solution Stability | 6 hours at room temperature followed by 139 days at 5°C ± 3°C |
| Spiking Solution Stability | 6 hours at room temperature followed by 139 days at 5°C ± 3°C |
| Internal Standard Stock Solution Stability | 6 hours at room temperature followed by 145 days at 5°C ± 3°C<br>(146 days at 5°C ± 3°C for 2-(1-Piperazinyl)pyrimidine) |
| Internal Standard Mixed Intermediate Solution Stability | 6 hours at room temperature followed by 145 days at 5°C ± 3°C |
| Other Experiments Performed | Stock accuracy and purity check, intra-and inter-assay precision and accuracy using freshly spiked calibration standards and QC samples in at least 3 runs, selectivity of blank matrix (including hemolyzed and lipemic), sensitivity at the LLOQ, OTC and OC specificity and quantitative interference check, carryover assessment, matrix effect and matrix factor and re-injection reproducibility. |

Source: Summary of Biopharmaceutics page 2

Method

Analytical method AP21-025 was developed and validated to determine the concentration of gepirone and its two major metabolites, 3-OH gepirone and 1-PP, in K2EDTA human plasma within the range of 20.00 to 20,000.00 pg/mL. Method AP21-025 was used to determine the pharmacokinetic parameters in clinical study FK-GBE-011, as well as bioequivalence of Exxua in clinical studies FK-GBE-012 (Study 2666) and FK-GBE-014 (Study 2667).

Results (Study 2666)

Gepirone

Inter-Assay Standard Precision (%CV): 1.3 to 6.2%

Inter-Assay Standard Accuracy (%Bias): -2.2 to 3.5%

r2≥0.9931

Inter-Assay QC Precision (%CV): 2.7 to 4.3%

Inter-Assay QC Accuracy (%Bias): 0.4 to 2.3%

Incurred Sample Reanalysis (ISR) was performed for gepirone using 278 subject samples. ISR showed 99.6% reproducibility for all calculable samples

3-OH-gepirone

Inter-Assay Standard Precision (%CV): 3.1 to 6.3%

Inter-Assay Standard Accuracy (%Bias): -0.9 to 1.6%

r2≥0.9935

Inter-Assay QC Precision (%CV): 4.1 to 5.1%

Inter-Assay QC Accuracy (%Bias): 0.5 to 3.4%

Incurred Sample Reanalysis (ISR) was performed for 3-Hydroxy gepirone using 278 subject samples. ISR showed 99.3% reproducibility for all calculable samples

2-(1-Piperazinyl) pyrimidine (1-PP)

Inter-Assay Standard Precision (%CV): 1.1 to 4.2%

Inter-Assay Standard Accuracy (%Bias): -6.5 to 5.4%

r2≥0.9963

Inter-Assay QC Precision (%CV): 1.8 to 3.9%

Inter-Assay QC Accuracy (%Bias): -9.0 to 8.6%

Incurred Sample Reanalysis (ISR) was performed for 2-(1- Piperazinyl) pyrimidine using 278 subject samples. ISR showed 99.6% reproducibility for all calculable samples

The results from calibration standards and quality control samples demonstrated acceptable performance of the method for all reported concentrations of gepirone, 3-Hydroxy gepirone and 2-(1-Piperazinyl) pyrimidine. The reviewer concurs.

***Reviewer Comment***

*The analytical method and its validation were reasonable and adequate. The analysis met the acceptance criteria. The analytical method and conditions were similar for Study 2667 and FK-GBE-011 and are acceptable.*

### 15.4.1. In Vitro Transporter Studies

**Study XT198036. Gepirone, 3-OH Metabolite or 1-PP: Transporter Inhibition and Substrate Potential**

Objective

The study was designed to evaluate gepirone, 3-OH metabolite or 1-PP metabolite as inhibitors and substrates of the human transporters P-gp, BCRP, BSEP< OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K

Methods and Results

Transporter inhibition was evaluated by measuring probe substrate transport in the presence and absence of the test article. Transporter substrate potential was evaluated by measuring test article transport in the presence and absence of transporter inhibitors.

