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*APPLICATION NUMBER:*

**021164Orig1s000**

**CLINICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name Earl Hearst, M.D.  
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Established Name Gepirone  
(Proposed) Trade Name Travivo  
Therapeutic Class Antidepressant  
Applicant Faber-Kramer, INC.

Priority Designation S

Formulation ER Tablets  
Dosing Regimen 40-80mg/day  
Indication MDD  
Intended Population ADULTS

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# **1 EXECUTIVE SUMMARY**

## **1.1 Recommendation on Regulatory Action**

I believe approving this drug would expose patients taking Gepirone ER to potential delay and risk which could be avoided if started immediately on an approved antidepressant with clear evidence of efficacy. I recommend we issue a nonapproval letter for Gepirone ER based on lack of evidence of efficacy.

## **1.2 Recommendation on Postmarketing Actions**

I do not believe this drug should be marketed.

## **1.3 Summary of Clinical Findings**

### **1.3.1 Brief Overview of Clinical Program**

A total of 25 clinical studies were conducted with gepirone ER.

- 9 placebo-controlled studies (Studies 134001, FK-GBE-007, 134002, 134023, FK-GBE-008, 28709, CN105-057, CN105-078, and CN105-083).
- 6 placebo- and active-controlled studies (Studies 134004, 134006, 134017, CN105-052, CN105-053, and CN105-064).
- 4 active-controlled studies (Studies 28715, 28722, 28723, and C-1762).
- 1 uncontrolled study (Study CN105-055).
- 4 long-term extension studies (Studies 134501, 134502, 134503, and 134506).
- 1 study in other indications (Study CN105-071).

A total of 28 clinical studies were conducted with gepirone IR:

- 6 placebo-controlled studies (Studies 03A7A-003, 03A7C-001A-2486, 03A7C-001A-2496, 03A7A-002, 03A7C-001B, and CN105-043).
- 4 placebo- and active-controlled studies (Studies CN105-037, CN105-022, CN105-028, and CN105-029).
- 5 uncontrolled studies (Studies 030L1-0004, 03A7A-001, CN105-019, CN105-039, and CN105-050)
- 13 studies in other indications (Studies 030L1-0003, 03A7B-001, 03A7B-002,

03A7B-004, CN105-001, CN105-041, CN105-045, CN105-031, CN105-017, CN105-003, CN105-004, CN105-018, and CN105-036).

### **1.3.2 Efficacy**

The sponsor now has 2 positive efficacy studies in the ER formulation (Studies FK-GBE-007 and 134001). They have not been able to provide the positive relapse prevention study we asked for in our previous nonapproval letter. This is a very unusual finding in that the enriched population of a relapse study almost always produces a positive result. Their meta-analysis for all 12 Gepirone ER DB PC studies is not positive.

There are five studies described as lacking assay sensitivity. Study 134004 was pointed out in our 6/23/04 nonapproval letter as being nearly significant for the active control fluoxetine over gepirone.

Fanhui Kong's statistical review indicates that in three out of the five so called "lack of assay sensitivity" studies, active control significantly outperformed gepirone ER. Active control significantly outperformed placebo in 2 out of 5 studies.

The efficacy of Gepirone ER has not been established with confidence and this drug would seem to be an unlikely choice over other approved antidepressants.

### **1.3.3 Safety**

There is no significant change in the safety data conclusions from the previous submission.

### **1.3.4 Dosing Regimen and Administration**

The proposed target dose of Gepirone ER is 60 to 80 mg/day. The sponsor also proposed recommended starting dose of 20 mg once daily. If the 20-mg initial dose is adequately tolerated, an increase to 40 mg given once daily may be made as early as Day 4 of dosing. 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. Gepirone ER should be taken with food at approximately the same time each day. The tablets should not be broken, crushed, chewed, or dissolved. Higher doses were not studied.

### **1.3.5 Drug-Drug Interactions**

Seven interaction studies were done, which included the following drugs: ketoconazole, verapamil, paroxetine, rifampin, warfarin, lithium, and glibenclamide.

In summary, ketoconazole, verapamil, paroxetine, and nefazodone inhibit the metabolism of gepirone, while rifampin induces metabolism. Coadministration of gepirone with warfarin, lithium, and glibenclamide was not associated with any clinically relevant changes in the action of these drugs.

### 1.3.6 Special Populations

There have been no new studies in special populations.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Gepirone hydrochloride is a member of the azapirone class of compounds and is an analog of buspirone.

The qualitative and quantitative composition of the drug product remains the same as previously submitted. It is formulated as Extended-Release (ER) tablets containing 20, 40, 60 and 80 mg of Gepirone hydrochloride. The inactive ingredients remain the same: hydroxypropyl methyl cellulose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate and iron oxide (red and/or yellow as coloring agents). These excipients are all pharmacopoeial (USP/EP) ingredients.

The shape of the tablets to be marketed, modified flat, remains the same as previously submitted. The only modification to the final market image is (b) (4). Comparative dissolution data (with f1 and f2 comparisons) for all four (4) strengths in multimedia demonstrating equivalence between the previous Organon market images (biconvex and modified flat) vs. the new Fabre-Kramer Pharmaceuticals, Inc., market image is provided in this NDA Amendment.

There have been no changes to tablet composition, size or shape since NDA 21-164 Amendment submission dated December 23, 2003.

### 2.2 Currently Available Treatment for Indications

Many drugs are approved for MDD.

### 2.3 Presubmission Regulatory Activity

The original New Drug Application (NDA) submitted by Organon on September 30, 1999 was not filed by the Food and Drug Administration (FDA), which issued a refusal to file letter dated November 30, 1999. Organon resubmitted the NDA on May 18, 2001 and included 2 short-term studies with the ER formulation in subjects with MDD along with 3 efficacy studies using the IR formulation. The Agency issued a nonapprovable letter dated March 15, 2002 citing inadequate evidence of effectiveness. Organon amended the NDA on December 23, 2003 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 nonapprovable letter issued to Organon on June 23, 2004.

During the time that the Organon amendment was in preparation and under FDA review, Fabre-Kramer, with Organon's approval, sponsored 2 double-blind, multicenter, randomized, placebo-controlled studies involving a total of 456 subjects with MDD (Studies FK-GBE-007

and FK-GBE-008). In June 2005, all rights to develop and market gepirone were reacquired by Fabre-Kramer Pharmaceuticals.

On October 12, 2005, Fabre-Kramer met with FDA to discuss the resubmission of the NDA for gepirone ER. The Agency advised that they would likely file an application based on the results of 2 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.

On May 31, 2006, Fabre-Kramer held a teleconference with FDA to further refine plans for the submission of an amendment to NDA 21-164 for gepirone ER. It was agreed that most of the analyses of routine safety data would focus on 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 non-inferiority to placebo for gepirone and inferiority for active controls may be sufficient to support a claim of lack of sexual dysfunction with gepirone. It was also agreed that the analysis of suicidality would follow FDA's August 2, 2005 advice document for identification of possible suicide-related adverse events; in addition, the suicide item from HAMD would be analyzed. The efficacy analysis would focus on 12 adequately designed ER studies, and would include summary information from IR studies as well. The relapse prevention study (Study 28709) is also submitted again. FDA agreed that the NDA amendment would be limited to adult only data; pediatric data will be submitted at a later date.

## **2.4 Other Relevant Background Information**

Gepirone was originally developed by Mead Johnson and Bristol-Myers Company for the treatment of both anxiety and depression. The development of gepirone IR was discontinued in favor of the reformulated extended-release, once daily dosage form.

In 1992, a business decision by Bristol-Myers Squibb (BMS) led to termination of the gepirone development program, resulting in discontinuation of ongoing Phase III studies in MDD. 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.

In June 2005, all rights to develop and market gepirone were reacquired by Fabre-Kramer Pharmaceuticals.

Gepirone has not been approved in any foreign country.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC**

There has been no significant change since the 2003 submission.

### **3.2 Animal Pharmacology/Toxicology**

There has been no change since the 2003 submission except a new in-vitro chromosomal aberration study report was submitted.

## **4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY**

### **4.1 Sources of Clinical Data**

#### *Clinical Studies*

A total of 25 clinical studies were conducted with gepirone ER.

- 9 placebo-controlled studies (Studies 134001, FK-GBE-007, 134002, 134023, FK-GBE-008, 28709, CN105-057, CN105-078, and CN105-083).
- 6 placebo- and active-controlled studies (Studies 134004, 134006, 134017, CN105-052, CN105-053, and CN105-064).
- 4 active-controlled studies (Studies 28715, 28722, 28723, and C-1762).
- 1 uncontrolled study (Study CN105-055).
- 4 long-term extension studies (Studies 134501, 134502, 134503, and 134506).
- 1 study in other indications (Study CN105-071).

A total of 28 clinical studies were conducted with gepirone IR:

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- 4 placebo- and active-controlled studies (Studies CN105-037, CN105-022, CN105-028, and CN105-029).
- 5 uncontrolled studies (Studies 030L1-0004, 03A7A-001, CN105-019, CN105-039, and CN105-050).
- 13 studies in other indications (Studies 030L1-0003, 03A7B-001, 03A7B-002, 03A7B-004, CN105-001, CN105-041, CN105-045, CN105-031, CN105-017, CN105-003, CN105-004, CN105-018, and CN105-036).

## 4.2 Tables of Clinical Studies

There were a total of 87 gepirone studies. The complete list of these 87 studies extracted from sponsor's submission can be found in Appendix 10.3 table 1. The list of 13 studies in the second NDA amendment detailed by the sponsor is attached in Appendix 10.3 table.2.

Clinical studies conducted since the 2003 submission added approximately 2200 new subjects to the safety database, including 1000 subjects exposed to gepirone. Approximately 850 healthy subjects have received single or multiple doses of gepirone IR or ER in Phase I studies. In Phase II and III studies in adults, 1859 subjects have been treated with gepirone IR and 3117 subjects with gepirone ER. The sponsor's table attached in Appendix 10.3 table 3 provides an overview of the distribution of the subjects by phase of clinical development and treatment group, and shows the approximate number of subjects included in the 2003 ISS and the number of subjects included in this amendment.

All 20 gepirone ER studies categorized by design are extracted from sponsor's submission in Table I below. This includes the complete set of randomized, placebo-controlled, double-blind studies conducted with gepirone ER, studies that lacked a placebo control (but may have included an active comparator), the long-term extension studies, and a relapse prevention study.

Table I- Sponsor's All Gepirone ER Studies in Major Depressive Disorder

| Study Number                                              | Sponsor Classification | Comments           | Date submitted to NDA 21-164 |
|-----------------------------------------------------------|------------------------|--------------------|------------------------------|
| <b>Adequate and Well Controlled (15)</b>                  |                        |                    |                              |
| FKGBE007                                                  | Positive               |                    | Current Amendment            |
| 134001                                                    | Positive               |                    | December 2003 Amendment      |
| FKGBE008                                                  | Supportive             |                    | Current Amendment            |
| 134002                                                    | Supportive             |                    | December 2003 Amendment      |
| CN105-078                                                 | Supportive             |                    | December 2003 Amendment      |
| CN105-083                                                 | Supportive             |                    | December 2003 Amendment      |
| CN105-052                                                 | Failed                 |                    | December 2003 Amendment      |
| CN105-053                                                 | Failed                 |                    | December 2003 Amendment      |
| CN105-064                                                 | Failed                 | Low Dose           | December 2003 Amendment      |
| CN105-057                                                 | Negative               | Low Dose           | December 2003 Amendment      |
| 134004                                                    | Failed                 |                    | December 2003 Amendment      |
| 134006                                                    | Failed                 |                    | Current Amendment            |
| 134017                                                    | Failed                 |                    | Current Amendment            |
| 134023                                                    | Negative               |                    | Current Amendment            |
| 28709                                                     | Supportive             | Relapse Prevention | December 2003 Amendment      |
| <b>Active Controlled Studies (2)</b>                      |                        |                    |                              |
| 28715                                                     | ER                     |                    | December 2003 Amendment      |
| C-1762                                                    | ER                     |                    | Current Amendment            |
| <b>Open Label Trials with Active Medication Group (2)</b> |                        |                    |                              |
| 28722                                                     | ER                     |                    |                              |
| 28723                                                     | ER                     |                    |                              |
| <b>Uncontrolled Studies (1)</b>                           |                        |                    |                              |
| CN105-055                                                 | ER                     |                    | December 2003 Amendment      |

### 4.3 Review Strategy

This review will concentrate on the 2007 submission efficacy and safety data. Many sections of this review have not changed since the 2003 submission and I will refer the reader to Tarek Hammad's previous safety review and my previous reviews for sections which have not been updated.

#### **4.4 Data Quality and Integrity**

DSI has inspected 2 sites in study FKGBE007. Robert J. Bielski, M.D., Okemos, MI, site 701: and. Kenneth Weiss, M.D., Bala Cynwyd, PA, site 706. The data appeared to be acceptable in support of this NDA.

#### **4.5 Compliance with Good Clinical Practices**

The submitted studies were conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, U.S. Food and Drug Administration (FDA) principles of Good Clinical Practice (GCP), and International Conference on Harmonization (ICH) guidelines.

In compliance with United States (U.S.) federal regulations (21 CFR 56), the protocols, informed consent forms, subject recruitment procedures, and any other written information provided to the subject were reviewed and approved by an Institutional Review Board (IRB) prior to the screening or enrollment of any study participants.

#### **4.6 Financial Disclosures**

The sponsor reports that there are no financial disclosures to make for any of the investigators.

### **5 CLINICAL PHARMACOLOGY**

Two new studies have been submitted and are listed below.

Protocol 28725

A single dose, randomized, four-way cross-over study to assess the effect of food on the pharmacokinetics of Org 33062 and its main metabolites in healthy male volunteers

Protocol 28725

A single dose, randomized, four-way cross-over study to assess the effect of food on the pharmacokinetics of Org 33062 and its main metabolites in healthy male volunteers

Ron Kavanagh, PhD. from the Office of Clinical Pharmacology/Division of Clinical Pharmacology reviewed these 2 studies and found acceptable. He has provided labeling comments. He recommended the sponsor provides written agreement to a phase IV commitment to perform a drug-drug interaction study of the effect of an intermediate CYP 3A4 inducer such as rifabutin within 1 year of approval.”

### **6 INTEGRATED REVIEW OF EFFICACY**

#### **6.1 Indication**

The sponsor would like Gepirone ER to be indicated for the treatment of Major Depressive Disorder (MDD).

### 6.1.1 Methods

The sponsor has presented efficacy findings for the newly submitted studies. They have also provided a meta-analysis of their efficacy studies and have resubmitted the relapse study we previously reviewed and rejected. They now claim there were protocol violations in this relapse study and 40 patients should be thrown out of the analysis. I will present and comment on all of the sponsor's efficacy data and provide an overview of the efficacy results for gepirone.

### 6.1.2 Efficacy Findings

#### Efficacy

The efficacy of gepirone (IR and ER formulations) in the treatment of subjects with MDD was assessed in 35 clinical studies; in 15 of these studies, the IR formulation was used, and in 20 of these studies, the ER formulation was used.

According to the sponsor, fifteen of the 20 gepirone ER studies were adequate and well-controlled studies in that they were randomized, double-blind and placebo-controlled. Three of the 20 studies (Studies 28722, 28723, and CN105-055) were not adequate and well-controlled. Two other studies (28715 and C-1762) were not placebo-controlled. Two of the 15 adequate and well-controlled trials, Studies CN105-064 and CN105-057, studied inadequate doses of gepirone ER.

The 13 studies included in the ISE were categorized by the sponsor as follows:

- **Pivotal Studies:** Two positive adequate and well-controlled gepirone ER studies that showed superior efficacy of gepirone over placebo in treatment of MDD: Study 134001 that the FDA has deemed as positive in a prior review, and a new study (FK-GBE-007) that is being submitted in the current amendment.
- **Supportive Studies:** Five studies conducted with adequate (i.e.,  $\geq 40$  mg/day) doses and provide evidence supportive of the efficacy of gepirone ER. Four studies (Studies CN105-078, CN105-083, 134002, and FK-GBE-008) were classified as supportive because gepirone ER separated from placebo in a statistically significant manner on one or more key outcome measures at one or more time points. The fifth study (Study 134023) is described below as a negative study. Additionally, the sponsor would like us to reconsider the long-term relapse prevention study (Study 28709).
- **Failed Studies:** Five studies (Studies 134004, 134006, CN105-052, CN105-053, and 134017) included an active comparator arm that failed to separate statistically from placebo on the primary endpoint. These studies are classified as failed studies because there was no demonstration of assay sensitivity. I would like to call attention that study 134004 was pointed out in our 6/23/04 nonapproval letter as being nearly significant for the active control fluoxetine over gepirone.
- **Negative Study:** Study 134023 is classified as negative because it did not produce evidence of statistical superiority of gepirone ER relative to placebo on any of the efficacy measures.

In addition, there were 4 gepirone ER long-term extension studies (Studies 134501, 134502, 134503, and 134506); these were continuations of some of the acute-phase studies.

There were 15 gepirone IR studies. These studies are presented for completeness.

- 10 adequate and well-controlled studies (Studies CN105-043, CN105-037, CN105-022, CN105-029, CN105-028, 03A7A-003, 03A7A-001A-2496, 03A7C-001B, 03A7C-001A-2486, and 03A7A-002).
- 5 uncontrolled studies (Studies CN105-039, CN105-050, CN105-019, 03A7A-001, and 030L1-0004).

## **Pivotal Positive Studies**

### **Study 134001**

This study (previously reviewed) was a trial with a flexible dose design (20-80 mg/day of gepirone ER with a starting dose of 20 mg/day; there was a mandatory dose increase from 20 mg to 40 mg daily on treatment Day 4 to 7; with an allowed weekly increases by 20 mg/day up to 80 mg/day). There were 102 subjects treated with gepirone ER and 106 treated with placebo. The primary analysis of change in HAMD-17 total score based on the ITT set and on the last-observation-carried-forward (LOCF) approach showed statistically significant difference in favor of gepirone ER of more than two points vs. placebo. The results were consistent across centers; no significant treatment-by-center interaction was detected. The primary result was supported by the result of the majority of the secondary endpoints.

As pivotal evidence of efficacy a new study (FK-GBE-007) is being submitted in the current amendment.

### **Study FK-GBE-007**

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study in which 248 moderately to severely depressed outpatients received Org 33062 ER tablets (doses ranged from 20 to 80 mg) or placebo tablets once each morning with food for 8 weeks (56 days).

All subjects participated in a placebo washout screening period during which subjects received 1 placebo tablet/day for 4 to 7 days. Subjects were titrated to study medication as follows: 1 Org 33062 ER 20 mg tablet or 1 placebo tablet on Days 1-3 and 2 Org 33062 ER 20 mg tablets or 2 placebo tablets on Days 4-7. Thereafter, the doses on the preferred dosing schedule were 40 to 60 mg Org 33062 ER or placebo qd (2-3 tablets) on Days 8-14 and 40 to 80 mg Org 33062 ER or placebo qd (2-4 tablets) on Days 15-56.

If a phone call to the subject on Day 3 revealed significant tolerability issues during Days 1-3, titration to 40 mg could be delayed until Day 8. On the alternate dosing schedule, the doses were 40 mg Org 33062 ER or placebo qd (2 tablets) on Days 8-14, 40 to 60 mg Org 33062 ER or placebo qd (2-3 tablets) on Days 15-21, and 40 to 80 mg Org 33062 ER or placebo qd (2-4 tablets) on Days 22-56. The minimum acceptable dose of Org 33062 ER was 40 mg qd

(2 tablets) after Day 3 on the preferred dosing schedule and 40 mg qd after Day 7 on the alternate dosing schedule.

At the conclusion of the study, subjects returned to the clinic for a follow-up assessment 7 days after the last dose of study medication, and were contacted 30 days after the last dose solely to determine if any SAEs had occurred since the final treatment.

The mean dose of gepirone ER was 58.2 mg/day. The results of this study showed statistically significant differences in favor of gepirone ER across virtually all of the efficacy parameters, including the primary efficacy parameter: HAMD-17 total score change from baseline LOCF, and the secondary parameters: CGI responders, HAMD-17 responders, HAMD-17 remitters, MADRS, total score change from baseline in the HAMD-21, HAMD-25, HAMD-28, and the HAMD item 1 (depressed mood).

More study details are included in the appendix 10.1 of my review and in Fanhui Kong's statistical review which I will not duplicate in this section.

With respect to the primary efficacy parameter in the ITT/LOCF population, a statistically significant difference between gepirone ER and placebo treatment groups was noted for the change from baseline HAMD-17 total score at Weeks 4 (Visit 4), 6 (Visit 5) and 8 (Visit 6). Also an insignificant difference between gepirone ER and placebo was found at Week 3 (Visit 3) ( $p=0.081$ ). Results based on the ITT/OC analysis were consistent with these findings.

The SAP for this ISE describes that individual study data were reanalyzed utilizing an analysis of covariance (ANCOVA) model which included terms for treatment, center and baseline HAMD-17 score. Baseline HAMD-17 score was not included in the original model for analyses planned for the Clinical Study Report but was included in analyses which were further undertaken to explore the treatment-by-center interaction.

The sponsor's results indicate that for Study FK-GBE-007, center 701 and center 706 were statistically significant alone ( $p=0.005$  and  $p=0.044$ , respectively). Five of the eight centers show that subjects treated with gepirone ER improved compared to placebo, except center 999 (pooled centers 703 and 707 due to the fact that each of these centers randomized less than 16 subjects), center 704, and center 705. Overall, the results are statistically significant ( $p=0.018$ ).

Both Fanhui Kong, Ph.D. and I consider this study positive. Please see his statistical review for a more detailed analysis.

### **Studies Lacking Assay Sensitivity**

There are five studies described by the sponsor as lacking assay sensitivity. These trials, 134004, 134006, 134017, CN105-052 and CN105-053, evaluated the efficacy of gepirone ER employing placebo and active comparator controls. In all of these clinical trials, the sponsor indicates that both gepirone ER and the active comparator failed to separate from placebo. Study 134004 was pointed out in our 6/23/04 nonapproval letter as being nearly significant for the active control fluoxetine over gepirone. In three of the remaining failed trials the active comparator showed more numerical improvement than gepirone and in the fourth trial they were equal. I have listed the primary efficacy variable for each of the other trials below.

134006 - The endpoint change from baseline of the HAMD-25 total score was 11.3 for the Org 33062 ER group, 12.6 for the paroxetine group, and 11.3 for the placebo group.

134017 - The endpoint change from baseline of the MADRAS total score was -12.23 for the Org 33062 ER group, -13.88 for the fluoxetine group, and -12.73 for the placebo group.

CN105-053 - The endpoint change from baseline of the HAMD-17 total score was -9.7 for the Org 33062 ER group, 11.00 for the imipramine group, and -9.00 for the placebo group. Imipramine had an endpoint p=.146 and Org 33062 ER had an endpoint p=.687.

CN105-052 - The endpoint change from baseline of the HAMD-17 total score was -11.00 for the Org 33062 ER group, -11.00 for the fluoxetine group, and 10.50 for the placebo group.

Dosing table for above studies can be seen in table II below.

Table II:

| TRIAL      | Proposed dose | Mean Dose   |
|------------|---------------|-------------|
| 134004     | 20-80mg/day   | 67.1 mg/day |
| 13406      | 20-80mg/day   | 55.3 mg/day |
| 134017     | 40-80mg/day   | 58.7 mg/day |
| CN 105-053 | 10-60mg/day   | 50.4 mg/day |
| CN105-052  | 10-40 mg/day  | 43.4 mg/day |

Fanhui Kong indicates in his stat review the following.

“Alternatively as explorative analyses, the reviewer reanalyzed the efficacy data sets by keeping all the subjects in the statistical model using the ANCOVA model with the baseline measure as covariate, center and treatment indicator as factors. The results are reported in Table 3.9. According to these results, perhaps only Study CN105-052 can be properly called “lack of assay sensitivity” at the nominal significance level of 0.05 based on the reduction of the HAMD-17 total score in which the active comparator arm failed to show superiority over placebo. In Studies CN105-053 and 134006, the active control was statistically significantly better than placebo in the change from baseline of the HAMD-17 total score. In all of the five studies, the active control showed more improvement than placebo, numerically. The improvement of the active control over gepirone ER in Studies 134004, 134006 and 134017 appeared to be statistically significant. In these three studies, the placebo appeared to be numerically better than gepirone ER, even though they were not statistically significant. In these studies and Study CN105-053, the numerical improvement of the active control over gepirone ER was all above 1.2 and was consistent with the rest of five studies.”

Although Fanhui Kong used the HAMD-17 in his review I believe that the studies mentioned above should be considered negative studies with the exception on CN105-52. The HAMD-17 is a reasonable scale to use and was used by the sponsor in their meta-analyses.

### Active Controlled Studies

The comparator beat gepirone numerically in both active controlled studies.

## Study C-1762

At endpoint of the acute phase, the improvement (based on changes from baseline in HAMD-25 total score) was 12.95 and 13.88, for Org 33062 and fluoxetine, respectively, and at endpoint of the extension phase 16.83 and 18.84, for Org 33062 and fluoxetine, respectively.

## Study 28715

The mean change from baseline on the HAMD-17 total score at the end of the acute treatment period was -12.5 for the Org 33062 group and -13.3 for the paroxetine group. During the extension period, a further decrease in HAMD-17 total score was found, resulting in a mean change from baseline of -18.7 for the Org 33062 group and -19.1 for the paroxetine group at the end of the extension period.

The studies presented above do not support the efficacy of gepirone.

## META-ANALYSIS

Table III presents results of the sponsor's meta-analysis for the primary efficacy parameter, HAMD-17 change from baseline to the end of the short-term, double-blind treatment period.

In separate analyses for each of the two pivotal studies (Studies 134001 and FK-GBE-007), the treatment differences between gepirone ER and placebo for the adjusted mean change in HAMD-17 from baseline to the end of the short-term, double-blind treatment period were statistically significant in favor of gepirone ER ( $p=0.013$  and  $0.018$ , respectively). The treatment differences were not statistically significant in the five supportive studies ( $p \geq 0.195$ ) or in the five studies lacking assay sensitivity ( $p \geq 0.167$ ) when analyzed on a per study basis.

When the two pivotal and five supportive studies were combined, the treatment difference between gepirone ER and placebo for the adjusted mean change in HAMD-17 total score from baseline to the end of the short-term double-blind treatment period was -1.22; this difference was statistically significant in favor of gepirone ER ( $p=0.002$ ). The treatment difference for the five supportive studies combined was not statistically significant ( $p=0.149$ ), and the treatment difference for all 12 studies combined was not statistically significant, although there was an apparent trend towards significance ( $p=0.093$ ).

I do not feel the meta-analyses add support for the efficacy of Gepirone. Not only are the 12 studies combined not statistically significant but the overall treatment effect for these studies is minimal to the point of clinical insignificance.

Sponsor Table III Sponsor's Analysis of Change in HAMD-17 from Baseline to End of Short-Term Double-Blind Treatment Period in Pivotal and Supportive Studies and Studies Lacking Assay Sensitivity (12 Studies)

| Study (1)                                                             | Number of subjects (N) (Adjusted) mean change |    |            |          | Treatment difference and 95% CI |         | SE                         | p-value     |                         |
|-----------------------------------------------------------------------|-----------------------------------------------|----|------------|----------|---------------------------------|---------|----------------------------|-------------|-------------------------|
|                                                                       | Gepirone                                      | ER | Placebo    | Gepirone | ER                              | Placebo |                            |             | (Gepirone ER - Placebo) |
| <b>Pivotal Studies</b>                                                |                                               |    |            |          |                                 |         |                            |             |                         |
| ORG 134001                                                            | 101                                           |    | 101        | -9.04    |                                 | -6.57   | -2.47 (-4.41, -0.53)       | 0.98        | 0.013                   |
| FKGBE007                                                              | 116                                           |    | 122        | -10.24   |                                 | -7.79   | -2.45 (-4.47, -0.43)       | 1.02        | 0.018                   |
| <b>Supportive Studies</b>                                             |                                               |    |            |          |                                 |         |                            |             |                         |
| ORG 134023 (2)                                                        | 123                                           |    | 123        | -7.93    |                                 | -8.05   | 0.13 (-1.79, 2.04)         | 0.97        | 0.898                   |
| FKGBE008                                                              | 96                                            |    | 99         | -9.86    |                                 | -8.48   | -1.38 (-3.48, 0.71)        | 1.06        | 0.195                   |
| ORG 134002                                                            | 102                                           |    | 103        | -9.95    |                                 | -9.24   | -0.71 (-2.44, 1.02)        | 0.88        | 0.417                   |
| CN105-078                                                             | 88                                            |    | 47         | -7.42    |                                 | -6.42   | -1.00 (-3.17, 1.16)        | 1.10        | 0.362                   |
| CN105-083                                                             | 73                                            |    | 39         | -9.46    |                                 | -8.97   | -0.49 (-3.52, 2.53)        | 1.53        | 0.747                   |
| <b>Studies Lacking AS</b>                                             |                                               |    |            |          |                                 |         |                            |             |                         |
| ORG 134017                                                            | 159                                           |    | 159        | -10.36   |                                 | -10.99  | 0.63 (-0.88, 2.13)         | 0.76        | 0.412                   |
| ORG 134004                                                            | 124                                           |    | 130        | -5.63    |                                 | -6.66   | 1.03 (-0.55, 2.61)         | 0.80        | 0.199                   |
| CN105-052                                                             | 35                                            |    | 37         | -10.94   |                                 | -10.28  | -0.66 (-4.86, 3.55)        | 2.11        | 0.757                   |
| ORG 134006                                                            | 140                                           |    | 143        | -6.89    |                                 | -7.13   | 0.24 (-1.18, 1.66)         | 0.72        | 0.742                   |
| CN105-053                                                             | 56                                            |    | 56         | -10.20   |                                 | -8.15   | -2.05 (-4.96, 0.87)        | 1.47        | 0.167                   |
| <b>Meta-analyses (3)</b>                                              |                                               |    |            |          |                                 |         |                            |             |                         |
| Supportive/Pivotal Studies Combined<br>Treatment by study interaction | 699                                           |    | 634        |          |                                 |         | -1.22 (-1.99, -0.45)       | 0.39        | 0.002<br>0.470          |
| <b>Supportive Studies Combined</b><br>Treatment by study interaction  | <b>482</b>                                    |    | <b>411</b> |          |                                 |         | <b>-0.68 (-1.60, 0.24)</b> | <b>0.47</b> | <b>0.149</b><br>0.874   |
| All 12 Studies Combined<br>Treatment by study interaction             | 1213                                          |    | 1159       |          |                                 |         | -0.48 (-1.03, 0.08)        | 0.28        | 0.093<br>0.108          |

- (1) Individual study statistics obtained using ANCOVA model with terms for treatment and center and baseline value (as a covariate).  
(2) Considered a negative study, but included with supportive studies for the purpose of meta-analysis.  
(3) Combined estimates of the gepirone-placebo difference obtained as weighted averages of the gepirone-placebo differences with reciprocals of the squares of the standard errors of the by-study differences used as the weights. The standard errors of the overall estimates are the reciprocals of the square roots of the sums of the weights.

Fanhui Kong concludes in his statistical review as follows.

“None of these analyses seems to give additional support for the effectiveness of gepirone ER over placebo in the treatment of MDD. So it seems that in a total of 12 short-term efficacy studies, only studies FKGBE007 and 134001 provide support for the efficacy of gepirone ER in the treatment of MDD. In addition, given that these are *post hoc* analyses, the multiplicity issue could be a concern if one only compares the p-values with the regular nominal significance level of 0.05. That means the adjusted pvalue could be even larger than what they are observed here.”

Please see further discussion on the meta-analyses in Fanhui Kong’s review.

## LONG-TERM EFFICACY

### Study 28709

I will present the sponsor’s revised analysis for Study 28709 which we have rejected before. In this analysis they have excluded 40 protocol violators in their 3<sup>rd</sup> version of who belongs in the study analysis.

### Original Results

In the original sponsor-conducted analysis (see September 2003 study report), a total of 303 subjects completed the open-label phase but only 250 subjects were randomized to receive double-blind treatment in the double-blind continuation period (126 gepirone ER and 124 placebo; see Table IV extracted from sponsor’s submission).

Table IV Disposition of Subjects, Original Analysis, Study 28709

| <b>Disposition</b>                      |                    |                |                |
|-----------------------------------------|--------------------|----------------|----------------|
| Screened                                | 435                |                |                |
| <b>Open-Label Phase</b>                 | <b>Gepirone ER</b> |                |                |
| Selected to participate                 | 428                |                |                |
| Treated with gepirone ER                | 420                |                |                |
| Discontinued prematurely                | 117                |                |                |
| Completed                               | 303                |                |                |
| In remission at the end of the OL phase | 250                |                |                |
| <b>Double-Blind Continuation Phase</b>  | <b>Gepirone ER</b> | <b>Placebo</b> | <b>Overall</b> |
| Randomized                              | 126                | 124            | 250            |
| Treated with double-blind study drug    | 126                | 124            | 250            |
| Discontinued prematurely                | 55                 | 54             | 109            |
| Completed                               | 71                 | 70             | 141            |

ER = extended-release, OL = open-label.

The results of the original analysis were 29/126 (23.0%) relapses in the gepirone ER group compared with 43/124 (34.7%) relapses in the placebo group (p=0.024).

The FDA letter of June 23, 2004 noted that five gepirone ER-treated subjects who appeared to meet relapse criteria were not included in the analysis, and that 32 subjects were excluded from the CMH analysis because they were enrolled at centers that had subjects in only one treatment group or had no relapsers. Appropriately considering these factors, the gepirone ER group in the double-blind continuation phase had a relapse rate of 27.0% compared with a rate of 34.7% for the placebo-treated group. The difference between the treatment groups was not statistically significant (p=0.10124).

### **Per Protocol Population**

This study is being included in the present application in support of short-term antidepressant efficacy and as evidence of maintenance of response having conducted an analysis based on a per protocol subject population. This modification of the original ITT population (n=250) was due to exclusion of 40 subjects, considered protocol violators, who had not met randomization criteria, yet had been included in the original ITT analysis, or who were major protocol violators during the continuation phase. The per protocol (PP) population consists of 210 subjects.

The protocol allowed a PP analysis if the difference between the ITT population and the PP population for the gepirone ER-treated subjects was greater than 15%. Considering 40 subjects to be protocol violators, there is a 17.5% difference. For the PP analysis, all subjects were included, including the 32 excluded previously from the original CMH analysis. In the PP analysis population, 13 subjects (9 gepirone ER and 4 placebo) identified as major protocol violators were excluded. Additionally, 13 gepirone ER-treated and 14 placebo-treated subjects who were not randomized in the 8-12-week window and who were protocol violators for that reason were excluded.

Specific details regarding the major protocol violators excluded from the PP analysis, other than for improper randomization, are listed in appendix 10.3.1 table 11.

The treatment groups were compared by means of the log-rank test for PP analysis dataset. In the PP analysis, gepirone ER separation from placebo occurs at approximately Day 110, with sustained antidepressant efficacy for the remainder of the treatment period. Gepirone ER achieved statistical significance relative to placebo in terms of time to relapse (p=0.032).

I do not feel that this study revision is acceptable and do not consider the relapse study to be positive. Section 7.1.2 of the protocol indicates that all protocol violations are to be determined prior to breaking the blind and this was not done. Fanhui Kong, Ph. D. agrees that the study is not supportive. Please see his statistical review.

## IR PROGRAM

I will mention that the IR program included 10 DB PC trials. They are CN105-043, CN105-037, CN105-022, CN105-029, CN105-028, 03A7A-003, 03A7C-001A-2496, 03A7C-001B, 03A7C-001A-2486, and 03A7A-002.

In our 6/23/04 nonapproval letter we indicated that only study 03A7A-003 was considered positive in the IR studies.

### 6.1.6 Efficacy Conclusions

The sponsor now has 2 positive efficacy studies in the ER formulation (Studies FK-GBE-007 and 134001). There are many failed and negative studies and in 3 the active comparator beats Geperione. In two of these trials the active comparator beats placebo. They have not been able to provide the positive relapse prevention study we asked for in our previous nonapproval letter. This is a very unusual finding in that the enriched population of a relapse study is almost always positive. Their meta-analysis for all 12 Gepirone ER DB PC studies is not positive.

The statistical review by Fanhui Kong concludes as follows:

**“The fact that only two out of a total of 12 short-term efficacy studies are positive in support of the effectiveness of gepirone ER during a period of 12 years raises concerns on the reproducibility of the treatment effect observed. “**

I feel the efficacy of Gepirone ER has not been established with confidence and this drug would seem to be an unlikely choice over other approved antidepressants.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

Safety was reviewed in detail by Tarek Hammad, MD, PhD in his 2/26/2002 review. I did a safety update in my 4/30/2004 review. In this review I will again present a safety update and provide safety summaries for selected sections.

Safety data were collected in all clinical studies of gepirone.

This application includes safety data from 87 studies, including 8858 subjects and 1030 healthy subjects (including 13 subjects with liver impairment and 28 subjects with renal impairment who participated in pharmacokinetic studies) who received gepirone, placebo, or other comparative agent. The cumulative experience with gepirone is 1288.01 subject years. In all Phase II/III studies, the population of 4976 subjects exposed to gepirone consists of approximately 63% females and 37% males, of 95% <65 years of age, and 5% ≥65 years of age, and of approximately 83% Caucasians, 8% Black, and 8% Other race.

As documented in the October 2005 and May 2006 pre NDA meeting minutes, the gepirone ER formulation is the focus for the AE tables and typical safety profile. All populations and analyses are based on the gepirone ER studies, with the exception of the following analyses which include both gepirone IR and ER studies:

- Demographics
- Disposition;
- Extent of exposure;
- Clinically significant liver function tests;
- QTc events of special interest (QTc intervals  $\geq 500$  msec or increases  $>60$  msec);
- Possibly suicide-related AEs (PSRAEs);
- Adverse events leading to discontinuation; and
- Serious AEs (SAEs).

In addition, selected AE summaries for Phase II/III studies and placebo-controlled Phase II/III studies in depression include both gepirone IR and ER studies.

Subject numbers in the ISS consist of 3 parts separated by hyphens. The first part is the protocol identifier; the second part is the site identifier; the third part is the subject identifier. In the 2003 ISS, the protocol and subject identifiers were 3 digits in length; the site identifier was 4 digits. In the new studies added to the ISS, the protocol identifier is the full length protocol number with non-alphanumeric characters removed. The site identifier remained 4 characters. The subject identifier was expanded to 6 characters to accommodate the length of subject numbers in some of the new studies. Subject numbers for Study 134501, which was incomplete but included in the 2003 ISS, use the 2003-ISS format. A listing of the ISS subject number along with the study-specific subject numbers has been provided.

### 7.1.1 Deaths

There were no deaths in Phase I studies. There were 9 deaths in subjects who participated in Phase II/III studies; 8 were treatment-emergent and 1 (Study 134004, Subject (b) (6)) occurred during a placebo wash-out period prior to randomization. Three of the deaths occurred during acute exposure to the study medications (ISS Subject (b) (6) [gepirone ER]; ISS Subject (b) (6) [paroxetine]; and ISS Subject (b) (6) [placebo]); 3 occurred during long-term exposure to study medication (ISS Subject (b) (6) [gepirone ER]; ISS Subject (b) (6) [gepirone ER]; and ISS Subject (b) (6) [fluoxetine subject]); and 2 occurred more than 30 days after the subject's final dose of study medication (ISS Subject (b) (6) [gepirone IR] and ISS Subject (b) (6) [gepirone ER]). See table V below.

## Sponsor's Table V Deaths During the Gepirone Development Program

| ISS Subject ID<br>(Study, Subject ID) | Study Drug  | Cause of Death         |
|---------------------------------------|-------------|------------------------|
| (b) (6)<br>(03A7A-002, (b) (6))       | Gepirone IR | Aortic dissection      |
| (b) (6)<br>(134501, (b) (6))          | Gepirone ER | Suicide                |
| (b) (6)<br>(28715, (b) (6))           | Paroxetine  | Heart arrest           |
| (b) (6)<br>(28715, (b) (6))           | Gepirone ER | Pulmonary embolus      |
| (b) (6)<br>(28715, (b) (6) 1)         | Gepirone ER | Coronary heart disease |
| (b) (6)<br>(C-1762, (b) (6))          | Gepirone ER | Suicide                |
| (b) (6)<br>(CN105-052, (b) (6))       | Fluoxetine  | Metastatic cancer      |
| (b) (6)<br>(CN105-031, (b) (6))       | Placebo     | Myocardial infarction  |
| (b) (6)<br>( (b) (6) )                | Placebo     | Suicide                |

\* Death occurred during a placebo wash-out period prior to randomization.

### Deaths with Gepirone ER

There were 4 deaths in subjects who were treated with gepirone ER in Phase II/III studies. These have been reviewed previously. I will highlight two of interest.

- ISS Subject (b) (6) (Study 134501, Subject (b) (6)) a 45-year old Caucasian male, who received gepirone ER and who had a history of multiple suicide attempts, committed suicide by hanging after 20 days' exposure to gepirone ER. This subject was a "category 2" subject; i.e., a direct entry into the extension study 134501, and had not been previously exposed to gepirone. He was also receiving diazepam as a concomitant medication. This death was judged to be unrelated to treatment with gepirone ER by both the investigator and the sponsor.
- ISS Subject (b) (6) (Study C-1762, Subject (b) (6)), a 50-year-old Caucasian male, who received gepirone ER and who had a history of suicide attempt died from a cardiorespiratory arrest after taking an overdose of alcohol and antidepressants (mirtazapine and maprotiline) after 184 days exposure to gepirone ER. He was also receiving atenolol (for hypertension), clonazepam (for anxiety), and vasten (for hypercholesteremia) as concomitant medication. This death was determined to be unrelated to study treatment by the investigator and unlikely related by the sponsor.

### Summary

There were 8 treatment-emergent deaths (4 gepirone ER subjects, 1 gepirone IR subject, 1 paroxetine subject, 1 fluoxetine subject, and 1 placebo subject). One additional subject

died during a placebo wash-out period prior to randomization. I have reviewed the narratives for the deaths. No new safety concerns are noted.

### **7.1.2 Other Serious Adverse Events**

The sponsor has updated the number (%) of subjects with SAE table for the increased database. There are no significant changes from prior submission.

There were no SAEs in gepirone ER and IR Phase I studies.

Across the 3 groups of Phase II/III studies, the incidence of SAEs in the gepirone ER+IR combined (2.1%-2.5%) group was consistently higher than the incidence in the placebo (0.9%-1.2%) and imipramine (0.8%) groups, and consistently lower than the incidence in the fluoxetine (3.1%-3.3%) and paroxetine (5.1%) groups. The most commonly reported SAEs in gepirone ER+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%).

I have reviewed the narratives for the SAEs. No new safety concerns are noted. Please see appendix 10.3 table 4.

### **7.1.3 Drop-outs and Other Significant Adverse Events**

The Drop-out table has been updated for the increased database. There are no significant changes.

The percentages of subjects with any AE leading to premature withdrawal were 23.8% (57/240) in the imipramine group, 18.1% (90/4976) in the gepirone ER+IR combined group (ER: 509/3117, 16.3%; IR: 392/1859, 21.1%), 11.6% (32/276) in the paroxetine group, 9.3% (65/700) in the fluoxetine group, and 6.8% (168/2483) in the placebo group.

The most frequent AEs ( $\geq 1\%$ ) leading to premature withdrawal in subjects receiving gepirone (ER+IR combined group) were dizziness (4.3%), nausea (3.7%), headache (2.5%), insomnia (1.4%), and anxiety (1.2%). Dizziness, nausea, headache, insomnia, and anxiety were reported for 3.0%, 2.6%, 1.3%, 1.1%, and 1.2% of gepirone ER subjects, and 0.5%, 0.8%, 1.0%, 0.6%, and 0.4% of placebo subjects, respectively.

I have reviewed the narratives for these drop-outs. No new safety concerns noted.

Please see appendix 10.3 tables 5 and 6.

#### **7.1.3.1 Adverse events associated with dropouts**

The drop-out data has been updated for the increased database. There are no significant changes.

In Phase II/III studies, controlled Phase II/III studies, and controlled Phase II/III the incidence of AEs leading to discontinuation in the gepirone groups were consistently higher than the incidence in the placebo (6.8%, 7.0%, and 6.4%, respectively), fluoxetine (9.3%, 9.6%, and 9.6%, respectively), and paroxetine (11.6%, 11.6%, and 11.6%, respectively) groups, and consistently lower than the incidence in the imipramine group (23.8%, 23.8%, and 23.8%, respectively).

The most commonly reported AEs leading to discontinuation in gepirone subjects (ER+IR combined group) were dizziness (approximately 4% to 5%), nausea (approximately 4%), headache (approximately 2% to 3%), insomnia (approximately 1%), and anxiety (approximately 1%). The most commonly reported AEs leading to discontinuation in gepirone ER subjects were dizziness (approximately 3%), nausea (approximately 3%), and headache, insomnia, and anxiety (each approximately 1%). The incidences were generally comparable to the active controls (fluoxetine: 0.3%, 0.7%, 0.9%, 0.3%, and 0.7%, respectively; paroxetine: 0.4%, 1.4%, 0%, 0.7%, and 0%, respectively; imipramine: 2.9%, 2.5%, 3.8%, 0.4%, and 0%, respectively).

Please see appendix 10.3 table 7.

#### **7.1.3.3 Other significant adverse events**

In placebo-controlled clinical trials in patients with MDD, there were no seizures reported in 1639 patients treated with gepirone ER and 1752 patients treated with placebo.

In 8-week controlled trials, the percentage of subjects with clinically significant weight gain (defined as  $\geq 7\%$  of baseline body weight) was greater for patients treated with gepirone ER (4%-6%) compared with placebo-treated patients (3%). The mean increase in body weight from baseline in patients treated with gepirone was small (0.52 kg) relative to placebo (0.06-0.07 kg).

#### **7.1.4 Other Search Strategies**

During the extension phase, 2088 subjects were exposed to gepirone (1571 gepirone ER and 517 gepirone IR). In long-term studies, 905 subjects were treated with gepirone for over 6 months (692 gepirone ER and 213 gepirone IR) and 261 subjects were treated for over 1 year (170 gepirone ER and 91 gepirone IR). The cumulative experience with gepirone is 1288.01 subject years.

In general, the extension phase and long-term (at least 6 months and at least 1 year of treatment) safety results are consistent with those reported during the acute phase. No new safety concerns with gepirone ER were noted.

#### **7.1.5 Common Adverse Events**

##### **7.1.5.1 Appropriateness of adverse event categorization and preferred terms**

Adverse reactions were classified using standard MedDRA terminology

### 7.1.5.2 Incidence of common adverse events

There has been no significant change from previous submissions.

### 7.1.5.3 Common adverse event tables

Table 33 below is extracted from sponsor's submission displays common adverse events.

**Table 33 Number (%) of Subjects with Adverse Events Regardless of Relationship to Study Drug by Preferred Term and Treatment for AEs Reported by  $\geq 5\%$  of Subjects in any Treatment Group (All Subjects Treated in Gepirone ER Controlled Phase II/III Studies)**

| Body System<br>Preferred Term                                 | Gepirone ER<br>(N=2060) | Placebo<br>(1315)  | Antidepressants       |                       |                      |
|---------------------------------------------------------------|-------------------------|--------------------|-----------------------|-----------------------|----------------------|
|                                                               |                         |                    | Fluoxetine<br>(N=595) | Paroxetine<br>(N=276) | Imipramine<br>(N=74) |
| Subjects with at Least 1 AE                                   | 1725 (83.7%)            | 1021 (77.6%)       | 449 (75.5%)           | 223 (80.8%)           | 71 (95.9%)           |
| <b>Nervous System Disorders</b>                               | <b>1158 (56.2%)</b>     | <b>541 (41.1%)</b> | <b>204 (34.3%)</b>    | <b>111 (40.2%)</b>    | <b>62 (83.8%)</b>    |
| Headache                                                      | 602 (29.2%)             | 332 (25.2%)        | 121 (20.3%)           | 44 (15.9%)            | 34 (45.9%)           |
| Dizziness                                                     | 637 (30.9%)             | 131 (10.0%)        | 36 (6.1%)             | 48 (17.4%)            | 29 (39.2%)           |
| Somnolence                                                    | 130 (6.3%)              | 80 (6.1%)          | 24 (4.0%)             | 27 (9.8%)             | 23 (31.1%)           |
| <b>Gastrointestinal Disorders</b>                             | <b>947 (46.0%)</b>      | <b>476 (36.2%)</b> | <b>227 (38.2%)</b>    | <b>119 (43.1%)</b>    | <b>63 (85.1%)</b>    |
| Nausea                                                        | 558 (27.1%)             | 158 (12.0%)        | 95 (16.0%)            | 53 (19.2%)            | 22 (29.7%)           |
| Diarrhea                                                      | 169 (8.2%)              | 114 (8.7%)         | 64 (10.8%)            | 19 (6.9%)             | 5 (6.8%)             |
| Dry Mouth                                                     | 142 (6.9%)              | 92 (7.0%)          | 38 (6.4%)             | 36 (13.0%)            | 56 (75.7%)           |
| Constipation                                                  | 99 (4.8%)               | 66 (5.0%)          | 15 (2.5%)             | 26 (9.4%)             | 30 (40.5%)           |
| <b>Psychiatric Disorders</b>                                  | <b>603 (29.3%)</b>      | <b>277 (21.1%)</b> | <b>160 (26.9%)</b>    | <b>99 (35.9%)</b>     | <b>34 (45.9%)</b>    |
| Insomnia                                                      | 247 (12.0%)             | 102 (7.8%)         | 56 (9.4%)             | 23 (8.3%)             | 6 (8.1%)             |
| <b>Infections &amp; Infestations</b>                          | <b>469 (22.8%)</b>      | <b>320 (24.3%)</b> | <b>134 (22.5%)</b>    | <b>62 (22.5%)</b>     | <b>13 (17.6%)</b>    |
| Upper Respiratory Tract Infection                             | 126 (6.1%)              | 94 (7.1%)          | 26 (4.4%)             | 15 (5.4%)             | 2 (2.7%)             |
| Nasopharyngitis                                               | 120 (5.8%)              | 74 (5.6%)          | 46 (7.7%)             | 14 (5.1%)             | 4 (5.4%)             |
| <b>General Disorders &amp; Administration Site Conditions</b> | <b>366 (17.8%)</b>      | <b>212 (16.1%)</b> | <b>92 (15.5%)</b>     | <b>46 (16.7%)</b>     | <b>25 (33.8%)</b>    |
| Fatigue                                                       | 116 (5.6%)              | 62 (4.7%)          | 45 (7.6%)             | 19 (6.9%)             | 8 (10.8%)            |

Source: [Statistical Table 5.2.2.](#)

### 7.1.5.5 Identifying common and drug-related adverse events

Adverse event summaries were also medically reviewed by representatives of the Sponsor for inclusion in the gepirone ER labeling. AEs that occurred in at least 2% of gepirone ER subjects receiving a modal dose of  $\geq 40$  mg/day, and at a rate greater than or equal to 1.5 times that of placebo subjects in Phase II/III placebo-controlled depression studies included dizziness, paraesthesia, tremor, nausea, dyspepsia, insomnia, abnormal dreams, middle insomnia, agitation, palpitations, weight increased, tinnitus, vision blurred, and feeling jittery.

Please see appendix 10.3 table 8.

There is no significant change from previous submissions.

#### **7.1.5.6 Additional analyses and explorations**

There have been no adequate studies to explore dose-response analysis.

#### **7.1.6 Less Common Adverse Events**

There is no significant change from previous submissions.

#### **7.1.7 Laboratory Findings**

During the short-term and long-term extension trials of gepirone ER, no clinically meaningful changes from baseline were seen in comparison to placebo for body temperature, pulse, or systolic or diastolic blood pressure.

Overall there are no significant changes from previous submissions in laboratory conclusions.

#### **7.1.12 Special Safety Studies**

Please see sexual dysfunction analyses and suicidality analyses in following sections.

#### **7.1.13 Sponsor's Sexual Dysfunction Analyses**

The studies that contain sexual dysfunction questionnaires are 134001, 134002, 134004, 134006, 134017, 134502, 134503 and 134506. Sexual dysfunction analyses were conducted only for the All Subjects Treated in Controlled Phase II/III Studies in Depression population. All of the above sexual dysfunction studies are in this population.

(b) (4)

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In summary, although gepirone ER seems to be superior to its active comparators (fluoxetine or paroxetine) in some active controlled studies, such superiority has not been able to be reproduced therefore doesn't substantiate the claim that gepirone ER did not reduce the quality of patient's sexual functioning in these studies..”

Please see additional details in the statistical review.

I believe that Fanhui Kong's analysis is correct. There is not consistent evidence as agreed to in the statistical analysis plan to establish a clear claim for Gepirone.

### **Sponsor's Suicidality Analysis**

There were 3 completed suicides (2 gepirone ER subjects and 1 placebo wash-out subject) reported in the studies included in this ISS, and 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) reported in the studies included in this ISS.

For the controlled Phase II/III studies population, the percentage of subjects with any PSRAE was highest in the gepirone ER group (2.8%) and ranged from 1.8% (placebo) to 2.7% (imipramine) in the remaining treatment groups.

Based on the grouping of Columbia rating categories, 0.1% to 0.2% of gepirone subjects (gepirone ER: 0.2%; gepirone IR: 0.1%) had suicidal behavior (categories 1-3) compared with no placebo subjects, and 0.6% of gepirone subjects (gepirone ER: 0.7% to 0.8%; gepirone IR: 0.4%) had suicidal behavior or ideation (categories 1-4) compared with 0.4% of placebo subjects.