**Table 74. Summary of Experimental Conditions**

| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as inhibitors** | | |
|---|---|---|
| Transporter | P-gp | BCRP |
| Test system | Caco-2 | MDCKII cells |
| Probe substrate | Digoxin (10 µM) | Prazosin (1 µM) |
| [Inhibitor (gepirone)] | 10 and 100 µM | 10 and 100 µM |
| [Inhibitor (3-OH metabolite)] | 5 µM | 5 µM |
| [Inhibitor (1-PP metabolite)] | 5 µM | 5 µM |
| Positive control inhibitor | Valspodar (1 µM) | Ko143 (1 µM) |
| Sampling time (min) | Donor: 0, 120<br>Receiver: 120 | Donor: 0, 120<br>Receiver: 120 |
| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as substrates** | | |
| Transporter | P-gp | BCRP |
| Test system | MDCKII cells | MDCKII cells |
| [Substrate (gepirone)] | 0.5 and 5 µM | 0.5 and 5 µM |
| [Substrate (3-OH metabolite)] | 5 µM | 5 µM |
| [Substrate (1-PP metabolite)] | 5 µM | 5 µM |
| Inhibitor | Valspodar (10 µM) | Ko143 (1 µM) |
| Positive control substrate | Digoxin (10 µM) | Prazosin (1 µM) |
| Test article sampling time (min) | Donor: 0, 120<br>Receiver: 15, 30, 120 | Donor: 0, 120<br>Receiver: 15, 30, 120 |
| Positive control substrate sampling time (min) | Donor: 0, 120<br>Receiver: 120 | Donor: 0, 120<br>Receiver: 120 |

Source: Study XT198036 page 23

**Table 75. Evaluation of Gepirone, 3-OH Metabolite or 1-PP Metabolites as Inhibitors and Substrates**

| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as inhibitors** | |
|---|---|
| Incubation medium | HEPES-Tris (10 mM), $KNO_3$ (100 mM), $Mg(NO_3)_2$ (10 mM) and sucrose (50 mM) |
| Wash buffer | HEPES-Tris (10 mM), $KNO_3$ (100 mM) and sucrose (50 mM) |
| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as substrates** | |
| Transporter | BSEP |
| [Substrate (gepirone)] | 0.5 and 5 µM |
| [Substrate (3-OH metabolite)] | 5 µM |
| [Substrate (1-PP metabolite)] | 5 µM |
| Inhibitor | Cyclosporine (20 µM) |
| Positive control substrate | [$^3$H]-Taurocholic acid (0.4 µM) |
| Test article incubation time (min) | 1 and 10 |
| Positive control incubation time (min) | 5 |
| Incubation medium | HEPES-Tris (10 mM), $KNO_3$ (100 mM), $Mg(NO_3)_2$ (10 mM) and sucrose (50 mM) |
| Wash buffer | HEPES-Tris (10 mM), $KNO_3$ (100 mM) and sucrose (50 mM) |

Source: Study XT198036 page 25

**Table 76. Evaluation of Gepirone, 3-OH Metabolite or 1-PP Metabolite as Inhibitors and Substrates**

| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as inhibitors** | | | | | |
|---|---|---|---|---|---|
| Transporter | OATP1B1/ OATP1B3 | OAT1 | OAT3 | OCT2 | MATE1/ MATE2-K |
| Probe substrate | [$^3$H]-Estradiol-17β-glucuronide (50 nM) | [$^3$H]-*p*-Aminohippurate (1 µM) | [$^3$H]-Estrone-3-sulfate (50 nM) | [$^{14}$C]-Metformin (10 µM) | [$^{14}$C]-Metformin (10 µM) |
| [Inhibitor (gepirone)] | 10 and 100 µM | 0.5 and 5 µM | 0.5 and 5 µM | 0.5 and 5 µM | 0.5 and 5 µM |
| [Inhibitor (3-OH metabolite)] | 5 µM | 5 µM | 5 µM | 5 µM | 5 µM |
| [Inhibitor (1-PP metabolite)] | 5 µM | 5 µM | 5 µM | 5 µM | 5 µM |
| Positive control inhibitor | Rifampin (10 µM) | Probenecid (100 µM) | Probenecid (100 µM) | Quinidine (300 µM) | Cimetidine (20 µM [a]; 300 µM [b]) |
| Incubation time (min) | 2 | 1 | 2 | 2 | 5 |
| **Evaluation of gepirone, 3-OH metabolite or 1-PP metabolite as substrates** | | | | | |
| Transporter | OATP1B1/ OATP1B3 | OAT1 | OAT3 | OCT2 | MATE1/ MATE2-K |
| [Substrate (gepirone)] | 0.5 and 5 µM | 0.5 and 5 µM | 0.5 and 5 µM | 0.5 and 5 µM | 0.5 and 5 µM |
| [Substrate (3-OH metabolite)] | 5 µM | 5 µM | 5 µM | 5 µM | 5 µM |
| [Substrate (1-PP metabolite)] | 5 µM | 5 µM | 5 µM | 5 µM | 5 µM |
| Inhibitor | Rifampin (10 µM) | Probenecid (100 µM) | Probenecid (100 µM) | Quinidine (300 µM) | Cimetidine (20 µM [a]; 300 µM [b]) |
| Positive control substrate | [$^3$H]-Estradiol-17β-glucuronide (50 nM) | [$^3$H]-*p*-Aminohippurate (1 µM) | [$^3$H]-Estrone-3-sulfate (50 nM) | [$^{14}$C]-Metformin (10 µM) | [$^{14}$C]-Metformin (10 µM) |
| Test article incubation time (min) | 1 and 10 | 1 and 10 | 1 and 10 | 1 and 10 | 1 and 10 |
| Positive control incubation time (min) | 2 | 1 | 2 | 2 | 5 |

a For MATE1
b For MATE2-K

Source: Study XT198036 page 26

Samples were analyzed by multiple reaction monitoring LC-MS/MS methods developed at the testing facility. The test article standard curves ranged from 0.3 to 20000 nM, each. The acceptable range for percent accuracy for calibration standards was 75 to 125%. Lactate dehydrogenase (LDH) leakage below 25% was considered evidence of negligible cytotoxicity. In all instances, less than 25% LDH was observed, establishing negligible cytotoxicity under the conditions used for the transporter assays.

Results

**Table 77. Inhibition**

| Transporter | Test system | Substrate | Experimental design | Test article (μM) | [Test article] (μM) | Maximum inhibition |
|---|---|---|---|---|---|---|
| P-gp | Caco-2 cells | Digoxin (10 μM) | Bidirectional permeability of substrate in cells | Gepirone | 10, 100 | 8.0% |
| | | | | 3-OH Metabolite | 5 | No inhibition |
| | | | | 1-PP Metabolite | 5 | No inhibition |
| BCRP | MDCKII cells | Prazosin (1 μM) | | Gepirone | 10, 100 | No inhibition |
| | | | | 3-OH Metabolite | 5 | 9.8% |
| | | | | 1-PP Metabolite | 5 | No inhibition |
| BSEP | Vesicles | [$^3$H]-Taurocholic acid (0.4 μM) | Accumulation of substrate in vesicles | Gepirone | 0.5, 5 | No inhibition |
| | | | | 3-OH Metabolite | 5 | No inhibition |
| | | | | 1-PP Metabolite | 5 | No inhibition |
| OATP1B1 | HEK293 cells | [$^3$H]-Estradiol-17β-glucuronide (50 nM) | Accumulation of substrate in cells | Gepirone | 10, 100 | 27.1% |
| | | | | 3-OH Metabolite | 5 | 26.8% |
| | | | | 1-PP Metabolite | 5 | 21.1% |
| OATP1B3 | | | | Gepirone | 10, 100 | 8.4% |
| | | | | 3-OH Metabolite | 5 | 35.4% |
| | | | | 1-PP Metabolite | 5 | 29.3% |
| OAT1 | | [$^3$H]-*p*-Aminohippurate (1 μM) | | Gepirone | 0.5, 5 | No inhibition |
| | | | | 3-OH Metabolite | 5 | 33.2% |
| | | | | 1-PP Metabolite | 5 | 54.0% |
| OAT3 | | [$^3$H]-Estrone-3-sulfate (50 nM) | | Gepirone | 0.5, 5 | 9.4% |
| | | | | 3-OH Metabolite | 5 | 37.7% |
| | | | | 1-PP Metabolite | 5 | 27.9% |
| OCT2 | | [$^{14}$C]-Metformin (10 μM) | | Gepirone | 0.5, 5 | 2.0% |
| | | | | 3-OH Metabolite | 5 | 0.2% |
| | | | | 1-PP Metabolite | 5 | 29.6% |
| MATE1 | | | | Gepirone | 0.5, 5 | 48.7% |
| | | | | 3-OH Metabolite | 5 | 34.9% |
| | | | | 1-PP Metabolite | 5 | 18.6% |
| MATE2-K | | | | Gepirone | 0.5, 5 | No inhibition |
| | | | | 3-OH Metabolite | 5 | No inhibition |
| | | | | 1-PP Metabolite | 5 | No inhibition |

Source: Study XT198036 page 16

A maximum of 27.1 and 48.7% inhibition of OATP1B1 and MATE1, respectively, was observed in the presence of up to 100 and 5 μM gepirone, respectively. Little to no inhibition of P-gp, BCRP, BSEP, OATP1B3, OAT1, OAT3, OCT2 or MATE2-K by gepirone was observed, under these experimental conditions.