For the controlled Phase II/III studies population, examination of the risk ratios suggest that treatment with gepirone ER did not increase the risk of PSRAEs relative to placebo (ratio: 1.263; CI: 0.801 to 1.992) or to active treatment (ratio: 1.203; CI: 0.659 to 2.198). The confidence limits around the relative risk ratios did not exclude 1.00.

Fanhui Kong concludes in his statistical review:

“Based on the grouping of Columbia rating categories, although examination of the risk ratios suggested that treatment with gepirone (ER, IR, or ER+IR combined group) did not statistically significantly increase the risk of suicidal behavior or ideation (categories 1-4) relative to placebo or to another active control, it seems to have increased the suicidal behavior (categories 1-3) and suicide attempt for gepirone ER compared to placebo. In fact, there were 5 patients with suicide behavior (who had a total of 8 suicide behaviors) in a total of 2143 gepirone ER patients compared none in a total of 2450 placebo patients. A Fisher’s exact test gives a statistically significant p-value of 0.022, indicating a possible increase of suicide behavior among gepirone ER patients. In the mean time, there were 4 patients with suicide attempt among a total of 2143 gepirone ER patients compared to none in a total of 2450 placebo patients. A Fisher’s exact test gives a statistically significant p-value of 0.048, indicating a possible increase of suicide attempt among gepirone ER patients.

In the controlled Phase II/III studies included in the PSRAE analysis, 1723 subjects received gepirone ER, 1393 subjects received gepirone IR, 2292 received placebo, 457 received fluoxetine, 142 received paroxetine, and 220 received imipramine.

Based on the grouping of Columbia rating categories, it 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 suicide behavior (who had a total of 3 suicide behaviors) and 2 suicide attempts in a total of 1723 gepirone ER patients compared 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.”

Please see additional details in the statistical review.

I agree with Fanhui Wong’s analysis that gepirone seems to have increased the suicidal behavior and suicide attempts for gepirone ER compared to placebo as pointed out in his review. This increase does not reach statistical significance based on the Columbia groupings.

### **7.1.13 Withdrawal Phenomena and/or Abuse Potential**

Gepirone is not a drug of abuse.

The available data on withdrawal effects, including data on subjects who abruptly discontinued the use of gepirone in relapse-prevention studies, indicate that the abrupt discontinuation of gepirone is not associated with the occurrence of withdrawal symptoms. Although there was a statistically significantly greater risk versus placebo of any posttreatment AE for gepirone (in the analysis of all integrated data), the most

frequently reported post-treatment AEs were similar in nature to the AEs frequently reported during treatment with gepirone (i.e., dizziness, nausea, headache).

The percentage of patients who experienced reactions that occurred between 1 and 7 days after the cessation of therapy for the 1138 patients receiving gepirone ER in the acute phase of controlled studies in depression (10.3%) was similar to that seen in the 830 patients receiving placebo (8.8%). The only individual adverse reaction reported within 7 days after discontinuing study drug by at least 1% of subjects receiving at least 40 mg/day of gepirone ER was headache (1.2%, placebo 1.1%).

#### **7.1.14 Human Reproduction and Pregnancy Data**

There has been no change since previous submissions.

#### **7.1.16 Overdose Experience**

There were no unexpected toxicities in rats and dogs who received gepirone at 20 times the maximum clinical dose estimated for humans. Intentional overdose occurred rarely in subjects who were treated with gepirone. Vomiting was the only AE reported by the investigator after the maximum recorded overdose in humans, 500 mg gepirone ER. However, 1 subject who overdosed on 200 mg gepirone ER experienced an incomplete right bundle branch block.

In clinical studies, cases of acute ingestions up to 500 mg (cases include extended-release and immediate-release 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.

#### **7.1.17 Postmarketing Experience**

There has been no postmarketing experience. The drug is not approved in any country.

### **7.2 Adequacy of Patient Exposure and Safety Assessments**

#### **7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

##### **7.2.1.1 Study type and design/patient enumeration**

A total of 8407 subjects are included in the Phase II/III studies population (acute and extension phases combined). Most subjects were treated with gepirone ER (3117, 37.1%) or placebo (2483, 29.5%). Sponsor table VI below presents a summary of subjects by treatment.

**Sponsor Table VI All Subjects Treated in Phase II/III Studies (Acute and Extension Phases Combined)**

| <b>Treatment</b> |            | <b>Number of Subjects (%)</b> |
|------------------|------------|-------------------------------|
| Gepirone         |            |                               |
|                  | ER         | 3117 (37.1%)                  |
|                  | IR         | 1859 (22.1%)                  |
|                  | ER+IR      | 4976 (59.2%)                  |
| Placebo          |            | 2483 (29.5%)                  |
| Antidepressants  |            |                               |
|                  | Fluoxetine | 700 (8.3%)                    |
|                  | Paroxetine | 276 (3.3%)                    |
|                  | Imipramine | 240 (2.9%)                    |
|                  | Overall    | 1216 (14.5%)                  |
| Anxiolytics      |            |                               |
|                  | Bromazepam | 73 (0.9%)                     |
|                  | Diazepam   | 110 (1.3%)                    |
|                  | Overall    | 183 (2.2%)                    |
| <b>TOTAL</b>     |            | <b>8407</b>                   |

During the acute phase, 4300 subjects were exposed to gepirone (2441 gepirone ER and 1859 gepirone IR) and 2325 were exposed to placebo. Active control agents included the antidepressants fluoxetine (653 subjects), paroxetine (276 subjects), and imipramine (240 subjects) and the anxiolytics bromazepam (73 subjects) and diazepam (110 subjects)

A total of 5868 individual subjects exposed to gepirone ER or IR in 87 clinical studies were included in the summaries of safety. A total of 8858 subjects participated in Phase II/III studies, and 4976 of these were exposed to gepirone (3117 to the ER formulation and 1859 to the IR formulation). Long-term exposure included 905 subjects (ER: 692; IR: 213) who were exposed to gepirone for at least 6 months, and 261 subjects (ER: 170; IR: 91) who were exposed to gepirone for at least 1 year.

In controlled Phase II/III studies in depression, 2677 subjects were exposed to gepirone (ER: 1976; IR: 701). Long-term exposure in controlled Phase II/III depression studies included 458 subjects (ER: 339; IR: 119) who were exposed to gepirone for at least 6 months, and 69 subjects (ER: 20; IR: 49) who were exposed to gepirone for at least 1 year. Please see table VII below.

**Sponsor Table VII All Subjects Treated in Controlled Phase II/III Studies in Depression (Acute and Extension Phases Combined)**

| Treatment       |            | Number of Subjects (%) |
|-----------------|------------|------------------------|
| Gepirone        |            |                        |
|                 | ER         | 1976 (36.2%)           |
|                 | IR         | 701 (12.9%)            |
|                 | ER+IR      | 2677 (49.1%)           |
| Placebo         |            | 1752 (32.1%)           |
| Antidepressants |            |                        |
|                 | Fluoxetine | 665 (12.2%)            |
|                 | Paroxetine | 276 (5.1%)             |
|                 | Imipramine | 240 (4.4%)             |
|                 | Overall    | 1181 (21.6%)           |
| <b>TOTAL</b>    |            | <b>5455</b>            |

**7.2.1.2 Demographics**

**All Subjects Treated in Gepirone ER and IR Phase II/III Studies**

Data for demographic characteristics for all subjects treated in Phase II/III studies are summarized by treatment group in sponsor's submission.

In Phase II/III studies, there were no apparent differences among treatment groups with respect to mean age or body weight, with the exception of mean age in the paroxetine group and mean weight in the bromazepam group. The mean age in the combined paroxetine group, which included subjects from Studies 28715, 134006, and 134503, was considerably higher (48.6% were  $\geq 65$  years old) compared with the other treatment groups (mean ages range from 38.4 years in the diazepam group to 41.9 years in the gepirone ER group). The mean weight in the bromazepam group was 67.8 kg (range 44-102 kg); mean weight in the other treatment groups ranged from 75.1 kg in the gepirone IR group to 79.6 kg in the gepirone ER group.

In most of the treatment groups, approximately two-thirds of the subjects were female; percentages ranged from 54.8% female in the bromazepam group to 77.5% in the paroxetine group. In all treatment groups, more than 80% of the subjects (of those with race reported) were Caucasian; percentages ranged from 78.2% Caucasian in the diazepam group to 90.2% Caucasian in the paroxetine group.

Please see appendix 10.3 table 9.

### **7.2.1.3 Extent of exposure (dose/duration)**

During acute Phase II/III studies, 4300 subjects were exposed to gepirone (ER+IR combined), the equivalent of 552.50 subject-years. In total, 2325 subjects were exposed to placebo (299.49 subject-years), 1169 subjects were exposed to control antidepressants (90.55 subject-years for fluoxetine, 37.99 subject-years for paroxetine, and 29.81 subject-years for imipramine), and 183 subjects were exposed to control anxiolytics (10.26 subject-years for bromazepam and 13.35 subject-years for diazepam).

The mean (SD) duration during the acute phase was 46.9 (21.49) days for gepirone treatment (50.8 [21.82] days for gepirone ER and 41.9 [19.96] days for gepirone IR) and 47.0 (17.95) days for placebo. The mean (SD) treatment duration for control antidepressants ranged from 45.4 (21.68) days in the imipramine group to 50.6 (17.05) days in the fluoxetine group, and for control anxiolytics from 44.3 (19.70) days for the diazepam group to 51.4 (11.18) days for the bromazepam group.

During the acute phase, the highest titrated dose of gepirone for most subjects was  $\geq 40$  mg/day (2593 subjects; 2116 gepirone ER and 477 gepirone IR). The mean (SD) highest titrated dose of gepirone in these subjects (ER+IR combined) was 65.1 (19.23) mg/day (66.9 [19.14] mg/day for gepirone ER and 57.3 [17.62] mg/day for gepirone IR).

The mean modal dose of gepirone ER in acute Phase II/III studies was 55.1 mg/day compared with 23.1 mg/day for gepirone IR. The modal dose of gepirone for most subjects during the acute phase was  $\geq 40$  mg/day (2365 subjects; 2016 gepirone ER and 349 gepirone IR). The mean (SD) modal dose of gepirone for these subjects was 62.2 (17.16) mg/day (63.3 [16.85] mg/day for gepirone ER and 56.1 [17.63] mg/day for gepirone IR). Total exposure for subjects with a modal dose gepirone  $\geq 40$  mg/day during the acute phase was 228.25 subject-years (208.66 subject-years for gepirone ER and 19.59 subject-years for gepirone IR).

Please see appendix 10.3 table 10.

### **7.2.2.2 Postmarketing experience**

There is no postmarketing experience. The drug is not approved in any country.

### **7.2.2.3 Literature**

See section 8.6

### **7.2.3 Adequacy of Overall Clinical Experience**

The clinical experience is adequate.

### **7.2.8 Assessment of Quality and Completeness of Data**

The data is of reasonable quality and completeness.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

The recent safety data has not changed the conclusions from previous reviews.

### **7.4 General Methodology**

#### **7.4.1 Explorations for drug-demographic interactions**

Fanhui Kong's review highlights some drug-demographic interactions in study FK-GBE-007. He states "Further *post hoc* subgroup analyses suggest that the treatment effect was mainly driven by Caucasians, and female patients."

I agree with his review and more details are provided there.

#### **7.4.2 Explorations for drug-disease interactions**

No additional analyses for drug-disease interactions were performed for the current submission.

#### **7.4.3 Explorations for drug-drug interactions**

Please see section 8.2.

## **8 ADDITIONAL CLINICAL ISSUES**

### **8.1 Dosing Regimen and Administration**

Both Study 134001 and Study FK-GBE-007 start dosing with 20 mg (one tablet) once a day for Days 1-3, then gradually increase dosing from 40 mg to 80 mg taken once per day. I believe this dosing is reasonably safe but it is unknown if higher dosing would be more efficacious. No fixed dose studies were done.

### **8.2 Drug-Drug Interactions**

Seven interaction studies were done, which included the following drugs: ketoconazole, verapamil, paroxetine, rifampin, warfarin, lithium, and glibenclamide.

In summary, ketoconazole, verapamil, paroxetine, and nefazodone inhibit the metabolism

of gepirone, while rifampin induces metabolism. Coadministration of gepirone with warfarin, lithium, and glibenclamide was not associated with any clinically relevant changes in the action of these drugs.

See section 7.4.3

### **8.3 Pediatrics**

Pediatric data will be submitted at a later date.

### **8.4 Literature Review**

A literature review performed for the 2003 NDA Amendment searched the Medline and Embase databases for publications with publication dates up to and including 1966 to 23 June 2003. The search terms that were used included gepirone, Org 33062 or Org33062, (b) (4), MJ 13805 or MJ 13805-1 or MJ13805 or MJ13805-1, BMY 13805 or BMY 13805-1 or BMY13805 or BMY13805-1, and CAS registry Number 83928-76-1. For this 2007 NDA Amendment, the same search terms were used, but publication dates used were 23 June 2003 through 13 December 2006. Only results from the 2003 to 2006 search are included here. Review articles and nonhuman studies are not included.

Abstracts (where available) were reviewed and when from the abstract (or title, if no abstract was available) it was clear that the article presented a clinical study or that the presence of clinical study data could not be excluded, the complete article was reviewed. Furthermore, reference lists of all articles containing clinical data were reviewed for additional references. When the description of the reference in the original publication or the titles of the additional references suggested the presence of clinical study data (or the presence of clinical study data could not be ruled out), these were reviewed as well.

In this literature review, data relevant to gepirone clinical safety are reported for those cases where the literature differed from the clinical study reports or this ISS. Quantitatively higher incidences of AEs and the presence of additional data relevant to safety are reported as well as qualitative differences.

I agree with the sponsor's conclusion that results from the literature search are consistent with the safety data of gepirone as presented in this submission and offer no new conclusions.

## **9 OVERALL ASSESSMENT**

### **9.1 Conclusions**

Gepirone is a serotonin (5-hydroxytryptamine, 5-HT) type1A receptor agonist and an analogue of buspirone. Bristol-Myers Squibb (BMS) and Organon dropped this drug from their development programs. Fabre-Kramer Pharmaceuticals, Inc. (Houston,

Texas) bought and sold the rights to this drug in 1998 and again bought the drug in 2005 after conducting their own additional studies.

We have sent out non-approval letters for Gepirone in 2002 and 2004. In the 2004 letter we pointed out that only 1 of 4 adequately designed short term ER studies was positive.

We asked for a positive relapse prevention study which has never been provided. This is a very unusual finding in that the enriched population of a relapse study is almost always positive. We stated in the 2004 letter that there was a “preponderance of negativity”.

The recent Faber Kramer Study 007 was positive but the similar study 008 only trended in the positive direction. Study 134023 did not produce evidence of superiority of gepirone ER in any of the efficacy parameters in spite of adequate dosing.

There are five studies described as lacking assay sensitivity. Study 134004 was pointed out in our 6/23/04 nonapproval letter as being nearly significant for the active control fluoxetine over gepirone. In three of the remaining failed trials the active comparator showed more numerical improvement than gepirone and in the fourth trial they were equal.

Fanhui Kong’s stat review states, “Furthermore, in three out of the five so called “lack of assay sensitivity” studies, active control significantly outperformed gepirone ER. Active control significantly outperformed the control in 2 out of 5 studies.”

Their meta-analysis for all 12 Gepirone ER DB PC studies is not positive.

Although there are now 2 positive studies for the ER formulation, the number of negative studies call into question the statistical meaning of the 2 positive studies.

## **9.2 Recommendation on Regulatory Action**

I believe approving this drug would expose patients taking Gepirone ER to potential delay and risk which could be avoided if started immediately on an approved antidepressant with clear evidence of efficacy. I recommend we issue a nonapproval letter for Gepirone ER based on lack of evidence of efficacy.

## **9.3 Recommendation on Postmarketing Actions**

### **9.3.1 Required Phase 4 Commitments**

A positive relapse prevention study is still needed.

OCP finds this application acceptable providing agreement can be reached on labeling and so long as the sponsor provides written agreement to a phase IV commitment to

perform a drug-drug interaction study of the effect of an intermediate CYP 3A4 inducer such as rifabutin within 1 year of approval.

### **9.3.2 Other Phase 4 Requests**

Pediatric data was deferred and would be needed.

### **9.4 Labeling Review**

The draft label has been provided in the current proper PLR format. If approved the efficacy section would need several changes. The 2 positive studies would need to be discussed within the context of the many failed and negative studies. The sponsor currently makes a maintenance claim based on the relapse study and this would have to be removed. The dosage section would need to be clarified as the summary page, dosage and administration section, and the clinical trial sections suggest slightly differing dosing strategies. The safety section is generally acceptable.

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Earl Hearst, MD  
HFD-130

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

#### **Study FK-GBE-007: A Double-Blind Multicenter, Randomized, Placebo-Controlled Efficacy and Safety Study of Org 33062 ER in Subjects with Major Depressive Disorder**

##### *Investigator sites*

Nine investigators conducted this study in the U.S. Investigators and sites listed in the table below were extracted from the sponsor's submission.

Table A: List of Investigators

|                                                                                                          |                                    |
|----------------------------------------------------------------------------------------------------------|------------------------------------|
| <b>Investigators:</b>                                                                                    |                                    |
| Site 701: Robert J. Bielski, M.D.                                                                        | Site 706: Kenneth Weiss, M.D.      |
| Site 702: Lynn Cunningham, M.D.                                                                          | Site 707: Dan L. Zimbroff, M.D.    |
| Site 703: Robert Bruce Lydiard, Ph.D., M.D.                                                              | Site 708: Ward T. Smith, M.D.      |
| Site 704: Dennis J. Munjack, M.D.                                                                        | Site 709: Peter D. Londeborg, M.D. |
| Site 705: Robert A. Riesenberg, M.D.                                                                     |                                    |
| <b>Trial Centers:</b>                                                                                    |                                    |
| Site 701: Summit Research Network (Michigan), Inc., 4084 Okemos Road, Okemos, MI 48864                   |                                    |
| Site 702: Cunningham Clinical Research, 1121 University Dr., Suite 4, Edwardsville, IL 62025             |                                    |
| Site 703: Southeast Health Consultants, Parkshore Centre, 1 Poston Road, Suite 150, Charleston, SC 29407 |                                    |
| Site 704: Southwestern Research, Inc., 2211 West Magnolia Blvd., Suite 270, Burbank, CA 91506            |                                    |
| Site 705: Atlanta Center for Medical Research, 811 Juniper Street NE, Atlanta, GA 30308                  |                                    |
| Site 706: Delaware Valley Research Associates, 922 Fayette Street, Conshohocken, PA 19428                |                                    |
| Site 707: Pacific Clinical Research Medical Group, 1317 W. Foothill Blvd., Suite 200, Upland, CA 91786   |                                    |
| Site 708: Summit Research Network (Oregon), Inc., 1849 NW Kearney, Suite 201, Portland, OR 97209         |                                    |
| Site 709: Summit Research Network (Seattle), Inc., 901 Boren Avenue, Suite 1800, Seattle, WA 98104       |                                    |

##### *Objectives*

According to the protocol, the primary objective of this trial was to evaluate the therapeutic efficacy of Org 33062 extended release (ER) tablets in comparison with placebo at the end of an 8-week treatment period in subjects with major depressive disorder (diagnosed according to DSM-IV criteria).

##### *Patient Sample*

Important inclusion criteria were:

- 18 to 64 years of age
- Diagnostic criteria for moderate-to-severe MDD according to the DSM-IV criteria (296.22, 296.23, 296.32, and 296.33 only)

- A total score of 20 or greater on the Hamilton Depression Rating Scale (HAMD-17) at both screening and baseline assessments. The HAMD-17 score was also evaluated by a computer-rated Interactive Voice Response System (IVRS) HAMD (which consisted only of yes/no responses). Only those subjects scoring 20 or more on the IVRS HAMD-17 were eligible for the study.
- A significant daily dysphoria for the 4 weeks prior to screening
- Written informed consent

Important exclusion criteria were:

- A  $\geq 20\%$  decrease on the HAMD-17 total score between screening and baseline
- Primary DSM-IV Axis I diagnosis other than MDD
- History or present condition of any DSM-IV Axis II disorder, seizure disorder, or bipolar disorder
- History of treatment-refractory major depressive episodes defined as incomplete or no therapeutic response to two prior courses of at least 1 month of conventional antidepressant drug treatment in adequate dosages
- Subjects currently in psychotherapy (at least one session in the past month with a plan for continuing)
- Subjects currently at significant suicidal risk according to the clinical judgment of the investigator
- Any clinically meaningful non-stable renal, hepatic, cardiovascular, respiratory, or cerebrovascular disease; any other serious, progressive, physical disease
- Positive result on the initial urine analysis for illegal drugs or alcohol
- Subjects who had electroconvulsive shock therapy in the last year
- Subjects who met DSM-IV criteria for psychoactive substance disorder (except nicotine dependency) or alcohol dependency
- Any of the following treatments within the indicated intervals before the start of active treatment:

| Treatment                                                                                         | Interval                           |
|---------------------------------------------------------------------------------------------------|------------------------------------|
| Monoamine oxidase (MAO) inhibitors                                                                | 3 weeks                            |
| Fluoxetine                                                                                        | 4 weeks                            |
| Other selective serotonin reuptake inhibitors (SSRIs)                                             | 4 weeks                            |
| Alternative psychoactive agents (e.g., melatonin, St. John's Wort, S-adenosyl methionine [SAM-e]) | 2 weeks                            |
| Other psychotropic drugs                                                                          | 5 times the half-life <sup>a</sup> |

<sup>a</sup> A minimum of a 2-week interval was required for drugs with no available pharmacokinetic data

- Subjects who were pregnant or lactating at screening
- Previous adverse reactions or allergic reactions to buspirone, Org 33062, or other azapirones
- History of treatment with an investigational drug within 6 months of enrollment in the trial

## *Design*

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study in which 248 moderately to severely depressed outpatients received Org 33062 ER tablets (doses ranged from 20 to 80 mg) or placebo tablets once each morning with food for 8 weeks (56 days).

The dosing schedule for each dose was described in the paragraph below as extracted from the sponsor's submission.

All subjects participated in a placebo washout screening period during which subjects received 1 placebo tablet/day for 4 to 7 days. Subjects were titrated to study medication as follows: 1 Org 33062 ER 20 mg tablet or 1 placebo tablet on Days 1-3 and 2 Org 33062 ER 20 mg tablets or 2 placebo tablets on Days 4-7. Thereafter, the doses on the preferred dosing schedule were 40 to 60 mg Org 33062 ER or placebo qd (2-3 tablets) on Days 8-14 and 40 to 80 mg Org 33062 ER or placebo qd (2-4 tablets) on Days 15-56. If a phone call to the subject on Day 3 revealed significant tolerability issues during Days 1-3, titration to 40 mg could be delayed until Day 8. On the alternate dosing schedule, the doses were 40 mg Org 33062 ER or placebo qd (2 tablets) on Days 8-14, 40 to 60 mg Org 33062 ER or placebo qd (2-3 tablets) on Days 15-21, and 40 to 80 mg Org 33062 ER or placebo qd (2-4 tablets) on Days 22-56. The minimum acceptable dose of Org 33062 ER was 40 mg qd (2 tablets) after Day 3 on the preferred dosing schedule and 40 mg qd after Day 7 on the alternate dosing schedule.

At the conclusion of the study, subjects returned to the clinic for a follow-up assessment 7 days after the last dose of study medication, and were contacted 30 days after the last dose solely to determine if any SAEs had occurred since the final treatment.

## *Efficacy Assessments*

The protocol-defined primary efficacy variable was change from baseline to endpoint in HAMD-17 total scores. No key secondary efficacy variable identified. Efficacy assessments included Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale (MADRS) and Clinical Global Impression Scale (CGI).

## *Efficacy Analysis*

The results for the Intent-to-Treat (ITT) Population using the LOCF approach were considered the primary evidence of efficacy. The primary efficacy variable was analyzed using an analysis of variance (ANOVA) model. The estimates of treatment effects and corresponding (two-sided) 95% CIs was based on the additive two-way ANOVA (including both treatment groups) with factors of treatment and study center. Treatment comparisons were presented for each visit. A test for interaction between treatment and center was performed by extending the additive model with the interaction term. In case of a significant interaction ( $p < 0.10$ ), the kind of interaction (the differences

between the centers with respect to the treatment effects) was explored to evaluate whether it was still justified to present an overall estimate of the treatment effect.

### *Baseline Demographics*

The table below displays the demographic characteristics of the ITT patient sample by treatment group. The mean (SD) age of all subjects was 38.1 (11.20) years and ranged from 18 to 64 years. The majority (nearly 70%) of subjects in both groups were female, and the majority of subjects were Caucasian (64.7%) or Black (23.1%). There were no major differences between the treatment groups with respect to age, gender, or race.

Table B: Demographics (ITT Population)

| Characteristic   | Treatment Group         |                    | Overall<br>(N=238) |
|------------------|-------------------------|--------------------|--------------------|
|                  | Org 33062 ER<br>(n=116) | Placebo<br>(n=122) |                    |
| Age (yrs)        |                         |                    |                    |
| Mean (SD)        | 38.2 (11.43)            | 38.0 (11.03)       | 38.1 (11.20)       |
| Median           | 39                      | 38                 | 38.5               |
| Minimum, Maximum | 18, 58                  | 18, 64             | 18, 64             |
| Gender           |                         |                    |                    |
| Male             | 37 (31.9)               | 37 (30.3)          | 74 (31.1)          |
| Female           | 79 (68.1)               | 85 (69.7)          | 164 (68.9)         |
| Race             |                         |                    |                    |
| Caucasian        | 73 (62.9)               | 81 (66.4)          | 154 (64.7)         |
| Black            | 28 (24.1)               | 27 (22.1)          | 55 (23.1)          |
| Asian            | --                      | 2 (1.6)            | 2 (0.8)            |
| Other            | 15 (12.9)               | 12 (9.8)           | 27 (11.3)          |

Source: Supportive Table 5-B

### *Baseline Severity of Illness*

Treatment groups had no major differences with respect to mean baseline HAMD-17 total score (mean scores of 24.2 in gepirone ER patients, and 23.9 in placebo patients). Overall, episodes of depression upon entering the study had lasted >12 months for 39.9% of the subjects, between 1 and 6 months for 36.6% of the subjects, and between 7 and 12 months for 23.5% of the subjects. Subjects had an overall mean (SD) age of 27.7 (11.92) years when they experienced their first episode of depression. Most subjects (58.8% overall) were suffering from recurrent depression with full recovery when they entered the study; 22.3% of subjects were suffering from their first episode of depression at baseline. The majority of subjects (95.4% overall) did not have a comorbid anxiety disorder; however, the incidence of comorbid anxiety disorder was higher for the gepirone ER (Org 33062) group compared to the placebo group (6.9% vs. 2.5%, respectively).

### *Patient Disposition*

A total of 248 subjects were randomized and treated in this study, 124 subjects each in the Org 33062 ER and placebo groups. Based on the information recorded on the end of trial CRF page, 199 subjects completed the study and 49 subjects discontinued. The

overall discontinuation rate was slightly higher for the Org 33062 ER group; [3.2% vs. 2.4%, respectively, for lack of efficacy; 4% vs. 2.4% for AE or SAE; and 14.5% vs. 12.9% for other reasons (lost to follow-up, withdrawal of consent, noncompliance with treatment, and other unspecified reasons)]. In addition to the discontinuations for AEs or SAEs noted on the end of trial page, 3 additional subjects were included because the AE form indicated they were discontinued for AEs. These subjects included Subject (b) (6) and Subject (b) (6) who completed at least 53 days of treatment and were listed as completers on the end of trial CRF, and one subject (Subject (b) (6)) for whom the investigator listed lack of efficacy as the primary reason for discontinuation on the end of trial form.

Of the 238 subjects in the ITT Population, 18 unique subjects had at least one major protocol violation. The most common protocol deviation was non-compliance with treatment (defined as taking less than 75% of the expected dose), with 9 subjects in the Org 33062 ER group considered noncompliant with treatment. Five subjects used concomitant anti-depressants, and 6 discontinued from the study before completing 14 days of treatment.

Table C: Subjects Discontinuation by Primary Reasons for Withdrawal in Study FKGBE007

| Disposition                               | Number (% , where applicable) of Subjects |          |          |
|-------------------------------------------|-------------------------------------------|----------|----------|
|                                           | Org 33062 ER                              | Placebo  | Overall  |
| Total number of subjects randomized       | 124                                       | 124      | 248      |
| Total number of subjects treated          | 124                                       | 124      | 248      |
| Total number of subjects completed        | 97                                        | 102      | 199      |
| Total number of subjects who discontinued | 27                                        | 22       | 49       |
| Lack of efficacy                          | 4 (3.2)                                   | 3 (2.4)  | 7 (2.8)  |
| AE or SAE                                 | 5 (4.0)                                   | 3 (2.4)  | 8 (3.2)  |
| Non compliance with treatment             | 1 (0.8)                                   | 0 (0.0)  | 1 (0.4)  |
| Withdrew consent                          | 5 (4.0)                                   | 2 (1.6)  | 7 (2.8)  |
| Lost to Follow-up                         | 11 (8.9)                                  | 12 (9.7) | 23 (9.3) |
| Other                                     | 1 (0.8)                                   | 2 (1.6)  | 3 (1.2)  |

Source: Sponsor's Table 9 in the Clinical Study Report of Study FKGBE007.

### *Dosing Information*

This was a flexible-dose study. The mean daily dose of gepirone ER was 58.2 mg/day.

### *Efficacy Results*

For the HAMD-17 total score mean change from baseline analysis, the differences were statistically significant in favor of gepirone ER in the LOCF analysis. The OC analysis was consistent with the LOCF analysis. Efficacy data displays may be found in the tables below extracted from sponsor's study report.

Table D: Summary of Primary and Secondary Efficacy Parameters

| Parameter<br>mean±SE             | Gepirone ER<br>Change from Baseline | Placebo<br>Change from Baseline | Difference | p-value at<br>Endpoint |
|----------------------------------|-------------------------------------|---------------------------------|------------|------------------------|
| HAMD-17 total score <sup>a</sup> | -10.22 ± 0.75                       | -7.96 ± 0.73                    | -2.26      | 0.032                  |
| HAMD-21 total score <sup>a</sup> | -11.07 ± 0.80                       | -8.79 ± 0.78                    | -2.28      | 0.043                  |
| HAMD-25 total score <sup>a</sup> | -12.65 ± 0.91                       | -9.85 ± 0.89                    | -2.80      | 0.029                  |
| HAMD-28 total score <sup>a</sup> | -15.04 ± 1.06                       | -11.83 ± 1.04                   | -3.21      | 0.032                  |
| CGI severity <sup>a</sup>        | -1.30 ± 0.11                        | -0.92 ± 0.11                    | -0.38      | 0.015                  |
| HAMD Item 1 <sup>a</sup>         | -1.39 ± 0.12                        | -1.07 ± 0.12                    | -0.32      | 0.056                  |
| MADRS total score <sup>a</sup>   |                                     | -10.86 ± 1.09                   |            |                        |
|                                  | -13.72 ± 1.01                       | -9.94 ± 0.99                    | -3.28      | 0.008                  |
| %HAMD-17 Remitters               | 34.5%                               | 20.5%                           | 14%        | 0.019                  |

Table E: Responder Rates at Visit 6/Endpoint

| Responder Rate at Week 8 (Visit 6)/ET (ITT, LOCF) |             |      |         |      |         |
|---------------------------------------------------|-------------|------|---------|------|---------|
| Variable                                          | Gepirone ER |      | Placebo |      | p-value |
|                                                   | n/N         | %    | n/N     | %    |         |
| HAMD-17 <sup>a</sup>                              | 53/116      | 45.7 | 36/122  | 29.5 | 0.014   |
| MADRS <sup>a</sup>                                | 59/116      | 50.9 | 39/121  | 32.2 | 0.005   |
| HAMD-21 <sup>a</sup>                              | 54/116      | 46.6 | 39/122  | 32.0 | 0.031   |
| HAMD-25 <sup>a</sup>                              | 56/116      | 48.3 | 37/122  | 30.3 | 0.007   |
| HAMD-28 <sup>a</sup>                              | 57/116      | 49.1 | 40/122  | 32.8 | 0.015   |
| CGI <sup>b</sup>                                  | 56/116      | 48.3 | 42/121  | 34.7 | 0.045   |

<sup>a</sup> Responder defined as a subject with a 50% or greater reduction in baseline HAMD-17, HAMD-25, or MADRS total score at any post-baseline assessment. <sup>b</sup> Responder defined as a subject who is much or very much improved based on the CGI improvement score at any post-baseline assessment.

Table F: Analysis of Treatment Differences at Visits 4, 5, and 6/ET (ITT, LOCF)

| Depression Scale                         | Visit 4 (Week 4) | Visit 5 (Week 6) | Visit 6/ET (Week 8) |
|------------------------------------------|------------------|------------------|---------------------|
| <u>HAMD-17</u>                           |                  |                  |                     |
| Treatment p-value <sup>a</sup>           | 0.004*           | 0.006*           | 0.032*              |
| Treatment-by-Center p-value <sup>b</sup> | 0.078**          | 0.163            | 0.070**             |
| <u>CGI</u>                               |                  |                  |                     |
| Treatment p-value <sup>a</sup>           | 0.002*           | 0.001*           | 0.015*              |
| Treatment-by-Center p-value <sup>b</sup> | 0.292            | 0.147            | 0.032**             |
| <u>MADRS</u>                             |                  |                  |                     |
| Treatment p-value <sup>a</sup>           | <0.001*          | 0.003*           | 0.008*              |
| Treatment-by-Center p-value <sup>b</sup> | 0.313            | 0.290            | 0.163               |
| <u>Bech Six-Item</u>                     |                  |                  |                     |
| Treatment p-value <sup>a</sup>           | 0.007*           | 0.006*           | 0.016*              |
| Treatment-by-Center p-value <sup>b</sup> | 0.066**          | 0.053**          | 0.026**             |

Source: Sponsor's Supportive Tables 21, 29, 73, and 99

<sup>a</sup> p-value for treatment based on the reduced model without interaction (treatment and center in the model)

<sup>b</sup> p-value for treatment-by-center interaction based on the full model (treatment, center, and treatment-by-center interaction in the model)

\* Indicates statistical significance  $p < 0.05$

\*\* Indicates statistical significance  $p < 0.10$

ET=End of treatment

### Treatment-by-Center Interaction

For Study FK-GBE-007, the protocol required an investigation of any significant treatment-by-center interactions (defined as a p-value  $\leq 0.10$ ). For the primary efficacy parameter (HAMD-17) as reported above, a significant p-value of 0.092 was found. Site variability in the treatment outcome of antidepressant trials is not uncommon (Amsterdam and Brunswick 2002).

Table G: Analysis of Change in HAMD-17 from Baseline to End of Short-Term Double-Blind Treatment Period (Pivotal Study FK-GBE-007)

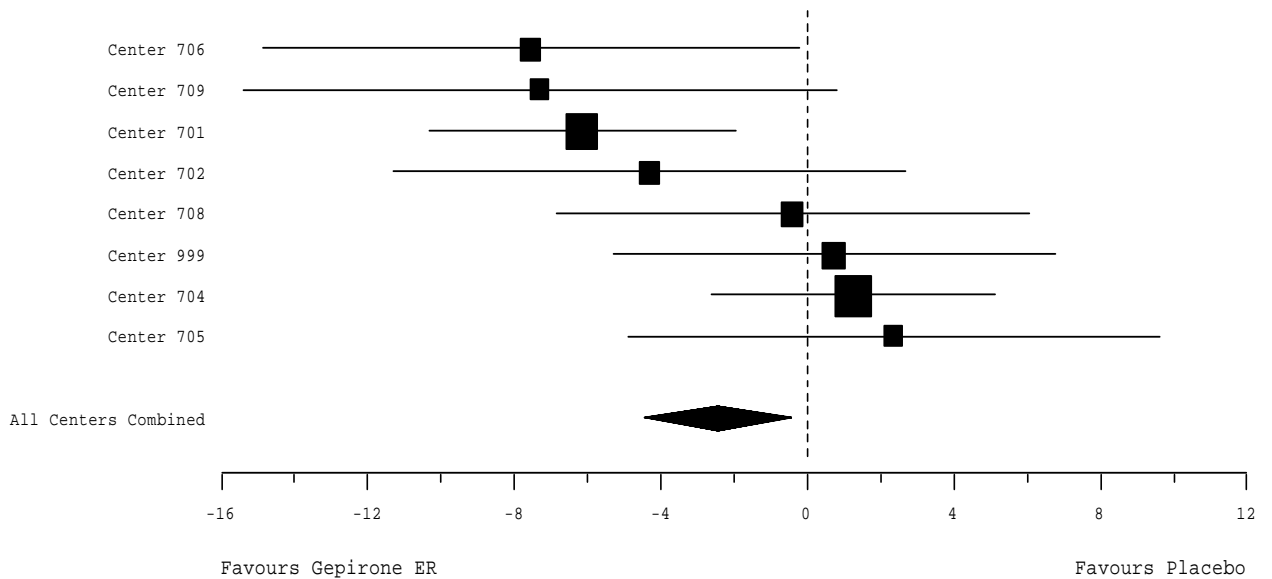
| Treatment difference and 95% CI     | Number of subjects |         | (Adjusted) mean change |         |
|-------------------------------------|--------------------|---------|------------------------|---------|
|                                     | Gepirone ER        | Placebo | Gepirone ER            | Placebo |
| Center<br>(Gepirone ER - Placebo)   | SE                 | p-value |                        |         |
| Center 701<br>-6.15 (-10.33, -1.97) | 2.07               | 0.005   | 21                     | 23      |
| Center 702<br>-4.31 (-11.30, 2.67)  | 3.40               | 0.216   | 14                     | 16      |
| Center 704<br>1.25 (-2.63, 5.13)    | 1.92               | 0.519   | 22                     | 20      |
| Center 705<br>2.36 (-4.88, 9.61)    | 3.53               | 0.509   | 14                     | 15      |
| Center 706<br>-7.55 (-14.85, -0.24) | 3.45               | 0.044   | 10                     | 9       |
| Center 708<br>-0.40 (-6.85, 6.05)   | 3.08               | 0.898   | 12                     | 10      |

|                                 |      |       |     |     |        |       |
|---------------------------------|------|-------|-----|-----|--------|-------|
| Center 709                      |      |       | 8   | 11  | -11.55 | -4.24 |
| -7.31 (-15.41, 0.79)            | 3.82 | 0.074 |     |     |        |       |
| Center 999                      |      |       | 15  | 18  | -7.20  | -7.94 |
| 0.74 (-5.28, 6.75)              | 2.95 | 0.804 |     |     |        |       |
| All Centers Combined            |      |       | 116 | 122 | -10.24 | -7.79 |
| -2.45 (-4.47, -0.43)            | 1.02 | 0.018 |     |     |        |       |
| Treatment by center interaction |      |       |     |     |        |       |
| 0.092                           |      |       |     |     |        |       |

Note: ANCOVA model was used with terms for treatment and center and baseline value (as a covariate).

Center 999 is a pooled center that combines centers 703 and 707.

Figure H: Forest Plot for the Change in HAMD-17 from Baseline to End of Short-Term Double-Blind Treatment Period (Pivotal Study FK-GBE-007)



### Conclusions

The results of Study FKGBE-007 provide evidence of the efficacy of gepirone ER vs placebo in treatment of MDD.

### **Study FK-GBE-008:**

This is a negative efficacy study. This will not be described in detail.

Study FK-GBE-008 had the same design as Study FK-GBE-007; however, the only difference was the planned sample size. Study FK-GBE-008 planned 100 subjects per treatment group. The primary analysis of change in HAMD-17 from baseline to the end of treatment showed no statistically significant difference between gepirone ER and placebo, although the results showed tendency towards significance in favor of gepirone ER (i.e., LS mean change of -9.86 in gepirone ER vs. -8.48 in placebo,  $p=0.20$ ). Statistically significant results in some efficacy parameters were observed intermittently at Weeks 2, 3 and 6.

## **10.2 Labeling Review**

The draft label has been provided in the current proper PLR format. If approved the efficacy section would need several changes. The 2 positive studies would need to be discussed within the context of the many failed and negative studies. The sponsor currently makes a maintenance claim based on the relapse study and this would have to be removed. The dosage section would need to be clarified as the summary page, dosage and administration section, and the clinical trial sections suggest slightly differing dosing strategies. The safety section is generally acceptable.

## **10.3 Appendix of Tables extracted from sponsor's submission**

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No.                  | Phase | Duration                                                    | Controlled?<br>(Control Drug)             | Blinded or Open?                                      | Indication                                                                                             | Gepirone Dose                                    | Population<br>(Adult, Elderly) |
|----------------------------|-------|-------------------------------------------------------------|-------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------|
| <b>Gepirone ER Studies</b> |       |                                                             |                                           |                                                       |                                                                                                        |                                                  |                                |
| CN105-049                  | I     | Acute<br>(8 days)                                           | Yes (placebo)                             | Double-blind                                          | PK Study                                                                                               | 10-75 mg/day                                     | Adult (18-40 years)            |
| CN105-085                  | I     | Acute<br>(7 days)                                           | Yes (placebo)                             | Double-blind                                          | PK study                                                                                               | 120 mg/day                                       | Adult (20-36 years)            |
| FK-GBE-003                 | I     | Acute<br>(2 doses)                                          | No                                        | Open-label                                            | PK study                                                                                               | 20 mg                                            | Adult (25-44 years)            |
| 134015                     | I     | Acute<br>(1 week)                                           | Yes (placebo)                             | Double-blind                                          | PK study                                                                                               | 40 mg                                            | Adult (22-62 years)            |
| 28703                      | I     | Acute<br>(8 weeks)                                          | No                                        | Double-blind                                          | Drug interaction with<br>paroxetine                                                                    | 20-40 mg                                         | Adult (20-45 years)            |
| 28704                      | I     | Acute<br>(4 weeks)                                          | Yes (placebo)                             | Double-blind                                          | Drug interaction with<br>warfarin                                                                      | 40 mg                                            | Adult (22-44 years)            |
| 28705                      | I     | Acute<br>(6 weeks)                                          | No                                        | Open-label                                            | Drug interaction with<br>rifampicin                                                                    | 20-40 mg                                         | Adult (22-45 years)            |
| 28706                      | I     | Acute<br>(12 weeks)                                         | No                                        | Double-blind                                          | Drug interaction with<br>lithium                                                                       | 40 mg                                            | Adult (18-39 years)            |
| 28707                      | I     | Acute<br>(Block I: 21 days)<br>(Block II: 6 days)           | Block I: Yes<br>(placebo)<br>Block II: No | Block I: Double-<br>blind<br>Block II: Open-<br>label | Block I: insulin<br>sensitivity in<br>diabetics<br>Block II: drug<br>interaction with<br>glibenclamide | Block I: 20-40 mg<br>Block II: 40 mg             | Adult (42-70 years)            |
| 28717                      | I     | Acute<br>(2 single doses + 5<br>days multiple dose)         | No                                        | Open-label                                            | Drug interaction with<br>ketoconazole                                                                  | 20-40 mg single<br>dose + 40 mg<br>multiple dose | Adult (24-43 years)            |
| 28724                      | I     | Acute<br>(Sequence I: 16 days)<br>(Sequence II: 23<br>days) | No                                        | Open-label                                            | Drug interaction with<br>verapamil                                                                     | 20 mg                                            | Adult (21-44 years)            |
| CN105-046                  | I     | Acute<br>(4 single doses)                                   | No                                        | Open-label                                            | Food effect                                                                                            | 20 mg                                            | Adult (19-40 years)            |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No.  | Phase  | Duration                  | Controlled?<br>(Control Drug) | Blinded or Open? | Indication                                     | Gepirone Dose | Population<br>(Adult, Elderly)                                                |
|------------|--------|---------------------------|-------------------------------|------------------|------------------------------------------------|---------------|-------------------------------------------------------------------------------|
| FK-GBE-002 | I      | Acute<br>(2 single doses) | No                            | Open-label       | Food effect                                    | 20 mg         | Adult (18-49 years)                                                           |
| 28725      | I      | Acute<br>(4 single doses) | No                            | Open-label       | Food effect                                    | 20 mg         | Adult (19-47 years)                                                           |
| 28727      | I      | Acute<br>(4 single doses) | No                            | Open-label       | Food effect                                    | 20 mg         | Adult (19-45 years)                                                           |
| CN105-026  | I      | Acute<br>(5 single doses) | No                            | Open-label       | Bioavailability ER<br>vs. IR*                  | 20-25 mg      | Adult (19-36 years)                                                           |
| CN105-060  | I      | Acute<br>(28 days)        | Yes (placebo)                 | Double-blind     | Bioavailability 3 ER<br>tablets and solution   | 5-20 mg       | Adult (19-40 years)                                                           |
| FK-GBE-001 | I      | Acute<br>(2 single doses) | No                            | Open-label       | Bioequivalence 2<br>manufacturers              | 20 mg         | Adult (19-45 years)                                                           |
| 28718      | I      | Acute<br>(4 single doses) | No                            | Open-label       | Bioavailability<br>20 mg, 40 mg, 80 mg<br>tabs | 40-80 mg      | Adult (18-44 years)                                                           |
| CN105-068  | I      | Acute<br>(21 days)        | Yes (placebo)                 | Double-blind     | Young vs. elderly PK                           | 20-80 mg/day  | Adult (19-40 years)<br>Elderly (65-79 years)                                  |
| FK-GBE-004 | I      | Acute<br>(8 days)         | No                            | Open-label       | Effect on race                                 | 20 mg/day     | Adult (18-48 years)                                                           |
| FK-GBE-005 | I      | Acute<br>(single dose)    | No                            | Open-label       | Hepatic impairment                             | 20 mg         | Adult (44-70 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| 28708      | I      | Acute<br>(single dose)    | No                            | Open-label       | Renal impairment                               | 40 mg         | Adult (35-65 years)                                                           |
| 134001     | II/III | Acute<br>(8 weeks)        | Yes (placebo)                 | Double-blind     | Depression                                     | 20-80 mg      | Adult (18-69 years)                                                           |
| FK-GBE-007 | II/III | Acute<br>(8 weeks)        | Yes (placebo)                 | Double-blind     | Depression                                     | 40-80 mg      | Adult (18-64 years)                                                           |
| 134002     | II/III | Acute<br>(8 weeks)        | Yes (placebo)                 | Double-blind     | Depression                                     | 20-80 mg      | Adult (18-69 years)                                                           |
| 134023     | II/III | Acute<br>(9 weeks)        | Yes (placebo)                 | Double-blind     | Depression                                     | 20-80 mg      | Adult (18-70 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| FK-GBE-008 | II/III | Acute<br>(8 weeks)        | Yes (placebo)                 | Double-blind     | Depression                                     | 40-80 mg      | Adult (18-65 years)                                                           |
| 28709      | II/III | Acute                     | Titration No                  | Open-label       | Depression, relapse                            | 20-80 mg      | Adult (17-72 years)                                                           |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No. | Phase  | Duration                                                                     | Controlled?<br>(Control Drug)       | Blinded or Open?                                | Indication | Gepirone Dose | Population<br>(Adult, Elderly)                                             |
|-----------|--------|------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------|------------|---------------|----------------------------------------------------------------------------|
|           |        | (8-12 week titration)<br>Extension ≥6 mos<br>(40-44 week relapse prevention) | Relapse prevention<br>Yes (placebo) | titration<br>Double-blind<br>relapse prevention | prevention |               | <i>Also Elderly, since some subjects ≥65 years</i>                         |
| CN105-057 | II/III | Acute<br>(8 week titration)<br>Extension<br>(42 weeks)                       | Yes (placebo)                       | Double-blind                                    | Depression | 2-40 mg       | Adult (18-79 years)<br><i>Also Elderly, since some subjects ≥65 years</i>  |
| CN105-078 | II/III | Acute<br>(6 week titration)<br>Extension ≥6 mos<br>(20 weeks)                | Yes (placebo)                       | Double-blind                                    | Depression | 10-100 mg     | Adult (17-77 years)<br><i>Also Elderly, since some subjects ≥65 years</i>  |
| CN105-083 | II/III | Acute<br>(6 week titration)<br>Extension<br>(20 weeks)                       | Yes (placebo)                       | Double-blind                                    | Depression | 10-100 mg     | Adult (15*-78 years)<br><i>Also Elderly, since some subjects ≥65 years</i> |
| 134004    | II/III | Acute<br>(8 weeks)                                                           | Yes (placebo and fluoxetine)        | Double-blind                                    | Depression | 20-80 mg      | Adult (18-65 years)                                                        |
| 134502    | II/III | Extension (for 004)<br>≥6 mos<br>(44 weeks)                                  | Yes (placebo and fluoxetine)        | Double-blind                                    | Depression | 20-80 mg      | Adult (18-65 years)                                                        |
| 134006    | II/III | Acute<br>(8 weeks)                                                           | Yes (placebo and paroxetine)        | Double-blind                                    | Depression | 20-80 mg      | Adult (18-64 years)                                                        |
| 134503    | II/III | Extension (for 006)<br>(16 weeks)                                            | Yes (placebo and paroxetine)        | Double-blind                                    | Depression | 40-80 mg      | Adult (18-64 years)                                                        |
| 134017    | II/III | Acute<br>(8 weeks)                                                           | Yes (placebo and fluoxetine)        | Double-blind                                    | Depression | 20-80 mg      | Adult (18-64 years)                                                        |
| 134506    | II/III | Extension (for 017)<br>(16 weeks)                                            | Yes (placebo and fluoxetine)        | Double-blind                                    | Depression | 20-80 mg      | Adult (18-64 years)                                                        |
| CN105-052 | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(42 weeks)                | Yes (placebo and fluoxetine)        | Double-blind                                    | Depression | 20-60 mg      | Adult (19-63 years)                                                        |
| CN105-053 | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                | Yes (placebo and imipramine)        | Double-blind                                    | Depression | 10-60 mg      | Adult (19-74 years)                                                        |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No.                  | Phase  | Duration                                                                                                                                                            | Controlled?<br>(Control Drug)   | Blinded or Open? | Indication                    | Gepirone Dose | Population<br>(Adult, Elderly)                                                                |
|----------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|------------------|-------------------------------|---------------|-----------------------------------------------------------------------------------------------|
| CN105-064                  | II/III | Acute<br>(8 week titration)<br>Extension $\geq$ 6 mos<br>(44 weeks)                                                                                                 | Yes (placebo and<br>imipramine) | Double-blind     | Depression                    | 5-40 mg       | Adult (20-78 years)<br><i>Also Elderly, since some<br/>subjects <math>\geq</math>65 years</i> |
| 28715                      | II/III | Long-term $\geq$ 6 mos<br>(26 weeks)                                                                                                                                | Yes (paroxetine)                | Double-blind     | Depression                    | 20-80 mg      | Elderly (64-92 years)                                                                         |
| 28722                      | II/III | Acute<br>(8 week titration)<br>Extension<br>(16 weeks)                                                                                                              | Yes (fluoxetine)                | Open-label       | Depression                    | 20-80 mg      | Adult (27-67 years)<br><i>Also Elderly, since some<br/>subjects <math>\geq</math>65 years</i> |
| 28723                      | II/III | Acute<br>(8 week titration)<br>Extension<br>(16 weeks)                                                                                                              | Yes (fluoxetine)                | Open-label       | Depression                    | 20-80 mg      | Adult (21-62 years)                                                                           |
| C-1762                     | II/III | Long-term $\geq$ 6 mos<br>(26 weeks)                                                                                                                                | Yes (fluoxetine)                | Double-blind     | Depression                    | 20-80 mg      | Adult (18-69 years)<br><i>Also Elderly, since some<br/>subjects <math>\geq</math>65 years</i> |
| 134501                     | II/III | Category 1<br>(extension for 001,<br>002, or 015)<br>Long-term $\geq$ 6 mos<br>(44 weeks)<br>Category 2 (naïve<br>subjects)<br>Long-term $\geq$ 1 yr<br>(104 weeks) | No                              | Open-label       | Depression                    | 20-80 mg      | Adult (18-69 years)                                                                           |
| CN105-055                  | II/III | Acute<br>(8 week titration)<br>Extension $\geq$ 6 mos<br>(44 weeks)                                                                                                 | No                              | Open-label       | Depression                    | 10-80 mg      | Adult (19-84 years)<br><i>Also Elderly, since some<br/>subjects <math>\geq</math>65 years</i> |
| CN105-071                  | II/III | 10 week double-blind<br>2 week placebo<br>withdrawal                                                                                                                | Yes (placebo)                   | Double-blind     | Mood-panic disorder           | 5-60 mg       | Adult (19-63 years)                                                                           |
| <b>Gepirone IR Studies</b> |        |                                                                                                                                                                     |                                 |                  |                               |               |                                                                                               |
| CN105-007                  | I      | Acute<br>(4 single doses)                                                                                                                                           | No                              | Open-label       | Absolute<br>bioavailability & | 1-20 mg       | Adult (18-39 years)                                                                           |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No.           | Phase  | Duration                                                      | Controlled?<br>(Control Drug) | Blinded or Open?        | Indication                                                         | Gepirone Dose          | Population<br>(Adult, Elderly)                                                |
|---------------------|--------|---------------------------------------------------------------|-------------------------------|-------------------------|--------------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------|
| CN105-012           | I      | Acute<br>(4 single doses)                                     | No                            | Open-label              | mass balance<br>Site of gepirone<br>absorption                     | 20 mg                  | Adult (20-35 years)                                                           |
| CN105-009           | I      | Acute<br>(7 days)                                             | No                            | Open-label              | Tolerance in healthy<br>subjects                                   | 5 mg                   | Adult (25-49 years)                                                           |
| 030L1-0002-<br>1869 | I      | Acute<br>(28 days)                                            | Yes (placebo)                 | Double-blind            | PK study                                                           | 10-50 mg               | Adult (18-43 years)                                                           |
| 59B4A-001-<br>2579  | I      | Acute<br>(10 days)                                            | No                            | Open-label              | PK study                                                           | 5-30 mg                | Adult (18-40 years)                                                           |
| 030L1-0001-<br>1700 | I      | Acute<br>(5 single doses)                                     | Yes (placebo)                 | Double-blind            | PK study                                                           | 5-100 mg               | Adult (18-38 years)                                                           |
| 59B4B-001-<br>2587  | I      | Acute<br>(2 single doses)                                     | No                            | Open-label              | Food effect                                                        | 20 mg                  | Adult (18-39 years)                                                           |
| CN105-026           | I      | Acute<br>(5 single doses)                                     | No                            | Open-label              | Bioavailability ER<br>vs. IR*                                      | 20 mg                  | Adult (19-36 years)                                                           |
| 03A7D-001           | I      | Acute<br>(3 single doses)                                     | Yes                           | Double-blind            | PK & neuroendocrine<br>effects                                     | 10-20 mg               | Adult (22-32 years)                                                           |
| CN105-005           | I      | Acute<br>(7 days)                                             | No                            | Open-label              | Young vs. elderly                                                  | 10 mg                  | Adult (18-40 years)<br>Elderly (64-81 years)                                  |
| CN105-025           | I      | Acute<br>(7 days)                                             | No                            | Open-label              | Effect of<br>dextromethorphan<br>metabolizer<br>polymorphism on PK | 5 mg and<br>10 mg/day  | Adult (18-35 years)                                                           |
| CN105-023           | I      | Acute<br>(9 days)                                             | No                            | Open-label              | Renal impairment                                                   | 15 mg and<br>30 mg/day | Only 1 subject treated                                                        |
| 03A7A-003           | II/III | Acute<br>(8 weeks)                                            | Yes (placebo)                 | Double-blind            | Depression                                                         | 10-90 mg               | Adult (24-64 years)                                                           |
| 03A7C-001A-<br>2486 | II/III | Acute<br>(8 weeks)                                            | Yes (placebo)                 | Double-blind            | Depression                                                         | 5-90 mg                | Adult (20-70 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| 03A7C-001A-<br>2496 | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks) | Yes (placebo)                 | Double-blind            | Depression                                                         | 5-90 mg                | Adult (20-73 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| 03A7A-002           | II/III | Acute<br>(6 week titration)                                   | Yes (placebo)                 | Open-label<br>titration | Depression                                                         | 10-90 mg               | Adult (25-75 years)<br><i>Also Elderly, since some</i>                        |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No.  | Phase  | Duration                                                                                | Controlled?<br>(Control Drug)   | Blinded or Open?                                 | Indication          | Gepirone Dose | Population<br>(Adult, Elderly)                                                                             |
|------------|--------|-----------------------------------------------------------------------------------------|---------------------------------|--------------------------------------------------|---------------------|---------------|------------------------------------------------------------------------------------------------------------|
| 03A7C-001B | II/III | Extension<br>(6 weeks)<br>Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks) | Yes (placebo)                   | Double-blind<br>randomized phase<br>Double-blind | Depression          | 5-90 mg       | <i>subjects ≥65 years</i><br>Adult (19-68 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| CN105-043  | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                           | Yes (placebo)                   | Double-blind                                     | Depression          | 5-30 mg       | Adult (21-62 years)                                                                                        |
| CN105-037  | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                           | Yes (placebo and<br>imipramine) | Double-blind                                     | Depression          | 2-30 mg       | Adult (18-71 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i>                              |
| CN105-022  | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                           | Yes (placebo and<br>fluoxetine) | Double-blind                                     | Depression          | 5-30 mg       | Adult (19-79 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i>                              |
| CN105-028  | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                           | Yes (placebo and<br>imipramine) | Double-blind                                     | Depression          | 5-30 mg       | Adult (18-73 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i>                              |
| CN105-029  | II/III | Acute<br>(8 week titration)<br>Extension ≥6 mos<br>(44 weeks)                           | Yes (placebo and<br>imipramine) | Double-blind                                     | Depression          | 5-45 mg       | Adult (21-72 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i>                              |
| 030L1-0004 | II/III | Acute<br>(6 weeks)                                                                      | No                              | Open-label                                       | Depression          | 5-90 mg       | Adult (26-67 years)                                                                                        |
| 03A7A-001  | II/III | Acute<br>(8 weeks)                                                                      | No                              | Open-label                                       | Atypical depression | 5-90 mg       | Adult (25-51 years)                                                                                        |
| CN105-039  | II/III | Acute<br>(3 weeks)                                                                      | No                              | Open-label                                       | Depression          | 5-50 mg       | Adult (36-68 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i>                              |
| 030L1-0003 | II/III | Acute<br>(6 weeks)                                                                      | No                              | Open-label                                       | Anxiety             | 10-60 mg      | Adult (24-58 years)                                                                                        |
| 03A7B-001  | II/III | Acute                                                                                   | Yes (placebo)                   | Double-blind                                     | Anxiety             | 10-60 mg      | Adult (20-65 years)                                                                                        |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No. | Phase  | Duration                                                                         | Controlled?<br>(Control Drug)   | Blinded or Open? | Indication                        | Gepirone Dose | Population<br>(Adult, Elderly)                                                            |
|-----------|--------|----------------------------------------------------------------------------------|---------------------------------|------------------|-----------------------------------|---------------|-------------------------------------------------------------------------------------------|
| 03A7B-002 | II/III | (6 weeks)<br>Acute<br>(8 week titration)<br>Extension $\geq$ 6 mos<br>(44 weeks) | Yes (placebo)                   | Double-blind     | Anxiety                           | 10-90 mg      | Adult (20-75 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| 03A7B-004 | II/III | Acute<br>(6 week titration)<br>Extension $\geq$ 6 mos<br>(46 weeks)              | Yes (placebo)                   | Double-blind     | Anxiety                           | 1-60 mg       | Adult (18-71 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-001 | II/III | Acute<br>(8 week DB phase)<br>Substitution phase<br>(2 weeks)                    | Yes (placebo and<br>diazepam)   | Double-blind     | Anxiety                           | 5-45 mg       | Adult (18-77 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-019 | II/III | Acute<br>(8 week titration)<br>Extension $\geq$ 6 mos<br>(44 weeks)              | No                              | Open-label       | Non-psychotic mood<br>disorder    | 5-30 mg       | Adult (18-77 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-041 | II/II  | Long-term<br>(10 weeks)                                                          | Yes (placebo)                   | Double-blind     | Obsessive-<br>compulsive disorder | 5-30 mg       | Adult (20-74 years)                                                                       |
| CN105-045 | II/II  | Long-term<br>(12 weeks)                                                          | Yes (placebo)                   | Double-blind     | Substance abuse                   | 5-30 mg       | Adult (21-52 years)                                                                       |
| CN105-031 | II/II  | Acute<br>(6 week double-<br>blind)<br>Extension<br>(12 weeks)                    | Yes (placebo)                   | Double-blind     | Anxiety                           | 2-12 mg       | Adult (23-74 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-017 | II/II  | Acute<br>(6 week double-<br>blind)<br>Withdrawal<br>(2 weeks)                    | Yes (placebo and<br>bromazepam) | Double-blind     | Anxiety                           | 5-30 mg       | Adult (19-70 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-050 | II/III | Acute<br>(8 week titration)<br>Extension $\geq$ 6 mos<br>(44 weeks)              | No                              | Open-label       | Mood disorder                     | 5-50 mg       | Adult (26-67 years)<br><i>Also Elderly, since some subjects <math>\geq</math>65 years</i> |
| CN105-003 | II/III | Acute<br>(8 week titration)                                                      | Yes (placebo)                   | Double-blind     | Anxiety                           | 5-45 mg       | Adult (22-68 years)<br><i>Also Elderly, since some</i>                                    |