A maximum of 26.8, 35.4, 33.2, 37.7 and 34.9% inhibition of OATP1B1, OATP1B3, OAT1, OAT3 and MATE1, respectively, was observed in the presence of up to 5 μM 3-OH metabolite. Little to no inhibition of P-gp, BCRP, BSEP, OCT2 or MATE2-K by 3-OH metabolite was observed, under these experimental conditions. A maximum of 21.1, 29.3, 54.0, 27.9, 29.6 and 18.6% inhibition of OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and MATE1, respectively, was observed in the presence of up to 5 μM 1-PP metabolite. Little to no inhibition of P-gp, BCRP, BSEP or MATE2-K

by 1-PP metabolite was observed, under these experimental conditions. Gepirone, 3-OH metabolite and 1-PP metabolite were not substrates for P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K under the conditions examined.

**Table 78. Substrate**

**Substrate**

| Transporter | Test system | Experimental design | Test article (µM) | [Test article] (µM) | Potential substrate [a] |
|---|---|---|---|---|---|
| P-gp | MDCKII cells | Bidirectional permeability of test article in cells | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| BCRP | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| BSEP | Vesicles | Accumulation of test article in vesicles | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| OATP1B1 | HEK293 cells | Accumulation of test article in cells | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| OATP1B3 | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| OAT1 | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| OAT3 | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| OCT2 | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| MATE1 | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |
| MATE2-K | | | Gepirone | 0.5, 5 | No |
| | | | 3-OH Metabolite | 5 | No |
| | | | 1-PP Metabolite | 5 | No |

a Uptake or efflux ratio ≥ 2 and reduced > 50% in presence of inhibitor

Source: Study XT198036 page 17

Conclusions

Gepirone and its metabolites were not substrates for any of the transporters tested. The uptake ratio of gepirone, 3-OH-gepirone and 1-PP in the transporter cells was less than 2 in the absence and presence of the transporter prototypical inhibitor.

Gepirone and its metabolites were not inhibitors of P-gp, BCRP, BSEP, OATP1B3, OAT1, OAT3, OCT2 or MATE2-K. A maximum of 27.1 and 48.7% inhibition of OATP1B1 and MATE1, respectively, was observed in the presence of up to 100 and 5 µM gepirone, respectively.

***Reviewer Comments***

*Based on the criteria established by the Sponsor, the studied gepirone and its metabolites appeared not to be substrate of the studied transporters. Little or no significant inhibition of the transporters studied was reported in these in vitro studies for gepirone and its metabolites. The in vitro inhibition of OATP1B1 and MATE1 by gepirone is not expected to be clinically meaningful.*

**Study XT193051. In Vitro Induction**

Title

Gepirone, 3-OH Metabolite and 1-PP Metabolite: P-gp Transporter Induction in Cultured Human Hepatocytes

Objective

The study was designed to evaluate the effect of gepirone (10 and 100 µM), 3-OH metabolite (5 µM) and 1-PP metabolite (5 µM) on the expression of P-gp transporter in three cultures of cryopreserved primary human hepatocytes. Transporter and enzyme expression were evaluated by mRNA expression determination.

Method

Individual cultures prepared in triplicate were treated once daily for three consecutive days with vehicle, gepirone, 3-OH metabolite, 1-PP metabolite, or the control compound. Approximately 24 h after the last treatment hepatocytes were lysed in Buffer RLT reagent containing β-mercaptoethanol (100:1), and cell lysates were stored at −80 ± 10 °C. The mechanistically distinct and clinically relevant control inducer rifampin (a PXR agonist and inducer of CYP3A4) was included as the positive control. Quantitative RT-PCR was performed in triplicate. A primer mix was prepared for each gene expression assay. The reaction mix was prepared by adding the primer mix to cDNA. No amplification control (NAC) samples were included. The change in mRNA expression in test samples relative to vehicle control samples was measured. This method assumes that the efficiency of the target amplification and the efficiency of the endogenous control amplification are approximately equal.

Results

Treatment with rifampin (1, 10 and 20 µM) resulted in 21.4- to 42.2-fold increase in CYP3A4 mRNA expression. There was little to no induction of P-gp transporter mRNA expression following treatment with 10 and 100 µM gepirone, 5 µM 3-OH metabolite, or 5 µM 1-PP metabolite with expression ranging from 0.777 to 1.47-fold. Treatment with rifampin (1, 10 and 20 µM) resulted in 2.08- to 3.50-fold increase in P-gp mRNA expression with one exception. Treatment of culture HC10-50 with 1 µM rifampin had little to no effect on P-gp mRNA expression (1.88-fold change).