**Table 1 Sponsor's Table of All Gepirone (ER & IR) Studies**

| Study No. | Phase  | Duration                                                                                 | Controlled?<br>(Control Drug) | Blinded or Open? | Indication | Gepirone Dose | Population<br>(Adult, Elderly)                                                |
|-----------|--------|------------------------------------------------------------------------------------------|-------------------------------|------------------|------------|---------------|-------------------------------------------------------------------------------|
| CN105-004 | II/III | Extension ≥6 mos<br>(44 weeks)<br>Acute<br>(8 week titration)<br>Extension<br>(18 weeks) | Yes (placebo and<br>diazepam) | Double-blind     | Anxiety    | 5-45 mg       | Adult (23-49 years)<br><i>subjects ≥65 years</i>                              |
| CN105-018 | II/III | Acute<br>(6 week titration)<br>Extension ≥6 mos<br>(46 weeks)                            | No                            | Open-label       | Anxiety    | 2-12 mg       | Adult (19-67 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |
| CN105-036 | II/III | Acute<br>(6 week)                                                                        | Yes (placebo and<br>diazepam) | Double-blind     | Anxiety    | 1-12 mg       | Adult (18-72 years)<br><i>Also Elderly, since some<br/>subjects ≥65 years</i> |

\*Study CN105-026 listed under ER and IR studies.

**Table 2 Studies Included in the Gepirone ER Second NDA Amendment**

| Study                                | Design                                                                                 | Treatments           | Number of Subjects* | Duration (weeks)  |
|--------------------------------------|----------------------------------------------------------------------------------------|----------------------|---------------------|-------------------|
| FK-GBE-007                           | R, DB, PC                                                                              | Gepirone ER 40-80 mg | 124                 | 8                 |
|                                      |                                                                                        | Placebo              | 124                 |                   |
| FK-GBE-008                           | R, DB, PC                                                                              | Gepirone ER 40-80 mg | 102                 | 8                 |
|                                      |                                                                                        | Placebo              | 104                 |                   |
| 134006                               | R, DB, PC, AC                                                                          | Gepirone ER 40-80 mg | 147                 | 8                 |
|                                      |                                                                                        | Paroxetine 10-40 mg  | 142                 |                   |
|                                      |                                                                                        | Placebo              | 148                 |                   |
| 134017                               | R, DB, PC                                                                              | Gepirone ER 40-80 mg | 165                 | 8                 |
|                                      |                                                                                        | Fluoxetine 20-40 mg  | 166                 |                   |
|                                      |                                                                                        | Placebo              | 164                 |                   |
| 134023                               | R, DB, PC                                                                              | Gepirone ER 40-80 mg | 127                 | 9                 |
|                                      |                                                                                        | Placebo              | 127                 |                   |
| C-1762                               | R, DB, AC, Long-term study                                                             | Gepirone ER 40-80 mg | 200                 | 26                |
|                                      |                                                                                        | Fluoxetine 20-40 mg  | 208                 |                   |
| 28722                                | OL, single center                                                                      | Gepirone ER 20-80 mg | 16                  | 8 + optional      |
|                                      |                                                                                        | Fluoxetine 20-40 mg  | 17                  | 16 week extension |
| 28723                                | OL, single center                                                                      | Gepirone ER 20-80 mg | 19                  | 8 + optional      |
|                                      |                                                                                        | Fluoxetine 20-40 mg  | 18                  | 16 week extension |
| <b>Extension Studies</b>             |                                                                                        |                      |                     |                   |
| 134501                               | OL extension of 134001, 134002, and 134015; includes 407 previously untreated subjects | Gepirone ER 20-80 mg | 684                 | 44-104            |
| 134503                               | R, DB extension of 134006                                                              | Gepirone ER 40-80 mg | 68                  | 20                |
|                                      |                                                                                        | Paroxetine 10-40 mg  | 72                  |                   |
|                                      |                                                                                        | Placebo              | 57                  |                   |
| 134506                               | R, DB extension of 134017                                                              | Gepirone ER 40-80 mg | 64                  | 20                |
|                                      |                                                                                        | Fluoxetine 20-40 mg  | 76                  |                   |
|                                      |                                                                                        | Placebo              | 68                  |                   |
| <b>Clinical Pharmacology Studies</b> |                                                                                        |                      |                     |                   |

**Table 2 Studies Included in the Gepirone ER Second NDA Amendment**

|       |                                                    |                                                        |    |   |
|-------|----------------------------------------------------|--------------------------------------------------------|----|---|
| 28725 | Single-dose, 4-period crossover, food effect study | Gepirone ER 20 mg (fasting, HF meal, MF meal, LF meal) | 32 | - |
| 28727 | Single-dose, 4-period crossover, food effect study | Gepirone ER 20 mg (fasting, HF meal, MF meal, LF meal) | 32 | - |

Abbreviations: AC = active-controlled; DB = double-blind; ER = extended-release; HF = high-fat; LF = low-fat; MF = medium-fat; OL = open-label; PC = placebo-controlled; R = randomized.

\*All subjects treated population.

**Table 3 Sponsor's Distribution of Participants in Gepirone Studies by Development Phase, Treatment Group, and 2003 vs. 2007 Safety Database**

| Study Phase                  | 2003 ISS |             |       | Control |         | Overall Total |
|------------------------------|----------|-------------|-------|---------|---------|---------------|
|                              | ER       | Gepirone IR | Total | Active  | Placebo |               |
| <b>Phase I</b>               | 582      | 204         | 786   | 30      | 108     | 924           |
| <b>Phase II/III</b>          | 2217     | 1859        | 4076  | 848     | 1816    | 6740          |
| <b>TOTAL</b>                 | 2799     | 2063        | 4862  | 878     | 1924    | 7664          |
| <b>Updated Exposure 2007</b> |          |             |       |         |         |               |
| <b>Phase I</b>               | 688      | 204         | 892   | 30      | 108     | 1030          |
| <b>Phase II/III</b>          | 3117     | 1859        | 4976  | 1399    | 2483    | 8858          |
| <b>TOTAL</b>                 | 3805     | 2063        | 5868  | 1429    | 2591    | 9888          |

Abbreviations: ISS = Integrated Summary of Safety.

Note: In Phase I cross-over studies, subjects may be counted twice in the total column. In Phase II/III studies, subjects who were given different treatments between the acute and extension phases may be counted twice in the total column.

**Sponsor's Table 4 Number (%) of Subjects with Serious Adverse Events Regardless of Relationship to Study Drug by Preferred Term and Treatment for Serious Adverse Events Reported by at Least 2 Subjects in any Treatment Group (All Subjects Treated in Gepirone ER and IR Phase II/III Studies)**

| Preferred Term                                          | Gepirone         |                  |                   | Placebo<br>(N=2483) | Antidepressants       |                       |                       |
|---------------------------------------------------------|------------------|------------------|-------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                                         | ER<br>(N=3117)   | IR<br>(N=1859)   | ER+IR<br>(N=4976) |                     | Fluoxetine<br>(N=700) | Paroxetine<br>(N=276) | Imipramine<br>(N=240) |
| <b>Subjects with at Least 1 SAE</b>                     | <b>77 (2.5%)</b> | <b>45 (2.4%)</b> | <b>122 (2.5%)</b> | <b>29 (1.2%)</b>    | <b>22 (3.1%)</b>      | <b>14 (5.1%)</b>      | <b>2 (0.8%)</b>       |
| <b>Psychiatric Disorders</b>                            | <b>27 (0.9%)</b> | <b>16 (0.9%)</b> | <b>43 (0.9%)</b>  | <b>6 (0.2%)</b>     | <b>6 (0.9%)</b>       | <b>6 (2.2%)</b>       | <b>0</b>              |
| 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                     |
| <b>Infections and Infestations</b>                      | <b>8 (0.3%)</b>  | <b>1(0.1%)</b>   | <b>9 (0.2%)</b>   | <b>7 (0.3%)</b>     | <b>3 (0.4%)</b>       | <b>3 (1.1%)</b>       | <b>0</b>              |
| 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                     |
| <b>Pregnancy, Puerperium, and Perinatal Conditions</b>  | <b>10 (0.3%)</b> | <b>4 (0.2%)</b>  | <b>14 (0.3%)</b>  | <b>1 (0.0%)</b>     | <b>5 (0.7%)</b>       | <b>0</b>              | <b>0</b>              |
| Pregnancy                                               | 10 (0.3%)        | 3 (0.2%)         | 13 (0.3%)         | 1 (0.0%)            | 5 (0.7%)              | 0                     | 0                     |
| <b>Injury, Poisoning &amp; Procedural Complications</b> | <b>6 (0.2%)</b>  | <b>4 (0.2%)</b>  | <b>10 (0.2%)</b>  | <b>3 (0.1%)</b>     | <b>4 (0.6%)</b>       | <b>0</b>              | <b>2 (0.8%)</b>       |
| 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                     |
| <b>Nervous System Disorders</b>                         | <b>8 (0.3%)</b>  | <b>5 (0.3%)</b>  | <b>13 (0.3%)</b>  | <b>2 (0.1%)</b>     | <b>0</b>              | <b>1 (0.4%)</b>       | <b>0</b>              |
| 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                     |
| <b>Cardiac Disorders</b>                                | <b>5 (0.2%)</b>  | <b>1 (0.1%)</b>  | <b>6 (0.1%)</b>   | <b>1 (0.0%)</b>     | <b>2 (0.3%)</b>       | <b>2 (0.7%)</b>       | <b>0</b>              |
| 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                     |
| <b>Reproductive System and Breast Disorders</b>         | <b>4 (0.1%)</b>  | <b>3 (0.2%)</b>  | <b>7 (0.1%)</b>   | <b>1 (0.0%)</b>     | <b>0</b>              | <b>3 (1.1%)</b>       | <b>0</b>              |
| Benign Prostatic Hyperplasia                            | 0                | 0                | 0                 | 0                   | 0                     | 2 (0.7%)              | 0                     |

**Sponsor's Table 4 Number (%) of Subjects with Serious Adverse Events Regardless of Relationship to Study Drug by Preferred Term and Treatment for Serious Adverse Events Reported by at Least 2 Subjects in any Treatment Group (All Subjects Treated in Gepirone ER and IR Phase II/III Studies)**

| Preferred Term                                              | Gepirone        |                 |                   | Placebo<br>(N=2483) | Antidepressants       |                       |                       |
|-------------------------------------------------------------|-----------------|-----------------|-------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                                             | ER<br>(N=3117)  | IR<br>(N=1859)  | ER+IR<br>(N=4976) |                     | Fluoxetine<br>(N=700) | Paroxetine<br>(N=276) | Imipramine<br>(N=240) |
| Breast Mass                                                 | 0               | 2 (0.1%)        | 2 (0.0%)          | 0                   | 0                     | 0                     | 0                     |
| <b>Renal and Urinary Disorders</b>                          | <b>5 (0.2%)</b> | <b>2 (0.1%)</b> | <b>7 (0.1%)</b>   | <b>0</b>            | <b>0</b>              | <b>1 (0.4%)</b>       | <b>0</b>              |
| Nephrolithiasis                                             | 3 (0.1%)        | 1 (0.1%)        | 4 (0.1%)          | 0                   | 0                     | 0                     | 0                     |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      | <b>1 (0.0%)</b> | <b>0</b>        | <b>1 (0.0%)</b>   | <b>3 (0.1%)</b>     | <b>2 (0.3%)</b>       | <b>2 (0.7%)</b>       | <b>0</b>              |
| Asthma                                                      | 0               | 0               | 0                 | 2 (0.1%)            | 0                     | 1 (0.4%)              | 0                     |
| <b>General Disorders and Administrative Site Conditions</b> | <b>1 (0.0%)</b> | <b>2 (0.1%)</b> | <b>3 (0.1%)</b>   | <b>2 (0.1%)</b>     | <b>2 (0.3%)</b>       | <b>0</b>              | <b>0</b>              |
| Hernia                                                      | 0               | 2 (0.1%)        | 2 (0.0%)          | 0                   | 0                     | 0                     | 0                     |
| <b>Hepatobiliary Disorders</b>                              | <b>2 (0.1%)</b> | <b>1 (0.1%)</b> | <b>3 (0.1%)</b>   | <b>1 (0.0%)</b>     | <b>1 (0.1%)</b>       | <b>1 (0.4%)</b>       | <b>0</b>              |
| Cholelithiasis                                              | 2 (0.1%)        | 0               | 2 (0.0%)          | 0                   | 1 (0.1%)              | 1 (0.4%)              | 0                     |
| <b>Investigations</b>                                       | <b>3 (0.1%)</b> | <b>2 (0.1%)</b> | <b>5 (0.1%)</b>   | <b>0</b>            | <b>0</b>              | <b>0</b>              | <b>0</b>              |
| 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                     |

WBC: white blood cell

**Sponsor Table 5 Number (%) of Subjects with Adverse Events Leading to Premature Withdrawal and Most Frequently Reported ( $\geq 1\%$  of all Gepirone Subjects) Body Systems and AEs (All Subjects Treated in Gepirone ER and IR Phase II/III Studies)**

| Body System<br>Preferred Term                                      | Gepirone           |                    |                    | Placebo<br>(N=2483) | Antidepressants       |                       |                       |
|--------------------------------------------------------------------|--------------------|--------------------|--------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                                                    | ER<br>(N=3117)     | IR<br>(N=1859)     | ER+IR<br>(N=4976)  |                     | Fluoxetine<br>(N=700) | Paroxetine<br>(N=276) | Imipramine<br>(N=240) |
| <b>Subjects with at Least 1 AE leading to Premature Withdrawal</b> | <b>509 (16.3%)</b> | <b>392 (21.1%)</b> | <b>901 (18.1%)</b> | <b>168 (6.8%)</b>   | <b>65 (9.3%)</b>      | <b>32 (11.6%)</b>     | <b>57 (23.8%)</b>     |
| <b>Nervous System Disorders</b>                                    | <b>168 (5.4%)</b>  | <b>229 (12.3%)</b> | <b>397 (8.0%)</b>  | <b>59 (2.4%)</b>    | <b>12 (1.7%)</b>      | <b>3 (1.1%)</b>       | <b>22 (9.2%)</b>      |
| Dizziness                                                          | 92 (3.0%)          | 124 (6.7%)         | 216 (4.3%)         | 13 (0.5%)           | 2 (0.3%)              | 1 (0.4%)              | 7 (2.9%)              |
| Headache                                                           | 42 (1.3%)          | 82 (4.4%)          | 124 (2.5%)         | 25 (1.0%)           | 6 (0.9%)              | 0                     | 9 (3.8%)              |
| <b>Psychiatric Disorders</b>                                       | <b>158 (5.1%)</b>  | <b>124 (6.7%)</b>  | <b>282 (5.7%)</b>  | <b>55 (2.2%)</b>    | <b>26 (3.7%)</b>      | <b>11 (4.0%)</b>      | <b>11 (4.6%)</b>      |
| Insomnia                                                           | 35 (1.1%)          | 35 (1.9%)          | 70 (1.4%)          | 15 (0.6%)           | 2 (0.3%)              | 2 (0.7%)              | 1 (0.4%)              |
| Anxiety                                                            | 37 (1.2%)          | 22 (1.2%)          | 59 (1.2%)          | 9 (0.4%)            | 5 (0.7%)              | 0                     | 0                     |
| <b>Gastrointestinal Disorders</b>                                  | <b>123 (3.9%)</b>  | <b>154 (8.3%)</b>  | <b>277 (5.6%)</b>  | <b>45 (1.8%)</b>    | <b>15 (2.1%)</b>      | <b>6 (2.2%)</b>       | <b>25 (10.4%)</b>     |
| Nausea                                                             | 82 (2.6%)          | 104 (5.6%)         | 186 (3.7%)         | 20 (0.8%)           | 5 (0.7%)              | 4 (1.4%)              | 6 (2.5%)              |
| <b>General Disorders &amp; Administrative Site Conditions</b>      | <b>55 (1.8%)</b>   | <b>72 (3.9%)</b>   | <b>127 (2.6%)</b>  | <b>23 (0.9%)</b>    | <b>2 (0.3%)</b>       | <b>1 (0.4%)</b>       | <b>9 (3.8%)</b>       |
| Investigations                                                     | 34 (1.1%)          | 22 (1.2%)          | 56 (1.1%)          | 15 (0.6%)           | 1 (0.1%)              | 1 (0.4%)              | 8 (3.3%)              |
| <b>Skin &amp; Subcutaneous Tissue Disorder</b>                     | <b>20 (0.6%)</b>   | <b>30 (1.6%)</b>   | <b>50 (1.0%)</b>   | <b>11 (0.4%)</b>    | <b>3 (0.4%)</b>       | <b>2 (0.7%)</b>       | <b>10 (4.2%)</b>      |

Subjects reporting the same AE more than once are counted only once.

**Sponsor's Table 6 Disposition of Subjects by Treatment Group: Acute Phase – All Phase II/III Studies**

|                  | Gepirone     |              |              | Placebo      | Antidepressants |             |             | Anxiolytics |            |
|------------------|--------------|--------------|--------------|--------------|-----------------|-------------|-------------|-------------|------------|
|                  | ER           | IR           | ER+IR        |              | Fluoxetine      | Paroxetine  | Imipramine  | Bromazepam  | Diazepam   |
| Treated          | <b>2441</b>  | <b>1859</b>  | <b>4300</b>  | <b>2325</b>  | <b>653</b>      | <b>276</b>  | <b>240</b>  | <b>73</b>   | <b>110</b> |
| Completed        | 1587 (65.0%) | 1023 (55.0%) | 2610 (60.7%) | 1548 (66.6%) | 492 (75.3%)     | 203 (73.6%) | 130 (54.2%) | 64 (87.7%)  | 68 (61.8%) |
| Discontinued     | 852 (34.9%)  | 836 (45.0%)  | 1688 (39.3%) | 777 (33.4%)  | 161 (24.7%)     | 73 (26.4%)  | 110 (45.8%) | 9 (12.3%)   | 42 (38.2%) |
| Adverse event    | 271 (11.1%)  | 341 (18.3%)  | 612 (14.2%)  | 125 (5.4%)   | 38 (5.8%)       | 22 (8.0%)   | 44 (18.3%)  | 3 (4.1%)    | 15 (13.6%) |
| Lack of efficacy | 148 (6.1%)   | 208 (11.2%)  | 356 (8.3%)   | 294 (12.6%)  | 34 (5.2%)       | 14 (5.1%)   | 15 (6.3%)   | 2 (2.7%)    | 5 (4.5%)   |
| Other            | 433 (17.7%)  | 287 (15.4%)  | 720 (16.7%)  | 358 (15.4%)  | 89 (13.6%)      | 37 (13.4%)  | 51 (21.3%)  | 4 (5.5%)    | 22 (20.0%) |

**Sponsor Table 7 Number (%) of Subjects with Adverse Events Leading to Premature Withdrawal and Most Frequently Reported ( $\geq 1\%$  of Gepirone Subjects) Body Systems and AEs by Severity (All Subjects Treated in Gepirone ER and IR Phase II/III Studies)**

| Body System<br>Preferred Term                            | Gepirone           |                    |                    |                     | Antidepressants       |                       |                       |
|----------------------------------------------------------|--------------------|--------------------|--------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                                          | ER<br>(N=3117)     | IR<br>(N=1859)     | ER+IR<br>(N=4976)  | Placebo<br>(N=2483) | Fluoxetine<br>(N=700) | Paroxetine<br>(N=276) | Imipramine<br>(N=240) |
| <b>Subjects with at Least 1 AE Leading to Withdrawal</b> | <b>509 (16.3%)</b> | <b>392 (21.1%)</b> | <b>901 (18.1%)</b> | <b>168 (6.8%)</b>   | <b>65 (9.3%)</b>      | <b>32 (11.6%)</b>     | <b>57 (23.8%)</b>     |
| Mild                                                     | 68 (2.2%)          | 64 (3.4%)          | 132 (2.7%)         | 21 (0.8%)           | 6 (0.9%)              | 4 (1.4%)              | 9 (3.8%)              |
| Moderate                                                 | 245 (7.9%)         | 175 (9.4%)         | 420 (8.4%)         | 74 (3.0%)           | 29 (4.1%)             | 17 (6.2%)             | 23 (9.6%)             |
| Severe                                                   | 196 (6.3%)         | 153 (8.2%)         | 349 (7.0%)         | 73 (2.9%)           | 30 (4.3%)             | 11 (4.0%)             | 25 (10.4%)            |
| <b>Nervous System Disorders</b>                          | <b>168 (5.4%)</b>  | <b>229 (12.3%)</b> | <b>397 (8.0%)</b>  | <b>59 (2.4%)</b>    | <b>12 (1.7%)</b>      | <b>3 (1.1%)</b>       | <b>22 (9.2%)</b>      |
| Mild                                                     | 29 (0.9%)          | 52 (2.8%)          | 81 (1.6%)          | 13 (0.5%)           | 3 (0.4%)              | 1 (0.4%)              | 4 (1.7%)              |
| Moderate                                                 | 84 (2.7%)          | 113 (6.1%)         | 197 (4.0%)         | 29 (1.2%)           | 6 (0.9%)              | 2 (0.7%)              | 6 (2.5%)              |
| Severe                                                   | 55 (1.8%)          | 64 (3.4%)          | 119 (2.4%)         | 17 (0.7%)           | 3 (0.4%)              | 0                     | 12 (5.0%)             |
| Dizziness                                                | 92 (3.0%)          | 124 (6.7%)         | 216 (4.3%)         | 13 (0.5%)           | 2 (0.3%)              | 1 (0.4%)              | 7 (2.9%)              |
| Mild                                                     | 25 (0.8%)          | 39 (2.1%)          | 64 (1.3%)          | 3 (0.1%)            | 1 (0.1%)              | 1 (0.4%)              | 1 (0.4%)              |
| Moderate                                                 | 45 (1.4%)          | 61 (3.3%)          | 106 (2.1%)         | 4 (0.2%)            | 1 (0.1%)              | 0                     | 6 (2.5%)              |
| Severe                                                   | 22 (0.7%)          | 24 (1.3%)          | 46 (0.9%)          | 6 (0.2%)            | 0                     | 0                     | 0                     |
| Headache                                                 | 42 (1.3%)          | 82 (4.4%)          | 124 (2.5%)         | 25 (1.0%)           | 6 (0.9%)              | 0                     | 9 (3.8%)              |
| Mild                                                     | 8 (0.3%)           | 19 (1.0%)          | 27 (0.5%)          | 4 (0.2%)            | 2 (0.3%)              | 0                     | 1 (0.4%)              |
| Moderate                                                 | 22 (0.7%)          | 41 (2.2%)          | 63 (1.3%)          | 16 (0.6%)           | 3 (0.4%)              | 0                     | 1 (0.4%)              |
| Severe                                                   | 12 (0.4%)          | 22 (1.2%)          | 34 (0.7%)          | 5 (0.2%)            | 1 (0.1%)              | 0                     | 7 (2.9%)              |
| <b>Psychiatric Disorders</b>                             | <b>158 (5.1%)</b>  | <b>124 (6.7%)</b>  | <b>282 (5.7%)</b>  | <b>55 (2.2%)</b>    | <b>26 (3.7%)</b>      | <b>11 (4.0%)</b>      | <b>11 (4.6%)</b>      |
| Mild                                                     | 14 (0.4%)          | 22 (1.2%)          | 36 (0.7%)          | 9 (0.4%)            | 2 (0.3%)              | 0                     | 3 (1.3%)              |
| Moderate                                                 | 72 (2.3%)          | 51 (2.7%)          | 123 (2.5%)         | 16 (0.6%)           | 11 (1.6%)             | 5 (1.8%)              | 6 (2.5%)              |
| Severe                                                   | 72 (2.3%)          | 51 (2.7%)          | 123 (2.5%)         | 30 (1.2%)           | 13 (1.9%)             | 6 (2.2%)              | 2 (0.8%)              |
| Insomnia                                                 | 35 (1.1%)          | 35 (1.9%)          | 70 (1.4%)          | 15 (0.6%)           | 2 (0.3%)              | 2 (0.7%)              | 1 (0.4%)              |
| Mild                                                     | 4 (0.1%)           | 6 (0.3%)           | 10 (0.2%)          | 2 (0.1%)            | 0                     | 0                     | 0                     |
| Moderate                                                 | 22 (0.7%)          | 18 (1.0%)          | 40 (0.8%)          | 7 (0.3%)            | 1 (0.1%)              | 0                     | 1 (0.4%)              |
| Severe                                                   | 9 (0.3%)           | 11 (0.6%)          | 20 (0.4%)          | 6 (0.2%)            | 1 (0.1%)              | 2 (0.7%)              | 0                     |
| Anxiety                                                  | 37 (1.2%)          | 22 (1.2%)          | 59 (1.2%)          | 9 (0.4%)            | 5 (0.7%)              | 0                     | 0                     |
| Mild                                                     | 2 (0.1%)           | 2 (0.1%)           | 4 (0.1%)           | 0                   | 0                     | 0                     | 0                     |
| Moderate                                                 | 18 (0.6%)          | 7 (0.4%)           | 25 (0.5%)          | 2 (0.1%)            | 1 (0.1%)              | 0                     | 0                     |

**Sponsor Table 7 Number (%) of Subjects with Adverse Events Leading to Premature Withdrawal and Most Frequently Reported ( $\geq 1\%$  of Gepirone Subjects) Body Systems and AEs by Severity (All Subjects Treated in Gepirone ER and IR Phase II/III Studies)**

| Body System<br>Preferred Term                                         | Gepirone          |                   |                   |                     | Antidepressants       |                       |                       |
|-----------------------------------------------------------------------|-------------------|-------------------|-------------------|---------------------|-----------------------|-----------------------|-----------------------|
|                                                                       | ER<br>(N=3117)    | IR<br>(N=1859)    | ER+IR<br>(N=4976) | Placebo<br>(N=2483) | Fluoxetine<br>(N=700) | Paroxetine<br>(N=276) | Imipramine<br>(N=240) |
| Severe                                                                | 17 (0.5%)         | 13 (0.7%)         | 30 (0.6%)         | 7 (0.3%)            | 4 (0.6%)              | 0                     | 0                     |
| <b>Gastrointestinal Disorders</b>                                     | <b>123 (3.9%)</b> | <b>154 (8.3%)</b> | <b>277 (5.6%)</b> | <b>45 (1.8%)</b>    | <b>15 (2.1%)</b>      | <b>6 (2.2%)</b>       | <b>25 (10.4%)</b>     |
| Mild                                                                  | 17 (0.5%)         | 46 (2.5%)         | 63 (1.3%)         | 11 (0.4%)           | 2 (0.3%)              | 1 (0.4%)              | 7 (2.9%)              |
| Moderate                                                              | 73 (2.3%)         | 71 (3.8%)         | 144 (2.9%)        | 21 (0.8%)           | 7 (1.0%)              | 3 (1.1%)              | 12 (5.0%)             |
| Severe                                                                | 33 (1.1%)         | 37 (2.0%)         | 70 (1.4%)         | 13 (0.5%)           | 6 (0.9%)              | 2 (0.7%)              | 6 (2.5%)              |
| Nausea                                                                | 82 (2.6%)         | 104 (5.6%)        | 186 (3.7%)        | 20 (0.8%)           | 5 (0.7%)              | 4 (1.4%)              | 6 (2.5%)              |
| Mild                                                                  | 13 (0.4%)         | 36 (1.9%)         | 49 (1.0%)         | 4 (0.2%)            | 1 (0.1%)              | 1 (0.4%)              | 1 (0.4%)              |
| Moderate                                                              | 51 (1.6%)         | 41 (2.2%)         | 92 (1.8%)         | 10 (0.4%)           | 3 (0.4%)              | 2 (0.7%)              | 4 (1.7%)              |
| Severe                                                                | 18 (0.6%)         | 27 (1.5%)         | 45 (0.9%)         | 6 (0.2%)            | 1 (0.1%)              | 1 (0.4%)              | 1 (0.4%)              |
| <b>General Disorders &amp;<br/>Administrative Site<br/>Conditions</b> | <b>55 (1.8%)</b>  | <b>72 (3.9%)</b>  | <b>127 (2.6%)</b> | <b>23 (0.9%)</b>    | <b>2 (0.3%)</b>       | <b>1 (0.4%)</b>       | <b>9 (3.8%)</b>       |
| Mild                                                                  | 14 (0.4%)         | 21 (1.1%)         | 35 (0.7%)         | 5 (0.2%)            | 1 (0.1%)              | 0                     | 3 (1.3%)              |
| Moderate                                                              | 30 (1.0%)         | 37 (2.0%)         | 67 (1.3%)         | 12 (0.5%)           | 1 (0.1%)              | 1 (0.4%)              | 5 (2.1%)              |
| Severe                                                                | 11 (0.4%)         | 14 (0.8%)         | 25 (0.5%)         | 6 (0.2%)            | 0                     | 0                     | 1 (0.4%)              |
| <b>Investigations</b>                                                 | <b>34 (1.1%)</b>  | <b>22 (1.2%)</b>  | <b>56 (1.1%)</b>  | <b>15 (0.6%)</b>    | <b>1 (0.1%)</b>       | <b>1 (0.4%)</b>       | <b>8 (3.3%)</b>       |
| Mild                                                                  | 7 (0.2%)          | 6 (0.3%)          | 13 (0.3%)         | 5 (0.2%)            | 0                     | 0                     | 0                     |
| Moderate                                                              | 16 (0.5%)         | 10 (0.5%)         | 26 (0.5%)         | 8 (0.3%)            | 1 (0.1%)              | 1 (0.4%)              | 7 (2.9%)              |
| Severe                                                                | 11 (0.4%)         | 6 (0.3%)          | 17 (0.3%)         | 2 (0.1%)            | 0                     | 0                     | 1 (0.4%)              |
| <b>Skin &amp; Subcutaneous Tissue<br/>Disorders</b>                   | <b>20 (0.6%)</b>  | <b>30 (1.6%)</b>  | <b>50 (1.0%)</b>  | <b>11 (0.4%)</b>    | <b>3 (0.4%)</b>       | <b>2 (0.7%)</b>       | <b>10 (4.2%)</b>      |
| Mild                                                                  | 6 (0.2%)          | 14 (0.8%)         | 20 (0.4%)         | 6 (0.2%)            | 1 (0.1%)              | 0                     | 2 (0.8%)              |
| Moderate                                                              | 10 (0.3%)         | 13 (0.7%)         | 23 (0.5%)         | 3 (0.1%)            | 1 (0.1%)              | 2 (0.7%)              | 6 (2.5%)              |
| Severe                                                                | 4 (0.1%)          | 3 (0.2%)          | 7 (0.1%)          | 2 (0.1%)            | 1 (0.1%)              | 0                     | 2 (0.8%)              |

Subjects reporting the same AE more than once are counted only once at the greatest severity. AEs missing severities were considered severe.

**Sponsor Table 8 Incidence of Adverse Reactions (GEPIRONE ER Rate  $\geq$  2% and  $\geq$  1.5x Placebo Rate) in Phase II/III Placebo-Controlled Depression Trials with GEPIRONE ER Modal Dose  $\geq$  40 mg/day**

| Body System<br>Adverse Reaction    | Percentage of Patients Experiencing Adverse Reaction |                     |
|------------------------------------|------------------------------------------------------|---------------------|
|                                    | GEPIRONE ER<br>(n=1300)<br>Modal Dose $\geq$ 40 mg   | Placebo<br>(n=1275) |
| <b>Nervous System Disorders</b>    |                                                      |                     |
| Dizziness                          | 38.2%                                                | 9.8%                |
| Paresthesia                        | 4.2%                                                 | 1.8%                |
| Tremor                             | 3.0%                                                 | 1.3%                |
| <b>Gastrointestinal Disorders</b>  |                                                      |                     |
| Nausea                             | 29.6%                                                | 11.8%               |
| Dyspepsia                          | 5.7%                                                 | 3.8%                |
| <b>Psychiatric Disorders</b>       |                                                      |                     |
| Insomnia                           | 12.7%                                                | 7.7%                |
| Abnormal dreams                    | 4.0%                                                 | 1.7%                |
| Middle insomnia                    | 3.0%                                                 | 0.8%                |
| Agitation                          | 2.5%                                                 | 1.6%                |
| <b>General Disorders</b>           |                                                      |                     |
| Feeling jittery                    | 2.5%                                                 | 0.8%                |
| <b>Investigations</b>              |                                                      |                     |
| Weight increased                   | 3.2%                                                 | 1.7%                |
| <b>Cardiac Disorders</b>           |                                                      |                     |
| Palpitations                       | 3.6%                                                 | 1.6%                |
| <b>Ear and Labyrinth Disorders</b> |                                                      |                     |
| Tinnitus                           | 2.7%                                                 | 1.5%                |
| <b>Eye Disorders</b>               |                                                      |                     |
| Vision blurred                     | 2.6%                                                 | 1.2%                |

**Sponsor Table 9 Summary of Demographics by Treatment Group –Phase II/III Studies**

| Demographic Characteristic | Gepirone     |              |                 | Placebo      | Antidepressants     |                     |                     | Anxiolytics        |                   |
|----------------------------|--------------|--------------|-----------------|--------------|---------------------|---------------------|---------------------|--------------------|-------------------|
|                            | ER<br>N=3117 | IR<br>N=1859 | ER+IR<br>N=4976 | N=2483       | Fluoxetine<br>N=700 | Paroxetine<br>N=276 | Imipramine<br>N=240 | Bromazepam<br>N=73 | Diazepam<br>N=110 |
| <b>Age (years)</b>         |              |              |                 |              |                     |                     |                     |                    |                   |
| N                          | 3113         | 1853         | 4966            | 2480         | 700                 | 276                 | 240                 | 71                 | 110               |
| Mean                       | 41.9         | 40.7         | 41.4            | 39.8         | 40.4                | 55.7                | 40.5                | 41.4               | 38.4              |
| Range                      | 15-87        | 18-79        | 15-87           | 18-79        | 18-71               | 18-92               | 18-78               | 19-69              | 19-77             |
| 17-64 yrs (n, %)           | 2919 (93.6%) | 1782 (95.9%) | 4701 (94.5%)    | 2435 (98.1%) | 685 (97.9%)         | 142 (51.4%)         | 234 (97.5%)         | 68 (93.2%)         | 104 (94.5%)       |
| ≥65 yrs (n, %)             | 193 (6.2%)   | 71 (3.8%)    | 264 (5.3%)      | 45 (1.8%)    | 15 (2.1%)           | 134 (48.6%)         | 6 (2.5%)            | 3 (4.1%)           | 6 (5.5%)          |
|                            |              |              |                 |              |                     |                     |                     |                    |                   |
| <b>Gender</b>              |              |              |                 |              |                     |                     |                     |                    |                   |
| Female (n, %)              | 2051 (65.8%) | 1064 (57.2%) | 3115 (62.6%)    | 1514 (61.0%) | 437 (62.4%)         | 214 (77.5%)         | 162 (67.5%)         | 40 (54.8%)         | 64 (58.2%)        |
| Male (n, %)                | 1061 (34.0%) | 789 (42.4%)  | 1850 (37.2%)    | 968 (39.0%)  | 262 (37.4%)         | 62 (22.5%)          | 78 (32.5%)          | 33 (45.2%)         | 46 (41.8%)        |
|                            |              |              |                 |              |                     |                     |                     |                    |                   |
| <b>Race</b>                |              |              |                 |              |                     |                     |                     |                    |                   |
| Caucasian (n, %)           | 2597 (83.3%) | 1553 (83.5%) | 4150 (83.4%)    | 2006 (80.8%) | 574 (82.0%)         | 249 (90.2%)         | 200 (83.3%)         | 0                  | 86 (78.2%)        |
| Black (n, %)               | 255 (8.2%)   | 158 (8.5%)   | 413 (8.3%)      | 236 (9.5%)   | 43 (6.1%)           | 14 (5.1%)           | 20 (8.3%)           | 0                  | 20 (18.2%)        |
| Other (n, %)*              | 265 (8.5%)   | 148 (8.0%)   | 413 (8.3%)      | 241 (9.7%)   | 83 (11.9%)          | 13 (4.7%)           | 20 (8.3%)           | 73 (100%)          | 4 (3.6%)          |
|                            |              |              |                 |              |                     |                     |                     |                    |                   |
| <b>Weight (kg)</b>         |              |              |                 |              |                     |                     |                     |                    |                   |
| N                          | 3091         | 1824         | 4915            | 2468         | 700                 | 276                 | 239                 | 72                 | 110               |
| Mean                       | 79.6         | 75.1         | 78.0            | 79.2         | 79.2                | 76.5                | 78.1                | 67.8               | 75.4              |
| Range                      | 30-202       | 40-177       | 30-202          | 37-197       | 44-172              | 37-141              | 42-188              | 44-102             | 47-134            |

\*Other includes missing values.

**Sponsor Table 10 Acute Phase: Number of Subjects Exposed to Study Drug by Duration of Treatment, Treatment Group, and Modal Dose – All Phase II/III Studies**

| Treatment Duration in Weeks       | Gepirone <40 mg/day |             | Gepirone ≥40 mg/day |             | Gepirone Total* | Placebo     | Antidepressants |             |             | Anxiolytics |            |
|-----------------------------------|---------------------|-------------|---------------------|-------------|-----------------|-------------|-----------------|-------------|-------------|-------------|------------|
|                                   | ER                  | IR          | ER                  | IR          |                 |             | Fluoxetine      | Paroxetine  | Imipramine  | Bromazepam  | Diazepam   |
| n                                 | 425                 | 1510        | 2016                | 349         | 4300            | 2325        | 653             | 276         | 240         | 73          | 110        |
| ≤1                                | 131 (30.8%)         | 310 (20.5%) | 124 (6.2%)          | 42 (12.0%)  | 306 (7.1%)      | 103 (4.4%)  | 31 (4.7%)       | 15 (5.4%)   | 19 (7.9%)   | 1 (1.4%)    | 8 (7.3%)   |
| >1 - ≤2                           | 36 (8.5%)           | 213 (14.1%) | 146 (7.2%)          | 80 (22.9%)  | 231 (5.4%)      | 108 (4.6%)  | 23 (3.5%)       | 10 (3.6%)   | 16 (6.7%)   | 0           | 6 (5.5%)   |
| >2 - ≤4                           | 62 (14.6%)          | 421 (27.9%) | 342 (17.0%)         | 139 (39.8%) | 399 (9.3%)      | 220 (9.5%)  | 31 (4.7%)       | 14 (5.1%)   | 32 (13.3%)  | 2 (2.7%)    | 8 (7.3%)   |
| >4 - ≤6                           | 91 (21.4%)          | 399 (26.4%) | 694 (34.4%)         | 75 (21.5%)  | 508 (11.8%)     | 259 (11.1%) | 38 (5.8%)       | 13 (4.7%)   | 18 (7.5%)   | 7 (9.6%)    | 19 (17.3%) |
| >6 - ≤8                           | 87 (20.5%)          | 152 (10.1%) | 488 (24.2%)         | 13 (3.7%)   | 1159 (27.0%)    | 755 (32.5%) | 271 (41.5%)     | 130 (47.1%) | 24 (10.0%)  | 32 (43.8%)  | 25 (22.7%) |
| >8 - ≤12                          | 14 (3.3%)           | 15 (1.0%)   | 200 (9.9%)          | 0           | 1553 (36.1%)    | 880 (37.8%) | 254 (38.9%)     | 92 (33.3%)  | 131 (54.6%) | 31 (42.5%)  | 44 (40.0%) |
| >12 - ≤16                         | 0                   | 0           | 22 (1.1%)           | 0           | 142 (3.3%)      | 0           | 5 (0.8%)        | 2 (0.7%)    | 0           | 0           | 0          |
| <b>Treatment Duration in Days</b> |                     |             |                     |             |                 |             |                 |             |             |             |            |
| n                                 | 421                 | 1510        | 2016                | 349         | 4300            | 2325        | 653             | 276         | 240         | 73          | 110        |
| Mean                              | 25.4                | 23.1        | 37.8                | 20.5        | 46.9            | 47.0        | 50.6            | 50.3        | 45.4        | 51.4        | 44.3       |
| SD                                | 19.50               | 15.06       | 18.14               | 11.60       | 21.49           | 17.95       | 17.05           | 17.67       | 21.68       | 11.18       | 19.70      |
| <b>Total Subject Years</b>        | 29.29               | 95.59       | 208.66              | 19.59       | 552.50          | 299.49      | 90.55           | 37.99       | 29.81       | 10.26       | 13.35      |

\*Gepirone Total column presents overall exposure to Gepirone at any dose (i.e., not limited to highest or modal doses) to allow direct comparison with exposure to the treatments other than Gepirone.

**10.3.1 Table 11-Study 28709: Randomized withdrawal study**

Table xx: Major Protocol Violators Excluded From the Per Protocol Analysis of Study 28709

| Subject Number                                                                                                                                                                                                                                                                                                                                                                        | Treatment Group | Reason for Exclusion from the Per Protocol Analysis |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------------------------------|
| (b) (6)                                                                                                                                                                                                                                                                                                                                                                               | Gepirone ER     | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Placebo         | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Placebo         | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Placebo         | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Placebo         | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 2 – Prohibited medication                           |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 1 – Non-compliance                                  |
|                                                                                                                                                                                                                                                                                                                                                                                       | Gepirone ER     | 1 – Non-compliance                                  |
| <ol style="list-style-type: none"> <li>1. Serious overall non-compliance with the intake of the trial medication defined as &lt;75% of the scheduled trial medication during the continuation phase.</li> <li>2. Use of disallowed concomitant medication between the last assessment of the open-label phase and the first efficacy assessment of the continuation phase.</li> </ol> |                 |                                                     |

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

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Earl Hearst  
10/24/2007 04:48:31 PM  
MEDICAL OFFICER

Ni Aye Khin  
10/24/2007 05:15:47 PM  
MEDICAL OFFICER

I agree that this NDA be considered for non-approval.  
See my memo to file dated 10/19/07 for  
additional comments.

## **Addendum to Previously Submitted Gepirone Review**

In this addendum I am including omitted sections that answer our safety requests from the 3/15/02 action letter. These sections are summaries of the sponsor's analyses.

### **Weight Changes**

(In this section the sponsor includes data from the Organon development program as requested.)

Findings for body weight were generally comparable across Phase II/III studies, controlled Phase II/III studies, and controlled Phase II/III studies in depression. The percentage of subjects with clinically significant weight gain was greater for the Org 33062 ER and ER  $\geq 40$  mg groups in comparison with the placebo group (approximately 1.0%, 1.3%, and 0.3% for the ER, ER  $\geq 40$  mg group, and placebo groups, respectively), with the risk for weight gain for the Org 33062 ER and ER  $\geq 40$  mg groups statistically significantly greater than placebo. Consistent with these findings, the mean change from baseline body weight was also greater in the Org 33062 ER  $\geq 40$  mg modal dose group than the placebo group. This was associated with a trend for mean body weight to increase during treatment in the Org 33062 ER  $\geq 40$  mg group; mean change from baseline at endpoint, approximately 0.51 kg compared to approximately 0.19 kg in the placebo group. Weight gain in the Org 33062 ER group appeared to be dose related (range for modal doses 0-80 mg/day, approximately 0.27 kg to 0.53 kg). Analyses of the control groups showed no clinically meaningful differences in comparison with the placebo group in the percentage of subjects with clinically significant body weight values. However, there was a general trend for mean body weight to decrease during treatment in the SSRI group, with statistically significant differences in mean change from baseline compared to placebo (approximate endpoint values: SSRI group, -0.83 kg vs. placebo group, 0.19 kg). 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.

### **ORTHOSTATIC BP CHANGES**

(In this section the sponsor includes data regarding risk ratios for orthostatic hypotension as requested.)

#### **All subjects in Phase II/III controlled studies**

Overall, the number of subjects with clinically significant orthostatic change in systolic blood pressure was generally comparable among the groups (Org 33062 ER, Org 33062 ER  $\leq 40$  mg modal dose, Org 33062 IR  $\leq 40$  mg modal dose, SSRI, and placebo). The only exception was a statistically significant increased risk of orthostatic change in the Org 33062 IR  $\leq 40$  mg modal dose group in comparison with the placebo group (IR  $\leq 40$  mg modal dose, 15%; placebo, 9%; risk ratio 1.67 [1.17, 2.39]); this effect was largely due to a statistically significant risk ratio at  $\delta 1$  minute (IR  $\leq 40$  mg modal dose, 15%; placebo, 8.1%; risk ratio 1.85 [1.28, 2.67]). At 3 minutes, there were no differences

among the groups ([Appendix A.8.10.3.41](#)).

The difference in change from baseline between the Org 33062 ER  $\geq 40$ mg and placebo group with respect to blood pressure was small and varied between 1.3 and 3.0 mmHg. There were no differences between the Org 33062 and placebo groups in the incidence of subjects with clinically significant increases in blood pressure as objectively measured in the clinical trial program, however the incidence of hypertension-related adverse events was slightly higher in the Org 33062 treated group compared to placebo. In controlled trials one Org 33062 subject discontinued due to increased blood pressure and two discontinued due to hypertension (as compared to none in the placebo group). Three cases of hypertensive crisis were reported during Org 33062 treatment, of which two had an onset after more than half a year of Org 33062 treatment. Upon careful review of the cases two of these events were mild and resolved spontaneously without treatment during continued Org 33062 treatment. Thus a relationship with Org 33062 in these cases would appear to be unlikely. In one case the subject was treated with antihypertensives for three days during continued Org 33062 treatment. This subject was discontinued from the trial one month later due to a severe panic attack, and therefore the reported hypertensive crisis could have been an unrecognized panic attack.

Consistent with the above, where no consistent decreases in blood pressure was seen, there were 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 three groups of trials was a greater risk of orthostatic change in systolic blood pressure for the Org 33062 IR  $\geq 40$  mg group vs. the placebo group. This difference was largely due to a statistically significant risk for the Org 33062 IR  $\geq 40$  mg vs. placebo groups at  $>1$  minute; at 3 minutes, there were no differences among the groups.

## **SUICIDE-RELATED AE**

(In this section the sponsor includes data with person-time as the denominator as requested.)

### **All subjects treated in controlled Phase II/III studies in depression**

The rate per subject-year for suicidal ideation was 0.07 for all Org 33062 subjects and 0.04 for placebo subjects ([Appendix Table A.3.6.4.4.A](#)). For intentional self-injury, non-accidental overdose, and overdose (ie suicide attempts) the rate per subject-year for all Org 33062 subjects was each 0.01. In paroxetine subjects, the rate per subject-year for suicide attempt was 0.05. There were no suicide attempts in the placebo group

Review of the suicide-related AE cases revealed that the majority of events (when there was adequate information to make an assessment) were indistinguishable from the natural consequences of depressive illness, which is the most common risk for

suicide-related events. Even with the most effective antidepressant therapies currently available, the incidence of suicide secondary to depression has not decreased over time. In a few cases of suicidal ideation/suicide attempts in subjects who received Org 33062, evidence of other mood disturbances, eg, anxiety, irritability and increased violent thoughts were present. Such mood disturbances have been associated with an increase risk of suicide. Relationship of these events to Org 33062 however, is confounded by the fact that there was limited information to make a proper assessment, and most of these subjects in each of these cases had pre-existing psychiatric symptoms. Moreover, sporadic paradoxical effects to psychotropic agents are a well-known phenomenon and therefore not unexpected in this patient population. With the limitations of retrospective review of adverse events, an objective evaluation of suicidality using the HAMD and MADRS suicide items was undertaken. The results showed no indication that Org 33062 causes suicide ideation.

## **SEXUAL DYSFUNCTION**

(In this section the sponsor identifies the rating scale as requested and refers us back to data previously submitted in studies 134001 and 134002.)

Sexual dysfunction can be secondary to depression and/or due to antidepressant therapy. There was no increased risk of adverse events associated with sexual dysfunction in subjects treated with Org 33062 compared to placebo, which was in contrast to the statistically significant increased risk observed in the SSRI and imipramine groups when compared to placebo. Consistent with this finding was the scores from the Derogatis Interview for Sexual Function Self Report, which was administered in studies 134001 and 134002. The scores indicated a trend toward improvement rather than worsening of sexual function providing further objective evidence that Org 33062 does not have the same deleterious effects on sexual performance compared to other psychotherapeutic agents.

## **ALLERGIC REACTION/HYPERSENSITIVITY ADVERSE EVENTS**

(In this section the sponsor includes the case definition for allergic reaction and provides data for eosinophilia as requested.)

The case definition for allergic reaction is discussed on ISS page 104 (Methods) and page 192: It can be further clarified as follows:

A case of allergic reaction was defined as:

1. the subject had a temporal clustering of AEs in the Hypersensitivity Reactions or Anaphylaxis SSCs or
2. the subject had any AE in these SSCs plus evidence of eosinophilia (as determined from the clinical laboratory data).

The final determination of whether an allergic reaction had indeed occurred was based on a medical review of all data available for the subjects who met either of the above criteria.

Seven cases in the ALL PHASE II/III data met case definition and are listed on ISS pages 193-194 (Section 6.5.2.2.1).

The incidence of individual allergic reaction/hypersensitivity AEs in acute Phase II/III studies was low in all treatment groups. In subjects who received any dose or formulation of Org 33062, the most frequent of these AEs included pruritus (1.1%), dyspnoea NOS (1.0%), hypersensitivity NOS (0.6%), and chest tightness (0.5%). The incidence of pruritus was slightly higher in the placebo group (1.8%), while the incidences of dyspnoea NOS, hypersensitivity NOS, and chest tightness were similar to the Org 33062 (Total) group.

The incidence of subjects with more than one of these AEs at any time during an acute Phase II/III trial was quite low and similar for the Org 33062 groups (4 Org 33062 ER, 4 Org 33062 IR) and the placebo group (n=4) ([Appendix Listing A.9.6.5.4](#)). During acute treatment, no subject in any treatment group had a cluster of more than two of the AEs. The subjects with a possible temporal relationship between the AEs are identified in the following list (2 Org 33062 ER, 3 Org 33062 IR, and 2 placebo).

\_ Org 33062 ER subject (b) (6) experienced chest tightness on Day 17 and bronchospasm on Day 19.

\_ Org 33062 ER subject (b) (6) 6 experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 4.

\_ Org 33062 IR subject (b) (6) experienced chest tightness on Day 1 and dyspnoea NOS on Day 4.

\_ Org 33062 IR subject (b) (6) experienced dyspnoea NOS and rash pruritic on Day 14.

\_ Org 33062 IR subject (b) (6) experienced dyspnoea NOS and pruritus on Day 21.

\_ Placebo subject (b) (6) experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 24.

\_ Placebo subject (b) (6) experienced pruritus and urticaria NOS on Day 4.

### **Analysis of eosinophil data**

In subjects treated with Org 33062, no trends over time were observed in mean change from baseline for eosinophils during acute Phase II/III studies ([Appendix Table A.4.9.3.7](#)). In addition, the mean changes were small and not clinically meaningful. At endpoint, the mean change was 0.08% in subjects who received any dose or formulation of Org 33062, -0.04% in the Org 33062 ER =40 mg modal dose group, 0.21% in the Org 33062 IR =40 mg modal dose group, and 0.1% in the placebo group. The percentage of subjects with at least one treatment-emergent clinically significant eosinophil value during acute treatment ranged from 0.5% to 0.9% in the Org 33062 groups, and was 0.6% in the placebo group ([Appendix Table A.4.9.3.2](#)). The maximum eosinophil value recorded for any Org 33062 subject was 19.4% at Week 6 and for placebo was 41.5% at Week 1 ([Appendix Table A.4.9.3.7](#)).

### **All subjects treated in controlled Phase II/III studies**

#### **Allergic reaction/hypersensitivity adverse events**

Six subjects in acute controlled Phase II/III trials experienced at least two allergic reaction/hypersensitivity AEs with a possible temporal relationship (2 Org 33062 ER, 2 Org 33062 IR, and 2 placebo).

\_ Org 33062 ER subject (b) (6) experienced chest tightness on Day 17 and bronchospasm on Day 19.

\_ Org 33062 ER subject (b) (6) experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 4.

\_ Org 33062 IR subject (b) (6) experienced chest tightness on Day 1 and dyspnoea NOS on Day 4.

\_ Org 33062 IR subject (b) (6) experienced dyspnoea NOS and pruritus on Day 21.

\_ Placebo subject (b) (6) experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 24.

\_ Placebo subject 7 (b) (6) experienced pruritus and urticaria NOS on Day 4.

### **Analysis of eosinophil data**

In subjects treated with Org 33062, no trends over time were observed in mean change from baseline for eosinophils during acute controlled Phase II/III studies ([Appendix Table A.4.9.3.8](#)). In addition, the mean changes were small and not clinically meaningful. At endpoint, the mean change was 0.07% in subjects who received any dose or formulation of Org 33062, -0.04% in the Org 33062 ER =40 mg modal dose group, 0.17% in the Org 33062 IR =40 mg modal dose group, and 0.1% in the placebo group. The percentage of subjects with at least one treatment-emergent clinically significant eosinophil value during acute treatment ranged from 0.5% to 0.9% in the Org 33062 groups, and was 0.6% in the placebo group ([Appendix Table A.4.9.3.4](#)). The maximum eosinophil value recorded for any Org 33062 subject was 19.4% at Week 6 and for placebo was 41.5% at Week 1 ([Appendix Table A.4.9.3.8](#)).

### **All subjects treated in controlled Phase II/III studies in depression**

#### **Allergic reaction/hypersensitivity adverse events**

Four subjects in acute controlled Phase II/III trials in depression experienced at least two allergic reaction/hypersensitivity AEs with a possible temporal relationship (2 Org 33062 ER, 1 Org 33062 IR, and 1 placebo).

\_ Org 33062 ER subject (b) (6) experienced chest tightness on Day 17 and bronchospasm on Day 19.

\_ Org 33062 ER subject (b) (6) experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 4.

\_ Org 33062 IR subject (b) (6) experienced dyspnoea NOS and pruritus on Day 21.

\_ Placebo subject (b) (6) experienced hypersensitivity NOS (verbatim .allergy.) and dyspnoea NOS on Day 24.

### **Analysis of eosinophil data**

In subjects treated with Org 33062, no trends over time were observed in mean change from baseline for eosinophils during acute controlled Phase II/III studies in depression ([Appendix Table A.4.9.3.9](#)). In addition, the mean changes were small

and not clinically meaningful. At endpoint, the mean change was 0.05% in subjects who received any dose or formulation of Org 33062, -0.04% in the Org 33062 ER =40 mg modal dose group, 0.17% in the Org 33062 IR =40 mg modal dose group, and 0.08% in the placebo group. The percentage of subjects with at least one treatment-emergent clinically significant eosinophil value during acute treatment ranged from 0.5% to 1.0% in the Org 33062 groups, and was 0.5% in the placebo group ([Appendix Table A.4.9.3.6.A](#)). The rate per subject-year ranged from 0.3 to 0.07 in the Org 33062 groups, and was 0.04 for placebo ([Appendix Table A.4.9.3.6.B](#)). The maximum eosinophil value recorded for any Org 33062 subject was 19.4% at Week 6 and for placebo was 41.5% at Week 1 ([Appendix Table A.4.9.3.9](#)).

## LIVER ENZYME ELEVATIONS

(We requested information on patient (b) (6) in study 28709, which is provided below.)

Two of the 12 possibly cases involved liver enzyme elevations. In one case, a subject experienced mild liver enzyme elevations after the subject stopped Org 33062 for a week and self-medicated himself with a monoamine oxidase inhibitor. In another case one subject, a 26-year-old male (race unknown), experienced severe hepatitis, liver dysfunction, .toxidermia., and low grade fever with mild lymphadenopathy after 15 days of Org 33062 IR (modal dose 20 mg) and numerous other psychotropic agents. A hepatic needle biopsy showed marked lesions on the liver with necrosis and mild intrahepatic cholestasis. The study medication was discontinued due to this SAE. The subject recovered after treatment with dexamethasone, vitamin K, and hydralazine. Two days before the case of hepatitis was diagnosed, the subject started acetaminophen, which is known to be hepatotoxic and may have contributed to the hepatic findings. Although Org 33062 exposure may be associated with mild changes in liver function tests with the exception of this case, which may be idiosyncratic, there is no clear evidence that Org 33062 is hepatotoxic. Further supporting this is that even in overdose situations (see section on overdose, [Section 16.2](#)) or exposure to high plasma levels due to inhibition of CYP3A4 (see drug-drug-interaction section, [Section 13](#)), no clinically relevant hepatic-related events have been reported ([12](#)).

We requested information on patient (b) (6) in study 28709 who had elevated LFTs. The narrative is reproduced below. There are LFTs dated FEB-05 showing a decrease in the previously high levels, (SGOT=24, SGPT=41, AP=102).

TRIAL AND TREATMENT DATA

Protocol no.: 28709
Centre: (b) (6)
Trial drug
- test product: Org 33062
- treatment: Org 33062/Org 33062

Subject no.: (b) (6)
Subject init.: (b) (6)

REASON FOR SUBJECT NARRATIVE SUMMARY

Serious Adverse Event

BASELINE DEMOGRAPHIC DATA

Date of birth: (b) (6) (Age: 41 yrs)
Gender: M
Height: 173 Cm
Weight: 78 Kg

EXPOSURE TO TRIAL MEDICATION

Table with 7 columns: Drug name, Tot d.dose, Unit, Route, Day start, Day stop, Days on drug. Rows show multiple administrations of Org 33062 at various doses (20, 40, 60, 80 mg) and routes (po).

DESCRIPTION EVENT

From (b) (6) until (b) (6) the dose of trial medication was increased to 80 mg maximum. However due to nervousness the dose was decreased to respectively 60 mg and 40 mg (not in detail reported). Three months after the start of trial medication, just before stopping, SGOT, SGPT and AP were slightly increased (SGOT increased; SGPT increased; alkaline phosphatase increased). Pre-treatment liver enzyme levels were normal. The subject decided for himself to stop the trial medication on (b) (6). At time of discontinuation the dose was 60 mg/day. On (b) (6) subject decided for himself to take ipronazid. On (b) (6) 0, 11 days after discontinuation of trial medication, subject was hospitalized for impairment of depression with suicidal ideation (depression aggravated; suicidal tendency). Subject was treated with thioridazine and citalopram. Four days before hospitalization, one week after discontinuation of trial medication, SGOT, SGPT and Ap were significantly increased. Subject had recovered and was discharged on (b) (6).

ADDITIONAL RELEVANT INFORMATION

SGOT (normal <37 IU/L): 21 (b) (6), 52 (b) (6), 148 (b) (6), 24 (b) (6)
SGPT (normal <40 IU/L): 33 (b) (6), 93 (b) (6), 393 (b) (6), 41 (b) (6)
AP (normal 80-250 IU/L): 91 (b) (6), 151 (b) (6), 485 (b) (6)

(b) (6)

RBC (normal 4.4 – 5.8 /mm3): 6.33 (b) (6)  
8.52 (b) (6)

MCV (normal 82 – 97 micr3): 70.5 (b) (6)  
70.1 (b) (6)

MCH (normal 27 - 33 pg): 22.9 (b) (6)  
32.9 (b) (6)

Neutrophils (2000 - 7000 /mm3): 1244 (b) (6)  
1915 (b) (6)

Lymphocytes (normal 1200-4000/mm3): 6586 (b) (6) (c)  
(05-Feb) (b)

Leucocytes (normal < 15.0): 15.5 (b) (6)  
15.6 (b) (6)

Eosinophils (normal 1200 – 4000 /mm3): 6586 (b) (6)

#### MEDICAL HISTORY

Several depressive episodes, treated with tricyclics (response not at all), tetracyclics (response not at all), MAOI (response very well), SSRIs (response not at all), venlafaxine (response not at all).

#### CONCOMITANT MEDICATION

| <u>Drug name</u> | <u>Tot d.dose</u> | <u>Unit</u> | <u>Route</u> | <u>Day start</u> | <u>Day stop</u> | <u>Indication</u>     |
|------------------|-------------------|-------------|--------------|------------------|-----------------|-----------------------|
| iproniazid       | 25                | mg          | po           | (b) (6)          | (b) (6)         | relapse of depression |

#### OTHER ADVERSE EVENTS

| <u>Adverse event</u> | <u>Day start</u> | <u>Day stop</u> | <u>Intensity</u> | <u>Action</u> | <u>Outcome</u> | <u>Causality</u> |
|----------------------|------------------|-----------------|------------------|---------------|----------------|------------------|
| nervousness          | (b) (6)          | (b) (6)         | Moderate         | reduced       | recovered      | probable         |

#### RELATION TO TRIAL DRUG

According to the investigator the event was **possibly related**.  
During in-house evaluation the event was judged as being **possibly related** to the trial medication, because a causal relationship cannot be excluded.

Conclusions:

The sponsor has provided the additional safety items we requested. The conclusions in my review remain unchanged from those previously submitted.

Earl Hearst, M.D.  
Medical Reviewer  
HFD-120

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this page is the manifestation of the electronic signature.**  
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/s/

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Earl Hearst  
5/12/04 03:27:53 PM  
MEDICAL OFFICER

Thomas Laughren  
5/20/04 08:18:57 AM  
MEDICAL OFFICER

I agree that this application remains nonapprovable; see memo  
to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 21-164  
Sponsor: Organon (AKZO NOBEL)

Drug Name

Generic Name Gepirone (Org 33062)  
Trade Name To be submitted

Drug Characterization

Pharmacological Category: Antidepressant Novel  
(selective partial 5-HT<sub>1A</sub> receptor agonist)  
Proposed Indication: Depression Dosage Forms,  
Strengths, and Routes of Administration: Oral  
Tablets 20mg, 40mg, 60mg and 80mg Extended  
Release

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.  
Review Completion Date: 4/30/2004

|                                                    |           |
|----------------------------------------------------|-----------|
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# EXECUTIVE SUMMARY

## EFFICACY

Study 28709 was a multicenter, placebo-controlled relapse prevention trial in adult depressed outpatients. The trial started with an open-label (OL) phase of 8-12 weeks, which was followed by a double-blind continuation phase of 40-44 weeks. Of the 303 subjects who completed the OL phase, 250 subjects were randomized into the double-blind continuation phase: 126 subjects to Org 33062 and 124 to placebo. The primary efficacy parameter was the number of subjects with a relapse at the end of the continuation phase defined as: HAMD-17 total score  $\geq 16$  or discontinuation due to relapse as judged by the investigator. The sponsor claims in their primary analysis that the relapse rate at endpoint of the continuation phase was 23.0% for subjects in the Org 33062 group compared to 34.7% for subjects in the placebo group ( $p=0.024$ ).

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. Please see Stat review by Rosewitha Kelly.

In an internal memo dated 27 February 2002 (prior to unbinding), it was noted that five subjects may have suffered a relapse and would therefore be redefined in the analysis as relapsers. Only after the blind was broken did the sponsor redefine these 5 subjects as non-relapsed patients saying their status could not be confirmed with the investigators anymore. I therefore believe these subjects should have been counted as relapsers and the alternate analysis is the correct one. According to this analysis, the number of subjects with a relapse at endpoint was 34 (27.0%) in the Org 33062 group and 43 (34.7%) in the placebo group. The difference between the treatment groups was not statistically significant. This analysis does not take into account the missing ITT patients noted in Rosewitha Kelly's review.

This study did not win based on the original primary efficacy variable and did not win even with the internal memo change prior to the breaking of the blind. It also does not win when taking all ITT patients into account.

Gepirone has still not produced a 2<sup>nd</sup> robustly positive study in the ER as required in the minutes of our 7/14/2003 meeting. I believe the drug should not be approved based on the large number of trails which have resulted in only one positive IR study and one positive ER study.

## SAFETY

As of the cutoff date of 23 June 2003, 4862 individual subjects have been exposed to Org 33062 in 75 clinical trials. A total of 4076 subjects participated in Phase II/III studies and 2217 of these subjects were exposed to the ER formulation. A total of 732 subjects were exposed to Org 33062 daily for at least 6 months, and 497 (476 Org 33062 ER) were exposed to a modal dose [dose (in mg/day) of Org 33062 that was most frequently prescribed for an individual subject during his/her study participation] of 40 mg or greater. A total of 260 subjects were exposed to Org 33062 daily for at least

one year, and 170 (161 Org 33062 ER) were exposed to a modal dose of 40 mg or greater.

There is nothing in the newly submitted safety material that would prevent the approval of Gepirone for MDD based on safety concerns.

## **CONCLUSIONS**

Gepirone has still not produced a 2<sup>nd</sup> robustly positive study in the ER as required in the minutes of our 7/14/2003 meeting. I recommend that Gepirone ER should not be approved based on the large number of trials which have resulted in only one positive IR study and one positive ER study.

## **BACKGROUND**

In our 3/15/2002 action letter we found only Study 134001 positive for the Gepirone ER formulation. During the 7/3/2002 meeting we agreed that Study 03A7A-003 was positive for the IR formulation but told the sponsor they needed an additional positive ER study before they could be approved. We agreed to accept the relapse prevention study as a second study if it was robustly positive, but told the sponsor this did not guarantee approval based on the large number of negative trials. In this submission the sponsor has submitted Study 28709 as an additional positive relapse prevention study in support of the ER formulation. In addition the sponsor has submitted safety material requested in the 3/15/2002 action letter.

## **REVIEW PLAN**

I will present the new efficacy data in Study 28709 which will include two analyses based on the status of 5 patients on Gepirone ER whose relapse status is questioned. I will also present conclusions in Rosewitha Kelly's independent statistical analysis. I will present the sponsor's reply to safety issues raised in our 3/15/2002 action letter. Also I will update the safety review previously done by Tarek Hammond, M.D. with the new exposure and present the deaths, SAEs and adverse events leading to discontinuation through the new cut-off date of 6/23/03.

## **HISTORY OF DRUG DEVELOPMENT**

The Phase II/III development program for Org 33062 was conducted by Bristol Myers Squibb from 1987 until 1992. Organon began development activities in mid-1998. All together, 43 Phase II/III trials were completed as of the clinical cut-off date of June 23, 2003: 11 in Anxiety, one in Obsessive-Compulsive Disorder, one in Substance Abuse, one in Mood/panic disorder, and 29 in Major Depressive Disorder. Of the 29 Phase II/III studies conducted in depression, 20 were placebo-controlled and designed to test the efficacy of Org 33062, including

9 placebo-controlled studies and 7 placebo- and active-controlled studies conducted in adult outpatients who met Research Diagnostic Criteria (RDC) or DSM-III-R or IV criteria for the following:

MDD not further specified (11 studies: Protocols CN105-078, CN105-083, CN105-052, CN105-053, CN105-064, CN105-057, CN105-037, 03A7A-003, 03A7C-001A-2496, 03A7C-001B, 03A7C-001A-2486)

MDD with an atypical profile (1 study: Protocol 03A7A-003)

MDD or dysthymia (mood disorder; 1 study: Protocol CN105-043)

MDD or bipolar disorder, depressed (3 studies: Protocols CN105-022, CN105-029, CN105-028).

6 uncontrolled studies conducted in adult inpatients or outpatients who met RDC or DSM-III-R criteria for MDD or mood disorders.

### **Organon Program Description**

The Phase II/III development of the extended release formulation of Org 33062 which was conducted by Organon up to June 23, 2003 include seven clinical trials in outpatient subjects with MDD. These studies were:

2 placebo-controlled efficacy trials (134001 and 134002) with their open-label extension treatment (134501)

1 placebo- and fluoxetine-controlled efficacy trial (134004) with its double-blind extension treatment (134502)

1 long-term relapse prevention trial (28709)

1 paroxetine-controlled geriatric trial (28715).

## **EFFICACY SECTION**

### **Study 28709**

The tables and text numbers in this study are based on the sponsor's assumption that we will accept the relapse status of patients as presented. It is also based on an analysis that excludes 32 ITT patients, (see Stat review). An alternate analysis is presented in my efficacy section for this study. All tables and data to follow are based on the sponsor's analysis except where otherwise noted.

### **STUDY SUMMARY**

Study 28709 was a multicenter, placebo-controlled relapse prevention trial in adult depressed outpatients. The trial started with an open-label (OL) phase of 8-12 weeks, which was followed by a double-blind continuation phase of 40-44 weeks. Of the 303 subjects who completed the OL phase, 250 subjects were randomized into the doubleblind continuation phase: 126 subjects to Org 33062 and 124 to placebo. The primary efficacy parameter was the number of subjects with a relapse at the end of the continuation phase defined as: HAMD-17 total score  $\geq 16$  or discontinuation due to

relapse as judged by the investigator.

In this trial, remission was defined as a HAMD-17 total score  $\leq 8$ . Subjects, who were in remission after the OL phase at Week 8 or Week 12, were randomized to placebo or Org 33062 for 40-44 weeks of double-blind continuation treatment. If the subject failed to show remission after 12 weeks of treatment with an adequate dose of Org 33062, the subject was withdrawn from the trial. The purpose of the continuation phase was to stabilize the remission and to prevent a relapse of the depressive episode. The dosage that led to remission was maintained during the continuation phase. Relapse was defined as having a HAMD-17 total score  $\geq 16$  or discontinuation due to lack of efficacy as determined by the investigator.

The relapse status of 5 patients places the outcome of this study in doubt.

### **Clinical trial objective(s)**

The primary objective of this trial was to compare the relapse rates of depression during the continuation phase between subjects receiving Org 33062 at the final titrated dose and subjects receiving placebo.

The secondary objectives were:

- . To compare the time to relapse during the continuation phase between subjects receiving Org 33062 at the final titrated dose and subjects receiving placebo;
- . To evaluate the therapeutic efficacy and the safety profile of Org 33062 at the final titrated dose during the continuation phase in comparison with placebo;
- . To investigate the effects of Org 33062 at the final titrated dose during the continuation phase on sexual functioning and quality of life in comparison with placebo;
- . To evaluate the therapeutic efficacy of Org 33062 at the final titrated dose during the continuation phase in subjects with atypical depression features in comparison with placebo.

Other objectives were:

- . To evaluate the therapeutic efficacy and safety profile of Org 33062 during a 8 to 12 weeks open-label phase;
- . To investigate the effects of Org 33062 on sexual functioning and quality of life during a 8 to 12 weeks open-label phase;
- . To evaluate the therapeutic efficacy of Org 33062 in subjects with atypical depression features during an 8 to 12 weeks open-label phase.

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The trial protocol (June, 1999) was approved by the Independent Ethics Committee (IEC) of each trial center. Name(s) and address(es) of the IEC(s) can be found in Appendix C "Investigator and ethics". The protocol was amended four times in

October, 1999 (Amendments I-III) and February, 2000 (Amendment IV). These amendments were approved by/sent for notification to the IECs. The protocol and amendments can be found in Appendix D “Protocol, amendments, specimen CRFs and interim analysis”.

The present trial was conducted in compliance with the current revision of the Declaration of Helsinki, ICH guideline and Good Clinical Practice (GCP) and current regulatory regulations.

## **Clinical trial design**

All subjects were to undergo a single-blind, placebo wash-out period of 3-14 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 Org 33062. The aim of the OL phase was to achieve remission of the depressive episode. In this trial, remission was defined as a HAMD-17 total score  $\leq 8$ . Subjects, who were in remission after the OL phase at Week 8 or Week 12, were to be randomized to placebo or Org 33062 for 40-44 weeks of double-blind continuation treatment. If the subject failed to show remission after 12 weeks of treatment with an adequate dose of Org 33062, the subject was to be withdrawn from the trial and the investigator was to consider an alternative treatment.

The purpose of the continuation phase was to stabilize the remission and to prevent a relapse of the depressive episode. The dosage that led to remission was maintained during the continuation phase. Since the primary objective of this trial was to evaluate the relapse preventing properties of Org 33062, the relapse rate and the time to relapse of patients treated with Org 33062 was to be compared to those of patients treated with placebo. Therefore, after the OL phase the subjects were to be randomized to Org 33062 or placebo.

Relapse was defined as having a HAMD-17 total score  $\geq 16$  OR discontinuation due to lack of efficacy. In addition to these criteria, the investigator had to have the opinion that the subject met the DSM-IV criteria for major depressive episode.

## **Subject Source and number**

The subjects were to be recruited from the patient population of the participating investigators. According to the protocol title the subjects participating were to be outpatients. Investigators could hospitalize subjects during initial screening and treatment, if needed.

It was estimated that about 650 subjects had to be enrolled into the OL phase to achieve the required number of subjects in the Intent-to-Treat (ITT) group, i.e., 2 x 100 subjects

## **Inclusion criteria**

. Primary diagnosis of recurrent MDD (DSM-IV 296.3);

- . At least 18 years and not older than 70 years of age;
- . Screening and baseline HAMD -17 total score  $\geq 20$ ;
- . Females had to be postmenopausal for at least one year, surgically sterile, or non-pregnant using a method of birth control that was acceptable to the investigator;
- . Written informed consent.

## Exclusion criteria

- . HAMD-17 total score decrease  $\geq 20\%$  between screening and baseline;
- . Treatment with additional psychotropics, except for stable use of short-acting benzodiazepines and/or sleep medication;
- . Currently in formal psychotherapy;
- . History of treatment refractory depression;
- . History or present condition of seizure disorder or bipolar disorder;
- . Drugs or alcohol abuse and/or addiction to benzodiazepines or use of high doses of benzodiazepines, i.e., more than 15 mg of diazepam or an equivalent dose of another benzodiazepine;
- . Significant suicidal risk according to the investigator;
- . Renal, hepatic, cardiovascular, respiratory, cerebrovascular or other serious, progressive physical disease;
- . Clinically meaningful abnormal findings during screening period;
- . Electroconvulsive therapy during the past year;
- . MAOI within 3 weeks, fluoxetine within 5 weeks, other psychotropic drugs within 2 weeks before start of active study treatment;
- . Pregnant or lactating women or women intending to become pregnant;
- . Previous adverse reactions or allergic reactions to azapirones;
- . Previous clinical experience with gepirone;
- . Participation in a clinical trial less than 3 months before date of screening.

The subjects' response to the trial drug was to be closely monitored throughout the trial. During the OL phase, subjects were to be excluded from the trial for any of the following reasons:

- . A score of more than 2 on Item [11] for suicidal risk of the HAMD -17 scale at any visit during the trial;
- . A decrease of  $\leq 20\%$  from baseline to Week 4 in the HAMD -17 total score;
- . A decrease of  $\leq 40\%$  from baseline to Week 8 in the HAMD -17 total score.

## DOSING

Org 33062 (gepirone HCl), the NV Organon code for 4,4-dimethyl-1-[4-[4-(2-pyrimidinyl)1-piperazinyl]butyl]-2,6-piperidinedione hydrochloride, was dispensed as ER tablets containing 20 mg of active drug (batch number CP099114). The dose range in this trial was 20-80 mg per day. During the OL phase every subject was to receive Org 33062, whereas during the double-blind continuation phase subjects were to be randomized to Org 33062 (at the last dose of the OL phase) or placebo.

Placebo tablets were identical to the Org 33062 tablets with regard to size, shape and color (batch number CP099113). All medication was to be taken orally, in the morning after breakfast (i.e., with food). During the first 14 days of dosing, subjects had the option of switching to evening administration if, in the opinion of the investigator, evening dosing would help the subject adjust for side effects. The starting dose was 20 mg/day with a forced titration up to 40 mg/day on Day 4. The minimal dose after Day 4 was 40 mg/day. The investigators could titrate the daily dose of Org 33062 to 60 mg on Day 8, and to 80 mg after Day 14. They were to use the subject's therapeutic response and tolerability as a guide for titration. The investigators were to strive to titrate the dose as high as possible (up to a maximum of 80 mg/day).

The dosing schedule is presented in Table 1. If the increased dose was not tolerated, the investigator could reduce back to the previous dosing, but the minimal dose was to be 40 mg/day. Starting from Week 8, the subjects' response to treatment was to be evaluated. If the subject had a HAMD-17 total score  $\leq 8$ , he/she fulfilled the criterion for remission and was to be randomized to double-blind treatment with Org 33062 or placebo. If the subject did not show remission at Week 12, the investigator was to withdraw the subject from the trial and offer appropriate alternative treatment.

**Table 1 Dosing schedule**

| Treatment day        | Org 33062 dose                                                 | Number of active tablets | Number of placebo tablets |
|----------------------|----------------------------------------------------------------|--------------------------|---------------------------|
| Screening / wash-out | --                                                             | --                       | 1                         |
| Day 1* - Day 3       | 20 mg                                                          | 1                        | --                        |
| Day 4 - Day 7        | 40 mg                                                          | 2                        | --                        |
| Day 8 - Day 14       | 40 or 60 mg                                                    | 2 or 3                   | --                        |
| Day 15 – Day 56/84   | 40, 60 or 80 mg                                                | 2, 3 or 4                | --                        |
| Day 56/84 – Day 365  | Final titrated dose or an equivalent number of placebo tablets |                          |                           |

\* First day of trial medication.

## Concomitant medication

Subjects participating in this trial were not permitted to use any other psychotropic drugs. Subjects already using short-acting benzodiazepines or sleep medication at regular doses could continue to use these during the OL phase. During the doubleblind phase, however, regular daily dosing (i.e., maximally 15 mg of diazepam per day or an equivalent dose of another benzodiazepine) was to be reduced to a frequency of twice weekly (or less). The use of benzodiazepines was not allowed on the night before a HAMD rating session. No new benzodiazepines or sleep medication was to be started during the trial. Subjects were to refrain from drinking alcoholic beverages and minimize caffeine. Formal psychotherapy was not allowed during the wash-out and treatment period.

## Flow chart of trial assessments

**Table 2** Flow chart of trial assessments

| Assessment                         | Week | Screen |    | Open-label phase |   |   |                                           |                | Double-blind continuation phase |                |                |                |                |                |                |                | FU             |                |                |  |
|------------------------------------|------|--------|----|------------------|---|---|-------------------------------------------|----------------|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|--|
|                                    |      | S      | BL | 1                | 2 | 4 | 8                                         | 12             | 16                              | 20             | 24             | 28             | 32             | 36             | 40             | 44             | 48             | 52             | 54             |  |
| Informed consent                   |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Medical history                    |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Lab data, pregnancy test, ECG      |      | X      |    |                  |   |   | X <sup>a</sup>                            |                |                                 | X              |                |                | X              |                |                |                |                |                | X <sup>b</sup> |  |
| DSM-IV checklist                   |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| HAMD-31                            |      | X      | X  | X                | X | X | X                                         | X              | X <sup>d</sup>                  | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> | X <sup>d</sup> |  |
| Psychiatric data inventory         |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Drug accountability                |      | X      | X  | X                | X | X | X                                         | X              | X                               | X              | X              | X              | X              | X              | X              | X              | X              | X              | X              |  |
| In-/exclusion checklist            |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Vital signs                        |      | X      | X  | X                | X | X | X                                         | X              | X                               | X              | X              | X              | X              | X              | X              | X              | X              | X              | X              |  |
| CGI                                |      | X      | X  | X                | X | X | X                                         | X              | X                               | X              | X              | X              | X              | X              | X              | X              | X              | X              | X              |  |
| Pre-treatment signs & symptoms     |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Selection checklist                |      | X      |    |                  |   |   |                                           |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Remission checklist                |      |        |    |                  |   |   | X <sup>c</sup>                            | X <sup>c</sup> |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Physical examination               |      | X      |    |                  |   |   | X <sup>a</sup>                            |                |                                 | X              |                |                | X              |                |                |                |                |                | X <sup>b</sup> |  |
| DISF-SR <sup>e</sup>               |      |        | X  |                  |   |   | X <sup>a</sup>                            |                |                                 | X              |                |                | X              |                |                |                |                |                | X <sup>b</sup> |  |
| SF-36                              |      |        | X  |                  |   |   | X <sup>a</sup>                            |                |                                 | X              |                |                | X              |                |                |                |                |                | X <sup>b</sup> |  |
| Pre-trial & concomitant medication |      | X      | X  | X                | X | X | X                                         | X              | X                               | X              | X              | X              | X              | X              | X              | X              | X              | X              | X              |  |
| Adverse events                     |      |        |    |                  |   |   | Whenever an adverse event occurred        |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| Serious adverse events             |      |        |    |                  |   |   | Whenever a serious adverse event occurred |                |                                 |                |                |                |                |                |                |                |                |                |                |  |
| End of trial                       |      |        |    |                  |   |   | X <sup>b</sup>                            |                |                                 |                |                |                |                |                |                |                |                |                | X <sup>b</sup> |  |

S = screening, BL = baseline, FU = follow-up, SF-36 = 36-Item Short Form Health Survey; <sup>a</sup> if the subject fulfilled the criteria for remission at Week 8, this assessment was to be done at Week 8; <sup>b</sup> or at time of discontinuation; <sup>c</sup> if the subject fulfilled the criteria for remission, he/she was to be randomized into the continuation phase; <sup>d</sup> in the continuation booklet, the HAMD scale ended with a check for the total score on the first items of the HAMD-31; if the subject was to have a relapse during this phase, he/she was to be withdrawn from the trial; <sup>e</sup> DISF-SR (=Derogatis Interview for Sexual Function - Self-Rated) was not to be assessed in Turkey.

## Protocol amendments

The protocol was amended four times. Amendment I (October, 1999) was a country specific amendment for investigators in Germany containing additional exclusion criteria, in order to comply with the requirements of the Ethics Committee of the Bavarian Chamber of Physicians. Per Amendment II (October, 1999) the SF-36 (instead of SF-12) was to be used as basic health status questionnaire and the quality of life scale was canceled. The DISF-SR and SF-36 were not to be assessed in Turkey. Per Amendment III (October, 1999), the content of Amendment I (i.e., additional exclusion criteria) was applicable for all trial centers. Per Amendment IV,

the use of benzodiazepines was restricted. A validated Turkish version of the SF-36 was to be assessed in Turkey (in contrast to the statement in Amendment II). In addition, if the investigator's clinical judgment demanded a hospitalization for monitoring the subject's safety during a screening period or initial treatment with the trial medication, it was justified to hospitalize the subject.

## **Efficacy Ratings**

For each visit, the efficacy assessments were to be performed by the same rater, to the extent possible. The primary efficacy parameter was the number of subjects that had a relapse during the continuation phase (i.e., the relapse rate). The following two efficacy scales were to be used:

The **31-item Hamilton Depression Rating Scale (HAMD-31)**: this is an observer rated scale for the quantitative assessment of depressed subjects. The HAMD [16] scoring was based on Dr. J. Williams' structured interview for the first 21 items of the HAMD [17]. The scale was to be completed at every visit.

The **Clinical Global Impression (CGI)**: this scale is used for risk-benefit evaluation of drug treatment of depressed subjects. The CGI [18] consisted of a 7-stage rating of the severity of the illness (taking into account the preceding two days), and global 7-stage ratings of the change in clinical status since the start of treatment. The scale was to be completed at baseline (only severity score) and at every further visit. In the continuation phase, an extra question was added to the CGI, which was to cover the change in clinical status since the start of the continuation phase.

Section 5.3 of the protocol defined relapse as: "Relapse is defined as having a HAMD-17 total score  $\geq 16$  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."

## **RESULTS**

### **Disposition of subjects**

The trial was conducted in 29 centers in Europe. The centers were located in Finland (6), France (9), Germany (4), Poland (5) and Turkey (5). In total 435 subjects were screened, of whom 428 subjects were selected to participate in the OL phase and 420 subjects were actually treated. In total, 117 subjects discontinued prematurely and therefore 303 subjects completed the OL phase of which 250 subjects fulfilled the criteria for remission.

At the end of the OL phase, 250 subjects were randomized, 126 to Org 33062 and 124 to placebo. All of those subjects were treated in the continuation phase. The number of subjects who completed the one-year treatment period is 141 (Org 33062: 71; placebo: 70). In Table 10, an overview of the disposition of subjects is presented by treatment group.

**Table 10**      **Disposition of subjects**

|                                            |                  |                  |                |
|--------------------------------------------|------------------|------------------|----------------|
| <b>Disposition</b>                         |                  |                  |                |
| Screened                                   |                  | 435              |                |
| <b>Open-label phase</b>                    |                  | <b>Org 33062</b> |                |
|                                            |                  | <b>N</b>         |                |
| Selected to participate                    |                  | 428              |                |
| Treated with Org 33062                     |                  | 420              |                |
| Discontinued prematurely                   |                  | 117              |                |
| Completed                                  |                  | 303              |                |
| In remission at the end of the OL phase    |                  | 250              |                |
| <b>Double-blind continuation phase</b>     | <b>Org 33062</b> | <b>Placebo</b>   | <b>Overall</b> |
|                                            | <b>N</b>         | <b>N</b>         | <b>N</b>       |
| Randomized                                 | 126              | 124              | 250            |
| Treated with double-blind trial medication | 126              | 124              | 250            |
| Discontinued prematurely                   | 55               | 54               | 109            |
| Completed                                  | 71               | 70               | 141            |

**Open-label phase**

## Treated subjects:

A total of 117 treated subjects (27.9%) discontinued the OL phase of the trial prematurely. The main reasons for discontinuation are presented in Table 11. The most important reason for premature discontinuation, as indicated on the EOT CRF, was occurrence of an (S)AE (46 subjects, 11.0%).

## Non-treated subjects:

Of the 428 subjects that were selected to participate in the OL phase, eight subjects (1.9%) discontinued prior to treatment with trial medication. Five subjects discontinued because they were not willing or could not cooperate for reasons not related to the trial. The other three subjects discontinued because of other reasons.

## Non-selected subjects:

Of all 435 subjects screened, seven subjects (1.6%) were not selected to enter the OL phase because they did not fulfill all inclusion criteria at screening or baseline.

**Double-blind continuation phase**

## Non-treated subjects:

All randomized subjects were treated with trial medication in the continuation phase.

## Non-randomized subjects:

Of all subjects who completed the OL phase, 53 subjects (17.5%) were not randomized to enter the (double-blind) continuation phase: fifty subjects were not qualified for continuation; one subject was not willing or could not cooperate for reasons not related to the trial; two subjects discontinued due to insufficient therapeutic effects, which made continuation of the trial conditions unjustifiable.

## Treated subjects:

In total, 109 (43.6%) treated subjects (Org 33062: 43.7%; placebo: 43.5%) discontinued from the continuation phase of the trial prematurely. The main reasons for discontinuation are presented in Table 11. According to the EOT CRF, the most important reason for early discontinuation was fulfillment of relapse criteria (61 subjects, 24.4%).

## Table of Premature Discontinuations

**Table 11** Reasons for premature discontinuation  
AST-OL group and AST group

| Reason for discontinuation (according to the EOT CRF)                                           | Open-label phase (AST-OL) |             | Double-blind continuation phase (AST) |             |                 |             |                 |             |
|-------------------------------------------------------------------------------------------------|---------------------------|-------------|---------------------------------------|-------------|-----------------|-------------|-----------------|-------------|
|                                                                                                 | Org 33062 (N=420)         |             | Org 33062 (N=126)                     |             | Placebo (N=124) |             | Overall (N=250) |             |
|                                                                                                 | n                         | %           | n                                     | %           | n               | %           | n               | %           |
| Adverse event / Serious adverse event                                                           | 46                        | 11.0        | 4                                     | 3.2         | 5               | 4.0         | 9               | 3.6         |
| Not willing or cannot cooperate for reasons not related to the study                            | 26                        | 6.2         | 11                                    | 8.7         | 7               | 5.6         | 18              | 7.2         |
| Insufficient therapeutic effects which makes continuation of the trial conditions unjustifiable | 26                        | 6.2         | -- <sup>a</sup>                       | --          | --              | --          | --              | --          |
| Relapse criteria fulfilled                                                                      | --                        | --          | 26                                    | 20.6        | 35              | 28.2        | 61              | 24.4        |
| Reason not mentioned above                                                                      | 19                        | 4.5         | 14                                    | 11.1        | 7               | 5.6         | 21              | 8.4         |
| <b>Total</b>                                                                                    | <b>117</b>                | <b>27.9</b> | <b>55</b>                             | <b>43.7</b> | <b>54</b>       | <b>43.5</b> | <b>109</b>      | <b>43.6</b> |

<sup>a</sup> not applicable.

## Major protocol violations

Major protocol violations were determined for nine subjects (7.1%) in the Org 33062 group and for four subjects (3.2%) in the placebo group. For seven subjects the major protocol violation was serious overall non-compliance (Org 33062: Subjects (b) (6); placebo: Subjects (b) (6)). The lowest compliance was 28% for Subject (b) (6). For the other six subjects the compliance was between 49% and 71%. Six subjects used disallowed concomitant medication between the last

assessment of the OL phase and the first efficacy assessment within the continuation phase (Org 33062: Subjects (b) (6); placebo: Subjects (b) (6)). The medications taken were Meprobamate (Subject (b) (6)), Zopiclone (Subject (b) (6)), Clonazepam (Subjects (b) (6)), Oxazepam (Subject (b) (6)), and Lorazepam (Subject (b) (6)).

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## DATA SETS

**Table 14** Number of subjects in various subject data sets

| Subject data set                       | Org 33062 |         |         |
|----------------------------------------|-----------|---------|---------|
|                                        |           | N       |         |
| All-Subjects -Treated-Open-Label group |           | 420     |         |
| Intent-to-Treat-Open-Label group       |           | 412     |         |
|                                        | Org 33062 | Placebo | Overall |
|                                        | N         | N       | N       |
| All-Subjects -Randomized group         | 126       | 124     | 250     |
| All-Subjects -Treated group            | 126       | 124     | 250     |
| Intent-to-Treat group                  | 126       | 124     | 250     |
| Per Protocol group                     | 117       | 120     | 237     |

### All-Subjects-Treated-Open-Label group

In total, 420 subjects received at least one dose of Org 33062.

### Intent-to-Treat-Open-Label group

Of the 420 subjects of the AST-OL group eight subjects did not have at least one post-baseline assessment on the HAM-D-17 total score during the OL phase. Therefore, 412 subjects were included in the ITT-OL group.

### All-Subjects-Randomized group

From all subjects of the ITT-OL group a total of 250 subjects was randomized and almost equally distributed over both treatment groups. The Org 33062 group consisted of 126 subjects, whereas the placebo group consisted of 124 subjects.

### All-Subjects-Treated group

All 250 subjects of the ASR group were treated with double-blind trial medication and therefore included in the AST group.

### Intent-to-Treat group

All 250 subjects of the AST group had at least one assessment on the primary

efficacy parameter and therefore were included in the ITT group (Org 33062: 126 subjects; placebo: 124 subjects).

## **Demographics**

Differences between the two treatment groups were only seen in the gender distribution: in the Org 33062 group 73.8% was female, whereas the placebo group consisted of 61.3% females. With regard to race, age, body height, body weight and Body Mass Index, both treatment groups showed comparable data.

## **Dosing Exposure**

The mean (median) number of days the subjects were exposed to trial medication during the OL phase was approximately 68 (83) days (see Table 20). Subjects who stopped during the OL phase generally discontinued at an early stage, which explains the large difference between mean and median exposure values. The modal (prescribed) dose of Org 33062 used by the largest number of subjects during the OL phase was 60 mg Org 33062 per day. During the OL phase, 142 of the 420 subjects were exposed to daily doses of 60 mg Org 33062 or more for at least 8 weeks.

With regard to exposure to trial medication in the continuation phase, both treatment groups were comparable. As shown in Table 20, the mean (median) number of days the subjects were exposed to trial medication during the continuation phase was approximately 217 (275) days in both treatment groups. During the total treatment period exposure was approximately 296 (356) days in the Org 33062 group and approximately 295 (356) days in the placebo group. The modal dose of Org 33062 used by the largest number of subjects during the continuation phase was 80 mg Org 33062 per day (see Table 21). During the continuation phase, 51 of the 126 subjects were exposed to daily doses of 60 mg Org 33062 or more for at least another 36 weeks.

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**Table 20 Duration of exposure (days)  
AST-OL group and AST group**

|                                        | Open-label phase (AST-OL) | Double-blind continuation phase (AST) |                            |                            |
|----------------------------------------|---------------------------|---------------------------------------|----------------------------|----------------------------|
|                                        | Org 33062 (N=420)         | Org 33062 (N=126)                     | Placebo (N=124)            | Overall (N=250)            |
| <b>Screening period</b>                |                           |                                       |                            |                            |
| N                                      | 420                       | 126                                   | 124                        | 250                        |
| Mean (SD)                              | 8.1 (3.3)                 | 8.4 (3.6)                             | 8.4 (3.4)                  | 8.4 (3.5)                  |
| Median (range)                         | 7 (1-19)                  | 7 (2-17)                              | 7 (1-19)                   | 7 (1-19)                   |
| <b>Open-label phase</b>                |                           |                                       |                            |                            |
| N                                      | 420                       | --                                    | --                         | --                         |
| Mean (SD)                              | 68.2 (25.0)               | --                                    | --                         | --                         |
| Median (range)                         | 83 (1-116)                | --                                    | --                         | --                         |
| <b>Double-blind continuation phase</b> |                           |                                       |                            |                            |
| N                                      | --                        | 126                                   | 124                        | 250                        |
| Mean (SD)                              | --                        | 217.1 (102.1)                         | 217.3 (98.9)               | 217.2 (100.3)              |
| Median (range)                         | --                        | 275 (6-363)                           | 275 (5-366)                | 275 (5-366)                |
| <b>Total treatment period</b>          |                           |                                       |                            |                            |
| N                                      | --                        | 126                                   | 124                        | 250                        |
| Mean (SD)                              | --                        | 296.2 (101.7)                         | 295.0 (100.0)              | 295.6 (100.7)              |
| Median (range)                         | --                        | 356 (77-421 <sup>a</sup> )            | 356 (62-421 <sup>a</sup> ) | 356 (62-421 <sup>a</sup> ) |

<sup>a</sup> Postponement of several assessments resulted in increased duration of exposure to trial medication.  
Data were taken from Tables 3.1-A, 3.1-B, 3.2-A.1, 3.2-B.1 and 3.2-C.1 in Appendix F.

**Table 21 Number of subjects with respect to duration of modal dose (mg Org 33062/day)  
AST-OL group and AST group**

| Open-label phase (AST-OL)<br>Duration | Org 33062  |            |            |            | Duration      | Double-blind continuation phase (AST) |                         |            | Placebo<br>0 mg |
|---------------------------------------|------------|------------|------------|------------|---------------|---------------------------------------|-------------------------|------------|-----------------|
|                                       | 20 mg<br>n | 40 mg<br>n | 60 mg<br>n | 80 mg<br>n |               | 40 mg<br>n                            | Org 33062<br>60 mg<br>n | 80 mg<br>n |                 |
| ≤ 1 week                              | 2          | 12         | 3          | 0          | ≤ 4 weeks     | 1                                     | 3                       | 9          | 2               |
| 1 – 2 weeks                           | 0          | 8          | 8          | 6          | 4 – 8 weeks   | 1                                     | 3                       | 4          | 11              |
| 2 – 4 weeks                           | 0          | 9          | 6          | 13         | 8 – 12 weeks  | 0                                     | 3                       | 0          | 5               |
| 4 – 6 weeks                           | 0          | 9          | 35         | 24         | 12 – 16 weeks | 2                                     | 1                       | 2          | 7               |
| 6 – 8 weeks                           | 0          | 24         | 41         | 26         | 16 – 20 weeks | 0                                     | 4                       | 0          | 9               |
| 8 – 10 weeks                          | 0          | 15         | 22         | 47         | 20 – 24 weeks | 1                                     | 2                       | 1          | 6               |
| > 10 weeks                            | 0          | 36         | 45         | 28         | 24 – 28 weeks | 1                                     | 1                       | 2          | 2               |
|                                       |            |            |            |            | 28 – 32 weeks | 0                                     | 1                       | 2          | 7               |
|                                       |            |            |            |            | 32 – 36 weeks | 0                                     | 1                       | 7          | 4               |
|                                       |            |            |            |            | 36 – 40 weeks | 11                                    | 11                      | 20         | 22              |
|                                       |            |            |            |            | > 40 weeks    | 12                                    | 13                      | 7          | 49              |
| Total                                 | 2          | 113        | 160        | 144        | Total         | 29                                    | 43                      | 54         | 124             |

Data were taken from Tables 3.1-C and 3.2-D.1 in Appendix F.

## CONCOMITANT MEDICATION USE

### Open-label phase

The most common concomitant medications taken by the subjects during the OL phase of the trial were central nervous system agents (30.2% of the subjects). Lorazepam (5.0% of the subjects) was most frequently used.

### Total treatment period and continuation phase

In both treatment groups, the most common concomitant medications taken by the subjects during the continuation phase of the trial were central nervous system agents (Org 33062: 31.7%; placebo: 25.0%). Aspirin (Org 33062: 5.6%; placebo: 3.2%) was most frequently used. During the total treatment period, Lorazepam was the most frequently used concomitant medication (Org 33062: 6.3%; placebo: 6.5%).

## EFFICACY

I will first present the sponsor's version of the efficacy findings based on the exclusion of 5 subjects whose relapse status is in question. I will then present the findings if these subjects are counted as relapsers. Finally I will present our statistical reviewer's (Rosewitha Kelly) conclusions.

## SPONSOR'S ANALYSIS

### Double-blind continuation phase

The analysis for all efficacy parameters was performed for the ITT group, and was based both on an OC and on an LOCF approach. Below, results of the LOCF approach are presented.

### Relapse rate at endpoint (primary analysis of primary parameter)

For subjects treated with Org 33062 in the continuation phase, the relapse rate was 23.0% at endpoint, compared to 34.7% for the placebo-treated group (Table 24). The difference between the treatment groups was statistically significant ( $p=0.024$  at endpoint).

**Table 24 Overall relapse rates (primary analysis of primary parameter)  
ITT group, LOCF approach**

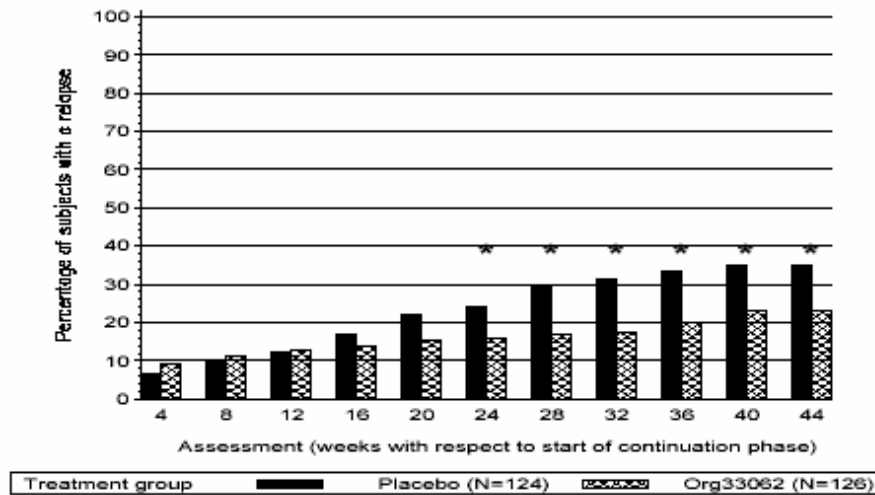
|         | Org 33062<br>(N=126) |      | Placebo<br>(N=124) |      | Between<br>treatments |
|---------|----------------------|------|--------------------|------|-----------------------|
|         | n                    | %    | n                  | %    | p-value               |
| Relapse | 29                   | 23.0 | 43                 | 34.7 | 0.024                 |

Data were taken from Table 6.2.1-A.2 and Analysis 6.2.1-A.3 in Appendix F.