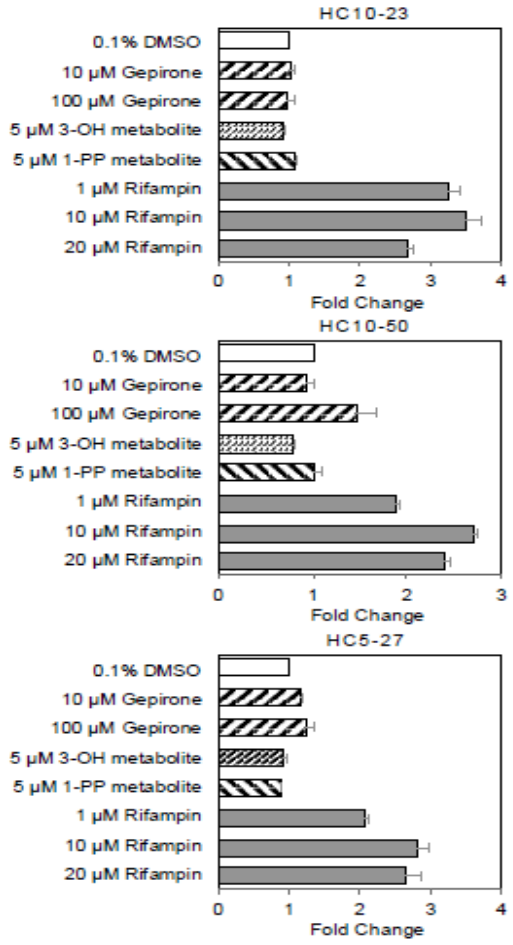
Conclusion

There was little to no induction of P-gp mRNA expression (< 2-fold change) following treatment with gepirone, 3-OH metabolite or 1-PP metabolite.

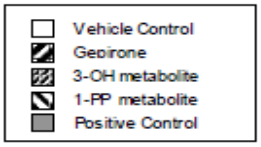
***Reviewer Comment***

*The Sponsor's conclusions appear reasonable.*

**Figure 29. Gepirone, 3-OH Metabolite and 1-PP Metabolite: P-gp mRNA Fold Change in Cultured Human Hepatocytes**




| Treatment | Fold change ± SD | n |
|---|---|---|
| 0.1% DMSO | 1.00 ± 0.00 | 3 |
| 10 µM Gepirone | 1.03 ± 0.06 | 3 |
| 100 µM Gepirone | 0.985 ± 0.107 | 3 |
| 5 µM 3-OH Metabolite | 0.903 ± 0.060 | 3 |
| 5 µM 1-PP Metabolite | 1.06 ± 0.11 | 3 |
| 1 µM Rifampin | 3.26 ± 0.16 | 3 |
| 10 µM Rifampin | 3.50 ± 0.22 | 3 |
| 20 µM Rifampin | 2.69 ± 0.06 | 3 |
| **Treatment** | **Fold change ± SD** | **n** |
| 0.1% DMSO | 1.00 ± 0.00 | 3 |
| 10 µM Gepirone | 0.939 ± 0.067 | 3 |
| 100 µM Gepirone | 1.47 ± 0.22 | 3 |
| 5 µM 3-OH Metabolite | 0.777 ± 0.036 | 3 |
| 5 µM 1-PP Metabolite | 1.02 ± 0.08 | 3 |
| 1 µM Rifampin | 1.88 ± 0.04 | 3 |
| 10 µM Rifampin | 2.70 ± 0.06 | 3 |
| 20 µM Rifampin | 2.39 ± 0.07 | 3 |
| **Treatment** | **Fold change ± SD** | **n** |
| 0.1% DMSO | 1.00 ± 0.00 | 3 |
| 10 µM Gepirone | 1.16 ± 0.02 | 3 |
| 100 µM Gepirone | 1.26 ± 0.11 | 3 |
| 5 µM 3-OH Metabolite | 0.912 ± 0.056 | 3 |
| 5 µM 1-PP Metabolite | 0.887 ± 0.005 | 3 |
| 1 µM Rifampin | 2.08 ± 0.04 | 3 |
| 10 µM Rifampin | 2.82 ± 0.16 | 3 |
| 20 µM Rifampin | 2.66 ± 0.20 | 3 |




n Number of replicates
SD Standard deviation
Fold change values are relative to vehicle control, normalized to GAPDH.

Source: Study XT193951 page 19

## 15.5. Additional Clinical Outcome Assessment Analyses

(b) (4)

See Section 8.3.5 for details.

DCOA notes that the Derogatis Interview for Sexual Functioning, Changes in Sexual Functioning Questionnaire, Derogatis Interview for Sexual Function – Self Report (DISF-SR), are considered patient reported outcome measures.

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/s/

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