In the continuation phase, a difference in relapse rate between the treatment groups

became apparent as of Week 16 (Figure 1). From Week 24 onward, the difference between the Org 33062 group and the placebo group was statistically significant in favor of Org 33062.

**Figure 1** Percentage of subjects with a relapse during the continuation phase  
ITT group, LOCF approach



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**Table 28 Change from baseline at the end of the continuation phase  
ITT group, LOCF approach**

| Parameter                                     | Statistic      | Org 33062     |                      | Placebo          |                      |
|-----------------------------------------------|----------------|---------------|----------------------|------------------|----------------------|
|                                               |                | Baseline      | Change from baseline | Baseline         | Change from baseline |
| HAMD Factor I<br>'anxiety /<br>somatization'  | n              | 126           | 124                  | 123 <sup>a</sup> | 123                  |
|                                               | Mean (SD)      | 9.0 (1.9)     | -5.5 (3.1)           | 9.1 (2.2)        | -4.9 (3.3)           |
|                                               | Median (range) | 9.0 (6 – 14)  | -6.0 (-13 – 2)       | 9.0 (1 – 15)     | -5.0 (-11 – 4)       |
| HAMD Factor III<br>'cognitive<br>disturbance' | n              | 126           | 124                  | 123              | 123                  |
|                                               | Mean (SD)      | 4.2 (1.9)     | -3.0 (2.3)           | 4.5 (2.4)        | -2.9 (2.5)           |
|                                               | Median (range) | 4.0 (0 – 11)  | -3.0 (-9 – 4)        | 4.0 (0 – 11)     | -3.0 (-9 – 3)        |
| HAMD Factor V<br>'retardation'                | n              | 126           | 124                  | 123              | 123                  |
|                                               | Mean (SD)      | 8.6 (1.8)     | -5.7 (3.0)           | 8.5 (1.9)        | -4.9 (3.2)           |
|                                               | Median (range) | 9.0 (4 – 12)  | -6.0 (-11 – 2)       | 9.0 (3 – 12)     | -5.0 (-12 – 2)       |
| HAMD Factor VI<br>'sleep disturbance'         | n              | 126           | 124                  | 123              | 123                  |
|                                               | Mean (SD)      | 4.1 (1.4)     | -2.7 (1.7)           | 4.1 (1.4)        | -2.5 (1.9)           |
|                                               | Median (range) | 4 (0 – 6)     | -3.0 (-6 – 2)        | 4.0 (1 – 6)      | -3.0 (-6 – 3)        |
| Bech six-item core<br>depression cluster      | n              | 126           | 124                  | 123              | 123                  |
|                                               | Mean (SD)      | 12.6 (2.0)    | -8.2 (4.4)           | 12.5 (2.2)       | -7.1 (4.4)           |
|                                               | Median (range) | 13.0 (8 – 18) | -9.0 (-16 – 2)       | 13.0 (6 – 19)    | -7.0 (-19 – 2)       |

<sup>a</sup> Subject (b) (6) (placebo) did not have an assessment within the allowed baseline window.

Data were taken from Tables 6.2.3-A.2, 6.2.3-B.2, 6.2.3-C.2, 6.2.3-D.2 and 6.2.3-F.2 in Appendix F.

## REANALYSIS OF RELAPSEERS

The efficacy of this study is called into question by the following sponsor statements in italics below.

*Relapse rate (additional analysis of primary parameter)*

***In an additional analysis on relapse rate, five subjects (Subjects (b) (6); all in the Org 33062 group) were redefined as having a relapse. For these subjects endpoint HAMD-17 total scores were below 16, but the information in the comment field associated with the EOT CRF Item “Reasons not mentioned above, please specify\_\_\_\_\_” suggested worsening of depressive symptoms (for details, see Section 7.13.1). According to this analysis, the number of subjects with a relapse at endpoint was 34 (27.0%) in the Org 33062 group and 43 (34.7%) in the placebo group. The difference between the treatment groups was not statistically significant.***

*Section 5.3 of the protocol defined relapse as: “Relapse is defined as having a HAMD-17 total score  $\geq$  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.”*

*The EOT CRF for the continuation phase consisted of the following items, one of which was to be checked by the Investigator for subjects discontinuing from the trial:*

- Adverse Event / Serious Adverse Event
- The subject is not willing or cannot cooperate for reasons not related to the study
- Relapse criteria fulfilled

- Reason not mentioned above, please specify \_\_\_\_\_  
 The protocol did not specifically instruct investigators to tick the EOT 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.

During the routine blind review of the data, the comment field associated with the EOT CRF Item "Reasons not mentioned above, please specify\_\_\_\_\_" was examined for every subject. A total of 21 subjects discontinued from the trial with this item ticked on the EOT CRF (see Listing 1.2.2.A in Appendix F) **It was found that eight subjects who were discontinued for "Reason not mentioned above" had information in the comment field for the item which suggested a re-emergence or worsening of depressive symptoms.** Three of these eight subjects (Subjects (b) (6)) had endpoint HAMD-17 total scores = 16 and five did not. These latter five subjects are listed in Table 9.

**Table 9** Subjects who discontinued due to other reason suggesting re-emergence or worsening of depressive symptoms

| Subject | HAMD-17 total score at endpoint | Comment on EOT CRF on reason for discontinuation                   |
|---------|---------------------------------|--------------------------------------------------------------------|
| (b) (6) | 13                              | Depression became worse again                                      |
| (b) (6) | 6                               | Depressive symptoms worsen                                         |
| (b) (6) | -- <sup>a</sup>                 | Stopped med. due to worsening of depression 5 d. before last visit |
| (b) (6) | 14 <sup>b</sup>                 | Stopped med. due to worsening of depression 4 d. before last visit |
| (b) (6) | 13                              | Insufficient effect: worsening of insomnia and depression          |

<sup>a</sup> No HAMD-17 total score available within the time frame for the continuation phase( i.e., up to 3 days after last trial medication intake). HAMD-17 total score 5 days after last drug intake was 22; <sup>b</sup> HAMD-17 total score 4 days after last drug intake was 23.

***In an internal memo dated 27 February 2002 (prior to unblinding), it was noted that these five subjects may have suffered a relapse and would therefore be redefined in the analysis as relapsers, even though they did not meet the protocol-defined relapse criteria. Due to logistical reasons, this procedure was adopted without queries to the concerned investigators or writing a protocol amendment (as stipulated by ICH guidelines). Consequently the study was unblinded with a memo on file that changed the definition of relapse to include any subject for whom the EOT CRF "Reasons not mentioned above, please specify\_\_\_\_\_" item was endorsed with comments suggesting worsening depression.***

***After unblinding and initial analyses were conducted, discrepancies were found in the findings of the five subjects who had been redefined as 'relapsers' (note the low HAMD-17 total score for Subject (b) (6), Table 9, for example). By then, investigators had been unblinded and could not be further queried. Subsequently, the procedures***

used to redefine the relapse status of the subjects in question were reviewed and determined to be invalid because the investigator comments were never queried to determine if they truly indicated relapse and the procedures were never authorized by protocol amendment.

After completion of the reviews and evaluations described above, the definition of relapse in the protocol pre-specified analysis plan for the primary efficacy parameter was determined to be consistent with the following programming algorithm: [Endpoint HAMD-17 total score  $\geq$  16] OR [EOT CRF Item 'Relapse criteria fulfilled' endorsed]. This definition, based on original intent of the protocol, is used in the primary analysis of the efficacy of Org 33062 in preventing relapse. The analysis based on the additional inclusion of subjects, who discontinued for 'Reasons not mentioned above' with comments suggesting worsening depression, is presented for completeness as an additional analysis.

## **FDA efficacy analysis**

Rosewitha Kelly in her statistical review makes the following points.

*“The primary endpoint in Study 28709-2003 was the proportion of relapse among the Gepirone-treated versus the placebo-treated patients. However, this reviewer did not observe a statistical significant treatment difference when using all ITT patients ( $p > 0.080$ ). When reclassifying five Gepirone patients identified by the sponsor as having relapsed, the treatment difference is even smaller and less significant.*

*The sponsor's statistical approach was not appropriate because it did not use all ITT patients. The main concerns with the trial and the sponsor's primary statistical analysis are:*

- *The Cochran-Mantel-Haenszel (CMH) test as performed by the sponsor is not appropriate because not all ITT patients were included in the primary analysis. The CMH test does not make use of centers that have either only one treatment arm or that have no relapses. Therefore, 32 ITT patients were not part of the sponsor's primary analysis. These patients need to be grouped into one center.*
- *Centers with less than 5 patients are usually grouped together as well. Grouping patients from centers with either only one treatment arm or no relapses or having at most 4 patients into one fictitious Center and performing the CMH test uses results of all ITT patients. This treatment comparison of relapse rates adjusted for Center is not statistically significant ( $p = 0.0971$ ).*
- *Grouping the original centers into countries also avoids the loss of any information. The treatment comparison of relapse rates adjusted for Country is also not statistically significant (CMH,  $p = 0.0805$ ).*

*As noted by the sponsor, five patients, who all received Gepirone, may have relapsed (based on information recorded under the investigator's discontinuation variable 'Reasons not mentioned above, please specify \_\_\_\_\_'), but were not classified as such it*

*the primary analysis. Classifying these patients as relapsed renders the treatment comparison non-significant whether adjusting for Center or for Country. “*

### **Summary of efficacy**

In an internal memo dated 27 February 2002 (prior to unbinding), it was noted that five subjects may have suffered a relapse and would therefore be redefined in the analysis as relapsers. Only after the blind was broken did the sponsor redefine these 5 subjects as non-relapsed patients saying their status could not be confirmed with the investigators anymore. I therefore believe these subjects should have been counted as relapsers. According to this analysis, the number of subjects with a relapse at endpoint was 34 (27.0%) in the Org 33062 group and 43 (34.7%) in the placebo group. The difference between the treatment groups was not statistically significant.

Rosewitha Kelly adds the following.

*“In this reviewer's opinion, Study 28709-2003, a relapse trial put forth by the sponsor as fulfilling the outstanding need for one more well-controlled positive trial in Gepirone ER, did not reach its goal. 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. “*

## **EFFICACY CONCLUSION**

Study28709 did not win based on the original primary efficacy variable and analysis plan.

### **Efficacy Addendum**

The sponsor provided us with data requested from Study 134004 which is one of their three acute pivotal placebo-controlled studies with the ER formulation. Four-hundred and ten subjects were randomized and 409 subjects received trial medication. There were 135 subjects randomized to the Org 33062 ER group, 138 subjects randomized to the fluoxetine group, and 136 subjects randomized to the placebo group.

In this study for the primary efficacy parameter (change from baseline in the HAMD-25 total score), there were no statistically significant differences between Org 33062 ER and placebo at any of the visits. It was also verified that there were no statistically significant differences between fluoxetine and placebo at any of the visits. The endpoint change from baseline values were -9.76 for Org 33062 ER, -11.66 for fluoxetine, and -10.63 for placebo.

The LOCF comparison of Fluoxetine vs. Gepirone just misses being significant at  $P=.068$  in favor of Fluoxetine. See table below.

**Table 1 HAMD-25 Total Score Change from Baseline  
LS Mean and P-Value by Visit and Treatment Group  
Org 33062 vs. Fluoxetine  
Intent-to-Treat Group (LOCF)**

| Treatment group        | Visit   |         |         |         |         |            |
|------------------------|---------|---------|---------|---------|---------|------------|
|                        | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6/ET |
| ORG 33062 (N=125)      |         |         |         |         |         |            |
| n                      | 124     | 124     | 124     | 124     | 124     | 124        |
| LS Mean                | -3.63   | -5.93   | -7.83   | -9.02   | -9.63   | -9.87      |
| SE                     | 0.43    | 0.52    | 0.58    | 0.64    | 0.71    | 0.76       |
| Fluoxetine (N=136)     |         |         |         |         |         |            |
| n                      | 134     | 134     | 134     | 134     | 134     | 134        |
| LS Mean                | -4.07   | -5.80   | -8.53   | -9.98   | -10.39  | -11.78     |
| SE                     | 0.41    | 0.50    | 0.56    | 0.62    | 0.69    | 0.73       |
| p-value                |         |         |         |         |         |            |
| Treatment (a)          | 0.457   | 0.852   | 0.379   | 0.276   | 0.437   | 0.068      |
| Treatment x Center (b) | 0.399   | 0.381   | 0.541   | 0.571   | 0.682   | 0.687      |

For the change from baseline in the HAMA total score, when the Org 33062 ER group was compared with the fluoxetine group using an LOCF approach, no statistically significant differences were found from Visits 1 through 5. However, at Visit 6, a statistically significant difference ( $p=0.025$ ) was found between the Org 33062 ER and fluoxetine groups, indicating that fluoxetine is better than Org 33062 ER at controlling anxiety.

## SAFETY SECTION

### DATABASE ORGANIZATION

The data cut-off date for this Integrated Summary of Safety is 23 June 2003.

The safety data from 75 clinical studies on Org 33062 are included in this integrated database. This group of studies includes:

- . 32 Phase I pharmacokinetic (PK) and pharmacodynamic (PD) studies (21 with Org 33062 ER and 11 with Org 33062 IR);
- . 34 Phase II/III double-blind, controlled studies (13 with Org 33062 ER and 21 with Org 33062 IR); and

. 9 Phase II/III open-label studies (2 with Org 33062 ER and 7 with Org 33062 IR).

For ongoing studies, data for serious adverse events (SAEs) that occurred through 23 June 2003 are included in this ISS.

Twenty-six of the 75 completed clinical trials provide long-term safety data for Org 33062. These studies include:

- . 20 Phase II/III double-blind, controlled studies (9 with Org 33062 ER and 11 with Org 33062 IR); and
- . 6 Phase II/III open-label studies (2 with Org 33062 ER and 4 with Org 33062 IR).

A total of 732 subjects were exposed to Org 33062 daily for at least 6 months, and 497 (476 Org 33062 ER) were exposed to a modal dose [dose (in mg/day) of Org 33062 that was most frequently prescribed for an individual subject during his/her study participation] of 40 mg or greater. A total of 260 subjects were exposed to Org 33062 daily for at least one year, and 170 (161 Org 33062 ER) were exposed to a modal dose of 40 mg or greater.

Table 3 provides an overview of the distribution of the subjects by phase of clinical development and treatment group. A total of 4862 subjects overall were exposed to Org 33062; the majority participated in Phase II/III clinical trials.

**Table 3**                      **Distribution of participants in Org 33062 studies by development phase and treatment group**

| Phase        | Org 33062 |      |       | Active   |         | Total subjects |
|--------------|-----------|------|-------|----------|---------|----------------|
|              | ER        | IR   | Total | Controls | Placebo |                |
| Phase I      | 582       | 204  | 786   | 30       | 108     | 924            |
| Phase II/III | 2217      | 1859 | 4076  | 848      | 1816    | 6740           |
| Total        | 2799      | 2063 | 4862  | 878      | 1924    | 7664           |

Source: Table A.1.2.2.

In Phase I cross-over studies, subjects may be counted twice in this table.

Subjects who were given different treatments between the acute and extension phases may be counted twice in this table.

## Exposure and Disposition

As of the cutoff date of 23 June 2003, 4862 individual subjects have been exposed to Org 33062 in 75 clinical trials. A total of 4076 subjects participated in Phase II/III studies and 2217 of these subjects were exposed to the ER formulation. Long-term exposure included 732 subjects who were exposed to Org 33062 for at least 6 months, and 261 subjects were exposed to Org 33062 for at least one year. In acute controlled Phase II/III studies in depression 1704 subjects were exposed to Org 33062 (1003 ER, 701 IR).

In terms of subject-years, exposure in the acute studies to Org 33062, placebo and control antidepressants (fluoxetine, paroxetine and imipramine combined) was

433.00, 205.74 and 83.42 subject-years respectively.

In the acute studies, including the Phase II/III controlled depression studies, the highest titrated doses of Org 33062 most frequently seen were doses of 40-80 mg/day. The mean modal dose of Org 33062 ER in Phase II/III controlled studies was 50.4 mg/day and similar to the mean modal dose (47.9 mg/day) in Phase II/III controlled depression studies; the mean modal dose was twice as high as for Org 33062 IR. More than half the subjects exposed to Org 33062 for 6 months to 1 year or greater received the ER formulation at doses of  $\geq 40$  mg/day.

Please see number of study participants table 5 below.

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Org 33062 (Gepirone Hydrochloride) ER Tablets  
Integrated Summary of Safety

Table 5 Number of study participants exposed to study drug by treatment phase, analysis population, and treatment group

| Analysis population                                                                                | Org 33062 |      |       | Antidepressants |            |            | Anxiolytics |          |         |
|----------------------------------------------------------------------------------------------------|-----------|------|-------|-----------------|------------|------------|-------------|----------|---------|
|                                                                                                    | ER        | IR   | Total | Fluoxetine      | Paroxetine | Imipramine | Bromazepam  | Diazepam | Placebo |
| All subjects treated in Phase I studies                                                            | 582       | 204  | 786   | 0               | 30         | 0          | 0           | 0        | 108     |
| All subjects treated in acute Phase II/III studies                                                 | 1541      | 1859 | 3400  | 244             | 134        | 240        | 73          | 110      | 1658    |
| All subjects treated in controlled acute Phase II/III studies                                      | 1087      | 1423 | 2510  | 244             | 134        | 240        | 73          | 110      | 1658    |
| All subjects treated in controlled acute Phase II/III studies in depression                        | 1003      | 701  | 1704  | 244             | 134        | 240        | 0           | 0        | 1065    |
| All subjects treated in extension Phase II/III studies                                             | 1278      | 517  | 1795  | 153             | 93         | 104        | 10          | 39       | 412     |
| All subjects treated in controlled extension Phase II/III studies                                  | 458       | 359  | 815   | 153             | 93         | 104        | 10          | 39       | 412     |
| All subjects treated in controlled extension Phase II/III studies in depression                    | 408       | 231  | 639   | 153             | 93         | 104        | 0           | 0        | 273     |
| All subjects treated in Phase II/III studies                                                       | 2217      | 1859 | 4076  | 291             | 134        | 240        | 73          | 110      | 1658    |
| All subjects treated in controlled Phase II/III studies acute and extension phases                 | 1195      | 1423 | 2618  | 291             | 134        | 240        | 73          | 110      | 1658    |
| All subjects treated in controlled Phase II/III studies in depression acute and extension phases   | 1111      | 701  | 1812  | 291             | 134        | 240        | 0           | 0        | 1065    |
| All subjects treated in uncontrolled Phase II/III studies in depression acute and extension phases | 1138      | 323  | 1461  | 0               | 0          | 0          | 0           | 0        | 0       |
| All subjects treated in Phase II/III studies 6 months                                              | 519       | 213  | 732   | 80              | 70         | 48         | 0           | 0        | 138     |
| All subjects treated in controlled Phase II/III studies 6 months                                   | 177       | 142  | 319   | 80              | 70         | 48         | 0           | 0        | 138     |
| All subjects treated in controlled Phase II/III studies in depression 6 months                     | 177       | 119  | 296   | 80              | 70         | 48         | 0           | 0        | 125     |
| All subjects treated in Phase II/III studies one year                                              | 170       | 91   | 261   | 28              | 0          | 25         | 0           | 0        | 64      |
| All subjects treated in controlled Phase II/III studies one year                                   | 20        | 59   | 79    | 28              | 0          | 25         | 0           | 0        | 64      |
| All subjects treated in controlled Phase II/III studies in depression one year                     | 20        | 49   | 69    | 28              | 0          | 25         | 0           | 0        | 59      |

Source: Table A.1.4.1, Listings A.9.4.2.2, A.9.4.3.2, A.9.4.3.3

In Phase I cross-over studies, subjects may be counted twice in this table. Subjects who were given different treatments between the acute and extension phases may be counted twice in this table. For the double-blind phase of relapse studies 03A7A-002 and 28709, only subjects randomized to Org 33062 are represented in this table. However, all-subjects who received Org 33062 during the open-label phase of these relapse studies are counted in this table.

Exposure and disposition data during the acute phase are presented for the All Subjects Treated population in: Phase I studies (primarily healthy volunteers), Phase II/III studies (the largest analysis population), controlled Phase II/III studies (a subset of All Subjects Treated in Phase II/III studies), and controlled Phase II/III studies in depression (a subset of All Subjects Treated in controlled Phase II/III studies). A summary of the exposure and disposition data for each population is provided below.

In Phase I studies 786 subjects received Org 33062, i.e., Org 33062 ER formulation (582 subjects) and Org 33062 IR formulation (204 subjects) combined, and 108 subjects received placebo. The discontinuation rates due to an AE were similar for subjects exposed to Org 33062 ER (2.9%) and placebo (2.8%). Of the subjects exposed to Org 33062 IR, 5.9% discontinued due to AE.

The mean duration of exposure was similar for Org 33062 ER (11.5 days) and placebo (11.1 days). The 786 subjects who were exposed to Org 33062 and the 108 subjects who received placebo were exposed for the equivalent of 23.82 subject years and 3.56 subject years, respectively. The highest titrated doses of Org 33062 most frequently seen were 20-39 mg/day (396 subjects), and mean modal dose of Org 33062 ER was 38.6 mg/day.

In acute Phase II/III studies, 3400 subjects received Org 33062 (1541 ER, 1859 IR) and 1658 subjects received placebo. The discontinuation rates were similar for Org 33062 ER (39.5%) and for placebo (38.3%). Approximately twice as many Org 33062 ER subjects as compared to placebo discontinued acute study participation due to an AE (12.1% vs. 6.8%), but half as many due to lack of efficacy (7.4% vs. 16.2%).

In terms of subject years, exposure to Org 33062 was 433.00 subject years (a total of 3400 subjects), exposure to placebo was 205.74 subject years (1658 subjects), and exposure to control antidepressants was 83.42 subject years (618 subjects for fluoxetine, imipramine and paroxetine combined). The highest titrated doses of Org 33062 most frequently seen were 40-80 mg/day (1453 subjects). Mean modal dose of Org 33062 ER was 50.4 mg/day, which was twice as high as Org 33062 IR. In total, 1165 subjects had a modal dose Org 33062 ER  $\geq$ 40 mg. Total exposure for modal dose Org 33062 ER  $\geq$ 40 mg was 178.78 subject years.

In controlled acute Phase II/III studies, 2510 subjects were exposed to Org 33062 (1087 ER, 1423 IR) and 1658 subjects received placebo. The percentages of subjects who discontinued were similar for the Org 33062 ER (38.5%) and the placebo (38.3%) groups. Approximately twice as many Org 33062 ER subjects as compared to placebo subjects discontinued due to an AE (12.6% vs. 6.8%), but half as many due to lack of efficacy (7.6% vs. 16.2%).

The 2510 subjects who were exposed to Org 33062 and the 1658 subjects who received placebo were exposed for the equivalent of 298.87 subject years and 205.74 subject years, respectively. Exposure to the control antidepressants was 83.42 subject years (a total of 618 subjects for fluoxetine, imipramine and paroxetine combined). The highest titrated doses of Org 33062 most frequently seen were <20 mg/day and 40-80 mg/day (in 930 and 927 subjects, respectively). Mean modal dose of Org 33062 ER was 46.5 mg/day, twice as high as with the IR formulation. In total, 732 subjects had modal dose of Org 33062 ER  $\geq$ 40 mg. Mean duration of treatment was 48.7 days for modal dose Org 33062 ER  $\geq$ 40 mg as compared to 45.3 days for placebo.

In controlled acute Phase II/III studies in depression, 1704 subjects were exposed to Org 33062 (1003 ER, 701 IR) and 1085 subjects received placebo. The

discontinuation rates were comparable for Org 33062 ER (38.2%) and for placebo (39.4%). Approximately twice as many Org 33062 ER subjects as compared to placebo discontinued due to an AE (13.0% vs. 6.4%), but half as many due to lack of efficacy (7.4% vs. 17.7%).

Exposure to Org 33062 was 210.02 subjects years (1704 subjects), exposure to placebo was 140.47 subject years (1085 subjects), and exposure to control antidepressants was 83.42 subject years (a total of 618 subjects for fluoxetine, imipramine and paroxetine combined). The highest titrated doses of Org 33062 most frequently seen were 40-80 mg/day, and the mean modal dose of Org 33062 ER was 47.9 mg/day, which was twice as high as with Org 33062 IR. In total, 697 subjects had a modal dose of Org 33062 ER  $\geq$  40 mg. Mean treatment duration for modal dose Org 33062 ER  $\geq$ 40 mg was 48.7 days.

Please see table below for acute phase dispositions in Depression studies.

Table 12 Acute phase: Disposition of subjects by treatment group (All subjects treated in controlled Phase II/III studies in depression)

|                      | Org 33062  |            |            |                         |                         | SSRIs      |            |            | Placebo    |
|----------------------|------------|------------|------------|-------------------------|-------------------------|------------|------------|------------|------------|
|                      | ER         | IR         | Total      | Modal dose ER $\geq$ 40 | Modal dose IR $\geq$ 40 | Fluoxetine | Paroxetine | Imipramine |            |
| Treated              | 1003       | 701        | 1704       | 697                     | 137                     | 244        | 134        | 240        | 1085       |
| Completed            | 620 (61.8) | 352 (50.2) | 972 (57.0) | 479 (68.7)              | 81 (59.1)               | 184 (75.4) | 102 (76.1) | 130 (54.2) | 658 (60.6) |
| Discontinued         | 363 (36.2) | 349 (49.8) | 732 (43.0) | 218 (31.3)              | 56 (40.9)               | 60 (24.6)  | 32 (23.9)  | 110 (45.8) | 427 (39.4) |
| --Adverse experience | 130 (13.0) | 146 (20.8) | 276 (16.2) | 80 (11.5)               | 23 (16.8)               | 12 (4.9)   | 14 (10.4)  | 44 (18.3)  | 69 (6.4)   |
| --Lack of efficacy   | 74 (7.4)   | 88 (12.6)  | 162 (9.5)  | 44 (6.3)                | 19 (13.9)               | 16 (6.6)   | 10 (7.5)   | 15 (6.3)   | 192 (17.7) |
| --Other              | 179 (17.8) | 115 (16.4) | 294 (17.3) | 94 (13.5)               | 14 (10.2)               | 32 (13.1)  | 8 (6.0)    | 51 (21.3)  | 166 (15.3) |

Source: Table A.1.4.4.1.B, Listing A.8.4.4.3

Org 33062 Total refers to Org 33062 ER and Org 33062 IR.

Treatment groups 'ER  $\geq$  40' and 'IR  $\geq$  40' are for subjects on Org 33062 with modal dose  $\geq$  40 mg/day in that formulation.

## Dosage and treatment duration during acute phase of treatment

Table 13 presents the number of subjects in controlled Phase II/III trials in depression according to treatment, treatment duration, and modal dose of Org 33062 for the acute phase.

In controlled acute Phase II/III studies in depression, exposure to Org 33062 was 210.02 subject years (1704 subjects), exposure to placebo was 140.47 subject years (1085 subjects), and exposure to the control antidepressants was 83.42 subject years (a total of 618 subjects for fluoxetine, paroxetine and imipramine combined) (Table 13).

The mean duration of treatment, which was 45.9 days for Org 33062 ER and 48.7 days for modal dose Org 33062 ER =40 mg, was comparable for all treatments. The highest titrated doses of Org 33062 most frequently administered were 40-80 mg/day (788 subjects), followed by <20 mg/day (449 subjects), 20-39 mg/day (421 subjects), and =80 mg/day (46 subjects) (Table 13).

Similar to the data for controlled Phase II/III studies, the mean modal dose for Org 33062 ER in controlled Phase II/III studies in depression was twice as high as for Org 33062 IR (47.9 vs. 25.2 mg/day). For the subjects with a modal dose =40 mg/day, however, the mean modal dose was similar for both formulations (62.1 vs. 60.8 mg/day for ER vs. IR formulation, respectively).

Table 13 Acute phase: Number of subjects exposed to study drug by duration treatment, treatment group, and modal dose (All subjects treated in controlled Phase II/III studies in depression)

| Treatment duration in weeks | Org 33062 dose (mg/day) |         |         |      | Org 33062 |         |         | SSRIs      |            |            | Placebo |
|-----------------------------|-------------------------|---------|---------|------|-----------|---------|---------|------------|------------|------------|---------|
|                             | < 20                    | 20 - 39 | 40 - 80 | > 80 | Total     | ER ≥ 40 | IR ≥ 40 | Fluoxetine | Paroxetine | Imipramine |         |
| ≤ 1                         | 77                      | 44      | 21      | 0    | 142       | 21      | 0       | 11         | 9          | 19         | 52      |
| > 1 - ≤ 2                   | 32                      | 24      | 38      | 0    | 94        | 36      | 2       | 9          | 1          | 16         | 50      |
| > 2 - ≤ 4                   | 61                      | 54      | 72      | 0    | 187       | 59      | 13      | 16         | 3          | 32         | 108     |
| > 4 - ≤ 6                   | 39                      | 41      | 71      | 12   | 163       | 61      | 22      | 12         | 5          | 18         | 110     |
| > 6 - ≤ 8                   | 63                      | 63      | 284     | 13   | 423       | 271     | 26      | 68         | 74         | 24         | 314     |
| > 8 - ≤ 12                  | 177                     | 195     | 301     | 21   | 694       | 248     | 74      | 128        | 40         | 131        | 451     |
| > 12 - ≤ 18                 | 0                       | 0       | 0       | 0    | 0         | 0       | 0       | 0          | 2          | 0          | 0       |
| > 18 - ≤ 24                 | 0                       | 0       | 1       | 0    | 1         | 1       | 0       | 0          | 0          | 0          | 0       |
| Total no. of subjects       | 449                     | 421     | 788     | 46   | 1704      | 897     | 137     | 244        | 134        | 240        | 1085    |
| Subject years               | 47.77                   | 50.27   | 105.41  | 6.57 | 210.02    | 93.00   | 18.98   | 34.12      | 19.47      | 29.83      | 140.47  |

Source: Table A.1.4.4.7.A, Listing A.9.4.4.4

Org 33062 treatment groups are determined by the given modal dose (mg/day) of Org 33062 in that formulation.

Org 33062 Total refers to Org 33062 ER and Org 33062 IR

Treatment groups 'ER ≥ 40' and 'IR ≥ 40' are for subjects on Org 33062 with modal dose ≥ 40 mg/day in that formulation.

## Deaths

There were no deaths in Phase I trials.

There were seven deaths in subjects who participated in Phase II/III studies. Three of the deaths occurred during acute exposure to the study medications (Org 33062 ER subject (b) (6), paroxetine subject (b) (6), and placebo subject (b) (6)); two occurred during long-term exposure to the study medication (Org 33062 ER subject (b) (6) and fluoxetine subject (b) (6)); and two occurred more than 30 days after the subject's final dose of study medication (Org 33062 IR subject (b) (6) and Org 33062 ER subject (b) (6)). A brief description of each death follows; additional details may be found in the subject narratives which I have reviewed.

Subject (b) (6) in the Org 33062 ER group, a 45-year old Caucasian male with a history of multiple suicide attempts, committed suicide by hanging after 20 days exposure to Org 33062 ER. This subject was a category 2 subject, ie a direct entry in the extension study 134-501, and had never been previously exposed to Org 33062. He was also receiving diazepam as a concomitant medication. This death was judged to be unrelated to treatment with Org 33062 ER by both the investigator and the sponsor.

Subject (b) (6), an 86-year old male subject who received paroxetine for 42 days, died as a consequence of heart arrest. The death was considered

unlikely related to the study medication by the investigator, but possibly related by the sponsor.

Subject (b) (6), a 62-year-old subject who received placebo for 13 days, died suddenly from an autopsy-confirmed myocardial infarction. The subject had no history of cardiovascular disease and was not receiving concomitant medications.

Subject (b) (6), an 83-year old male subject who received Org 33062 ER (modal dose 60 mg) for 191 days, died during the tapering period of study 28715 with pre-existing coronary heart disease. Both the investigator and the sponsor considered the death unrelated to treatment with the study medication.

Subject (b) (6), a 45-year old Caucasian male in the fluoxetine group, died of metastatic cancer after approximately 314 days on study. The cancer was of the lungs, liver, pancreas, and gall bladder. The subject was a moderate smoker. The metastatic cancer was thought not to be related to fluoxetine treatment.

Subject (b) (6) died on (b) (6) of an aortic dissection approximately 40 days after his last dose of Org 33062 IR. The subject had been treated with Org 33062 IR for approximately 35 days ((b) (6)) and had been treated for eight years for hypertension with furosemide and metoprolol. The circumstances of this case do not support a conclusion that Org 33062 was associated with this serious and unexpected adverse event.

Subject (b) (6), a 79-year old male subject, died approximately 30 days after the last dose of trial medication due to pulmonary embolism. The subject had received Org 33062 ER (modal dose 60 mg) for 90 days during the trial. Both the investigator and the sponsor considered the death unrelated to treatment with the study medication.

## **Serious adverse events**

This section of the ISS presents treatment-emergent SAEs (MedDRA 5.1 preferred terms) during acute phase treatment through the cut-off date of 23 June 2003, including those that occurred in ongoing trials (even if the treatment blind has not been broken). A treatment-emergent SAE is one that occurred after the first dose of study medication up to 30 days after the final dose of study medication. A narrative for each SAE can be found in Appendix B which I have reviewed.

All subjects treated in Phase I studies

There were no SAEs in Phase I trials.

All subjects treated in Phase II/III studies

The number and percentage of subjects with SAEs during acute phase treatment are presented in Table 28. The risk of experiencing at least one SAE was statistically significantly greater vs. placebo only in the SSRI group. The overall incidence of SAEs in

the Org 33062 ER =40 mg group was 1.4%; the incidence among the other analysis groups differed from the ER =40 mg incidence by approximately  $\pm 1\%$ . The only individual SAE with a statistically significant greater risk of occurrence vs. placebo was road traffic accident in the imipramine group. The most frequent SAEs in the Org 33062 ER group or the ER =40 mg modal dose group were depression aggravated, suicidal ideation, and major depressive disorder NOS. Tables of SAEs follows.

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Table 28 Acute phase: Number (%) of subjects with serious adverse events regardless of relationship to study drug by preferred term (in descending order) and treatment group (All subjects treated in Phase II/III studies)

| Preferred Term                      | Org 33062 N(%) |            |            |            |            | Control N(%) |            |            |
|-------------------------------------|----------------|------------|------------|------------|------------|--------------|------------|------------|
|                                     | ER             | IR         | Total      | ER ≥ 40 mg | IR ≥ 40 mg | SSRI         | Imipramine | Placebo    |
| Total number of subjects            | 1541           | 1859       | 3400       | 1165       | 349        | 378          | 240        | 1658       |
| Subjects with at least 1 AE         | 1184(76.8)     | 1615(86.9) | 2799(82.3) | 870(74.7)  | 329(94.3)  | 293(77.5)    | 221(92.1)  | 1291(77.9) |
| Subjects with at least 1 serious AE | 21(1.4)        | 32(1.7)    | 53(1.6)    | 16(1.4)    | 4(1.1)     | 9(2.4)       | 2(0.8)     | 15(0.9)    |
| DEPRESSION AGGRAVATED               | 3(0.2)         | 2(0.1)     | 5(0.1)     | 3(0.3)     | 0          | 0            | 0          | 0          |
| SUICIDAL IDEATION                   | 3(0.2)         | 2(0.1)     | 5(0.1)     | 3(0.3)     | 1(0.3)     | 0            | 0          | 0          |
| MAJOR DEPRESSIVE DISORDER NOS       | 2(0.1)         | 0          | 2(0.1)     | 2(0.2)     | 0          | 1(0.3)       | 0          | 0          |
| ANGINA PECTORIS                     | 1(0.1)         | 1(0.1)     | 2(0.1)     | 1(0.1)     | 1(0.3)     | 0            | 0          | 0          |
| LOSS OF CONSCIOUSNESS               | 1(0.1)         | 1(0.1)     | 2(0.1)     | 0          | 0          | 0            | 0          | 0          |
| SUICIDE ATTEMPT                     | 1(0.1)         | 1(0.1)     | 2(0.1)     | 1(0.1)     | 0          | 1(0.3)       | 0          | 0          |
| OVARIAN CYST                        | 1(0.1)         | 0          | 1(0.0)     | 0          | 0          | 0            | 0          | 1(0.1)     |
| CHEST PAIN                          | 1(0.1)         | 0          | 1(0.0)     | 0          | 0          | 0            | 0          | 0          |
| CHOLELITHIASIS                      | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| CYSTITIS CHRONIC NOS                | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| ELECTROCARDIOGRAM ABNORMAL NOS      | 1(0.1)         | 0          | 1(0.0)     | 0          | 0          | 0            | 0          | 0          |
| EPILEPSY NOS                        | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| HALLUCINATION NOS                   | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| INTENTIONAL SELF-INJURY             | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| NON-ACCIDENTAL OVERDOSE             | 1(0.1)         | 0          | 1(0.0)     | 0          | 0          | 0            | 0          | 0          |
| PANIC ATTACK                        | 1(0.1)         | 0          | 1(0.0)     | 1(0.1)     | 0          | 0            | 0          | 0          |
| PROSTATE CANCER NOS                 | 1(0.1)         | 0          | 1(0.0)     | 0          | 0          | 0            | 0          | 0          |

Table 28 Acute phase: Number (%) of subjects with serious adverse events regardless of relationship to study drug by preferred term (in descending order) and treatment group (All subjects treated in Phase II/III studies)

| Preferred Term                       | Org 33062 N(%) |        |        |            |            | Control N(%) |            |         |
|--------------------------------------|----------------|--------|--------|------------|------------|--------------|------------|---------|
|                                      | ER             | IR     | Total  | ER ≥ 40 mg | IR ≥ 40 mg | SSRI         | Imipramine | Placebo |
| PSYCHOGENIC PAIN DISORDER            | 1(0.1)         | 0      | 1(0.0) | 1(0.1)     | 0          | 0            | 0          | 0       |
| STERNAL FRACTURE                     | 1(0.1)         | 0      | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| SYNCOPE                              | 1(0.1)         | 0      | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| WHITE BLOOD CELL COUNT DECREASED     | 1(0.1)         | 0      | 1(0.0) | 1(0.1)     | 0          | 0            | 0          | 0       |
| PSYCHIATRIC SYMPTOM NOS              | 0              | 6(0.3) | 6(0.2) | 0          | 1(0.3)     | 0            | 0          | 1(0.1)  |
| HERNIA NOS                           | 0              | 2(0.1) | 2(0.1) | 0          | 1(0.3)     | 0            | 0          | 0       |
| ROAD TRAFFIC ACCIDENT                | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 2(0.8)     | 1(0.1)  |
| ALANINE AMINOTRANSFERASE INCREASED   | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| ASPARTATE AMINOTRANSFERASE INCREASED | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| BACK PAIN                            | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| CONFUSIONAL STATE                    | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| DEPRESSION                           | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| DYSMENORRHOEA                        | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| FEAR, FOCUS                          | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| HEPATITIS NOS                        | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| HERPES ZOSTER                        | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| HOSPITALISATION                      | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| HYPERTENSION NOS                     | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| MANIA                                | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| MENORRHAGIA                          | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| MENTAL DISORDER NOS                  | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| MIGRAINE NOS                         | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| NEPHROLITHIASIS                      | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| NERVOUSNESS                          | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| OVERDOSE NOS                         | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |

Table 28 Acute phase: Number (%) of subjects with serious adverse events regardless of relationship to study drug by preferred term (in descending order) and treatment group (All subjects treated in Phase II/III studies)

| Preferred Term               | Org 33062 N(%) |        |        |            |            | Control N(%) |            |         |
|------------------------------|----------------|--------|--------|------------|------------|--------------|------------|---------|
|                              | ER             | IR     | Total  | ER ≥ 40 mg | IR ≥ 40 mg | SSRI         | Imipramine | Placebo |
| PAIN IN LIMB                 | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| RENAL PAIN                   | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| TRANSIENT ISCHAEMIC ATTACK   | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| VERTIGO                      | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| VOMITING NOS                 | 0              | 1(0.1) | 1(0.0) | 0          | 0          | 0            | 0          | 0       |
| APPENDICITIS                 | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| ASTHMA NOS                   | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| CARTILAGE INJURY             | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| CHOLECYSTITIS ACUTE NOS      | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| CONVULSIONS NOS              | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| DRUG HYPERSENSITIVITY        | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| HEPATITIS B                  | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| HUMERUS FRACTURE             | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| INFECTED CYST                | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| LIGAMENT INJURY NOS          | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| MENINGITIS VIRAL NOS         | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| MYOCARDIAL INFARCTION        | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| OEDEMA NOS                   | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| PAPILLARY THYROID CANCER     | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| PNEUMOTHORAX NOS             | 0              | 0      | 0      | 0          | 0          | 0            | 0          | 1(0.1)  |
| ATRIAL FLUTTER               | 0              | 0      | 0      | 0          | 0          | 1(0.3)       | 0          | 0       |
| BENIGN PROSTATIC HYPERPLASIA | 0              | 0      | 0      | 0          | 0          | 1(0.3)       | 0          | 0       |
| BRADYCARDIA NOS              | 0              | 0      | 0      | 0          | 0          | 1(0.3)       | 0          | 0       |
| CALCULUS BLADDER             | 0              | 0      | 0      | 0          | 0          | 1(0.3)       | 0          | 0       |
| CARDIAC ARREST               | 0              | 0      | 0      | 0          | 0          | 1(0.3)       | 0          | 0       |

Table 28 Acute phase: Number (%) of subjects with serious adverse events regardless of relationship to study drug by preferred term (in descending order) and treatment group (All subjects treated in Phase II/III studies)

| Preferred Term                                  | Org 33062 N(%) |    |       |            |            | Control N(%) |            |         |
|-------------------------------------------------|----------------|----|-------|------------|------------|--------------|------------|---------|
|                                                 | ER             | IR | Total | ER ≥ 40 mg | IR ≥ 40 mg | SSRI         | Imipramine | Placebo |
| CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED | 0              | 0  | 0     | 0          | 0          | 1(0.3)       | 0          | 0       |
| LEFT VENTRICULAR FAILURE                        | 0              | 0  | 0     | 0          | 0          | 1(0.3)       | 0          | 0       |
| POLYTRAUMATISM                                  | 0              | 0  | 0     | 0          | 0          | 1(0.3)       | 0          | 0       |
| PREGNANCY NOS                                   | 0              | 0  | 0     | 0          | 0          | 2(0.5)       | 0          | 0       |
| SUPRAVENTRICULAR TACHYCARDIA                    | 0              | 0  | 0     | 0          | 0          | 1(0.3)       | 0          | 0       |

Source: Table A.3.7.3.4, Listing A.9.7.3.2

Adverse events were coded using MedDRA version 5.1.

Treatment groups "ER ≥ 40" and "IR ≥ 40" are for subjects on Org 33062 with modal dose ≥ 40 mg/day in that formulation.

## Discontinuations due to adverse events.

In Phase I studies the discontinuation rates were similar for subjects exposed to Org 33062 ER (2.9%) and placebo (2.8%); 5.9% of subjects exposed to Org 33062 IR discontinued due to an AE.

In acute Phase II/III studies approximately twice as many Org 33062 ER subjects compared to placebo discontinued due to an AE (12.1% vs. 6.8%), half as many discontinued to lack of efficacy (7.4% vs. 16.2%).

Furthermore 15% of subjects in the combined Org 33062 treatment group, 18% in the Org 33062 IR group, 18% in the imipramine group and 7% in the SSRI group discontinued prematurely due to adverse experiences. The risk of experiencing any adverse experience leading to discontinuation was statistically significantly greater in the Org 33062 and imipramine groups compared to placebo. The incidence of withdrawal due to any adverse experience in the Org 33062 ER treatment group was only slightly higher than in the placebo group.

A narrative for each adverse drop-out is available and I have reviewed these without finding any unusual events.

The most common events (≥1%) leading to discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) are included in the table below.

| <b>TABLE I: COMMON ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN ALL SHORT-TERM CONTROLLED DEPRESSION TRIALS WITH BRAND NAME<sup>™</sup> (gepirone HCl) EXTENDED-RELEASE TABLETS<sup>1</sup></b> |                                                         |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------|
| Adverse Event                                                                                                                                                                                                     | Percentage of Patients Discontinuing with Adverse Event |                     |
|                                                                                                                                                                                                                   | BRAND NAME <sup>™</sup><br>(n=697 )<br>Dose ≥ 40 mg     | Placebo<br>(n=608 ) |
| Nausea                                                                                                                                                                                                            | 2%                                                      | <1%                 |
| Dizziness <sup>1</sup>                                                                                                                                                                                            | 2%                                                      | <1%                 |
| Headache                                                                                                                                                                                                          | 1%                                                      | <1%                 |
| Irritability                                                                                                                                                                                                      | 1%                                                      | <1%                 |

<sup>1</sup>Please note any reported light-headedness is translated to dizziness in MedDRA terminology

## ADVERSE EVENTS OF SPECIAL INTEREST

### DIZZINESS

There were no serious reports of dizziness in acute controlled Phase II/III trials.

Dizziness most frequently led to the discontinuation of subjects in the Org 33062 Total group and the Org 33062 IR ≥40 mg modal dose group. In the Org 33062 ER ≥40 mg modal dose group similar percentages of subjects discontinued due to either dizziness or nausea. The risk of discontinuation due to dizziness was statistically significantly greater vs. placebo in each Org 33062 analysis group. The incidence of discontinuation in the Org 33062 Total group (4.3%) was about 10 times the placebo incidence (0.4%). The incidence of discontinuation due to dizziness in the Org 33062 IR ≥40 mg modal dose group (6.1%) was about 3 times the incidence in the Org 33062 ER ≥40 mg modal dose group (1.8%). Most discontinuations due to dizziness in Org 33062-treated subjects occurred during the first three weeks of treatment.

### Incidence by demographic subgroup

There was no statistically significant difference in the incidence of dizziness between young and old subjects, male and female subject or Caucasian and non-Caucasian subjects. However, the incidence of dizziness in the younger Org 33062 subjects (37.6%) was much higher than the incidence in the older Org 33062 subjects (15.2%), while the incidence in the young and old placebo subjects was similar (12% and 10%, respectively).

## **Incidence of dizziness, syncope, accidental injury, and orthostatic hypotension**

This section presents the sponsor's discussion of the relationship, or lack thereof, among Org 33062-associated dizziness, syncope, accidental injury, and objectively measured orthostatic change. No consistent association among these events was observed during acute phase treatment in Phase II/III trials. Orthostatic change was not measured in every study, may have been measured for selected subjects even if not planned per protocol, and even if planned per protocol the method of measurement was not standardized across protocols. Also, the orthostatic change data were collected as part of routine trial visits and not necessarily at the time of AEs. In addition, many of the subjects who received the IR formulation of Org 33062 came from the older BMS trials, and there is limited information on these subjects.

In order to provide the broadest possible search, subjects with the following AEs were identified by the sponsor from the all Phase II/III studies database:

- \_ for dizziness . dizziness, dizziness aggravated, dizziness exertional, dizziness postural, vertigo, vertigo positional
- \_ for syncope . loss of consciousness, syncope
- \_ for accidental injury . fall, and any AE in the Injury, Poisoning, and Procedural
- \_ for orthostatic hypotension . orthostatic hypotension, blood pressure orthostatic abnormal, dizziness postural, vertigo positional

In this sponsor analysis, subjects who experienced dizziness and/or syncope and/or accidental injury and/or orthostatic hypotension no more than 1 day apart (ie had a .temporal association. between these AEs) during acute exposure in Phase II/III trials were identified. Objectively measured orthostatic change data were examined to determine if orthostatic change contributed to the AEs.

Only one subject had a cluster of greater than two of the four AEs during acute exposure; placebo subject (b) (6) had one AE from each of the four AE categories. The search identified 9 subjects who had an AE of dizziness and an AE of syncope or loss of consciousness during acute exposure in Phase II/III trials (4 Org 33062 IR, 2 Org 33062 ER, 2 placebo, and 1 diazepam). Five of these cases were temporally-associated (2 Org 33062 IR, 2 Org 33062 ER, and 1 placebo); these are identified in the following list. None of the five had a record of a clinically significant orthostatic change during their respective trials.

- \_ Org 33062 IR subject (b) (6) (dizziness on Day 1, syncope on Day 2)
- \_ Org 33062 IR subject (b) (6) (both AEs on Day 44)
- \_ Org 33062 ER subject (b) (6) (both AEs on Day 11)
- \_ Org 33062 ER subject (b) (6) (direct entry into extension trial exposed for only 42 days; both AEs on Day 42; this is subject (b) (6) at site (b) (6))
- \_ Placebo subject (b) (6) (both AEs on Day 27)

The search identified 30 subjects who had an AE of dizziness and an AE of fall or any AE in the SOC of Injury, Poisoning, and Procedural Complications during acute exposure in Phase II/III trials (10 Org 33062 IR, 9 Org 33062 ER, 6 placebo, 1 fluoxetine, and 4 imipramine). Three of these cases showed a reasonable temporal association (2 Org 33062 ER and 1 placebo); these are identified in the following list.

None had a record of a clinically significant orthostatic change during their respective trials (Appendix Listing A.9.10.3.5).

\_ Org 33062 ER subject (b) (6) (both eye injury NOS [verbatim .right eye injury.] and dizziness on Day 4)

\_ Org 33062 ER subject (b) (6) (both fall and dizziness on Day 30)

\_ Placebo subject (b) (6) (both post procedural pain [verbatim .pain, root canal.] and dizziness on Day 13)

The search identified 13 subjects who had an AE of dizziness and an AE of orthostatic hypotension (4 Org 33062 IR, 2 Org 33062 ER, 4 placebo, 1 paroxetine, and 2 imipramine) during acute exposure in Phase II/III trials. Four of these cases were temporally-associated (1 Org 33062 ER, 1 placebo, 1 paroxetine, and 1 imipramine); these are identified in the following list. Only the paroxetine subject had a record of an objectively measured clinically significant orthostatic change.

\_ Org 33062 ER subject (b) (6) (both AEs on Day 23)

\_ Placebo subject (b) (6) (both AEs on Day 1)

\_ Paroxetine subject (b) (6) (an elderly subject with both AEs on Day 20, plus a clinically significant, objectively measured orthostatic change on Days 12 and 26)

\_ Imipramine subject (b) (6) (AEs occurred on Day 10 and Day 11)

The search identified only 2 subjects with the AE of orthostatic hypotension and the AE of fall or any AE in the SOC of Injury, Poisoning, and Procedural Complications (1 placebo subject and 1 imipramine subject); there was no temporal relationship between the two AEs and neither had a record of an objectively measured clinically significant orthostatic change.

The search identified 4 subjects with the AE of syncope and the AE of fall or any AE in the SOC of Injury, Poisoning, and Procedural Complications (1 Org 33062 IR subject, 2 Org 33062 ER subjects, and 1 placebo subject). A temporal relationship was observed for the Org 33062 IR subject and for one Org 33062 ER subject, identified in the list below. Neither had a record of a clinically significant orthostatic change.

\_ Org 33062 IR subject (b) (6) experienced a loss of consciousness, fell, and suffered lacerations to the elbow and scalp as a result on Day 45.

\_ Org 33062 ER subject (b) (6) suffered a 4-5 minute loss of consciousness, a concussion, and a fractured sternum after her car was rear-ended at a traffic light on Day 14.

There was no association among dizziness and syncope, accidental injury, and orthostatic hypotension.

Regarding dizziness, the majority of events occurred within the first two weeks of treatment, with the mean duration of the first occurrence being approximately 17 days; however the IR  $\geq$  40 mg group had a mean duration of approximately 26 days. The incidence of dizziness was also dose-related. The distribution of severity for dizziness was not clinically or statistically significantly different than placebo except for the IR  $\geq$  40 mg subjects who had more mild and fewer moderate and severe occurrences than placebo subjects. For subjects with more than one episode of dizziness, severity did not appear to worsen with the second episode of dizziness. Of interest, the incidence of dizziness appeared to be higher in young subjects less than 65

years old compared to elderly subjects  $\geq 65$  years old; however, this difference may be due to the small number of elderly subjects compared to the young. There was no increased risk of postural hypotension, syncope or an increased risk of associated falls or accidental injuries. Moreover there was no evidence of increased risk of bradycardia, tachycardia, conduction defects or arrhythmias that could be the basis for the observed dizziness. Based on these data, a CNS etiology rather than a cardiovascular etiology for dizziness is suggested.

The sponsors feels the most likely explanation of dizziness is that it is related to the drug's CNS properties since there is no relationship between dizziness, syncope, orthostasis, decreased blood pressure upon standing, or arrhythmias. The incidence of postural hypotension in the Org 33062 ER group was not significantly different from placebo. This was in contrast to imipramine where a ten-fold (statistically significant) increase in incidence of postural hypotension compared to placebo was noted. Furthermore dizziness has not been associated with an increased risk of falls or other accidents and consequently dizziness, although it may be an unpleasant side effect for some subjects, has not been associated with clinically important outcomes.

Incidence, dose-response, time to onset, and duration in acute controlled Phase II/III studies dizziness was the most frequent drug-related AE in each Org 33062 analysis group. The incidence of dizziness in all Org 33062 subjects (35.8%) was about 3 times the placebo incidence (11.7%). There was a strong dose trend for dizziness both for incidence and risk of occurrence vs. placebo). The incidence in the Org 33062 IR =40 mg modal dose group (59.8%) was nearly twice the Org 33062 ER =40 mg modal dose group incidence (34.6%).

In the Org 33062 ER group and in the Org 33062 ER and IR =40 mg modal dose groups, approximately 75% of all first reports of dizziness occurred in the first two weeks of treatment. The mean duration of the first occurrence of dizziness in all Org 33062 subjects was approximately 17 days. In the Org 33062 ER =40 mg modal dose group the mean duration of dizziness was approximately 16 days, while in the Org 33062 IR =40 mg group it was 10 days longer (26 days).

The distribution of severity for dizziness was not clinically or statistically significant different between the Org 33062 analysis groups and the placebo group, except for the Org 33062 IR =40 mg modal dose group. The Org 33062 IR =40 mg subjects had more mild and fewer moderate and severe occurrences of dizziness than placebo subjects. Also, the severity of dizziness did not increase with increasing modal dose of Org 33062.

There were few occurrences of dizziness that were reported to be a worsening of dizziness (ie dizziness aggravated. In order to determine if the severity of dizziness changed with subsequent episodes, an analysis was performed on all occurrences of dizziness in the Phase II/III database (acute and extension phases combined). In this analysis shift tables were prepared to compare the distribution of the severity classes between the first and subsequent occurrences of dizziness. More than 60% of placebo subjects who experienced exactly 2 episodes of dizziness had no change in severity with the second episode, and exactly the same percentage (19.5%) showed improvement (ie shift from moderate/severe to mild/moderate) or worsening (ie shift from mild/moderate to moderate/severe). In all Org 33062 analysis groups there was a trend for a shift to milder second episodes that was most prominent in the Org 33062 IR =40 mg modal

dose group (21.9% with improvement; 9.4% with worsening). A total of 48.8% of subjects in the Org 33062 ER =40 mg modal dose group had no change in severity with the second episode, 29.9% showed improvement and 21.2% showed worsening.

There were no clear trends towards improvement or worsening in the data for subjects with at least 2 episodes of dizziness and the data for subjects with exactly 3 or at least 3 episodes is difficult to interpret because there were few placebo subjects in this category. I have reviewed this data and believe it to be accurately represented by the sponsor.

## **Electrocardiographic data**

Electrocardiographic data collected during the acute phase of treatment in the Phase II/III studies were analyzed for 3 different subject groups: subjects in all Phase II/III studies, subjects in the controlled Phase II/III studies, and subjects in the controlled Phase II/III studies in depression. The sponsor's results did not differ appreciably among the 3 groups.

For subjects in the controlled Phase II/III studies, the incidence of clinically significant decreases in ECG heart rate was higher in the Org 33062 groups compared with placebo (0.7% for ER =40 mg, 1.3% for IR =40 mg, and 0.2% for placebo). The risk of a clinically significant decrease in ECG heart rate was statistically significantly greater for IR =40 mg compared with placebo, although clinically significant decreases were seen in only 3 of 224 IR =40 mg subjects. Mean change from baseline in ECG heart rate at the last visit was similar for the Org 33062 groups compared with placebo. The SSRI group had a statistically significant decrease in ECG heart rate from baseline at the last visit compared with placebo, while the imipramine group had a statistically significant increase in ECG heart rate from baseline at the last visit compared with placebo.

The incidence of clinically significant values for PR interval in subjects in the controlled Phase II/III studies was less than 1% for each treatment group. There was no statistically significant increased risk (compared with placebo) of a clinically significant value for PR interval for any treatment group. Mean change from baseline in PR interval at the last visit for the Org 33062 groups was comparable to that of placebo.

The incidence of clinically significant values for QRS interval was higher for the IR =40 mg (2.7%) and imipramine (2.8%) groups compared with the ER =40 mg (1.8%), SSRIs (1.5%), and placebo (1.9%) groups. However, the risk of a clinically significant value for QRS interval was not statistically significantly greater for any treatment group compared with placebo. For the Org 33062 groups, the mean change from baseline in QRS interval at the last visit was relatively small and comparable to placebo.

For subjects in the controlled Phase II/III studies, the incidence of clinically significant QTc interval values in the ER =40 mg group was slightly lower than that of placebo (6.5% vs 7.7%). The incidence of clinically significant values was somewhat higher than that of placebo for SSRIs (11.5%) and imipramine (9.0%), and highest for the IR

=40 mg group (21.0%). Compared with placebo, the risk of a clinically significant QTc interval value was statistically significantly greater for both the SSRI and IR =40 mg groups. The ER =40 mg group had a statistically significant smaller risk of increases from baseline of =30 msec and =60 msec compared with placebo. In contrast, the risk of a clinically significant increase in QTc interval was statistically significantly greater for the IR =40 mg group compared with placebo using each of 5 criteria for clinical significance. Imipramine produced a statistically significant greater risk of increases from baseline (or first evaluation) of =30 msec and =60 msec compared with placebo. The incidences of clinically significant QTc increases were generally higher at greater doses of Org 33062, especially for the IR formulation. Caucasians had similar incidences of clinically significant increases than non-Caucasians for most of the treatment groups, including placebo. Analysis by gender and age did not produce consistent results.

In the mean change analysis, the ER =40 mg group had a marginally statistically significant decrease from baseline in QTc interval at last visit compared with placebo. The imipramine group had a statistically significant increase from baseline compared with placebo at the last visit. Although the IR =40 mg group had a statistically significant greater risk of a clinically significant increase in QTc interval compared with placebo, mean change from baseline at the last visit for the IR =40 mg group was actually quite small (+0.6 msec) and comparable to that of placebo (-0.4 msec). For both the ER and IR formulations, there was no obvious relationship between change from baseline in QTc interval at last visit and dose of Org 33062 received. Similarly, analysis by gender did not reveal striking differences between males and females for any of the treatment groups, nor did analysis by race. For all treatment groups including placebo, subjects =65 years of age had numerically greater mean decreases in QTc interval compared with subjects <65 years of age.

For the original analysis, the Bazett correction algorithm was used to convert QT interval data into the corrected QTc interval data. However, because of the inconsistent QTc results obtained for the IR =40 mg and ER =40 mg groups, QTc data from the controlled Phase II/III studies were re-analyzed using the Fridericia correction formula. Although the re-analysis produced numerically different results from the original analysis, a similar pattern of an increased risk of clinically significant increases in QTc interval was seen for the IR =40 mg group, as was a decrease in the incidence of such events for the ER =40 mg group.

Table 90 Acute phase: Summary of expanded analysis of QTc interval by treatment group (All patients treated in controlled Phase II/III studies)

| ECG Parameter                    | Org 33062   |             |                |                                      |                                      | Active controls |                     | Placebo<br>N (%) |
|----------------------------------|-------------|-------------|----------------|--------------------------------------|--------------------------------------|-----------------|---------------------|------------------|
|                                  | ER<br>N (%) | IR<br>N (%) | Total<br>N (%) | ER<br>modal dose<br>≥ 40 mg<br>N (%) | IR<br>modal dose<br>≥ 40 mg<br>N (%) | SSRIs<br>N (%)  | Imipramine<br>N (%) |                  |
| <b>Baseline</b>                  |             |             |                |                                      |                                      |                 |                     |                  |
| N                                | 981         | 1125        | 2106           | 664                                  | 221                                  | 334             | 190                 | 1341             |
| Mean                             | 414.17      | 414.51      | 414.35         | 416.63                               | 421.00                               | 421.23          | 403.62              | 411.44           |
| S.D.                             | 25.04       | 32.90       | 29.49          | 24.17                                | 37.65                                | 27.55           | 28.47               | 30.85            |
| Min                              | 335.41      | 261.85      | 261.85         | 338.35                               | 293.94                               | 176.97          | 320.00              | 277.13           |
| Max                              | 511.00      | 590.11      | 590.11         | 511.00                               | 565.19                               | 516.15          | 495.70              | 581.38           |
| <b>Last Visit</b>                |             |             |                |                                      |                                      |                 |                     |                  |
| N                                | 764         | 936         | 1702           | 570                                  | 224                                  | 296             | 135                 | 1116             |
| Mean                             | 412.12      | 415.18      | 413.81         | 414.57                               | 421.19                               | 421.67          | 418.69              | 411.23           |
| S.D.                             | 25.99       | 35.49       | 31.81          | 25.18                                | 36.69                                | 23.42           | 28.11               | 28.90            |
| Min                              | 340.00      | 60.90       | 60.90          | 340.00                               | 317.54                               | 355.79          | 320.52              | 268.33           |
| Max                              | 536.77      | 582.07      | 582.07         | 487.34                               | 582.07                               | 508.07          | 499.90              | 575.85           |
| p-value vs. placebo <sup>2</sup> | 0.4941      | 0.0055      | 0.0289         | 0.0195                               | 0.0000                               | 0.0000          | 0.0380              | -                |
| <b>Change from bsl</b>           |             |             |                |                                      |                                      |                 |                     |                  |
| N                                | 749         | 916         | 1667           | 559                                  | 216                                  | 290             | 133                 | 1095             |
| Mean                             | -2.76       | -0.67       | -1.61          | -2.97                                | 0.56                                 | -1.27           | 13.39               | -0.35            |
| S.D.                             | 24.59       | 31.12       | 28.39          | 23.61                                | 33.12                                | 23.91           | 32.38               | 26.78            |
| Min                              | -131.11     | -338.75     | -338.75        | -131.11                              | -136.45                              | -81.98          | -100.66             | -191.38          |
| Max                              | 177.10      | 159.00      | 177.10         | 88.14                                | 89.33                                | 203.03          | 130.64              | 173.96           |
| p-value vs. placebo <sup>2</sup> | 0.0506      | 0.8053      | 0.2451         | 0.0513                               | 0.6590                               | 0.5955          | 0.0000              | -                |
| N <sup>a</sup>                   | 764         | 936         | 1702           | 570                                  | 224                                  | 296             | 135                 | 1116             |

Table 90 Acute phase: Summary of expanded analysis of QTc interval by treatment group (All patients treated in (continued) controlled Phase II/III studies)

| ECG Parameter                                                                | Org 33062 |                        |             |                                  |                                  | Active controls |                       | Placebo N (%) |
|------------------------------------------------------------------------------|-----------|------------------------|-------------|----------------------------------|----------------------------------|-----------------|-----------------------|---------------|
|                                                                              | ER N (%)  | IR N (%)               | Total N (%) | ER modal dose $\geq$ 40 mg N (%) | IR modal dose $\geq$ 40 mg N (%) | SSRIs N (%)     | Imipramine N (%)      |               |
| $\geq$ 450 msec at any time post-baseline <sup>a</sup>                       | 39(5.10)  | 66(8.36) <sup>a</sup>  | 127(7.46)   | 32(5.61)                         | 33(14.7) <sup>a</sup>            | 25(8.45)        | 14(10.4)              | 89(6.18)      |
| $\geq$ 480 msec at any time post-baseline <sup>a</sup>                       | 2(0.26)   | 21(2.24) <sup>a</sup>  | 23(1.35)    | 1(0.18)                          | 13(5.80) <sup>a</sup>            | 3(1.01)         | 2(1.48)               | 8(0.72)       |
| $\geq$ 500 msec at any time post-baseline <sup>a</sup>                       | 1(0.13)   | 8(0.85)                | 9(0.53)     | 0(0.00)                          | 5(2.23) <sup>a</sup>             | 1(0.34)         | 0(0.00)               | 3(0.27)       |
| $\geq$ 30 msec increase from baseline to any time post-baseline <sup>b</sup> | 50(6.54)  | 143(15.2) <sup>a</sup> | 193(11.3)   | 38(6.67)                         | 50(22.3) <sup>a</sup>            | 23(7.77)        | 38(28.1) <sup>a</sup> | 121(10.8)     |
| $\geq$ 60 msec increase from baseline to any time post-baseline <sup>b</sup> | 6(0.79)   | 26(2.99)               | 34(2.00)    | 4(0.70)                          | 13(5.80) <sup>a</sup>            | 4(1.35)         | 9(6.67) <sup>a</sup>  | 23(2.06)      |

Source: Table A.8.10.2.25, Table A.8.10.2.26, Table A.8.10.2.38, Listing A.9.10.2.5 and Listing A.9.10.2.6

Org33062 Total includes Org33062 ER and Org33062 IR.

<sup>a</sup> Includes subjects with at least one non-missing QTc interval at post-baseline.

<sup>b</sup> Includes subjects with a baseline QTc < 450 msec or missing.

<sup>c</sup> If baseline QTc is missing, this includes increase from the first QTc evaluation.

<sup>d</sup> P-values come from T-test assuming equal variances.

\* Relative Risk  $\geq$  1 and 95% CI does not include 1.

## ADVERSE EVENTS

In acute Phase II/III trials, controlled Phase II/III trials, and controlled Phase II/III trials in depression, the incidence of AEs overall during exposure to any dose or formulation of Org 33062 (82% to 86%) was 4-7% higher than the placebo incidence and 4-10% higher than the incidence for SSRIs, while 6-10% less than the incidence for imipramine. The risk of at least one AE for any dose or formulation of Org 33062 was statistically significantly greater vs. placebo only in the group of all controlled trials.

For the Org 33062 ER  $\geq$ 40 mg modal dose group, the overall incidence of AEs across the three groups of trials (75% to 84%) was 9-19% lower than the incidence for the Org 33062 IR  $\geq$ 40 mg modal dose group. In each of the three populations of Phase II/III subjects, the risk of at least one AE was statistically significantly greater vs. placebo for the IR formulation of Org 33062, but not the ER formulation.

During acute, controlled Phase II/III trials, the individual AEs at a 5% incidence with a statistically significant greater risk of occurrence vs. placebo in the Org 33062 ER  $\geq$ 40 mg or IR  $\geq$ 40 mg modal dose groups included:

- \_ for both formulations of Org 33062 . dizziness and nausea;
- \_ for ER  $\geq$ 40 mg only - vomiting NOS;
- \_ for IR  $\geq$ 40 mg only . headache, somnolence, paraesthesia, palpitations, tinnitus, sedation, sweating increased, and hot flushes NOS.

## Common Adverse Events

### Common adverse experiences during treatment with Org 33062 ER at daily doses $\geq$ 40 mg.

The common Org 33062 related adverse events, occurring at an incidence of  $\geq$ 5% of subjects treated with the ER formulation at a daily dose of > 40 mg are nausea, dizziness and vomiting. The fact that the incidence for these events is statistically

significantly higher compared to placebo treatment leads to their identification as being likely related to Org 33062 ER treatment.

Nausea, dizziness and vomiting are, together with headache and insomnia, also the major Org 33062 ER  $\geq 40$  mg related adverse events leading to discontinuation. The average duration of nausea is ten days and most frequently nausea starts in the first two weeks of treatment. The incidence of vomiting is much lower than the incidence of nausea and on average vomiting, if it occurs, lasts for three days. After the third treatment week the incidence of nausea declines considerably (indicating adaptation to Org 33062) whereas vomiting tends to occur at an approximately similar frequency throughout the first eight weeks of Org 33062 treatment. Although nausea and vomiting are unpleasant events for patients, these events have not led to medically serious sequelae like dehydration.

Dizziness is the third common adverse event likely related to Org 33062 treatment and is mostly described by patients as lightheadedness. The average duration of an episode of dizziness is two weeks and in the majority of cases starts in the first few weeks of treatment, indicating adaptation to Org 33062. The sponsor feels that the most likely explanation of dizziness is that it is related to the drug's CNS properties since there is no relationship between dizziness, syncope, orthostasis, decreased blood pressure upon standing, or arrhythmias. The incidence of postural hypotension in the Org 33062 ER group was not significantly different from placebo. This was in contrast to imipramine (well known for causing orthostasis) where a ten-fold (statistically significant) increase in incidence of postural hypotension compared to placebo was noted. Furthermore dizziness has not been associated with an increased risk of falls or other accidents and consequently dizziness, although it may be an unpleasant side effect for some subjects, has not been associated with clinically important outcomes.

#### **Adverse Events Occurring at an Incidence of 2% or More in Gepirone**

##### **Treated Depressed Patients**

Table II enumerates the incidence of treatment-emergent adverse events that occurred at an incidence of 2% or more, and were more frequent than in the placebo group, among BRAND NAME™-treated depressed patients (dose  $\geq 40$  mg daily) who participated in placebo-controlled trials, rounded to the nearest percent. This table shows the percentage of patients in each group who experienced at least one event at some time during their treatment. Reported adverse events were classified using standard MedDRA terminology.

**TABLE II: INCIDENCE OF ADVERSE CLINICAL EXPERIENCES<sup>1</sup> (≥2%)  
IN PLACEBO-CONTROLLED DEPRESSION STUDIES<sup>2</sup>**

| Body System<br>Adverse Clinical Experience                    | BRAND<br>NAME™<br>dose ≥ 40 mg<br>(n=697) | Placebo<br>(n=608) |
|---------------------------------------------------------------|-------------------------------------------|--------------------|
| <b>Cardiac Disorders</b>                                      |                                           |                    |
| Palpitations                                                  | 5%                                        | 2%                 |
| <b><i>Ear and Labyrinth Disorders</i></b>                     |                                           |                    |
| Tinnitus                                                      | 3%                                        | 2%                 |
| <b>Gastrointestinal Disorders</b>                             |                                           |                    |
| Nausea                                                        | 27%                                       | 13%                |
| Dry Mouth                                                     | 8%                                        | 7%                 |
| Dyspepsia                                                     | 6%                                        | 4%                 |
| Vomiting nos                                                  | 6%                                        | 4%                 |
| Flatulence                                                    | 4%                                        | 3%                 |
| Abdominal Pain Upper                                          | 3%                                        | 1%                 |
| <b>General Disorders and Administration Site Conditions</b>   |                                           |                    |
| <b>Feeling Jittery</b>                                        | 2%                                        | <1%                |
| Weight Increased                                              | 3%                                        | 2%                 |
| <b>Metabolism and Nutritional Disorders</b>                   |                                           |                    |
| <b>Appetite Increased nos</b>                                 | 3%                                        | 2%                 |
| <b><i>Musculoskeletal and Connective Tissue Disorders</i></b> |                                           |                    |
| <i>Pain in Limb</i>                                           | 2%                                        | 1%                 |

|                                        |     |     |
|----------------------------------------|-----|-----|
| <b><i>Nervous System Disorders</i></b> |     |     |
| <i>Dizziness</i> <sup>2</sup>          | 34% | 11% |
| <i>Paraesthesias</i>                   | 4%  | 2%  |
| <i>Tremor</i>                          | 4%  | <1% |
| <i>Sedation</i>                        | 3%  | 2%  |
| <b><i>Psychiatric Disorders</i></b>    |     |     |
| <i>Insomnia</i>                        | 10% | 8%  |
| <i>Abnormal Dreams</i>                 | 4%  | 2%  |
| <i>Insomnia Exacerbated</i>            | 3%  | 2%  |
| <i>Middle Insomnia</i>                 | 3%  | 1%  |
| <i>Anxiety</i>                         | 3%  | 2%  |
| <i>Nightmare</i>                       | 2%  | 1%  |
| <i>Nervousness</i>                     | 2%  | 1%  |
| <i>Restlessness</i>                    | 2%  | <1% |

<sup>1</sup>Events reported by at least 2% of patients (after rounding to the nearest whole percent) treated with BRAND NAME<sup>TM</sup> are included, except the following events which had an incidence on placebo  $\geq$  BRAND NAME<sup>TM</sup>: Headache, Diarrhea nos, Constipation, Somnolence, Nasopharyngitis, Irritability, Fatigue, Myalgia, Back Pain, Pharyngitis, Upper Respiratory Tract Infection nos, Abdominal Pain, Cough, Arthralgia, Sinusitis nos, Urinary Frequency, Agitation, Nasal Congestion, Heart Rate Increased, Vision Blurred, Sweating Increased, Rash, Appetite Decreased nos.<sup>3</sup>

### **Dose response.**

No clear dose-response relationship was observed for the total number of reported AEs in the recommended dose range; however, a dose-response relationship appears to be present for the AEs of dizziness and nausea. These events also occurred at statistically significant increased incidences during Org 33062 treatment as compared to placebo, which further suggests the probable relationship to Org 33062. In interaction studies with ketoconazole and verapamil, both inhibitors of CYP 3A4, a higher plasma level of Org

33062 indeed resulted in a higher incidence and severity of these AEs. Especially in the study with ketoconazole, the stronger inhibitor of the two, the incidence and severity of dizziness, nausea and vomiting increased.

Daily doses over 80 mg of Org 33062 have not been systematically studied, although in some Org 33062 IR trials dose escalation up to 120 mg was allowed. Adverse experiences at Org 33062 doses higher than the recommended dose range of 40-80 mg were similar in type to the common adverse experiences observed in the recommended dose range, although generally at higher incidences.

## **Recommended Dose**

The recommended dose range of Org 33062 is 40 to 80 mg/day. Extended release tablets containing 20, 40, 60 and 80 mg of Org 33062 will be marketed. The initial daily dose will be 20 mg, which is recommended to be subsequently increased to 40 mg (b) (4) and then up to 80 mg in a stepwise fashion based on individual clinical response and tolerance. Org 33062 is to be administered once daily (b) (4). Dose decreases should be considered when subjects are treated with concomitant CYP450 3A4 inhibitors or have renal or hepatic impairment.

## **Literature review of Org 33062**

For this review a search was conducted in the Medline and Embase database for publications with publication dates up to and including 1966 to June 23, 2003. The search terms that were used were: gepirone, Org 33062, (b) (4), MJ13805-1, BMY13805-1.

Abstracts (where available) were reviewed and when from the abstract (or title, if no abstract was available) it was clear that the article presented a clinical trial or that the presence of clinical trial data could not be excluded, the complete article was reviewed. Furthermore reference lists of all articles containing clinical data were reviewed for additional references. When the description of the reference in the original publication or the titles of the additional references suggested the presence of clinical trial data (or the presence of clinical data could not be ruled out), these were reviewed as well.

In this literature review data relevant to Org 33062 clinical safety are reported for those cases where the literature differed from the clinical trial reports (CTRs) or this ISS. Quantitatively higher incidences of adverse events and the presence of additional data relevant to safety are reported as well as qualitative differences.

The sponsor provides 617 citations, some with abstracts. I have reviewed this and agree with the sponsor that there are no new findings that will add to the evaluation of this drug.

## **WORLDWIDE REGULATORY STATUS**

There has been no change since the May 18th, 2001 submission.

## **SAFETY UPDATE CORRECTION**

On 4/12/04 I received a 3 volume safety correction of acute and long term data pertaining to Vital Signs and Weight sections of the ISS. The sponsor claims that the ISS had programming errors but the data had been submitted correctly to the original study reports. These changes do not appear to significantly affect the safety profile for Gepirone.

## **Study 28718- BIOPHARM SAFETY ISSUE**

The Agency stated in the 3/15/02 action letter that the 40-, 60-, and 80-mg strengths were not approvable based on the bioequivalence study data (28718). During the July 3, 2002 Meeting the Agency stated that these tablet strengths could be approvable if the difference in the safety data for patients who were treated with 4 20-mg tablets was not clinically relevant compared to patients whose plasma levels were to those attained with the 80 mg strength. The sponsor has provided study 28718 data to make the safety comparison.

### **Title of the study**

An open label, randomized, four way cross-over, single dose, dosage strength equivalence study to determine the bioequivalence of Org 33062 (Gepirone HCl) 40 or 80 mg ER tablets versus multiple 20 mg ER tablets in healthy, young, extensive metabolizers for dextromethorphan, male volunteers

### **Methodology**

An open label, randomized, four-way crossover single dose study design was used with a washout phase of one week between the different treatments. During each period, a single dose of one formulation strength of Org 33062 was administered followed by frequent blood sampling for a 72 hours period for the analysis of Org 33062 and its metabolites.

### **Number of Subjects (total and for each treatment)**

In total, 37 subjects were enrolled and 32 subjects completed the study. The completed subjects received the following treatments in a randomized order: Oral administration of Org 33062, as a single dose of

- A) 1x 40 mg ER tablet;
- B) 2 x 20 mg ER tablets;
- C) 1 x 80 mg ER tablet;
- D) 4 x 20 mg ER tablets.

### **Deaths**

There were no deaths in this trial.

### **Serious Adverse Events**

There were no serious adverse events in this trial.

### **Discontinuation Due to Adverse Events**

The incidence of AEs causing discontinuation is given in Table 3.5, Appendix F. In agreement with the sponsor, four subjects were discontinued from the trial because of vomiting soon after dosing during the first study period: two (nos. (b) (6) and (b) (6)) after having received 1 x 80 mg and two (nos. (b) (6) and (b) (6)) after having received 4 x 20 mg. It was assumed that their vomiting could affect the outcome of the pharmacokinetic evaluation. Since safety was not an argument in the decision to discontinue the study for these subjects, no subjects' narratives (Appendix A) are presented.

### Incidence of Adverse Events

The incidence of AEs is detailed in Tables 3.2 to 3.8, Appendix F. The incidence of adverse events are summarized with respect to the relationship assessment given by the investigator in Tables 3.6 to 3.8 and with respect to severity in Tables 3.9 to 3.11. The most commonly reported AEs are summarized by treatment in the Table 22 below.

**Table 22 Incidence of the Most Commonly Reported Adverse Events**

|                | Treatment A<br>(N = 32) |    | Treatment B<br>(N = 33) |    | Treatment C<br>(N = 34) |    | Treatment D<br>(N = 35) |    |
|----------------|-------------------------|----|-------------------------|----|-------------------------|----|-------------------------|----|
|                | n                       | %  | n                       | %  | n                       | %  | n                       | %  |
| Dizziness      | 7                       | 22 | 6                       | 18 | 18                      | 53 | 22                      | 63 |
| Headache       | 5                       | 16 | 3                       | 9  | 7                       | 21 | 8                       | 23 |
| Nausea         | 2                       | 6  | 2                       | 6  | 12                      | 35 | 7                       | 20 |
| Somnolence     | 7                       | 22 | 5                       | 15 | 6                       | 18 | 5                       | 14 |
| Vomiting       | 0                       | 0  | 0                       | 0  | 9                       | 26 | 3                       | 9  |
| Fatigue        | 2                       | 6  | 3                       | 9  | 3                       | 9  | 3                       | 9  |
| Malaise        | 0                       | 0  | 2                       | 6  | 5                       | 15 | 4                       | 11 |
| Abdominal pain | 1                       | 3  | 1                       | 3  | 5                       | 15 | 3                       | 9  |

Treatment A: 1 x Org 33062 40 mg ER tablet

Treatment B: 2 x Org 33062 20 mg ER tablet

Treatment C: 1 x Org 33062 80 mg ER tablet

Treatment D: 4 x Org 33062 20 mg ER tablet

### Summary of Safety

The most prominent AEs were CNS effects (dizziness, headache), gastro-intestinal disorders (nausea, vomiting, abdominal pain), psychiatric disorders (somnolence) and general disorders (fatigue, malaise). Except for headache, these adverse events were generally drug-related. The incidence of adverse events was higher after intake of 1 x 80 mg or 4 x 20 mg Org 33062 than after 1 x 40 mg or 2 x 20 mg, especially for CNS and gastro-intestinal disorders.

No clinically relevant changes were observed by physical examination, in vital signs, in ECGs or in the laboratory parameters.

## SAFETY CONCLUSION

As of the cutoff date of 23 June 2003, 4862 individual subjects have been exposed to Org 33062 in 75 clinical trials. A total of 4076 subjects participated in Phase II/III

studies and 2217 of these subjects were exposed to the ER formulation. A total of 732 subjects were exposed to Org 33062 daily for at least 6 months, and 497 (476 Org 33062 ER) were exposed to a modal dose [dose (in mg/day) of Org 33062 that was most frequently prescribed for an individual subject during his/her study participation] of 40 mg or greater. A total of 260 subjects were exposed to Org 33062 daily for at least one year, and 170 (161 Org 33062 ER) were exposed to a modal dose of 40 mg or greater.

There is nothing in the newly submitted safety material that would prevent the approval of Gepirone for MDD based on safety concerns.

## **RECOMMENDATION**

In an internal memo dated 27 February 2002 (prior to unbinding), it was noted that five subjects may have suffered a relapse and would therefore be redefined in the analysis as relapsers. Only after the blind was broken did the sponsor redefine these 5 subjects as non-relapsed patients saying their status could not be confirmed with the investigators anymore. I therefore believe these subjects should have been counted as relapsers and the alternate analysis is the correct one. According to this analysis, the number of subjects with a relapse at endpoint was 34 (27.0%) in the Org 33062 group and 43 (34.7%) in the placebo group. The difference between the treatment groups was not statistically significant.

Rosewitha Kelly points out that using all ITT patients, the comparison of relapse rates between Gepirone-treated patients and placebo-treated patients did not reach statistical significance.

Gepirone has still not produced a 2<sup>nd</sup> robustly positive study in the ER as required in the minutes of our 7/14/2003 meeting. I believe the drug should not be approved based on the large number of trials which have resulted in only one positive IR study and one positive ER study.

Earl D. Hearst, M.D.  
Medical Reviewer  
HFD-120

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

-----  
Earl Hearst  
4/30/04 01:28:34 PM  
MEDICAL OFFICER

Thomas Laughren  
5/20/04 08:16:40 AM  
MEDICAL OFFICER

I agree that this application remains nonapprovable; see memo  
to file for more detailed comments.--TPL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA: 21-164  
Sponsor: Organon (AKZO NOBEL)  
Clock Date: 05/18/2001

Drug Name

Generic Name Gepirone (Org 33062)  
Trade Name ARIZA(will be changed)

Drug Characterization

Pharmacological Category: Antidepressant Novel  
(selective partial 5-HT<sub>1A</sub> receptor agonist)  
Proposed Indication: Depression  
Dosage Forms, Strengths, and Routes of Administration:  
Oral Tablets 20mg, 40mg, 60mg and 80mg Extended Release

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.  
Review Completion Date: 02/19/2002

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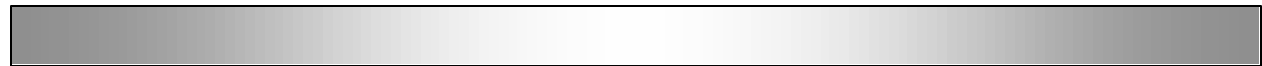
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# Clinical Review for NDA 21-164

## Executive Summary

### **I. Recommendations**

#### **A. Recommendation on Approvability**

If the safety issues can be resolved favorably the sponsor has provided two or more positive efficacy studies for this drug and it is approvable. See statistical and safety reviews for further information.

#### **B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

The sponsor has future studies suggested in the current Clinical Development Plan. I would agree that these studies are worthwhile:

1. Two placebo-controlled clinical trials in pediatric patients (age groups 7-11 and 12-17 years) with depression aimed at establishing the efficacy of Org 33062 ER in treating depression in children and adolescents. Preparation associated with these studies commenced in the beginning of 2001. The pediatric studies are scheduled to begin enrolling patients in September 2001.

2. A pilot tolerability study aimed at establishing preliminarily the tolerability and safety of an initial dose of 40 mg Org 33062 ER in depressed patients. Preparation associated with this study commenced in the beginning of 2001. The study is scheduled to begin enrolling patients in May 2001.

3. A pharmacokinetic study aimed at establishing the pharmacokinetics of Org 33062 ER in male and female children and adolescents. Preparation associated with this study commenced at the end of 2000. This study is scheduled to start in July 2001.

## CLINICAL REVIEW

### Executive Summary Section

4. A number of drug-drug interaction studies assessing the possibility of a drug-drug interaction between Org 33062 ER and rifampicine, paroxetine, lithium, warfarin, and glibenclamide. Preparation associated with these studies commenced in the course of 2000. This series of studies is scheduled to be complete by the first quarter of 2002.

5. An active and placebo-controlled clinical trial of Org 33062 ER aimed at establishing the efficacy of Org 33062 in treating depression in the elderly.

6. Three SSRI-controlled comparative studies aimed at further profiling the efficacy and side effects of Org 33062 ER as compared to SSRI's.

7. An open-label switching study with Org 33062 ER aimed at preliminarily establishing the efficacy of Org 33062 ER in patients not responding to SSRIs.

8. A placebo-controlled SSRI augmentation study aimed at evaluating the efficacy of Org 33062 ER added to an SSRI in patients not responding to an SSRI.

9. A placebo-controlled clinical trial of Org 33062 ER aimed at establishing the efficacy of Org 33062 ER in the treatment of depression in primary care.

10. Humanitarian and extension studies in the U.S. and Europe with the aim to allow continuation of treatment with Org 33062 ER in clinical trials listed above.

Per biopharm reviewer Gerald J. Fetterly, Ph.D. the following should be performed.

1. Since gepirone is metabolized mainly by CYP3A4, the sponsor is requested to perform an in vitro assessment of potential drug-drug interactions with common CYP3A4 substrates, inhibitors and inducers in conjunction with gepirone.

2. In vitro assessment of Phase 2 metabolism of gepirone should be assessed with hepatocytes. This study could provide information to explain the multiple peaks observed among subjects that received gepirone.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

Org 33062 is a novel azapirone derivative that the sponsor feels has both antidepressant and antianxiety activity. Org 33062 is a relatively selective partial serotonin 5-HT<sub>1A</sub> receptor agonist, and has relatively lower affinity for 5-HT<sub>1B</sub> and other CNS receptors. The clinical trials were performed in a total of 677 subjects who were not psychiatric patients (636 healthy subjects, 28 patients with renal failure, and 13 patients with hepatic impairment) and 4761 psychiatric patients. Of this population, 623 non-psychiatric subjects and 2709 psychiatric patients received Org 33062, 54 healthy subjects and 1523 psychiatric patients received placebo, and 529 psychiatric patients received active comparative agents. The worldwide program consisted of 65 studies.

### B. Efficacy

Org 33062 was efficacious in the treatment of patients with MDD in 4 of the 18 adequate and well controlled studies based on the LOCF analysis of the Intent-to-Treat population at Endpoint (ie, the primary time point established for evaluating efficacy; Table 1). In 3 of these 4 studies, the efficacy of Org 33062 was established based on the change from baseline in the Hamilton Depression (HAMD) 17 total score and/or the percentage of Clinical Global Impression (CGI) responders. In the 1 remaining study (a relapse prevention study), Org 33062 prevented relapse in patients who had previously responded to this drug during an open-label treatment phase. In the 4 studies overall, Org 33062 was administered at doses ranging from 5 to 120 mg/day.

**Table 1 Studies that Provide Proof of Efficacy of Org 33062 in the Treatment of MDD**

| Study Number | Formulation | Description of Findings                   |
|--------------|-------------|-------------------------------------------|
| 134001       | ER          | Primary and secondary efficacy parameters |

| Study Number           | Formulation | Description of Findings                                         |
|------------------------|-------------|-----------------------------------------------------------------|
|                        |             | positive <sup>a</sup>                                           |
| 03A7A-003              | IR          | Primary and secondary efficacy parameters positive <sup>a</sup> |
| 03A7C-001B             | IR          | Primary and secondary efficacy parameters positive <sup>a</sup> |
| 03A7A-002 <sup>b</sup> | IR          | Primary and secondary efficacy parameters positive <sup>a</sup> |

ER = Extended release; IR = Immediate release; MDD = Major depressive disorder

<sup>a</sup> One or more secondary efficacy parameters positive

<sup>b</sup> This was a relapse prevention study.

### C. Safety

Please refer to safety team review.

### D. Dosing

The sponsor's recommended starting dose for Org 33062 ER is 20 mg/day, titrated to 40 mg/day (b) (4). The dose may be subsequently increased up to 80 mg/day, depending on clinical response and tolerability. The recommended dose is one tablet once daily, (b) (4). Dosing below 40 mg/day tended to produce negative studies in this submission. See dosing tables for studies in appendix.

### E. Special Populations

There are no efficacy differences based on the special populations evaluations done by the sponsor and by the FDA statistical team for gender, age, race or treatment severity. See special population main section in the body of my review.

## **Clinical Review**

### **I. Introduction and Background**

#### **A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

Org 33062 Extended Release Tablets, 20 mg, 40 mg, 60 mg and 80 mg, represent a pharmaceutical dosage form for oral administration that is comprised of Org 33062 (Gepirone HCl, an azapirone compound). Gepirone HCl interacts principally with serotonin (5-HT)<sub>1A</sub> receptors and acts as a partial agonist at these sites for use as an antidepressant. It is the first compound of this class indicated for depression.

#### **B. State of Armamentarium for Indication(s)**

There are many approved drugs for the treatment of depression but none of this particular chemical family with this presumed novel mechanism of action.

#### **C. Important Milestones in Product Development**

Org 33062 was originally developed by Bristol-Myers Squibb (BMS). During the clinical development program, it was first studied in an immediate-release (IR) formulation primarily in Anxiety Disorders and Major Depression, but also in other indications such as obsessive-compulsive disorder and substance abuse. After review of the safety data for this formulation, an extended-release (ER) formulation was developed to reduce the incidence of troublesome adverse experiences such as dizziness, nausea, and insomnia. Clinical trials that employed the ER formulation were designed primarily as double-blind, randomized, active- and/or placebo-controlled trials for the treatment of depression. In 1992, BMS discontinued all work on Org 33062 ER due to other priorities and as a result, discontinued the ongoing Phase III trials in Major Depression.

In 1993, Fabre-Kramer Pharmaceuticals, Inc., Houston, Texas, acquired rights to Org 33062 ER; they instituted and completed a series of Phase I trials in special populations. In May 1998, Organon Inc. signed an agreement with Fabre-Kramer

Pharmaceuticals, Inc., granting Organon rights to further develop and market Org 33062.

An NDA (NDA 21-164) for the use of Org 33062 ER in depression was submitted to the Food and Drug Administration by Organon Inc. on October 1, 1999. The original NDA contained an Integrated Summary of Safety (ISS) that covered the safety data generated by BMS and Fabre-Kramer Pharmaceuticals. This ISS is henceforth referred to in this document as the BMS experience. This ISS pooled and analyzed the results of 22 Phase I studies conducted in 579 healthy subjects and 36 Phase II/III studies (8 conducted with the ER formulation and 28 with the IR formulation) conducted in 4,333 patients. A total of 53 studies were sponsored and conducted by BMS and five Phase I trials were sponsored and conducted by Fabre-Kramer Pharmaceuticals.

The following INDs have been submitted for this drug.

IND No. 23952 Gepirone hydrochloride immediate release formulation (formerly held by Bristol-Myers Squibb and later by Fabre-Kramer Pharmaceuticals, Inc.)

IND No. 33626 Gepirone hydrochloride extended release formulation (formerly held by Bristol-Myers Squibb and later by Fabre-Kramer Pharmaceuticals, Inc.)

IND No. (b) (4) Gepirone hydrochloride (b) (4)  
(formerly held by Bristol-Myers Squibb and later by Fabre-Kramer Pharmaceuticals, Inc.)

Key meetings and correspondences are listed below.

Pre-NDA Meeting on March 20, 1998, meeting minutes dated April 15, 1998 and subsequent acceptance of these minutes by the FDA in a letter dated April 29, 1998:

At the Pre-NDA Meeting the Agency stated that the following issues would be a matter for review:

- 1) efficacy data from studies using the IR formulation could be used to support approval of the ER formulation;
- 2) effects of premature termination of studies by BMS; and
- 3) single centers from selected multicenter studies may be allowed to stand alone in support of superiority of Org 33062 when adequate justification is provided.

Meeting with the FDA on February 2, 2000 and subsequent meeting minutes as contained in the Agency letter to Organon dated February 9, 2000:

The Agency confirmed that Organon would need either 1) two adequate and well controlled studies using gepirone immediate release (IR) and one bridging study using gepirone ER, or 2) two adequate and well controlled studies using gepirone ER in order to satisfy the efficacy requirements for filing of the NDA. During the February 2, 2000, meeting and documented in Organon's meeting minutes submitted in Org 33062 IND Amendment No. 071 (February 14, 2000), the Agency concurred with Organon's proposal for an ISS supplement. The proposal specified that integration of safety data for the supplement would be limited to an analysis of the combined adverse event data from studies 134001 and 134002 and to a combined analysis of the adverse events from all phase 2/3 ER studies. The incidence of AEs from the latter analysis would be used for development of the product labeling.

Information obtained during teleconferences with Paul David, Regulatory Project Manager:

April 17, 2000: Safety information for ongoing studies may be limited to SAEs.

June 13, 2000:

- 1) Results of an in-vivo CYP-450 inducer study are not required at the time of submission but may be submitted during the review period.
- 2) Copies of publications are only required for those referenced in the technical summaries. The Agency would request publications of interest from the literature search provided.

FDA Letter dated August 25, 2000:

Notification that the Office of Post-Marketing Drug Risk Assessment (OPDRA) had completed its review of the Org 33062 IND Amendment No. 068 requesting trademark review and had no objections to the use of the proprietary name, Ariza. The Agency noted that the name would be re-evaluated within 90 days prior to the expected approval of the NDA. (see next section)

FDA Letter dated April 9, 2001:

Agency notification that the request to defer submission of pediatric assessments of safety and effectiveness has been granted until April 1, 2003.

#### **D. Other Relevant Information**

This drug is not approved or currently submitted in any other countries. [REDACTED] (b) (4)

OPDRA does not recommend the use of the proposed proprietary name Ariza. Although they initially had no objections to the use of the proprietary name, Ariza (see consult 00-0086) they now believe that there is potential risk of product mix-ups between Arava and Ariza.

#### **E. Important Issues with Pharmacologically Related Agents**

This is the first drug in this pharmacologic class.

### **II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

The immediate release and extended release are not considered bioequivalent. See biopharm review. My efficacy review is consistent with the statistical review. Please see statistical review.

### **III. Human Pharmacokinetics and Pharmacodynamics**

#### **A. Pharmacokinetics**

The sponsor states that in vitro metabolism studies have verified that both 1-PP and 3'-OH-gepirone are formed by CYP450 3A4. It is estimated that 2D6 contributes only about 2% of net gepirone clearance. The bioavailability of gepirone is enhanced by administration with food, irrespective of the dosage form. AUC was increased by an average of 37% for Org 33062 IR and 32% for Org 33062 ER when administered 15 minutes after a standard

high-fat breakfast. In general, the studies demonstrate that steady-state conditions are achieved within two to four days following administration of Org 33062 ER once daily. The binding of Gepirone to human plasma protein was determined in vitro using ultrafiltration methods. Binding was linear across the range of 30.4 to 152.2 ng/mL, and averaged 71.8% bound.

Please see the biopharm review (Gerald J. Fetterly, Ph.D.) for more details.

## **B. Pharmacodynamics**

Please see biopharm review (Gerald J. Fetterly, Ph.D.) for details in this area.

# **IV. Description of Clinical Data and Sources**

## **A. Overall Data**

The Phase II and Phase III clinical program consisted of 18 controlled (11 placebo-controlled studies and 7 placebo- and active-controlled studies) and 6 uncontrolled clinical trials. The sponsor feels these studies were sufficiently diverse to include most population subgroups that have significant potential to need antidepressant therapy. Selection of patients was based on the diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders 3rd revised or 4th edition (DSM-III-R/IV) and the Research Diagnostic Criteria. The clinical development program for Org 33062 focused on randomized, double-blind, placebo-controlled 6- or 8-week studies, with or without active control.

To evaluate long-term safety of this drug, double-blind extensions of 13 studies were conducted with durations of 20 or 44 weeks (the sponsor may revise these numbers- -see safety review). A total of 2263 patients were randomized to study medication during the conduct of 18 adequate and well controlled trials; 1168 patients received Org 33062, 350 patients received active control medication, and 745 patients received placebo. A total of 122 patients received Org 33062 for periods longer than 48 weeks (not all of these patients were exposed to the therapeutic dose). One study that is currently in progress has been designed to assess the safety and efficacy of Org 33062 in the elderly (i.e., 65 or more years of age).

Eighty-six patients aged 65 years or older were administered Org 33062 in the course of the completed clinical trials (including trials in generalized anxiety disorder). A placebo substitution study began with a six-week open label phase in which 134 depressed patients received Org 33062 ER prior to randomization to placebo or active medication. The standard antidepressants used as active controls in these studies were imipramine and fluoxetine.

Org 33062 was investigated in several therapeutic areas related to depression including generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and substance-abuse.

Clinical studies initiated before 1990 were conducted with an immediate-release (IR) capsule, which was to be taken 2-3 times daily.

The studies break down as follows:

MDD not further specified (13 studies: Protocols 134001, 134002, CN105-078, CN105-083, CN105-052, CN105-053, CN105-064, CN105-057, CN105-037, 03A7A-003, 03A7C-001A-2496, 03A7C-001B, 03A7C-001A-2486)

MDD with an atypical profile (1 study: Protocol 03A7A-003) or MDD or dysthymia (mood disorder; 1 study: Protocol CN105-043)

MDD or bipolar disorder, depressed (3 studies: Protocols CN105-022, CN105-029, CN105-028).

6 uncontrolled studies conducted in adult inpatients or outpatients who met RDC or DSM-III-R criteria for MDD or mood disorders.

**B. Tables Listing the Clinical Trials**

**Table 2 Clinical Studies in which the Efficacy of Org 33062 in the Treatment of MDD was Assessed**

| Study Number                                     | Formulation | Sponsor | IND Number |
|--------------------------------------------------|-------------|---------|------------|
| <b>Adequate and well controlled studies (18)</b> |             |         |            |

| Study Number                    | Formulation | Sponsor | IND Number |
|---------------------------------|-------------|---------|------------|
| 134001                          | ER          | Organon | 33626      |
| 134002                          | ER          | Organon | 33626      |
| CN105-078                       | ER          | BMS     | 33626      |
| CN105-083                       | ER          | BMS     | 33626      |
| CN105-052                       | ER          | BMS     | 33626      |
| CN105-053                       | ER          | BMS     | 33626      |
| CN105-064                       | ER          | BMS     | 33626      |
| CN105-057                       | ER          | BMS     | 33626      |
| CN105-043                       | IR          | BMS     | 23952      |
| CN105-037                       | IR          | BMS     | 23952      |
| CN105-022                       | IR          | BMS     | 23952      |
| CN105-029                       | IR          | BMS     | 23952      |
| CN105-028                       | IR          | BMS     | 23952      |
| 03A7A-003                       | IR          | BMS     | 23952      |
| 03A7C-001A-2496                 | IR          | BMS     | 23952      |
| 03A7C-001B                      | IR          | BMS     | 23952      |
| 03A7C-001A-2486                 | IR          | BMS     | 23952      |
| 03A7A-002                       | IR          | BMS     | 23952      |
| <b>Uncontrolled studies (6)</b> |             |         |            |
| CN105-055                       | ER          | BMS     | 33626      |
| CN105-039                       | IR          | BMS     | NA         |
| CN105-050                       | IR          | BMS     | NA         |
| CN105-019                       | IR          | BMS     | 23952      |
| 03A7A-001                       | IR          | BMS     | 23952      |
| 030L1-0004                      | IR          | BMS     | 23952      |

Note: Studies listed by design (adequate and well controlled or uncontrolled) and start date, from most recent to least recent

BMS = Bristol-Myers Squibb; ER = Extended release; IND = Investigational New Drug Application; IR = Immediate release; NA = Not applicable: study conducted in Europe

### C. Postmarketing Experience

This drug is not approved in any country and there is no post marketing data.

### D. Literature Review

Please see safety review for details of the literature review. There is no relevant literature related to efficacy.

## **V. Clinical Review Methods**

### **A. How the Review was Conducted**

My review deals with efficacy only. I will review the sponsor's 4 pivotal trials in detail with comments on the other trials done in this database. Please see appendix for DSI audit remarks.

### **B. Overview of Materials Consulted in Review**

311 volumes were submitted to this NDA. In addition the electronic document room contains copies of these volumes with electronic CRFs and data sets. CDROMs with word copies of key tables and text were provided also. Additional data was provided to the EDR in May, Oct, Nov, Dec of 2001 and Jan of 2002.

### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

DSI will audit and submit their report independently of key studies that were requested in our consults. DSI has audited study #03A7C-001B (see report in review) and is in the process of auditing the sponsor.

### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

Of the sixty-eight (68) clinical studies identified in this application, fifty-eight (58) were conducted under an IND. The clinical investigators for the fifty-eight (58) studies agreed to comply with Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards) of Title 21, Code of Federal Regulations.

The sponsor reports that for the ten (10) clinical studies not performed under an IND in France, Germany, Sweden, Poland, Belgium, Turkey, Finland and Italy, the protocol and supporting documents (those protocol amendments likely to affect subject safety, scope of investigation, or quality of the study; consent forms; ect.) were reviewed by appropriate local ethics committees. For these studies, potential research subjects or when necessary, family or legal representatives were notified of the purpose of these clinical investigations through a process addressing the elements of informed consent on the Declaration of

Helsinki and/or local requirements, whichever afforded greater protection to the subject.

**E. Evaluation of Financial Disclosure**

The sponsor has submitted financial disclosure information for studies since 2/2/99. There is nothing that appears to be improper in this area.

**VI. Integrated Review of Efficacy**

**A. Brief Statement of Conclusions**

The sponsor's analyses demonstrate efficacy in the 4 selected key studies. Our FDA statisticians have verified the sponsor's analyses and confirmed 3 of the 4 studies with other statistical analyses of their own. In addition, their Meta analysis, which used the combined data of the 4 studies, showed all Gepirone doses statistically significantly superior to placebo.

**B. General Approach to Review of the Efficacy of the Drug**

I will review the sponsor's 4 pivotal trials in detail with comments on the other trials done in this database. Trials for other indications will not be reviewed in the efficacy section.

**C. Detailed Review of Trials by Indication**

Before reviewing the clinical trials I will provide several tables describing the data base.

**Table 3**  
**Enumeration of the Number of Unique Study Participants by ER Treatment Group**

| Study Phase                                             | Treatment Group <sup>a</sup> |         |
|---------------------------------------------------------|------------------------------|---------|
|                                                         | Org 33062 ER                 | Placebo |
| <b>Phase I Clinical Trials</b>                          |                              |         |
| Single-Dose Studies <sup>b</sup>                        | 74                           | 0       |
| Multiple-Dose Studies <sup>c</sup>                      | 24                           | 0       |
| <b>Phase I Subtotal</b>                                 | 98                           | 0       |
| <b>Phase III Short-Term Clinical Trials<sup>d</sup></b> |                              |         |
| Placebo-Controlled, Flexible Dose                       | 212                          | 214     |
| <b>Phase III Subtotal</b>                               | 212                          | 214     |
| <b>Grand Total</b>                                      | 310                          | 214     |

- a: Includes all study subjects who received at least one dose of study drug.
- b: Includes subjects treated in Studies 28708 and 28718.
- c: Includes subjects treated in Study 28717.
- d: Includes Studies 134001 and 134002 without long-term extensions.

# TABLE 4

## Populations for Phase I and Phase II/III Depression Trials

| Phase                 | ORG 33062<br>ER | ORG 33062<br>IR | Org 33062<br>Total | FLUOXETIN<br>E | IMIPRAMINE | PLACEBO     |
|-----------------------|-----------------|-----------------|--------------------|----------------|------------|-------------|
| Phase I AST           | 419             | 204             | 623                | 0              | 0          | 54          |
| Phase II/III AST(ITT) | 765(736)        | 926(890)        | 1691(1626)         | 106(103)       | 240(228)   | 983(946)    |
| <b>Total AST</b>      | <b>1184</b>     | <b>1130</b>     | <b>2314</b>        | <b>106</b>     | <b>240</b> | <b>1037</b> |
| Extensions            | 235             | 320             | 555                | 68             | 114        | 267         |

### NOTES:

- This table includes subjects from the following studies:

#### Phase I

030L1-0001-1700, 030L1-0002-1869, 59B4A-001-2579, 59B4B-001-2587, CN105-005, CN105-007, CN105-012, CN105-023, CN105-025, CN105-026, CN105-046, CN105-049, CN105-060, CN105-068, CN105-085, FK-GBE-001, FK-GBE-002, FK-GBE-003, FK-GBE-004, FK-GBE-005, 28708, 28717, 28718

#### Phase II/III Depression Trials

- Double-blind ER studies: 134001, 134002, CN105-052, CN105-053, CN105-057, CN105-064, CN105-078, CN105-083.
  - Open-label ER study: CN105-055.
  - Double-blind IR studies: 03A7C-001A-2586 (Fabre), 03A7C-001A-2496 (Mendels), 03A7C-001B, 03A7A-002, 03A7A-003, CN105-022, CN105-028, CN105-029, CN105-037, CN105-043.
  - Open-label IR studies: 030L1-0004, 03A7A-001, CN105-019, CN105-039, CN105-050.
- All Subjects Treated (AST) populations are listed and tallied because an Intent-to-Treat (ITT) population was not identified for Phase I or Phase II/III extension studies.
  - Re: Org 33062 ER numbers for Phase II/III AST (ITT): 765 (736):  
- The count of 736 for ITT also includes all 34 treated subjects in CN105-055. An ITT group was not identified in the report for this uncontrolled study.
  - Re: Org 33062 IR numbers for Phase II/III AST(ITT): 926 (890):  
- The count of 890 for ITT also includes 189 subjects in the 5 uncontrolled studies: 030L1-0004, 03A7A-001, CN105-019, CN105-039, CN105-050. ITT groups were not identified in the reports for these uncontrolled studies.

**TABLE 1-A**  
**DEMOGRAPHICS FOR ALL SUBJECTS IN PHASE II/III DEPRESSION STUDIES**  
**ER FORMULATION**  
**(INTENT-TO-TREAT GROUP)**

| Parameter        | Org 33062<br>(N=736) |        | Placebo<br>(N=456) |        | Fluoxetine<br>(N=36) |        | Imipramine<br>(N=73) |        |
|------------------|----------------------|--------|--------------------|--------|----------------------|--------|----------------------|--------|
|                  | n                    | %      | n                  | %      | n                    | %      | n                    | %      |
| Sex [n (%)]      |                      |        |                    |        |                      |        |                      |        |
| Male             | 267                  | (36.3) | 184                | (40.4) | 14                   | (38.9) | 29                   | (39.7) |
| Female           | 466                  | (63.3) | 272                | (59.7) | 21                   | (58.3) | 44                   | (60.3) |
| Missing data     | 3                    | (0.4)  | 0                  |        | 1                    | (2.8)  | 0                    |        |
| Origin [n (%)]   |                      |        |                    |        |                      |        |                      |        |
| Caucasian        | 599                  | (81.4) | 379                | (83.1) | 33                   | (91.7) | 67                   | (91.8) |
| African descent  | 56                   | (7.6)  | 30                 | (6.6)  | 0                    |        | 1                    | (1.4)  |
| Asian descent    | 6                    | (0.8)  | 6                  | (1.3)  | 1                    | (2.8)  | 2                    | (2.7)  |
| Hispanic         | 56                   | (7.6)  | 36                 | (7.9)  | 1                    | (2.8)  | 3                    | (4.1)  |
| Other origin     | 17                   | (2.3)  | 4                  | (0.9)  | 0                    |        | 0                    |        |
| Missing data     | 2                    | (0.3)  | 1                  | (0.2)  | 1                    | (2.8)  | 0                    |        |
| Age (years)      |                      |        |                    |        |                      |        |                      |        |
| Mean             | 39.5                 |        | 40.0               |        | 40.5                 |        | 41.0                 |        |
| Range            | 1 - 84               |        | 18 - 79            |        | 19 - 63              |        | 19 - 78              |        |
| Age [n (%)]      |                      |        |                    |        |                      |        |                      |        |
| < 40 years       | 399                  | (54.2) | 219                | (48.0) | 18                   | (50.0) | 36                   | (49.3) |
| 40 to < 65 years | 322                  | (43.8) | 227                | (49.8) | 18                   | (50.0) | 33                   | (45.2) |
| ≥ 65 years       | 15                   | (2.0)  | 10                 | (2.2)  | 0                    |        | 4                    | (5.5)  |

- This table includes subjects from the following studies:  
Double-blind ER studies: 134001, 134002, CN105-052, CN105-053, CN105-057, CN105-064, CN105-078, CN105-083.  
Open-label ER study: CN105-055.
- For Study CN105-055 (uncontrolled ER study), an ITT group was not identified in the report. This summary includes all 34 subjects in the AST group of CN105-055, even though 4 of these subjects did not have post-baseline HAMD assessments.
- In Study CN105-083, subject (b) (6) (Org 33062) was recorded as having the age of 1 on the database. If this subject were excluded, the minimum age in the Org 33062 group would be 15 and the mean age would be 39.5.
- In Study 134001, 16 Org 33062 subjects and 12 Placebo subjects are listed here as being HISPANIC in origin, although they were listed in the study report under the "Other" category for race. The Hispanic categorization was obtained from comments on the demographics CRF.
- In Study 134002, 2 Org 33062 subjects and 1 Placebo subject are listed here as being HISPANIC in origin, although they were listed in the study report under the "Other" category for race. The Hispanic categorization was obtained from comments on the demographics CRF.

**TABLE 1-B**  
**DEMOGRAPHICS FOR ALL SUBJECTS IN PHASE II/III DEPRESSION STUDIES**  
**IR FORMULATION**  
**(INTENT-TO-TREAT GROUP)**

| Parameter        | Org 33062<br>(N=890) |         | Placebo<br>(N=490) |         | Fluoxetine<br>(N=67) |         | Imipramine<br>(N=155) |         |
|------------------|----------------------|---------|--------------------|---------|----------------------|---------|-----------------------|---------|
|                  | n                    | %       | n                  | %       | n                    | %       | n                     | %       |
| Sex [n (%)]      |                      |         |                    |         |                      |         |                       |         |
| Male             | 363                  | (40.8)  | 193                | (39.4)  | 22                   | (32.8)  | 44                    | (28.4)  |
| Female           | 524                  | (58.9)  | 296                | (60.4)  | 45                   | (67.2)  | 111                   | (71.6)  |
| Missing data     | 3                    | (0.3)   | 1                  | (0.2)   | 0                    |         |                       |         |
| Origin [n (%)]   |                      |         |                    |         |                      |         |                       |         |
| Caucasian        | 771                  | (86.6)  | 438                | (89.4)  | 60                   | (89.6)  | 124                   | (80.0)  |
| African descent  | 76                   | (8.5)   | 32                 | (6.5)   | 3                    | (4.5)   | 17                    | (11.0)  |
| Asian descent    | 3                    | (0.3)   | 6                  | (1.2)   | 1                    | (1.5)   | 0                     |         |
| Hispanic         | 16                   | (1.8)   | 9                  | (1.8)   | 1                    | (1.5)   | 14                    | (9.0)   |
| Other origin     | 5                    | (0.6)   | 4                  | (0.8)   | 2                    | (3.0)   | 0                     |         |
| Missing data     | 19                   | (2.1)   | 1                  | (0.2)   | 0                    |         | 0                     |         |
| Age (years)      |                      |         |                    |         |                      |         |                       |         |
| Mean             |                      | 41.1    |                    | 40.4    |                      | 38.0    |                       | 40.5    |
| Range            |                      | 18 - 79 |                    | 18 - 73 |                      | 20 - 71 |                       | 18 - 71 |
| Age [n (%)]      |                      |         |                    |         |                      |         |                       |         |
| < 40 years       | 441                  | (49.6)  | 252                | (51.4)  | 42                   | (62.7)  | 72                    | (46.5)  |
| 40 to < 65 years | 419                  | (47.1)  | 228                | (46.5)  | 23                   | (34.3)  | 81                    | (52.3)  |
| ≥ 65 years       | 30                   | (3.4)   | 10                 | (2.0)   | 2                    | (3.0)   | 2                     | (1.3)   |

- This table includes subjects from the following studies:  
 Double-blind IR studies: 03A7C-001A-2586 (Fabre), 03A7C-001A-2496 (Mendels), 03A7C-001B, 03A7A-002 (double-blind phase only), 03A7A-003, CN105-022, CN105-028, CN105-029, CN105-037, CN105-043.  
 Open-label IR studies: 030L1-0004, 03A7A-001, CN105-019, CN105-039, CN105-050.
- For uncontrolled studies 030L1-0004, 03A7A-001, CN105-019, CN105-039 and CN105-050, ITT groups were not identified in the study reports. This summary provides subjects from these studies who belonged to the AST group.
- All 13 subjects in study CN105-050 did not have any data for race (origin).
- In Study CN105-019, subjects (b) (6) are listed on the database as having RACE='1', an undefined value for race. The study report and the table above counts these subjects as having missing data for race (origin). The ISS counts these subjects as having RACE='White' (Caucasian).

**Table 4**  
**Distribution of All Study Participants<sup>a</sup> in the Org 33062 Development Program by Treatment Group**

| Study Group                                | ER    | Org 33062<br>IR | Total            | Antidepressants |            | Anxiolytics |          | Placebo |
|--------------------------------------------|-------|-----------------|------------------|-----------------|------------|-------------|----------|---------|
|                                            |       |                 |                  | Fluoxetine      | Imipramine | Bromazepam  | Diazepam |         |
| <b>Phase I Clinical Trials</b>             |       |                 |                  |                 |            |             |          |         |
| Single-Dose Trials                         | 139   | 67              | 206              | 0               | 0          | 0           | 0        | 6       |
| Multiple-Dose Trials                       | 182   | 137             | 319              | 0               | 0          | 0           | 0        | 48      |
| <b>Phase 1 Subtotal</b>                    | 321   | 204             | 525 <sup>d</sup> | 0               | 0          | 0           | 0        | 54      |
| <b>Phase II/III Clinical Trials</b>        |       |                 |                  |                 |            |             |          |         |
| <b>Flexible Dose</b>                       |       |                 |                  |                 |            |             |          |         |
| Placebo-Controlled                         |       |                 |                  |                 |            |             |          |         |
| Short-term                                 | 603   | 1557            | 2160             | 106             | 240        | 73          | 110      | 1308    |
| Long-term <sup>b</sup>                     | (233) | (409)           | (642)            | (64)            | (104)      | (10)        | (39)     | (371)   |
| Uncontrolled Studies                       |       |                 |                  |                 |            |             |          |         |
| Short-term                                 | 34    | 302             | 336              | 0               | 0          | 0           | 0        | 0       |
| Long-term <sup>b</sup>                     | (12)  | (122)           | (134)            | 0               | 0          | 0           | 0        | 0       |
| <b>Phase II – III Subtotal<sup>c</sup></b> | 637   | 1859            | 2496             | 106             | 240        | 73          | 110      | 1308    |
| <b>Grand Total<sup>c</sup></b>             | 958   | 2063            | 3021             | 106             | 240        | 73          | 110      | 1362    |

a: Includes all study subjects who received at least one dose of study medication. Subjects in crossover study 03A7A-002 were counted only in the treatment group they were first exposed to.

b: Includes studies with a short-term phase and a long-term extension phase (numbers in parentheses indicate subjects in short-term phase previously counted)

c: Excludes subjects in long-term extension phase previously counted in short-term phase

d: One additional patient was treated with Org 33062 IR for 8 days in Study CN105-023 before the study was terminated. No CRF is available, thus the subject does not contribute to the safety database.

**Table 3 Disposition of Subjects in Proof-of-Efficacy Studies by Study and Treatment Group**

| Study Number           | Treatment Group           | Randomized | All-Subjects-Treated | Completed | ITT |
|------------------------|---------------------------|------------|----------------------|-----------|-----|
| 134001 <sup>a</sup>    | Org 33062 ER 20-80 mg/day | 103        | 102                  | 74        | 101 |
|                        | Placebo                   | 106        | 106                  | 81        | 103 |
| 03A7A-003              | Org 33062 IR 10-90 mg/day | 30         | 30                   | 17        | 30  |
|                        | Placebo                   | 30         | 30                   | 19        | 30  |
| 03A7C-001B             | Total Org 33062 IR        | 141        | 141                  | 73        | 137 |
|                        | Org 33062 IR 5-45 mg/day  | 71         | 71                   | 41        | 70  |
|                        | Org 33062 IR 10-90 mg/day | 70         | 70                   | 32        | 67  |
|                        | Placebo                   | 70         | 70                   | 32        | 69  |
| 03A7A-002 <sup>b</sup> | Org 33062 IR 10-90 mg/day | 36         | 36                   | 21        | 36  |
|                        | Placebo                   | 34         | 34                   | 18        | 34  |

Note: Data shown were obtained from Appendices F8.1.1-1 and F8.1.4-1 of the clinical study report for Protocol 134001 and from Appendix F, Table 6.1-1, of the clinical study reports for all other studies.

ER = Extended release; IR = Immediate release; ITT = Intent-to-Treat

<sup>a</sup>Three subjects in each treatment group received study medication different than the treatment they were randomized to receive. These subjects were included in the All-Subjects-Treated population based on the study medication they received. They were included in the ITT population based on the treatment group to which they were randomized.

<sup>b</sup>A total of 134 subjects were treated with Org 33062 in the open-label phase of the study; 64 of those subjects discontinued. Information on discontinuations in the open-label phase of the study is provided in the clinical study report.

**Table 4 Reasons for Discontinuation in Proof-of-Efficacy Studies by Study and Treatment Group (All-Subjects-Treated)**

| Treatment Group           | N   | Subjects Discontinued Due to <sup>a</sup> |      |                  |      |                    |     |       |      |       |      |
|---------------------------|-----|-------------------------------------------|------|------------------|------|--------------------|-----|-------|------|-------|------|
|                           |     | Adverse Event <sup>b</sup>                |      | Lack of Efficacy |      | Termination by BMS |     | Other |      | Total |      |
|                           |     | n                                         | %    | n                | %    | n                  | %   | n     | %    | n     | %    |
| 134001                    |     |                                           |      |                  |      |                    |     |       |      |       |      |
| Org 33062 ER 20-80 mg/day | 102 | 10                                        | 9.8  | 4                | 3.9  | NA                 |     | 14    | 13.7 | 28    | 27.5 |
| Placebo                   | 106 | 3                                         | 2.8  | 4                | 3.8  | NA                 |     | 18    | 17.0 | 25    | 23.6 |
| 03A7A-003                 |     |                                           |      |                  |      |                    |     |       |      |       |      |
| Org 33062 IR 10-90 mg/day | 30  | 8                                         | 26.7 | 1                | 3.3  | 0                  | 0   | 4     | 13.3 | 13    | 43.3 |
| Placebo                   | 30  | 4                                         | 13.3 | 6                | 20.0 | 0                  | 0   | 1     | 3.3  | 11    | 36.7 |
| 03A7C-001B                |     |                                           |      |                  |      |                    |     |       |      |       |      |
| Total Org 33062 IR        | 141 | 45                                        | 31.9 | 13               | 9.2  | 0                  | 0   | 10    | 7.1  | 68    | 48.2 |
| Org 33062 IR 5-45 mg/day  | 71  | 17                                        | 23.9 | 8                | 11.3 | 0                  | 0   | 5     | 7.1  | 30    | 42.3 |
| Org 33062 IR 10-90 mg/day | 70  | 28                                        | 40.0 | 5                | 7.1  | 0                  | 0   | 5     | 7.1  | 38    | 54.3 |
| Placebo                   | 70  | 8                                         | 11.4 | 21               | 30.0 | 0                  | 0   | 9     | 12.9 | 38    | 54.3 |
| 03A7A-002 <sup>c</sup>    |     |                                           |      |                  |      |                    |     |       |      |       |      |
| Org 33062 IR 10-90 mg/day | 36  | 4                                         | 11.1 | 9                | 25.0 | 0                  | 0   | 2     | 5.6  | 15    | 41.7 |
| Placebo                   | 34  | 1                                         | 2.9  | 10               | 29.4 | 2 <sup>d</sup>     | 5.9 | 3     | 8.8  | 16    | 47.1 |

Note: Data shown were obtained from Appendices F8.1.2-1 and F8.1.4-1 of the clinical study report for Protocol 134001 and from Appendix F, Supplement to Report Table on Reasons for Discontinuation, of the clinical study reports for all other studies.  
 BMS = Bristol-Myers Squibb; ER = Extended release; IR = Immediate release; NA = Not applicable  
<sup>a</sup> For BMS studies, >1 reason for discontinuation could be recorded. The reason for discontinuation shown was the primary reason recorded on the Case Report Form (CRF), unless the reason for discontinuation was due to an AE. If AE was recorded as the reason for discontinuation, even if recorded as a secondary or tertiary reason, then AE was the reason for discontinuation included in this table.  
<sup>b</sup> Including serious adverse event  
<sup>c</sup> Refers to subjects who participated in double-blind phase of the study  
<sup>d</sup> Based on the CRF, these subjects discontinued for factors related to design (primary reason) and withdrawal of consent (secondary reason). These discontinuations were recorded in the database as "BMS termination."

## Adequate and well controlled studies that provide proof of the efficacy of Org 33062

Table 14 provides a summary of the demographic characteristics of subjects in the 4 placebo-controlled studies that provide proof of the efficacy of Org 33062.

**Table 14 Demographic Characteristics at Baseline in Proof-of-Efficacy Studies by Study and Treatment Group (Intent-to-Treat)**

| Treatment Group           | N   | Age                | Height             | Weight             | Gender | Race  |    |     |     |    |
|---------------------------|-----|--------------------|--------------------|--------------------|--------|-------|----|-----|-----|----|
|                           |     | (yr.)<br>Mean ± SD | (in.)<br>Mean ± SD | (lb.)<br>Mean ± SD |        | % F/M | Bl | His | Ori | Wh |
| 134001                    |     |                    |                    |                    |        |       |    |     |     |    |
| Org 33062 ER 20-80 mg/day | 101 | 39.9 ± 11.3        | 66.6 ± 3.6         | 183 ± 42.7         | 66/34  | 8     | NA | 1   | 72  | 19 |
| Placebo                   | 103 | 40.2 ± 11.9        | 66.8 ± 4.3         | 182 ± 53.0         | 54/46  | 11    | NA | 3   | 75  | 12 |
| 03A7A-003                 |     |                    |                    |                    |        |       |    |     |     |    |
| Org 33062 IR 10-90 mg/day | 30  | 41.4 ± 10.0        | 67.8 ± 6.0         | 162 ± 28.8         | 33/67  | 3     | 0  | 0   | 97  | 0  |
| Placebo                   | 30  | 37.4 ± 8.8         | 69.2 ± 4.6         | 168 ± 40.1         | 37/63  | 3     | 0  | 0   | 93  | 3  |
| 03A7C-001B                |     |                    |                    |                    |        |       |    |     |     |    |
| Total Org 33062 IR        | 137 | 41.7 ± 9.9         | 67.7 ± 3.9         | 167 ± 39.4         | 55/45  | 7     | 0  | 0   | 93  | 0  |
| Org 33062 IR 5-45 mg/day  | 70  | 43.0 ± 10.1        | 67.3 ± 3.9         | 159 ± 35.1         | 54/46  | 3     | 0  | 0   | 97  | 0  |
| Org 33062 IR 10-90 mg/day | 67  | 40.3 ± 9.6         | 68.1 ± 3.7         | 175 ± 42.3         | 55/45  | 10    | 0  | 0   | 90  | 0  |
| Placebo                   | 69  | 44.0 ± 11.3        | 66.5 ± 3.6         | 169 ± 38.7         | 67/33  | 4     | 0  | 0   | 96  | 0  |
| 03A7A-002 <sup>a</sup>    |     |                    |                    |                    |        |       |    |     |     |    |
| Org 33062 IR 10-90 mg/day | 36  | 42.7 ± 9.1         | 67.5 ± 3.9         | 169 ± 38.1         | 47/53  | 8     | 0  | 0   | 92  | 0  |
| Placebo                   | 34  | 42.7 ± 10.1        | 67.5 ± 3.5         | 174 ± 37.6         | 41/59  | 0     | 0  | 3   | 97  | 0  |

Note: Data shown were obtained from Appendix F8.2-1B of the clinical study report and from Appendices B.1 and B.2 of the Integrated Summary of Efficacy for Protocol 134001 and from Appendix F, Tables 6.6-3, of the clinical study reports for all other studies.

ER = Extended release; IR = Immediate release

For race, Bl = Black; His = Hispanic; Ori = Oriental; Wh = White; NA = Not applicable: recorded as "Other" on CRF for Protocol 134001.

<sup>a</sup> Refers to subjects who participated in double-blind phase of the study

Overall, there were no major differences among these 4 studies with respect to demographic characteristics of subjects in the Intent-to-Treat population.

**Table 5 Maximum Modal Dose and Mean Dose of Org 33062 in Proof-of-Efficacy Studies by Study and Treatment Group (Intent-to-Treat)**

| Study Number           | Treatment Group                        | N   | Maximum Modal Dose <sup>a</sup> in mg/day |        |          | Mean Dose <sup>a</sup> in mg/day |        |             |
|------------------------|----------------------------------------|-----|-------------------------------------------|--------|----------|----------------------------------|--------|-------------|
|                        |                                        |     | Mean ± SD                                 | Median | Min-Max  | Mean ± SD                        | Median | Min-Max     |
| 134001                 | Org 33062 ER 20-80 mg/day              | 101 | 68.3 ± 16.1                               | 80.0   | 40 - 80  | 70.3 ± 14.9                      | 80.0   | 40.0 - 80.0 |
| 03A7A-003              | Org 33062 IR 10-90 mg/day <sup>b</sup> | 30  | 47.0 ± 29.1                               | 35.0   | 10 - 110 | 40.6 ± 21.3                      | 35.6   | 10 - 87.1   |
| 03A7C-001B             | Total Org 33062 IR                     | 137 | 33.3 ± 24.7                               | 25.0   | 0 - 120  | 27.2 ± 17.6                      | 22.1   | 1.3 - 87.0  |
|                        | Org 33062 IR 5-45 mg/day <sup>c</sup>  | 70  | 26.7 ± 15.1                               | 25.0   | 0 - 60   | 21.4 ± 10.1                      | 19.3   | 1.3 - 45.9  |
|                        | Org 33062 IR 10-90 mg/day <sup>b</sup> | 67  | 40.1 ± 30.5                               | 40.0   | 0 - 120  | 33.3 ± 21.4                      | 29.6   | 3.0 - 87.0  |
| 03A7A-002 <sup>d</sup> | Org 33062 IR 10-90 mg/day              | 36  | 42.2 ± 22.7                               | 40.0   | 0 - 90   | 39.9 ± 20.3                      | 40.0   | 9.0 - 86.1  |

Note: Data shown were those based on short-term, double-blind treatment and were obtained from Appendix F8.3-8 of the clinical study report and Appendix B.5 of the Integrated Summary of Efficacy for Protocol 134001 and from Appendix F, Tables 6.10-5 and 6.10-7, of the clinical study report for all other studies.

ER = Extended release; IR = Immediate release

<sup>a</sup> The mean of the maximum modal dose and the mean dose were calculated for the duration of short-term, double-blind treatment. The maximum modal dose was defined as the dose most frequently prescribed. In a case of a tie, the highest modal dose was selected.

<sup>b</sup> The dose could be increased up to 120 mg/day.

<sup>c</sup> The dose could be increased up to 60 mg/day.

<sup>d</sup> Refers to subjects who participated in double-blind phase of the study

**Individual study reviews**  
**STUDY 134001**

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**A double-blind, multicenter, randomized, placebo-controlled, efficacy and safety study of Org 33062 ER in subjects with major depressive disorder**

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The trial was to be a double-blind, placebo-controlled, parallel group, multicenter, trial of Org 33062 ER in the treatment of moderately to severely depressed outpatients. Each subject was to participate in a 7-day screening (placebo wash-out) period designed to ensure that all eligibility criteria had been met. Subjects who met all eligibility requirements were to be randomized to receive either placebo or Org 33062 ER (20 mg to 80 mg) once per day in the morning. Those who completed the 8-week trial were to be offered enrollment in the 44-week open-label Org 33062 ER extension trial. This was a 5-center, double-blind study of Org 33062 ER 20-80 mg/day and placebo in subjects meeting DSM-IV criteria for MDD. The study had a flexible-dose design with 1 forced-titration step from 20 mg/day to 40 mg/day at Day 4. The minimum dose of Org 33062 allowed was 40 mg/day.

**Investigators**

Investigators and Institutional Review Boards

| Site # | Investigator/Site                                                                                                    | EC/IRB  |
|--------|----------------------------------------------------------------------------------------------------------------------|---------|
| 01     | Alan D. Feiger, M.D.<br>Feiger Health Research Center<br>3555 Lutheran Parkway<br>Suite 320<br>Wheat Ridge, CO 80033 | (b) (4) |
| 02     | Jon F. Heiser, M.D.<br>Pharmacology Research Institute<br>1000 Dove Street, Suite 200<br>Newport Beach, CA 90720-    |         |

|    |                                                                                                                      |         |
|----|----------------------------------------------------------------------------------------------------------------------|---------|
|    | 2149                                                                                                                 |         |
| 03 | Ram K. Shrivastava, M.D.<br>Eastside Comprehensive<br>Medical Services<br>133 East 73rd Street<br>New York, NY 10021 | (b) (4) |

|    |                                                                                                                          |         |
|----|--------------------------------------------------------------------------------------------------------------------------|---------|
|    |                                                                                                                          |         |
| 04 | Kenneth J. Weiss, M.D.<br>Delaware Valley Research<br>Associates, Inc.<br>922 Fayette Street a<br>Conshohocken, PA 19428 | (b) (4) |
| 05 | Ward Smith, M.D. b<br>Northwest Research<br>Clinics<br>1849 N. W. Kearny<br>Suite 201<br>Portland, OR 97209              |         |

a As per Amendment 2 (April 19, 2000) the address was changed

b As per Amendment 2 (April 19, 2000) Site 05 was added

### Subjects

Prospective subjects were to meet all of the following criteria for inclusion in the trial:

- at least 18 and not more than 70 years of age (as per Amendment 2 [April 19, 2000] the maximum age of subjects was changed from 64 to 70 years of age)
- meet diagnostic criteria for moderate to severe major depressive disorder according to the DSM-IV criteria (296.22, 296.23, 296.32, 296.33 only)
- have a total score of 20 or greater on the HAMD-17 at both screening and baseline assessments
- have significant daily dysphoria for the past four weeks, and
- provide written informed consent.

### Dosing Schedule

|                             | Org 33062 group                       | Placebo group       |
|-----------------------------|---------------------------------------|---------------------|
| Washout (day -7/-4 - day 0) | 2 placebo tablets                     | 2 placebo tablets   |
| day 1 - day 3               | 1 20 mg Org 33062<br>1 placebo tablet | 2 placebo tablets   |
| day 4 - day 6               | 2 20 mg Org 33062                     | 2 placebo tablets   |
| day 7 - day 14              | 2-3 20 mg Org 33062                   | 2-3 placebo tablets |
| day 15 - day 56             | 2-4 20 mg Org 33062                   | 2-4 placebo tablets |

### Protocol amendments

The protocol was amended three times after it was approved on November 11, 1998. Amendment 1 (June 24, 1999) was to result in the Derogatis Inventory for Sexual Dysfunction - Self-Report (DISF-SR) at baseline and at endpoint to be included in section of the safety evaluations; ECG was to be done at screening instead of at baseline; a reference for DISF-SR was to be included in the reference list; the statistical plan was to include an outline for the analysis and interpretation of the DISF-SR; and the names of the first 4 investigators and centers were provided.

The protocol was amended the second time (April 19, 2000) to include subjects at least 18 years of and of not more than 70 years of age. The amendment was to reduce the number of months that elapsed between a subject's involvement in a former clinical trial and current trial from 6 months to 1 month; to exclude subjects 65 years old and older diagnosed with or taking any medication for any chronic illness (other than psychiatric disorders), and subjects with a history of treatment with an investigational drug within 1 month of enrollment to the trial. Also, investigators were to verify that the prior investigational compound had had a sufficient wash-out period prior to enrolling the subject. Due to Amendment 2, subjects who were enrolled after February 2, 2000 were to have a 30-day follow-up assessment to inquire about

SAEs. An SAE or death was to be recorded on the follow-up record. The address of Dr. Kenneth Weiss was updated (Site 04) and Dr. Ward Smith was included in the trial, increasing the number of sites to 5. The planned clinical trial period was increased to October, 2000.

Amendment 3 (December 21, 2000) resulted in the blood samples being assayed for 3'-OH gepirone in addition to Org 33062 and 1-PP. Due to this amendment, placebo samples were not to be assayed for Org 33062, 3'-OH-gepirone, or 1-PP. Assays were done after the blind was broken; treatment codes were not made available to (b) (4) until after the blind was broken. Amendment 3 also resulted in the initial statistics plan being replaced in by the final statistical plan.

### **Efficacy Assessments**

The Hamilton Depression Rating Scale (HAMD): This is an observer rated scale for the quantitative assessment of depression in subjects with MDD. The HAMD (Hamilton, 1960) scoring was to be based on Dr. J. Williams' structured interview for the HAMD-21 (Williams, 1988). Additional HAMD items were to be administered according to guidelines provided at the Investigator's Meeting. The scale was to be completed at screening, baseline, and at Visits 1 through 6. Items for the HAMD have been developed for various purposes. Raters were to administer the following items whenever the HAMD was specified: the common 17 items composing the HAMD-17; one diurnal variation item; three items unique to the HAMD-21; and 10 items unique to the HAMD-28. In total, there are 31 recognized HAMD items. Each of these was to be administered at each HAMD assessment. The 10 items unique to the HAMD-28 were to be administered as part of an unstructured interview conducted immediately after the HAMD-21.

The Clinical Global Impression Scale (CGI): The CGI (Guy, 1976) consists of a rating of the severity of the illness, and global ratings of the change in clinical status since the start of treatment. The scale was to be completed at baseline (severity only) and at Visits 1 through 6.

Montgomery-Åsberg Depression Rating Scale (MADRS): This scale is an observer rating scale for the quantitative assessment of depression in subjects with MDD. The

MADRS (Montgomery and Åsberg, 1979) is a 10-item rating scale. The scale was to be completed at baseline and at Visits 1 through 6.

### **Analysis**

The primary efficacy parameter was the change from baseline on the HAMD-17 total score. The primary time-point for treatment comparisons was the endpoint assessment based on the Intent-to-Treat Group.

The primary efficacy parameter was analyzed at each visit by means of an analysis of variance (ANOVA) model. The estimates of treatment effects were based upon the additive two-way ANOVA with factors treatment and center. A test for interaction between treatment and center was performed by extending the additive model with the interaction term. In case of a significant interaction ( $p \leq 0.10$ ) the kind of interaction (i.e., the differences between the centers with respect to the treatment effects) was to be discussed and further explored to evaluate whether it was still justified to present an overall estimate of the treatment effect.

The analysis of the secondary efficacy parameters was considered supportive to the main conclusions based on the primary efficacy. The following variables were considered as secondary efficacy parameters:

- a) Number of 'HAMD-17 responders' (defined by a decrease on a post-baseline assessment of at least 50% on the HAMD total score [17 items] as compared to the baseline value);
- b) Number of 'CGI responders' (defined as subjects who were 'much' or 'very much improved' according to the CGI change score on a post-baseline assessment);
- c) Number of 'remitters' (defined as subjects with a HAMD-17 total score  $\leq 7$  on a post-baseline assessment);
- d) Number of 'HAMD-25 responders' (defined by a decrease on the endpoint assessment of at least 50% on the HAMD total score [25 items] as compared to the baseline value) for subjects who satisfied DSM-IV criteria for MDD with atypical depression;
- e) Change from baseline on the MADRS total score;

- f) Change from baseline on the HAMD total score [21, 25, and 28 items];
- g) Change from baseline on the HAMD item [1] 'Depressed mood';
- h) Change from baseline on the HAMD Anxiety/Somatization Factor (Factor I)
- i) Change from baseline on the global impression of severity (CGI item [1]); and  
Global impression of change (CGI item [2]).

**RESULTS**  
**Disposition**

**Disposition of subjects by treatment group**

| Number of subjects                               | Treatment group |         |       |
|--------------------------------------------------|-----------------|---------|-------|
|                                                  | Org 33062       | Placebo | Total |
| Randomized to treatment                          | 103             | 106     | 209   |
| Treated (Actual Treatment Received) <sup>a</sup> | 102             | 106     | 208   |
| Discontinued treatment by <sup>b</sup>           |                 |         |       |
| Week 1                                           | 4               | 4       | 8     |
| Week 2                                           | 6               | 3       | 9     |
| Week 3                                           | 4               | 4       | 8     |
| Week 4                                           | 4               | 3       | 7     |
| Week 5                                           | 0               | 5       | 5     |
| Week 6                                           | 3               | 3       | 6     |
| Week 7                                           | 4               | 1       | 5     |
| Week 8                                           | 3               | 2       | 5     |
| Total discontinued treatment                     | 28              | 25      | 53    |
| Completed treatment                              | 74              | 81      | 155   |

<sup>a</sup> Subjects [REDACTED] (b) (6) were randomized to Org 33062 but were treated with Placebo. Subjects [REDACTED] (b) (6) were randomized to Placebo but were treated with Org 33062.

<sup>b</sup> All-Subjects-Treated Group

A total of 209 subjects were randomized to the Org 33062 and the placebo treatment groups. Of these subjects, 103 were randomized to the Org 33062 treatment group and 106 were randomized to the placebo treatment group. Of the 209 subjects who were randomized, 208 received at least 1 dose of trial medication and were included in the All-Subjects-Treated Group; 102 subjects in the Org 33062 treatment group and 106 subjects in the placebo treatment group.

Six subjects did not receive the treatment to which they were randomized. Of these 6 subjects all from the same site, 3 subjects ( (b)(6) ) were randomized to the Org 33062 treatment group, but received placebo. The remaining 3 subjects ( (b)(6) ) were randomized to the placebo treatment group, but received Org 33062. Subject (b)(6) was excluded from the All-Subjects-Treated Group because the subject did not ingest any of the trial medication (Org 33062) she received (i.e., all trial medication was returned by this subject).

## Dicontinuations

**Number (%) of subjects who discontinued by reason for discontinuation and treatment group  
All-Subjects-Treated Group**

| Reason for discontinuation | Treatment group    |      |                  |      |                |      |
|----------------------------|--------------------|------|------------------|------|----------------|------|
|                            | Org 33062<br>N=102 |      | Placebo<br>N=106 |      | Total<br>N=208 |      |
|                            | n                  | %    | n                | %    | n              | %    |
| Adverse Events/SAE         | 10                 | 9.8  | 3                | 2.8  | 13             | 6.3  |
| Lack of efficacy           | 4                  | 3.9  | 4                | 3.8  | 8              | 3.8  |
| Reason not mentioned above | 14                 | 13.7 | 18               | 17.0 | 32             | 15.4 |

Of the 208 subjects in the All-Subjects-Treated Group, 53 (25.5%) discontinued the trial. Of the 102 and 106 subjects in the Org 33062 treatment and placebo treatment groups 28 (27.5%) and 25 (23.6%) discontinued the trial, respectively.

A total of 13 (6.3%) subjects discontinued the trial due to AEs/SAEs. A higher proportion of subjects in the Org 33062 treatment group (10 [9.8%] subjects) discontinued due to AEs/SAEs than in the placebo treatment group (3 [2.8%] subjects). Four (3.9% and 3.8% in the Org 33062 and placebo

treatment groups, respectively) subjects in each treatment group discontinued due to lack of efficacy.

A total of 32 (15.4%) subjects withdrew from the trial for reasons not mentioned above, including 14 (13.7%) subjects in the Org 33062 treatment group and 18 (17.0%) subjects in the placebo treatment group. Most of these 32 subjects were lost to follow-up, withdrew consent, were non-compliant, or had moved out of the area.

## Demographics

**Table 6 Demographics by treatment group  
All-Subjects-Treated Group**

| Demographics  | Treatment group    |      |                  |      |                |      |
|---------------|--------------------|------|------------------|------|----------------|------|
|               | Org 33062<br>N=102 |      | Placebo<br>N=106 |      | Total<br>N=208 |      |
| Age: yrs      |                    |      |                  |      |                |      |
| n             | 102                |      | 106              |      | 208            |      |
| Mean          | 39.5               |      | 40.6             |      | 40             |      |
| SD            | 11.3               |      | 11.7             |      | 11.5           |      |
| Median        | 37                 |      | 41               |      | 39             |      |
| Minimum       | 18                 |      | 19               |      | 18             |      |
| Maximum       | 63                 |      | 69               |      | 69             |      |
| Weight: kg    |                    |      |                  |      |                |      |
| n             | 101                |      | 105              |      | 206            |      |
| Mean          | 83.1               |      | 82.6             |      | 82.8           |      |
| SD            | 20                 |      | 23.5             |      | 21.8           |      |
| Median        | 81.8               |      | 78.6             |      | 79.3           |      |
| Minimum       | 40                 |      | 36.8             |      | 36.8           |      |
| Maximum       | 133.8              |      | 167.8            |      | 167.8          |      |
| Height: cm    |                    |      |                  |      |                |      |
| n             | 101                |      | 106              |      | 207            |      |
| Mean          | 168.9              |      | 169.7            |      | 169.3          |      |
| SD            | 9.3                |      | 10.9             |      | 10.1           |      |
| Median        | 170                |      | 170              |      | 170            |      |
| Minimum       | 134                |      | 108              |      | 108            |      |
| Maximum       | 190                |      | 196              |      | 196            |      |
| Gender: n (%) |                    |      |                  |      |                |      |
| Female        | 69                 | 67.6 | 57               | 53.8 | 126            | 60.6 |
| Male          | 33                 | 32.4 | 49               | 46.2 | 82             | 39.4 |
| Race: n (%)   |                    |      |                  |      |                |      |
| Asian         | 1                  | 1    | 3                | 2.8  | 4              | 1.9  |
| Black         | 8                  | 7.8  | 11               | 10.4 | 19             | 9.1  |

| Demographics | Treatment group    |      |                  |      |                |      |
|--------------|--------------------|------|------------------|------|----------------|------|
|              | Org 33062<br>N=102 |      | Placebo<br>N=106 |      | Total<br>N=208 |      |
| Caucasian    | 74                 | 72.5 | 78               | 73.6 | 152            | 73.1 |
| Other        | 19                 | 18.6 | 14               | 13.2 | 33             | 15.9 |

Of the 208 subjects in the All-Subjects-Treated Group, 60.6% were female and 39.4% were male. The age of subjects ranged from 18 to 69 years. The majority of subjects (73.1%) were Caucasian. The demographic characteristics of subjects in the 2 treatment groups were similar.

The baseline characteristics of subjects in the 2 treatment groups of the Intent-to-Treat Group were similar to those of the All-Subjects-Treated Group.

Table 8 provides a summary of other subject baseline characteristics for the All-Subjects-Treated Group by treatment group.

**Table 8 Other subject baseline characteristics by treatment group**  
**All-Subjects-Treated Group**

| Baseline characteristics                      | Treatment Group    |      |                  |      |                |      |
|-----------------------------------------------|--------------------|------|------------------|------|----------------|------|
|                                               | Org 33062<br>N=102 |      | Placebo<br>N=106 |      | Total<br>N=208 |      |
| Duration of present episode: n (%)            |                    |      |                  |      |                |      |
| 1 to 6 months                                 | 32                 | 31.4 | 23               | 21.7 | 55             | 26.4 |
| 7 to 12 months                                | 16                 | 15.7 | 20               | 18.9 | 36             | 17.3 |
| >1 year                                       | 54                 | 52.9 | 63               | 59.4 | 117            | 56.3 |
| Age at first episode of depression            |                    |      |                  |      |                |      |
| n                                             | 60                 |      | 51               |      | 111            |      |
| Mean                                          | 27.8               |      | 26.2             |      | 27.0           |      |
| SD                                            | 12.8               |      | 11.2             |      | 12.1           |      |
| Median                                        | 24.5               |      | 24               |      | 24             |      |
| Minimum                                       | 10                 |      | 10               |      | 10             |      |
| Maximum                                       | 60                 |      | 56               |      | 60             |      |
| Course of illness: n (%)                      |                    |      |                  |      |                |      |
| First episode                                 | 29                 | 28.4 | 39               | 36.8 | 68             | 32.7 |
| Chronic                                       | 13                 | 12.7 | 19               | 17.9 | 32             | 15.4 |
| Recurrent with partial inter-episode recovery | 25                 | 24.5 | 14               | 13.2 | 39             | 18.8 |
| Recurrent with full inter-episode recovery    | 35                 | 34.3 | 34               | 32.1 | 69             | 33.2 |
| Precipitating life events present: n (%)      |                    |      |                  |      |                |      |
| Yes                                           | 51                 | 50.0 | 56               | 52.8 | 107            | 51.4 |
| No                                            | 51                 | 50.0 | 50               | 47.2 | 101            | 48.6 |
| Prior treatment with antidepressants: n (%)   |                    |      |                  |      |                |      |
| Yes                                           | 48                 | 78.7 | 35               | 68.6 | 83             | 74.1 |
| No                                            | 13                 | 21.3 | 16               | 31.4 | 29             | 25.9 |

Table 9 provides a frequency distribution of the duration of exposure to Org 33062 and placebo for the All-Subjects-Treated Group by days and treatment group.

**Table 9 Frequency distribution of duration of exposure to Org 33062 and placebo by days and treatment group All-Subjects-Treated Group**

| Exposure (days) <sup>a</sup> | Treatment group    |      |                  |      |
|------------------------------|--------------------|------|------------------|------|
|                              | Org 33062<br>N=102 |      | Placebo<br>N=106 |      |
|                              | n                  | %    | n                | %    |
| 1 - 7                        | 4                  | 3.9  | 4                | 3.8  |
| 8 - 14                       | 6                  | 5.9  | 3                | 2.8  |
| 15 - 21                      | 4                  | 3.9  | 4                | 3.8  |
| 22 - 28                      | 4                  | 3.9  | 3                | 2.8  |
| 29 - 35                      | 0                  | 0    | 5                | 4.7  |
| 36 - 42                      | 3                  | 2.9  | 4                | 3.8  |
| 43 - 49                      | 4                  | 3.9  | 1                | 0.9  |
| 50 - 56                      | 48                 | 47.1 | 50               | 47.2 |
| > 56                         | 29                 | 28.4 | 32               | 30.2 |

<sup>a</sup> The duration of exposure (total number of days) to trial medication = the date of last trial medication intake (according to the End-of-Trial Form) - the date of the first intake (according to the Drug Accountability Form) + 1.

Table 11 provides the frequency distribution for mean actual Org 33062 dose for the All-Subjects-Treated Group.

**Table 11 Frequency distribution for the mean actual Org 33062 dose All-Subjects-Treated Group**

| Mean dose<br>(mg/day) | Visit      |    |            |          |            |          |            |          |            |          |               |          |
|-----------------------|------------|----|------------|----------|------------|----------|------------|----------|------------|----------|---------------|----------|
|                       | Visit<br>1 |    | Visit<br>2 |          | Visit<br>3 |          | Visit<br>4 |          | Visit<br>5 |          | Visit<br>6/ET |          |
|                       | n          | %  | n          | %        | n          | %        | n          | %        | n          | %        | n             | %        |
| >20-40                | 10<br>0    | 98 | 21         | 22<br>.1 | 9          | 10<br>.3 | 4          | 4.<br>7  | 5          | 6        | 3             | 3.<br>9  |
| >40-60                | 2          | 2  | 71         | 74<br>.7 | 21         | 24<br>.1 | 22         | 25<br>.6 | 18         | 21<br>.4 | 19            | 24<br>.7 |
| >60-80                | 0          | 0  | 3          | 3.<br>2  | 52         | 59<br>.8 | 57         | 66<br>.3 | 54         | 64<br>.3 | 48            | 62<br>.3 |
| >80                   | 0          | 0  | 0          | 0        | 5          | 5.<br>7  | 3          | 3.<br>5  | 7          | 8.<br>3  | 7             | 9.<br>1  |

## Concomitant Medications

The most common concomitant medications taken by the Org 33062 and placebo treatment groups were ibuprofen (26.5% and 39.6% subjects, respectively), acetaminophen (25.5% and 21.7% subjects, respectively), multivitamins (21.6% and 33.0% subjects, respectively), aspirin (19.6% and 13.2% subjects, respectively), naproxen (10.8% and 9.4% subjects, respectively) and Vitamin C (7.8% and 11.3% subjects, respectively). All other concomitant medications were taken by fewer than 10% of subjects in either treatment group.

## Efficacy Results

Table 12 provides the change from baseline in the HAM-D-17 total score by visit and treatment group for the Intent-to-Treat Group (LOCF analysis).

**Table 12 Change from baseline in the HAMD-17 total score by visit and treatment group  
Intent-to-Treat Group (LOCF)**

|                   |                       | Visit   |         |         |         |         |            |
|-------------------|-----------------------|---------|---------|---------|---------|---------|------------|
|                   |                       | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6/ET |
| Treatment group   | Statistical parameter |         |         |         |         |         |            |
| Org 33062 (N=101) | N                     | 98      | 100     | 101     | 101     | 101     | 101        |
|                   | LS Mean               | 3.3     | 5.74    | 7.86    | 8.23    | 8.44    | 9.04       |
|                   | SE                    | 0.47    | 0.58    | 0.65    | 0.67    | 0.75    | 0.78       |
| Placebo (N=103)   | n                     | 99      | 101     | 101     | 101     | 101     | 101        |
|                   | LS Mean               | 2.17    | 4.4     | 5.86    | 6.78    | 6.63    | 6.75       |
|                   | SE                    | 0.46    | 0.57    | 0.64    | 0.66    | 0.74    | 0.77       |
| p value           |                       | 0.052   | 0.059   | 0.013   | 0.078   | 0.051   | 0.018      |

Note: Change = (total score at the baseline) - (total score at the post-baseline visit)

ET = end of trial; LS = least squares; SE = standard error of the mean

A statistically significant difference between the Org 33062 and placebo treatment groups was noted for the change from baseline in the HAMD-17 total score at Visit 3 (p = 0.013; 2.00 points difference in favor of Org 33062) and at Visit 6/end of trial (p = 0.018; 2.29 points difference in favor of Org 33062) based on the LOCF analysis for the Intent-to-Treat Group. Results based on the LOCF and OC analyses for the Intent-to-Treat Group were consistent.

**Table 7** Number (%) of CGI responders (subjects "much" or "very much" improved) by visit and treatment group Intent-to-Treat Group (LOCF)

|                 |                       | Visit   |         |         |         |         |            |
|-----------------|-----------------------|---------|---------|---------|---------|---------|------------|
|                 |                       | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6/ET |
| Treatment group | Statistical parameter |         |         |         |         |         |            |
| Org 33062       | N                     | 98      | 100     | 101     | 101     | 101     | 101        |
|                 | n                     | 10      | 24      | 34      | 41      | 39      | 44         |
|                 | %                     | 10.2    | 24      | 33.7    | 40.6    | 38.6    | 43.6       |
| Placebo         | N                     | 99      | 101     | 101     | 101     | 101     | 101        |
|                 | n                     | 6       | 14      | 24      | 35      | 37      | 36         |
|                 | %                     | 6.1     | 13.9    | 23.8    | 34.7    | 36.6    | 35.6       |
| p value         |                       | 0.288   | 0.067   | 0.121   | 0.385   | 0.772   | 0.251      |

Note:ET = end of trial

There was no statistically difference between the Org 33062 and placebo treatment groups at any visit. Results based on the LOCF and OC analyses for the Intent-to-Treat Group were consistent.

**Table 8** Overview of the differences in treatment effect for efficacy parameters Intent-to-Treat Group (LOCF)

| Efficacy parameter                              | Visit       |             |           |             |             |                         |
|-------------------------------------------------|-------------|-------------|-----------|-------------|-------------|-------------------------|
|                                                 | 1           | 2           | 3         | 4           | 5           | 6/ET                    |
| Change from baseline in the HAMD-17 total score | <u>1.13</u> | <u>1.34</u> | 2.00      | <u>1.45</u> | <u>1.81</u> | 2.29                    |
| HAMD-17 responders (%)                          | 4.13        | 7.14        | 14.8<br>5 | 13.8<br>6   | 4.95        | <u>12.8</u><br><u>7</u> |
| HAMD-17 remitters (%)                           | <u>3.06</u> | 4.05        | 6.93      | 4.95        | 10.8<br>9   | 13.8<br>6               |

|                                                                         |                  |                  |           |             |             |                  |
|-------------------------------------------------------------------------|------------------|------------------|-----------|-------------|-------------|------------------|
| Change from baseline in the HAMD-21 total score                         | 1.38             | 1.63             | 2.27      | 1.46        | <u>1.84</u> | 2.51             |
| Change from baseline in the HAMD-28 total score                         | 1.98             | 2.48             | 3.26      | <u>2.37</u> | <u>2.59</u> | 3.68             |
| Change from baseline in the HAMD item 1 score (depressed mood)          | 0.08             | 0.17             | 0.34      | 0.25        | <u>0.24</u> | 0.39             |
| CGI responders (%)                                                      | 4.14             | <u>10.1</u><br>4 | 9.90      | 5.94        | 1.98        | 7.92             |
| Change from baseline in CGI severity                                    | 0.20             | 0.25             | 0.34      | 0.35        | 0.29        | 0.39             |
| Change from baseline in CGI of improvement                              | <u>-</u><br>0.18 | -                | -         | -           | -           | <u>-</u><br>0.29 |
| Change from baseline in the HAMD anxiety/somatization factor (Factor I) | 0.34             | 0.35             | 0.74      | 0.42        | 0.25        | 0.58             |
| Change from baseline in the HAMD item 12 (psychic anxiety)              | 0.34             | 0.28             | 0.35      | 0.28        | 0.30        | 0.43             |
| HAMD-25 responders (%)                                                  | 5.16             | <u>9.13</u>      | 14.8<br>5 | 10.8<br>9   | 10.8<br>9   | 16.8<br>3        |
| Change from baseline in the HAMD-25 total score                         | 1.65             | 2.17             | 2.80      | 2.14        | <u>2.29</u> | 3.37             |

Note: The statistically significant ( $p \leq 0.05$ ) differences between the Org 33062 and placebo treatment groups, in favor of Org 33062, are shaded, marginally significant differences ( $0.05 < p \leq 0.10$ ) are underlined.

For the HAMD-17 change from baseline, the raw magnitude of response at endpoint was 2.29 HAMD-17 points.

See appendix for additional efficacy tables.

This study is positive as per the sponsor's analysis above and is confirmed by the FDA statistical analysis (see stat review.)

### **Study 03A7A-003**

A Double-Blind Trial of Org 33062 vs. Placebo in the Treatment of Outpatients with Atypical Depression

This was a single-center, double-blind study of Org 33062 IR 10-90 mg/day and placebo in subjects meeting RDC criteria for major, minor, or intermittent depression with a specified atypical profile. (Note: Based on a protocol amendment, the Org 33062 dose range was changed to 10-120 mg/day).

### **Study Period (Years)**

March 7, 1988 (first dose of study drug) to March 14, 1990 (last dose of study drug).

### **Objectives**

The objective of this 8-week study was to investigate the safety and efficacy of Org 33062 compared to placebo in the treatment of depression in outpatients who met Research Diagnostic Criteria (RDC) for a major, minor, or intermittent depression and who had an atypical profile.

### **Methodology**

This was a double-blind, randomized, parallel-group, single center comparison of the safety and efficacy of Org 33062 and placebo in the treatment of depressed outpatients who met RDC criteria for a major, minor, or intermittent depression. Subjects participated in a 7 to 14 day baseline phase. Subjects who at baseline had atypical depression and met the entry criteria were randomly assigned to one of two treatment groups: Org 33062 10 to 90 mg (up to 120 mg/day if necessary) or placebo. The duration of the baseline phase was to be two weeks for subjects who had been treated with a monoamine oxidase inhibitor (MAOI) or any other long-duration psychotropic medication. Subjects who at baseline had atypical depression [ $\geq 10$  on the HAMD 21 (amended from  $\geq 18$  on the HAMD 25 in Amendment No. 1)] were to be randomly assigned

to one of two treatment groups: Org 33062 (1-9 capsules/day) 10 to 90 or placebo. If a subject was unresponsive, with the permission of BMS, the maximum allowable dose could have been increased to 120 mg/day. Subjects were to receive one to nine capsules/day (amended up to 12 capsules/day). The dose was to be individualized for each subject. Double-blind treatment was to be administered BID. The protocol was amended (Amendment No. 1) to allow a TID schedule, a QID schedule could also be used if necessary, to reduce the incidence of side effects. Subjects were to receive eight weeks of double-blind treatment.

### **Diagnosis and Criteria for Inclusion**

Outpatients  $\geq 18$  years of age, females of child bearing potential using contraception (amendment 2) meeting RDC criteria for major, minor, or intermittent depression with a minimum score of  $\geq 10$  on the first 21 items of the 25 item Hamilton Depression Scale (HAMD 25) (amended from  $\geq 18$  items on the HAMD 25 in Amendment No. 1) at baseline who maintained mood reactivity while depressed and had one or more of the following: increased appetite or weight gain while depressed, oversleeping, or spending more time in bed while depressed, severe fatigue, creating a sensation of leaden paralysis, or extreme heaviness of arms or legs when depressed, or hypersensitivity to rejection as a trait throughout adulthood. Subjects received eight weeks of double-blind treatment.

### **Inclusion Criteria**

The following criteria allowed subjects to enter the baseline phase:

- Male or female outpatients  $\geq 18$  years of age. Females of child-bearing potential must not have been pregnant and must have been practicing an acceptable form of birth control to be included in the study.
- Subjects who had a RDC diagnosis of major, minor, or intermittent depression with a severity score of at least 10 on the HAMD 21 scale (amended from at least 18 on the HAMD 25 in Amendment No. 1).
- Subjects must have maintained mood reactivity while depressed (the ability to be at least temporarily cheered by pleasant events).
- Subjects who showed one or more of the following:
  - increased appetite or weight gain while depressed

- oversleeping or spending more time in bed while depressed
- severe fatigue, creating a sensation of leaden paralysis, or extreme heaviness of arms or legs while depressed.
- hypersensitivity to rejection as a trait throughout adulthood.
- Subjects who gave written informed consent prior to study participation.

## **Criteria for Evaluation**

Efficacy Evaluations: The following were the efficacy outcome measures used: HAMD 21, HAMD 25, HAMD 17, Clinical Global Impression (CGI), Montgomery Åsberg Depression Rating Scale (MADRS), Symptom Checklist 87-item Version (SCL-87), Comprehensive Psychopathologic Rating Scale (CPRS) subscale, and the Hamilton Anxiety Scale (HAM-A).

The primary efficacy variables were the HAMD 17 change from baseline score and the proportion of responders based on the CGI Global Improvement score; the other efficacy variables were secondary.

The HAMD 21, HAMD 17, HAMD 25 and CGI were completed at baseline and Weeks 1, 2, 3, 4, 5, 6, 7, and 8 (or early termination). The SCL-87 and HAM-A were completed at baseline and at Weeks 2, 4, and 8 (or early termination). The MADRS and CPRS were completed at baseline and Week 8 (or early termination) (amended from baseline and at Weeks 2 and 4 in Amendment No. 1).

## **Statistical Methods**

Demographic and other subject characterization, duration of exposure to study medication, medication compliance, and dosing information were summarized by treatment group.

The primary efficacy variables were the HAMD 17 change from baseline score and the proportion of responders based on the CGI Global Improvement score, with the endpoint as the primary time point. Other efficacy variables included HAMD 25 total score, HAMD 21 total score, HAMD factors, proportion of responders based on HAMD 17 total score, MADRS, SCL-87, HAM-A

and CPRS. For all analyses of continuous variables, an ANOVA was carried out with treatment as factor. For categorical variables, analyses were performed using the CMH test. All statistical tests were two-sided and considered statistically significant if the overall p-value  $\leq 0.05$ .

#### HAMD 17

The change from baseline in HAMD 17 total score was considered to be a primary efficacy parameter. Post-baseline HAMD 17 total scores were not computed if more than two items were missing. If one or two items were missing, or if the assessment was obtained at baseline, then the HAMD 17 total score was computed in the following manner:

$$\frac{\text{Total for non-missing items} \times \text{Total number of items (17)}}{\text{Number of non-missing items}} .$$

#### CGI Responders

Responders based on the Clinical Global Impression - Global Improvement item was the second primary efficacy parameter. A responder based on the CGI - Improvement item is defined as a subject who has a CGI Global Improvement score of 1 or 2 ("very much improved" or "much improved", respectively). A score of 0 ("Not Assessed") on the CGI Improvement item was interpreted as a missing assessment for purposes of statistical analysis.

## RESULTS

### Investigator

| Site | Investigator                                                                                                   |
|------|----------------------------------------------------------------------------------------------------------------|
| 2518 | Frederick Quitkin, M.D.<br>New York State Psychiatric<br>Institute<br>722 West 168th St.<br>New York, NY 10032 |

### Number of Subjects (total and for each treatment)

Sixty subjects were randomized at a single study center. Subjects per treatment group included in each data set were:

| Data Set                           | Org 33062<br>10-90<br>mg/day | Placebo | Total |
|------------------------------------|------------------------------|---------|-------|
| Randomized                         | 30                           | 30      | 60    |
| All-Subjects-Treated<br>Population | 30                           | 30      | 60    |
| Intent-to-Treat<br>Population      | 30                           | 30      | 60    |
| Evaluable<br>Population            | 29                           | 29      | 58    |

## Demographic Data

Table 7 presents the summary of baseline demographics and other baseline characteristics by treatment group for the All-Subjects-Treated population

**Table 7 Demographic and Other Baseline Characteristics by Treatment Group (All-Subjects-Treated Population)**

| Parameter                      | Org 33062<br>10-90<br>mg/day<br>(N=30) | Placebo<br>(N=30) | Total<br>(N=60) |
|--------------------------------|----------------------------------------|-------------------|-----------------|
| Gender: Female                 | 10 (33%)                               | 11 (37%)          | 21 (35%)        |
| Male                           | 20 (67%)                               | 19 (63%)          | 39 (65%)        |
| Race: Black                    | 1 (3%)                                 | 1 (3%)            | 2 (3%)          |
| Oriental                       | 0 (0%)                                 | 0 (0%)            | 0 (0%)          |
| White                          | 29 (97%)                               | 28 (93%)          | 57 (95%)        |
| Other                          | 0 (0%)                                 | 1 (3%)            | 1 (2%)          |
| Age (years): Mean ± SD         | 41.4 " 10.0                            | 37.4 " 8.8        | 39.4 " 9.6      |
| Weight (Ibs): Mean ± SD        | 162 " 28.8                             | 168 " 40.1        | 165 " 34.8      |
| Major Depressive Disorder:     |                                        |                   |                 |
| No                             | 5 (17%)                                | 9 (30%)           | 14 (23%)        |
| Probable                       | 2 (7%)                                 | 3 (10%)           | 5 (8%)          |
|                                | 23 (77%)                               | 18 (60%)          | 41 (68%)        |
| Onset of Symptoms:             |                                        |                   |                 |
| 4 weeks to < 3 months          | 3 (10%)                                | 0 (0%)            | 3 (5%)          |
| 3 months to < 6 months         | 6 (20%)                                | 2 (7%)            | 8 (13%)         |
| 6 months to < 1 year           | 2 (7%)                                 | 1 (3%)            | 3 (5%)          |
| 1 year to < 2 years            | 2 (7%)                                 | 2 (7%)            | 4 (7%)          |
| 2 years to < 3 years           | 1 (3%)                                 | 2 (7%)            | 3 (5%)          |
| ≥ 3 years                      | 16 (53%)                               | 23 (77%)          | 39 (65%)        |
| Prior Psychotropic Medication: |                                        |                   |                 |
| No                             | 20 (67%)                               | 19 (63%)          | 39 (65%)        |
| Yes                            | 8 (27%)                                | 10 (33%)          | 18 (30%)        |
| No. Missing                    | 2 (7%)                                 | 1 (3%)            | 3 (5%)          |

There were no important demographic and other baseline characteristic differences between the treatment groups in the All-Subjects-Treated population. Of the 60 subjects, the majority were white (95%) males (65%). The subjects ranged in age from 25 to 64 years (mean age 39.4 " 9.6 years). A similar percentage of subjects in both treatment groups had a history of prior psychotropic therapy.

Seventy-six percent of the patients had a probable or definite diagnosis of Major Depressive Disorder by RDC criteria.

## DOSING

The average daily dose for each subject was calculated from the total number of capsules taken by that subject at each dosing interval. Summary statistics were calculated for the maximum modal dose (the most frequently taken dose) for the Org 33062 group. The maximal modal dose by Org 33062 10-90 mg treatment group in the ITT population is presented in Table 11.

**Table 11 Maximal Modal Dose for the Org 33062 10-90 mg/day Treatment Group (Intent-to-Treat Population)**

| Maximum Modal Dose | Org 33062 10-90 mg/day<br>(N=30) |
|--------------------|----------------------------------|
| Mean $\pm$ SD      | 47.7 $\pm$ 29.4                  |
| Median             | 35.0                             |
| Range              | 10.0-110                         |

The mean maximum modal dose in the Org 33062 10-90 mg group was 47.7 mg/day. No subject received a modal dose equivalent to the maximum allowable dose (120 mg/day); the highest modal dose was 110 mg/day.

## DISPOSITION

The disposition of subjects by treatment group is presented in Table 4.

**Table 4 Disposition of Subjects by Treatment Group (All-Subjects-Treated)**

| Treatment Group                      | Org 33062<br>10-90 mg/day | Placebo    | Total      |
|--------------------------------------|---------------------------|------------|------------|
| Randomized                           | 30                        | 30         | 60         |
| All-Subjects-Treated<br>Population   | 30 (100%)                 | 30 (100%)  | 60 (100%)  |
| Intent-to-Treat<br>Population        | 30 (100%)                 | 30 (100%)  | 60 (100%)  |
| Evaluable<br>Population <sup>a</sup> | 29 (96.7%)                | 29 (96.7%) | 58 (96.7%) |
| Discontinued<br>Treatment by:        |                           |            |            |
| Week 1                               | 1 (3.3%)                  | 0 (0.0%)   | 1 (1.7%)   |
| Week 2                               | 5 (16.7%)                 | 1 (3.3%)   | 6 (10.0%)  |
| Week 3                               | 2 (6.7%)                  | 1 (3.3%)   | 3 (5.0%)   |
| Week 4                               | 0 (0.0%)                  | 3 (10.0%)  | 3 (5.0%)   |
| Week 5                               | 1 (3.3%)                  | 0 (0.0%)   | 1 (1.7%)   |
| Week 6                               | 1 (3.3%)                  | 0 (0.0%)   | 1 (1.7%)   |
| Week 7                               | 0 (0.0%)                  | 3 (10.0%)  | 3 (5.0%)   |
| Week 8                               | 3 (10.0%)                 | 3 (10.0%)  | 6 (10.0%)  |
| Total<br>Discontinued <sup>b</sup>   | 13 (43.3%)                | 11 (36.7%) | 24 (40.0%) |
| Completed Study                      | 17 (56.7%)                | 19 (63.3%) | 36 (60.0%) |

<sup>a</sup> Subjects from the ITT population who had a minimum of two weeks of documented exposure to study medication.

<sup>b</sup> One placebo subject ( (b) (6) ) discontinued the study after > 59 days of treatment and is included in the total discontinued group and in discontinuations at week 8.

A total of 60 subjects were randomized in the study: 30 subjects to Org 33062 10-90 mg and 30 subjects to placebo. All subjects randomized were included in the All-Subjects-Treated population and ITT population. A total of 36 subjects completed the study: 17 (56.7%) Org 33062 10-90 mg and 19 (63.3%) placebo subjects. One subject ( (b) (6) ) in the placebo group discontinued after being on study medication for greater than 59 days, but was included in the total discontinued calculation and the discontinued treatment by Week 8 calculation.

## DISCONTINUATIONS

The number and percentage of subjects in the All-Subjects-Treated population who discontinued from the

study are presented by treatment group and reason for discontinuation in Table 6.

**Table 6 Number (%) of Subjects who Discontinued from the Study by Treatment Group and Reason for Discontinuation (All-Subjects-Treated Population)**

| Reason for Discontinuation | Org 33062<br>10-90 mg/day<br>(N=30) | Placebo<br>(N=30) | Total<br>(N=60)   |
|----------------------------|-------------------------------------|-------------------|-------------------|
| Adverse Event              | 8 (26.7%)                           | 4 (13.3%)         | 12 (20.0%)        |
| Death                      | 0 (0.0%)                            | 0 (0.0%)          | 0 (0.0%)          |
| Lack of Efficacy           | 1 (3.3%)                            | 6 (20.0%)         | 7 (11.7%)         |
| Withdrew Consent           | 2 (6.7%)                            | 0 (0.0%)          | 2 (3.3%)          |
| Randomized in Error        | 1 (3.3%)                            | 0 (0.0%)          | 1 (1.7%)          |
| Lost to Follow-up          | 1 (3.3%)                            | 1 (3.3%)          | 2 (3.3%)          |
| <b>Total Discontinued</b>  | <b>13 (43.3%)</b>                   | <b>11 (36.7%)</b> | <b>24 (40.0%)</b> |

A total of 24 (40.0%) subjects discontinued the study, including 13 (43.3%) Org 33062 10-90 mg and 11 (36.7%) placebo subjects. The most frequent reason for subjects discontinuing treatment was AEs (eight subjects or 26.7%) in the Org 33062 10-90 mg and lack of efficacy (six subjects or 20.0%) in the placebo subjects. More Org 33062 10-90 mg subjects (26.7%) than placebo subjects (13.3%) discontinued the study because of an AE. On the other hand, more placebo treated subjects (20.0%) discontinued due to lack of efficacy than Org 33062 treated subjects (3.3%).

## CONCOMITANT MEDICATIONS

A summary of concomitant medications taken by at least 10% of subjects in either treatment group is presented by therapeutic classification and treatment group in the All-Subjects-Treated population in Table 8.

**Table 8 Concomitant Medications Taken by at Least 10% of Subjects in Any Treatment Group During the Study by Therapeutic Classification and Treatment Group (All-Subjects-Treated Population)**

| Therapeutic Classification<br>Medication Category | Org 33062<br>10-90 mg/day<br>(N=30)<br>N (%) | Placebo<br>(N=30)<br>N (%) |
|---------------------------------------------------|----------------------------------------------|----------------------------|
| Any Concomitant Medication                        | 30 (100%)                                    | 30 (100%)                  |
| Anti-Infective Agents                             | 3 (10.0%)                                    | 5 (16.7%)                  |
| Antibiotics                                       | 2 (6.7%)                                     | 4 (13.3%)                  |
| Central Nervous System Agents                     | 14 (46.7%)                                   | 13 (43.3%)                 |
| Analgesics and Antipyretics                       | 14 (46.7%)                                   | 13 (43.3%)                 |
| Nonsteroidal                                      | 10 (33.3%)                                   | 11 (36.7%)                 |
| Anti-Inflammatory Agents                          | 4 (13.3%)                                    | 5 (16.7%)                  |
| Other Analgesics and<br>Antipyretics              |                                              |                            |
| Respiratory Drugs                                 | 3 (10.0%)                                    | 9 (30.0%)                  |
| Antihistamines                                    | 0 (0.0%)                                     | 4 (13.3%)                  |
| Cough/Cold Combination<br>Products                | 2 (6.7%)                                     | 5 (16.7%)                  |
| Gastrointestinal Drugs                            | 3 (10.0%)                                    | 4 (13.3%)                  |
| Antacids and Adsorbents                           | 3 (10.0%)                                    | 1 (3.3%)                   |

Overall, 100% Org 33062 10-90 mg subjects and 100% placebo subjects took one or more concomitant medications during the study. The most common concomitant medications were central nervous system agents (46.7% Org 33062 10-90 mg and 43.3% placebo subjects). Within this category, analgesics and antipyretics (46.7% Org 33062 10-90 mg and 43.3% placebo subjects) were most frequently taken by subjects in both treatment groups.

The only concomitant medications by therapeutic classification taken by at least 5% more Org 33062 10-90 mg subjects than placebo subjects were electrolytic, caloric and water balance agents (6.7% Org 33062 10-90 mg and no placebo subjects). Concomitant medications taken by at least 5% more placebo subjects than Org 33062 10-90 mg subjects included: anti-infective agents (10.0% Org 33062 10-90 mg and 16.7% placebo), skin and mucous membrane agents (no Org 33062 10-90 mg and 6.7% placebo), vitamin and minerals (no Org 33062 10-90 mg and 6.7% placebo), and respiratory drugs (10.0% Org 33062 10-90 mg and 30.0% placebo).

## **EXTENT OF EXPOSURE**

A summary of the duration of exposure to study drug by treatment group in the ITT population is presented in Table 9.

**Table 9 Duration of Exposure to Study Medication by Treatment Group (Intent-to-Treat Population)**

| Duration (Days) | Org 33062 10-90 mg/day (N=30) | Placebo (N=30) |
|-----------------|-------------------------------|----------------|
| Mean ± SD       | 45.3 ± 19.6                   | 52.0 ± 13.7    |
| Median          | 56.0                          | 56.5           |
| Range           | 1-68                          | 12-67          |

The mean (days) duration of exposure to study medication was 45.3 days for the Org 33062 10-90 mg and 52.0 days for the placebo group. The mean number of days that placebo subjects received study medication was slightly more than the Org 33062 10-90 mg subjects.

## **Efficacy Evaluation**

Primary parameters: In the ITT population (LOCF analysis), there were statistically significant differences between the Org 33062 10-90 mg/day group and the placebo group at Week 2 (p=0.036), Week 5 (p=0.004), Week 7 (p=0.038), and Week 8/endpoint (p=0.009) for the primary efficacy parameter HAMD 17. For the CGI: Global Improvement Responders, statistically significant differences between the Org 33062 10-90 mg/day group and the placebo group were present at Week 5 (p=0.010) and at Week 8/endpoint (p=0.009).

There was a statistically significant difference for the HAMD 17 total score between the Org 33062 10-90 mg/day and placebo groups in the MDD subset (ITT/LOCF analysis) at Week 2 (p=0.005), Week 3 (p=.011), Week 4 (p=.005), Week 5 (p=0.001), Week 7 (p=0.027), and Week 8/endpoint (p=0.007) providing evidence of the antidepressant efficacy of Org 33062 in Major Depressive Disorder with atypical features.

Secondary parameters: There were statistically significant differences between the Org 33062 10-90 mg/day group and the placebo group at endpoint for the secondary efficacy parameters, HAMD 25 (p=0.002), the HAMD Item 1 (p=0.007), the HAMD Responders (p=0.003), and the MADRS (p=0.026), in the ITT population (LOCF analysis).

### HAMD 17: Mean Change from Baseline

The HAMD 17 total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) are presented in Table 12.

**Table 12 HAMD 17: Mean Change from Baseline Score by Week and Treatment Group (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD 17 Score: LOCF |        |        |        |         |        |        |                              |
|------------------------|-------------------|-------------------------------------------------------|--------|--------|--------|---------|--------|--------|------------------------------|
|                        |                   | Week 1                                                | Week 2 | Week 3 | Week 4 | Week 5  | Week 6 | Week 7 | Week 8/Endpoint <sup>a</sup> |
| Org 33062 10-90 mg/day | 30 (13.8)         | -2.2                                                  | -4.7 * | -4.3   | -4.8   | -6.5 ** | -5.1   | -6.2 * | -6.7**                       |
| Placebo                | 30 (13.7)         | -1.3                                                  | -2.1   | -2.2   | -2.8   | -2.7    | -3.5   | -3.2   | -2.7                         |

<sup>a</sup> Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendices F 7.1.1-1 and 7.1.1-3.

\* p-value #0.05 vs. placebo.

\*\* p-value ≤0.01 vs. placebo

These results are consistent with the other analyses, including the OC analysis in the ITT population, and the LOCF and OC analyses in the Evaluable population for the MDD subset.

### CGI: Global Improvement Responders

The number and percentage of subjects "much improved" or "very much improved" for the CGI: Global Improvement at each assessment week by treatment group in the ITT population (LOCF analysis) are presented in Table 13.

**Table 93 CGI: Global Improvement Responders: Number (%) of Subjects "Much Improved" or "Very Much Improved" by Week and Treatment Group (Intent-to-Treat Population)**

| Treatment Group        | N  | N (%) of Subjects "Much Improved" or "Very Much Improved": LOCF |            |             |             |                   |             |             |                              |
|------------------------|----|-----------------------------------------------------------------|------------|-------------|-------------|-------------------|-------------|-------------|------------------------------|
|                        |    | Week 1                                                          | Week 2     | Week 3      | Week 4      | Week 5            | Week 6      | Week 7      | Week 8/Endpoint <sup>a</sup> |
| Org 33062 10-90 mg/day | 30 | 3<br>(12%)                                                      | 8<br>(27%) | 11<br>(37%) | 14<br>(47%) | 18<br>(60%)<br>** | 14<br>(47%) | 16<br>(53%) | 17 (57%)**                   |
| Placebo                | 30 | 2<br>(9%)                                                       | 7<br>(24%) | 7<br>(23%)  | 8<br>(27%)  | 8<br>(27%)        | 11<br>(37%) | 9<br>(30%)  | 7 (23%)                      |

<sup>a</sup>Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendix F 7.1.2-1.

\*p-value #0.05 vs. placebo.

\*\*p-value ≤0.01 vs. Placebo.

There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 10-90 mg/day and placebo groups at Week 5 (p=0.010), Week 8/endpoint (p=0.009). These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 10-90 mg/day and placebo groups in the MDD subset (ITT/LOCF analysis) at Week 3 (p=.012), Week 4 (p=.006), Week 5 (p=.001), Week 7 (p=.029), Week 8/endpoint (p=.005). These results are consistent with the other analyses, including the OC analysis in the ITT population, and the LOCF and OC analyses in the Evaluable population for the MDD subset.

## SECONDARY EFFICACY PARAMETERS

The secondary efficacy parameters included the mean change from baseline to endpoint for the HAMD 25 total score, the mean change from baseline to endpoint for the HAMD Item 1 (Depressed Mood) score, the mean change from baseline to endpoint for the MADRS total score, and the percentage of HAMD 17 Responders.

### HAMD 25: Mean Change from Baseline

The HAMD 25 total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment

group in the ITT population (LOCF analysis) are presented in Table 14.

**Table 104 HAMD 25: Mean Change from Baseline Score by Week and Treatment Group (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD 25 Total Score: LOCF |        |        |        |        |        |        |                              |
|------------------------|-------------------|-------------------------------------------------------------|--------|--------|--------|--------|--------|--------|------------------------------|
|                        |                   | Week 1                                                      | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8/Endpoint <sup>a</sup> |
| Org 33062 10-90 mg/day | 30 (18.2)         | -2.8                                                        | -6.9** | -6.6*  | -7.5*  | -9.5** | -8.3*  | -9.4** | -9.8**                       |
| Placebo                | 30 (17.4)         | -1.8                                                        | -2.3   | -2.1   | -2.7   | -2.6   | -3.9   | -3.6   | -3.0                         |

<sup>a</sup> Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendices F 7.2.1-25 and 7.2.1-27.

\* p-value # 0.05 vs. placebo.

\*\* p-value ≤0.01 vs. placebo.

There was a statistically significant difference for the HAMD 25 total score between the Org 33062 10-90 mg/day and placebo groups in the ITT population (LOCF analysis) at Week 2 (p=0.008), Week 3 (p=0.018), Week 4 (p=0.019), Week 5 (p#0.001), Week 6 (p=0.041), Week 7 (p=0.005), and Week 8/endpoint (p=0.002 ).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

**HAMD Item 1 (Depressed Mood): Mean Change from Baseline**

The HAMD Item 1 (Depressed Mood) total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) are presented in Table 15.

**Table 15 HAMD Item 1 (Depressed Mood): Mean Change from Baseline Score by Week and Treatment Group (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD Item 1 Score: LOCF |        |        |        |        |        |        |                              |
|------------------------|-------------------|-----------------------------------------------------------|--------|--------|--------|--------|--------|--------|------------------------------|
|                        |                   | Week 1                                                    | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | Week 8/Endpoint <sup>a</sup> |
| Org 33062 10-90 mg/day | 30 (2.1)          | -0.5                                                      | -0.8   | -1.0   | -1.0   | -1.2*  | -1.0   | -1.2*  | -1.2**                       |
| Placebo                | 30 (2.1)          | -0.3                                                      | -0.5   | -0.6   | -0.6   | -0.6   | -0.6   | -0.6   | -0.5                         |

<sup>a</sup> Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendices F 7.2.2-1 and 7.2.2-3.

\* p-value #0.05 vs. placebo.

\*\* p-value ≤0.01 vs. placebo.

There were statistically significant differences for the HAMD Item 1 score between the Org 33062 10-90 mg/day and placebo groups in the ITT population (LOCF analysis) at Week 5 (p=0.044), Week 7 (p=0.038), and Week 8/endpoint (p=0.007).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

**HAMD 17 Responders**

The number and percentage of subjects with at least a 50% reduction in HAMD 17 scores from baseline to endpoint by treatment group in the ITT population (LOCF analysis) are presented in Table 16.

**Table 16 HAMD 17 Responders: Subjects Displaying \$50% Reduction in HAMD 17 Score at Endpoint by Treatment Group (LOCF) (Intent-to-Treat Population)**

| Treatment Group                  | N (%)<br>Responders | p-Value vs.<br>Placebo <sup>a</sup> |
|----------------------------------|---------------------|-------------------------------------|
| Org 33062 10-90<br>mg/day (N=30) | 16 (53%)            | 0.003                               |
| Placebo (N=30)                   | 5 (17%)             | - -                                 |

<sup>a</sup> Analyzed using the CMH test.

Note: Data for this table were derived from Appendix F 7.2.3-1.

There was a statistically significant difference for the HAMD 17 Responders between the Org 33062 10-90 mg/day and the placebo group in the ITT (LOCF analysis) population at the following visits: Week 3 (p=0.005), Week 4 (p=0.047), Week 5 (p<0.001), Week 6 (p=0.025), Week 7 (p=0.030), and at Week 8/endpoint (p=0.003).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

**MADRS: Mean Change from Baseline**

The MADRS total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) are presented in Table 17.

**Table 117 MADRS: Mean Change from Baseline Score by Week and Treatment Group (Intent-to-Treat Population)**

| Treatment Group           | Baseline<br>N (Mean) | Mean Change from Baseline for<br>the MADRS Total Score: LOCF |                                  |
|---------------------------|----------------------|--------------------------------------------------------------|----------------------------------|
|                           |                      | Week 4                                                       | Week 8/<br>Endpoint <sup>a</sup> |
| Org 33062<br>10-90 mg/day | 30 (22.1)            | -11.7                                                        | -12.4*                           |
| Placebo                   | 30 (20.3)            | 4.0                                                          | -3.8                             |

<sup>a</sup> Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendices F 7.2.4-1 and 7.2.4-3.

\* p-value #0.05 vs. placebo.

There were statistically significant differences for the MADRS total score between the Org 33062 10-90 mg/day group and the

placebo group in the ITT (LOCF analysis) population at Week 8/endpoint (p=0.026).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

**SUMMARY OF EFFICACY**

Table 18 summarizes selected primary and secondary efficacy parameters at endpoint by treatment group in the ITT population (LOCF analysis).

**Table 18 Summary of Endpoint Results for Selected Efficacy Parameters by Treatment Group (Intent-to-Treat Population)**

| Parameters                                                 | Mean Change from Baseline to Endpoint and Percent Responders |         |
|------------------------------------------------------------|--------------------------------------------------------------|---------|
|                                                            | Org 33062 10-90 mg/day                                       | Placebo |
| Primary Efficacy Parameters in the ITT Population (LOCF)   |                                                              |         |
| HAMD 17                                                    | -6.7**                                                       | -2.7    |
| CGI: Global Improvement Responders                         | 57%**                                                        | 23%     |
| Secondary Efficacy Parameters in the ITT Population (LOCF) |                                                              |         |
| HAMD 25                                                    | -9.8**                                                       | -3.0    |
| HAMD Item 1                                                | -1.2**                                                       | -0.5    |
| HAMD 17 Responders                                         | 53%**                                                        | 17%     |
| MADRS                                                      | -12.4*                                                       | -3.8    |

Note: Data for this table were derived from Appendices F 7.1 and 7.2.

\* p-value #0.05 vs placebo.

\*\* p-value ≤0.01 vs. placebo.

There were statistically significant differences between the Org 33062 10-90 mg/day and placebo groups for the primary efficacy parameters, HAMD 17 (p=0.009) and CGI: Global Improvement Responders (p=0.009) in the ITT population (LOCF analysis) at endpoint.

There were statistically significant differences between the Org 33062 10-90 mg/day and placebo groups for the secondary efficacy parameters, HAMD 25 (p=0.002), HAMD Item 1 (p=0.007), HAMD 17 Responders (p=0.003), and MADRS (p=0.026), in the ITT population (LOCF dataset) at endpoint. These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

Sixty-five percent of subjects met criteria for Major Depressive Disorder. Primary efficacy results in this subset were consistent with those found in the full study sample, indicating that the efficacy results are valid for subjects with MDD.

See appendix for additional efficacy tables.

This study is positive as per the sponsor's analysis above and is confirmed by the FDA statistical analysis (see stat review.)

## **Study 03A7A-002**

### **Multicenter Comparison of Org 33062 with Placebo in Major Depressive Disorder (Relapse Study)**

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#### **Methodology**

The open-label phase of the study was a 6-week, multicenter, open-dose titration. Doses of all enrolled subjects were to be individually titrated with Org 33062 starting at 10 mg twice daily and increasing to 90 mg per day (twice daily or three times daily) depending on therapeutic response and tolerance at the discretion of the investigator. Amendment No. 3 started subjects using the 5 mg BID capsule for the first week and switched to 10 mg during the second week.

The double-blind phase of the study was a 4-week (amended to six weeks after the start of the study Amendment 3), double-blind, multicenter, placebo substitution, randomized withdrawal. All responders who completed the open-label phase were to be randomized to receive Org 33062 or placebo. Subjects were to continue taking the same number of capsules daily they received at the time of randomization. The placebo substitution design of the double-blind phase allowed for comparison of the relapse rates between subjects

who continued on Org 33062 and subjects who were switched to placebo after having responded to Org 33062 in the open-label phase.

### Number of Subjects (total each treatment)

A total of 134 subjects were enrolled in the open-label phase and 70 subjects were randomized in the double-blind phase. Subjects per treatment group included in each data set for the open-label phase and the double-blind phase were:

| Data Set                         | Open-Label Phase         | Double-Blind Phase       |         |       |
|----------------------------------|--------------------------|--------------------------|---------|-------|
|                                  | Org 33062<br>20 to 90 mg | Org 33062<br>20 to 90 mg | Placebo | Total |
| All-Subjects-Enrolled population | 134                      | - -                      | - -     | - -   |
| All-Subjects-Treated population  | - -                      | 36                       | 34      | 70    |
| Intent-to-Treat population       | - -                      | 36                       | 34      | 70    |
| Evaluable Population             | - -                      | 33                       | 25      | 58    |

### Diagnosis and Criteria for Inclusion

Open-Label Phase: Subjects  $\geq 18$  (amended from between 18 and 65 Amendment 1) with a diagnosis of major depressive disorder (MDD) according to Research Diagnostic Criteria (RDC), modified to require at least four weeks duration. Subjects with a baseline HAMD score  $\geq 22$  on the first 17 items, later amended to require a  $\geq 20$  on all 25 items of the HAMD (Amendment No. 4).

Double-Blind Phase: Completion of the open-label phase with a reduction on the HAMD 17 Total Score of  $\leq 12$  or by  $\geq 50\%$  and a Clinical Global Impression (CGI): Global Improvement Score of at least "moderately improved." (Amendment No. 1).

### Inclusion Criteria (Open-Label Phase)

The following criteria allowed subjects to enter the baseline phase:

- Subjects between the ages of 18 and 65, inclusive. (Amendment No. 1, approved before the start of the study, changed the age requirements to 18 years of age and above.)
- Subjects who were male or female. Female subjects were not of childbearing potential (i.e., postmenopausal, as defined as a history of no menses for at least one year) or surgically sterilized.
- Subjects with a MDD according to RDC, modified to require at least four weeks duration.
- Subjects who were outpatients.

Subjects with a required baseline HAMD score  $\geq 20$  (amended from  $\geq 22$ , Amendment 1) on the first 17 items of the HAMD 25. Amendment No. 4, approved after the start of the study, changed the minimum score to 20 on all 25 items of the HAMD.

## **Duration of Treatment**

Subjects received six weeks of Org 33062 during the open-label phase. Subjects responding received an additional four weeks (Amendment No. 3 extended the double-blind phase to six weeks after the start of the study) of treatment (with either Org 33062 or placebo) during the double-blind phase.

## **Dosing Regimen**

During the 6-week, open-label phase, subjects were to take one capsule BID with meals initially. The dosage was to be increased gradually (not more than one capsule every other day) over the first two to three weeks depending on response and tolerance, to a total of not more than 90 mg per day. The investigator could divide the total daily dose into either a BID or TID schedule. (Study medication was to be taken with food, if tolerance or compliance was enhanced by doing so.) For example, tolerance could be increased in some subjects by taking three doses per day with meals and a fourth at bedtime. Amendment No. 3, approved after the start of the study, changed the dosing regimen to 5 mg for the first week of open treatment, and subjects were to take one capsule (5mg) BID with meals initially and titrated gradually (not more than one capsule every other day). The subjects were to be crossed over to the 10 mg capsule by the second week and continued titration until an optimal dosage was reached.

In the double-blind phase, responding subjects were to be randomized to receive Org 33062 or placebo at the same dose (number of capsules per day) they were taking at the end of the open-label phase. In the open-label phase, all subjects received Org 33062 for six weeks. Responders who were randomized to Org 33062 received active drug for an additional four weeks for a total of 10 weeks (unless relapse occurred before this time). Amendment No. 3 extended the double-blind phase to six weeks for a total of 12 weeks.

## **Criteria for Evaluation**

Efficacy Evaluations: efficacy outcome measures were HAMD, Hamilton Anxiety Scale (HAM-A), CGI, and Symptom Checklist 90-item (SCL-90). For the open-label phase, the HAMD, HAM-A, and CGI were to be performed at baseline and Weeks 1, 2, 3, 4, 5, and 6, or early termination. The SCL-90 was to be performed at baseline and Weeks 2 and 4 or early termination. For the double-blind phase, the HAMD, HAM-A, and CGI were to be performed at Weeks 7, 8, 9, 10, 11, and 12, or early termination. The SCL-90 was to be performed Weeks at 6, 8, 10, 11, and 12, or early termination.

## **Statistical Methods**

Demographic and other subject characterization, duration of exposure to study medication, medication compliance, and dosing information were summarized by treatment group.

For the double-blind phase, the primary efficacy variables were the time to relapse (using 6 definitions of relapse, based either on the HAMD 17 total score, CGI Improvement score, or discontinuation), the HAMD 17 change from baseline score and the proportion of responders based on the CGI Global Improvement score, with the endpoint as the primary time point. Other efficacy variables included HAMD 25 total score, HAMD factors, proportion of responders based on HAMD 17 total score, SCL-90, and HAM-A. For the analyses of relapse, the log-rank test was performed with fixed right censoring. For all other analyses of continuous variables, an ANOVA was carried out with treatment as factor. For categorical variables, analyses were performed using the CMH test. All statistical tests were two-sided and considered statistically significant if the overall p-value  $\leq 0.05$ .

## Relapse

Survival or life-table analyses, which take into account the time (visit) to an event, were used to evaluate the first time to relapse during the double-blind phase. These indices were considered the primary efficacy parameter in this relapse study. There were six definitions of relapse used in the analyses:

- A. Return to  $\geq 75\%$  of the (pre-treatment) baseline HAMD 17 total score.
- B. CGI Improvement score of "No Change" or "Worse than (pre-treatment) Baseline" ( $\geq 4$ ).
- C. Return to  $\geq 75\%$  of the (pre-treatment) baseline HAMD 17 total score, or discontinuation.
- D. CGI Improvement score of "No Change" or "Worse than (pre-treatment) Baseline" ( $\geq 4$ ), or discontinuation.
- E. Return to  $\geq 75\%$  of the (pre-treatment) baseline HAMD 17 total score, or discontinuation due to lack of efficacy.
- F. CGI-Improvement score of "No Change" or "Worse than (pre-treatment) Baseline" ( $\geq 4$ ), or discontinuation due to lack of efficacy.

## HAMD 17

The change from baseline in HAMD 17 total score was analyzed as a secondary parameter. Post-baseline HAMD 17 total scores were not computed if more than two items were missing. If one or two items were missing, or if the assessment was obtained at baseline, then the HAMD 17 total score was computed in the following manner:

$$\frac{\text{Total for non-missing items} \times \text{Total number of items (17)}}{\text{Number of non-missing items}}$$

## Investigators

| Site | Investigator                            |
|------|-----------------------------------------|
| 2416 | Jay Amsterdam, M.D.<br>Philadelphia, PA |
| 2417 | John J. Schwab, M.D.                    |

|      |                                                                 |
|------|-----------------------------------------------------------------|
|      | Elizabeth Lin, Ph.D.<br>Louisville, KY                          |
| 2418 | John S. Carmen, M.D.<br>Smyrna, GA                              |
| 2419 | Bradley Evans, M.D.<br>Helen Pettinati, Ph.D.<br>Belle Mead, NJ |
| 2424 | Jeffrey Rausch, M.D.<br>La Jolla, CA                            |

## Demographic Data

A majority of subjects who participated in the open-label phase were male (57%) and Caucasian (97%) and ranged in age from 26 to 75 years (mean age 44.4 ± 11.3 years). Most subjects who participated in the double-blind phase were male (56%) and Caucasian (94%) and ranged in age from 26 to 67 (mean age 42.7 ± 9.5 years). The mean (days) duration of exposure to study drug in the open-label phase was 25.8 days and in the double-blind phase was 27.1 days in Org 33062 20-90 mg and 24.9 days in placebo subjects. The mean maximum modal dose in the double-blind phase was 41.4 mg/day of an allowable 90 mg/day in the Org 33062 20-90 mg group.

Table 8 (open-label phase) presents the summary of baseline demographics and other baseline characteristics in subjects participating in the open-label phase only (did not participate in the double-blind phase) and the total population for the open-label phase, and Table 9 (double-blind phase) presents the summary of baseline demographics and other baseline characteristics by treatment group in the double-blind phase in the Intent-to-Treat population.

**Table 8 Demographic and Other Baseline Characteristics in the Open-Label Phase**

| Parameter    | Org 33062<br>20-90 mg/day<br>Open-Label Only <sup>a</sup><br>(N=64) | Org 33062<br>20-90 mg/day<br>Open-Label Total <sup>b</sup><br>(N=134) |
|--------------|---------------------------------------------------------------------|-----------------------------------------------------------------------|
| Gender: Male | 38 (59%)                                                            | 77 (57%)                                                              |
| Female       | 26 (41%)                                                            | 57 (43%)                                                              |
| Race: Black  | 0 (0%)                                                              | 3 (2%)                                                                |
| Asian        | 0 (0%)                                                              | 1 (1%)                                                                |

|                             |             |             |
|-----------------------------|-------------|-------------|
| Caucasian                   | 64 (100%)   | 130 (97%)   |
| Other                       | 0 (0%)      | 0 (0%)      |
| Age (years): Mean ± SD      | 46.2 (12.7) | 44.4 (11.3) |
| Weight (kg): Mean ± SD      | 170 (33.0)  | 171 (35.4)  |
| Prior Psychotropic Therapy: |             |             |
| Yes                         | 51 (80%)    | 86 (64%)    |
| No                          | 1 (2%)      | 4 (3%)      |
| Missing                     | 12 (19%)    | 44 (33%)    |

<sup>a</sup>Only those subjects participating in the open-label phase and did not participate in the double-blind phase.

<sup>b</sup>All subjects participating in the open-label phase. This treatment group also includes subject (b) (6) who received placebo during the last 10 days of the participation in the study.

There were no important demographic and other baseline characteristic differences in the open-label only phase subjects and the total open-label phase subjects. Of the 134 subjects who participated in the open-label phase, 57% were male and 97% were Caucasian. The mean age of all subjects was 44.4 " 11.3 years. Approximately 64% (33% missing data) of all open-label subjects had a history of prior psychotropic therapy.

**Table 9 Demographic and Other Baseline Characteristics by Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Parameter                   | Org 33062<br>20-90 mg/day<br>(N=36) | Placebo<br>(N=34) | Total<br>(N=70) |
|-----------------------------|-------------------------------------|-------------------|-----------------|
| Gender: Male                | 19 (53%)                            | 20 (59%)          | 39 (56%)        |
| Female                      | 17 (47%)                            | 14 (41%)          | 31 (44%)        |
| Race: Black                 | 3 (8%)                              | 0 (0%)            | 3 (4%)          |
| Asian                       | 0 (0%)                              | 1 (3%)            | 1 (1%)          |
| Caucasian                   | 33 (92%)                            | 33 (97%)          | 66 (94%)        |
| Age (years):<br>Mean ± SD   | 42.7 (9.1)                          | 42.7 (10.1)       | 42.7 (9.5)      |
| Weight (kg):<br>Mean ± SD   | 169 (38.1)                          | 174 (37.6)        | 171 (37.6)      |
| Prior Psychotropic Therapy: |                                     |                   |                 |
| Yes                         | 18 (50%)                            | 17 (50%)          | 35 (50%)        |
| No                          | 3 (8%)                              | 0 (0%)            | 3 (4%)          |
| Missing                     | 15 (42%)                            | 17 (50%)          | 32 (46%)        |

Note: The Intent-to-Treat population is the same as the All-Subjects-Treated population. The Org 33062 group includes Subject (b) (6) who received placebo during the last 10 days of participation in the study.

There were no important demographic and other baseline characteristic differences between the treatment groups in the Intent-to-Treat population of the double-blind phase of the study. Of the 70 subjects enrolled, 39 (56%) were male and 66 (94%) were Caucasian. The subjects ranged in age from 26 to 67 years (mean age 42.7 " 9.5 years). Approximately 50% (46% data missing) of subject had prior psychotropic therapy.

### **Open-Label Phase**

The disposition of all subjects in the open-label phase are presented in Table 3. The table displays the number of subjects who discontinued by week and the number of subjects who completed the open-label phase

**Table 3 Disposition of All Subjects for the Open-Label Phase**

|                            |                              |
|----------------------------|------------------------------|
| Treatment Group            | Org 33062<br>20 to 90 mg/day |
| All-Subjects-Enrolled      | 134                          |
| Discontinued Treatment by: |                              |
| Week 1                     | 16 (25.0%)                   |
| Week 2                     | 8 (12.5%)                    |
| Week 3                     | 4 (6.3%)                     |
| Week 4                     | 7 (10.9%)                    |
| Week 5                     | 12 (18.8%)                   |
| Week 6                     | 14 (21.9%)                   |
| >45 Days                   | 3 (4.7%)                     |
| Total Discontinued         | 64 (47.8%)                   |
| Completed Open-Label phase | 70 (52.2%)                   |

Percentages for discontinuations at each week are for the subjects who participated in the open-label phase only.

A total of 134 subjects were enrolled. A total of 64 (47.8%) subjects discontinued and 70 (52.2%) subjects completed the open-label phase.

#### **Double-Blind Phase**

The disposition of all subjects by treatment group in the double-blind phase are presented in Table 4.

**Table 4 Disposition of All Subjects for the Double-Blind Phase by Treatment Group**

| Treatment Group                   | Org 33062<br>20 to 90<br>mg/day | Placebo    | Total      |
|-----------------------------------|---------------------------------|------------|------------|
| All-Subjects-Treated Population   | 36 (100%)                       | 34 (100%)  | 70 (100%)  |
| Intent-to-Treat Population        | 36 (100%)                       | 34 (100%)  | 70 (100%)  |
| Evaluable Population <sup>a</sup> | 33 (91.7%)                      | 25 (73.5%) | 58 (82.9%) |
| Discontinued Treatment by:        |                                 |            |            |
| Week 7                            | 6 (16.7%)                       | 3 (8.8%)   | 9 (12.9%)  |
| Week 8                            | 4 (11.1%)                       | 6 (17.7%)  | 10 (14.3%) |
| Week 9                            | 2 (5.6%)                        | 4 (11.8%)  | 6 (8.6%)   |
| Week 10                           | 1 (2.8%)                        | 2 (5.9%)   | 3 (4.3%)   |
| Week 11                           | 1 (2.8%)                        | 1 (2.9%)   | 2 (2.9%)   |
| Week 12                           | 1 (2.8%)                        | 0 (0.0%)   | 1 (1.4%)   |
| Total Discontinued                | 15 (41.7%)                      | 16 (47.1%) | 31 (44.3%) |
| Completed Double-Blind Phase      | 21 (58.3%)                      | 18 (52.9%) | 39 (55.7%) |

<sup>a</sup>Subjects from the ITT population who had a minimum of two weeks of documented exposure to study medication.

A total of 70 subjects were randomized in the double-blind phase: 36 subjects to Org 33062 20-90 mg and 34 subjects to placebo. All randomized subjects ingested at least one dose of study drug and are included in the All-Subject-Treated population, and all randomized subjects had at least one post-baseline efficacy evaluation and are included in the ITT population. A total of 39 (55.7%) randomized subjects completed the double-blind phase: 21 (58.3%) Org 33062 20-90 mg and 18 (52.9%) placebo subjects.

## **DISCONTINUATIONS**

The number and percentage of subjects who discontinued are presented by treatment group and reason for discontinuation in Table 6 for the All-Subjects-Enrolled population (open-label phase) in Table 7 for the All-Subjects-Treated population in (double-blind phase).

**Table 6 Number (%) of Subjects who Discontinued from the Open-Label Phase by Reason for Discontinuation (All-Subjects-Enrolled Population)**

| Reason for Discontinuation | Org 33062<br>20-90 mg/day<br>(N=134) |
|----------------------------|--------------------------------------|
| Adverse Event              | 36 (26.9%) <sup>b</sup>              |
| Lack of Efficacy           | 16 (11.9%)                           |
| Patient Withdrew Consent   | 6 (0.5%)                             |
| Other <sup>a</sup>         | 6 (0.5%)                             |
| Total                      | 64 (47.8%)                           |

<sup>a</sup> Reason includes subject unreliability, lost to follow-up, and other known cause.

<sup>b</sup> This number does not include Subjects (b) (6) who discontinued due to AE because their final dispositions were given as "Completed" and "Other Known Cause", respectively.

A total of 64 (47.8%) subjects in the All-Subjects-Enrolled population discontinued the open-label phase. The most frequent reasons for subject discontinuing treatment were AEs (26.9%) and lack of efficacy (11.9%). No deaths were reported in the open-label phase.

**Table 7 Number (%) of Subjects who Discontinued from the Double-Blind Phase by Treatment Group and Reason for Discontinuation (All-Subjects-Treated Population)**

| Reason for Discontinuation   | Org 33062<br>20-90 mg/day<br>(N=36) | Placebo<br>(N=34)     | Total<br>(N=70) |
|------------------------------|-------------------------------------|-----------------------|-----------------|
| Adverse Event                | 4 (11.1%)                           | 1 <sup>c</sup> (2.9%) | 5 (7.1%)        |
| Lack of Efficacy             | 9 (25.0%)                           | 10 (29.4%)            | 19 (27.1%)      |
| BMS Termination <sup>a</sup> | 0 (0.0%)                            | 2 (5.9%)              | 2 (2.9%)        |
| Other <sup>b</sup>           | 2 (5.6%)                            | 3 (8.8%)              | 5 (7.1%)        |
| Total                        | 15 (41.7%)                          | 16 (47.1%)            | 31 (44.3%)      |

<sup>a</sup> Subjects originally listed as Discontinued for "factors related to study design" as primary and "withdrew consent" as secondary. <sup>b</sup> Reason includes improvement, subject unreliability, lost to follow-up, and other known cause.

<sup>c</sup> Although subject (b) (6) withdrew after randomization to placebo, the AE leading to early termination began during the

open-label phase of the study and ended the day that placebo began. Therefore, in the safety section of this report (Section 8), this subject is counted as a withdrawal from Org 33062.

A total of 31 (44.3%) subjects in the All-Subjects-Treated population discontinued the double-blind phase, including 15 (41.7%) Org 33062 20-90 mg and 16 (47.1%) placebo subjects. The most frequent reason for subjects discontinuing treatment for both treatment groups was lack of efficacy: 9 (25.0%) in Org 33062 20-90 mg and 10 (29.4%) placebo subjects. No deaths were reported in the double-blind phase.

Overall, 47.8% of subjects in the open-label phase and 44.3% of subjects in the double-blind phase (41.7% Org 33062 20-90 mg and 47.1% placebo subjects) discontinued treatment. The most frequent reason for discontinuation during the open-label phase was AEs (26.9%), and during the double-blind phase was lack of efficacy (25.0%) Org 33062 20-90 mg subjects and (29.4%) placebo subjects.

## **CONCOMITANT MEDICATIONS**

A summary of concomitant medications taken by at least 10% of subjects in any treatment group during the study (open-label phase and double-blind phase) by therapeutic classification and treatment group in the All-Subjects-Treated population is presented in Table 10.

**Table 10 Concomitant Medications Taken by 10% of Subjects in Any Treatment Group During the Study by Therapeutic Classification by Treatment Group (All-Subjects-Treated Population)**

| Therapeutic Classification/<br>Medication Category | Org 33062<br>20-90 mg/day<br>(N=134) | Placebo<br>(N=34) |
|----------------------------------------------------|--------------------------------------|-------------------|
| Any Concomitant Medication                         | 106 (79.1%)                          | 7 (20.6%)         |
| Anti-infective Agents                              | 17 (12.7%)                           | 0 (0.0%)          |
| Antibiotics                                        | 15 (11.2%)                           | 0 (0.0%)          |
| Cardiovascular Drugs                               | 23 (17.2%)                           | 0 (0.0%)          |
| Diuretics                                          | 15 (11.2%)                           | 0 (0.0%)          |
| Central Nervous System Agents                      | 79 (59.0%)                           | 4 (11.8%)         |
| Analgesics and Antipyretics                        | 59 (44.0%)                           | 3 (8.8%)          |
| Nonsteroidal Anti-inflammatory Agents              | 51 (38.1%)                           | 3 (8.8%)          |
| Other Analgesics and Antipyretics                  | 15 (11.2%)                           | 0 (0.0%)          |
| Anxiolytics, Sedatives and Hypnotics               | 34 (25.4%)                           | 1 (2.9%)          |
| Respiratory Drugs                                  | 44 (32.8%)                           | 1 (2.9%)          |
| Antihistamines                                     | 20 (14.9%)                           | 0 (0.0%)          |
| Cough/Cold                                         | 23 (17.2%)                           | 0 (0.0%)          |
| Combination Products                               |                                      |                   |

Overall, during both phases of the study 79.1% Org 33062 20-90 mg subjects took one or more concomitant medications during the study. The most common concomitant medications were central nervous system agents (59.0%), and within this category analgesics and antipyretics (44.0%) were most frequently used. After randomization to placebo, 20.6% of subjects received one or more concomitant medications. Those most frequently received were central nervous system agents (11.8%), and within this category analgesics and antipyretics and nonsteroidal anti-inflammatory agents were most frequently used (each 8.8%).

**EXTENT OF EXPOSURE**

A summary of the duration of exposure to study drug for the open-label phase only is presented in Table 11 and the double-blind phase by treatment group in the ITT population is presented in Table 12.

**Table 11 Duration of Exposure to Study Medication for the Open-Label Phase**

|                 |                        |                 |
|-----------------|------------------------|-----------------|
| Duration (Days) | Org<br>20-90<br>(N=64) | 33062<br>mg/day |
| Mean " SD       | 25.8 (15.8)            |                 |
| Median          | 27.0                   |                 |
| Range           | 1-56                   |                 |

The mean (days) duration of exposure to Org 33062 was 25.8 days for those subjects who participated in the open-label phase only.

**Table 12 Duration of Exposure to Study Medication for the Double-Blind Phase by Treatment Group (Intent-to-Treat Population)**

|                 |                                  |                 |                             |
|-----------------|----------------------------------|-----------------|-----------------------------|
| Duration (Days) | Org<br>20-90<br>(N=36)<br>mg/day | 33062<br>mg/day | Placebo<br>(N=34)<br>mg/day |
| Mean " SD       | 27.1 (12.9)                      |                 | 24.9 (10.0)                 |
| Median          | 29.0                             |                 | 27.0                        |
| Range           | 7-50                             |                 | 5-44                        |

The mean (days) duration of exposure to study medication was 27.1 days for the Org 33062 20-90 mg and 24.9 days for the placebo group. The mean number of days that Org 33062 20-90 mg subjects received study medication was slightly more than the placebo subjects.

## **MEDICATION DOSES**

The average daily dose for each subject during the double-blind phase was calculated from the total number of capsules taken by that subject at each dosing interval. Summary statistics were calculated for the maximum modal dose (the most frequently taken dose) by Org 33062 subjects. The

maximum modal dose by the Org 33062 treatment group in the ITT population is presented in Table 14.

**Table 14 Maximum Modal Dose by Org 33062 Treatment Group for the Double-Blind Phase (Intent-to-Treat Population)**

|                    | Org 33062<br>20-90<br>(N=36) | mg/day |
|--------------------|------------------------------|--------|
| Maximum Modal Dose |                              |        |
| Mean $\pm$ SD      | 41.4 (21.4)                  |        |
| Median             | 40.0                         |        |
| Range              | 10.0-90.0                    |        |

Note: The Org 33062 treatment group includes subject (b) (6) who received placebo during the last 10 days of participation in the study.

The mean maximum modal dose in the Org 33062 20-90 mg group was 41.4 mg/day.

**AMENDMENTS:**

This protocol was amended five times after it was approved. The details of the amendment are summarized below.

Amendment No.1: This amendment approved before start of study, changed the age requirements for participation in the study from 18 to 65, inclusive to  $\geq 18$ ; changed the baseline minimum score for the HAMD from 22 on the 17-item HAMD to 20 on the 25-item HAMD, and changed the criteria for response from a 50% or greater reduction of the HAMD score on the first 17 items and from a CGI Improvement rating of at least "moderately improved" to a HAMD 17 score of  $\leq 12$  or reduction by  $\geq 50\%$ , and a CGI Improvement rating of at least "moderately improved".

Amendment No. 2: Changed study staff at site 2419. Helen Pettinati, Ph.D. replaced Frederick Evans, Ph.D. as co-investigator.

Amendment No. 3: Extended the double-blind phase of the study from 4 to 6 weeks. This amendment also changed the titration of Org 33062 in the open treatment phase. The dosing regimen

was changed to 5 mg for the first week of open treatment, and subjects were to take one capsule (5 mg) BID with meals initially and titrated gradually (not more than one capsule every other day). The subjects were to be crossed over to the 10 mg capsule by the second week and continued titration until an optimal dosage (no >90 mg/day) was reached.

Amendment No. 4: Changed the inclusion criteria from a minimum of 20 on the first 17 items of the HAMD to a minimum of 20 on all 25 items of the HAMD.

Amendment No. 5: Changed study staff at site 2417. John J. Schwab, M.D. and Elizabeth Lin, Ph.D. replaced Steven Barton, M.D. and Manochehr Manshadi, M.D. as principal investigators.

## **Efficacy Evaluation**

### Open-Label Phase:

The baseline mean HAMD 17 total score was 25.2 in the Org 33062 20-90 mg/day subjects. The mean change from baseline to endpoint was a decrease of 10.6 points in the ITT population (LOCF analysis) during the open-label phase.

### Double-Blind Phase:

Of the 134 subjects who entered the open-label phase, 70 subjects were considered responders and entered the double-blind phase. Subjects receiving Org 33062 20-90 mg/day had a statistically significant lower incidence of relapse according to four of the six definitions of relapse in the ITT population (LOCF analysis) at endpoint during the double-blind phase. Although not statistically significant, the Org 33062 mg/day subjects had a greater reduction in HAMD 17 (-13.0 vs. -9.0) score and a greater percentage of CGI: Global Improvement Responders (56% vs. 42%) than the placebo subjects in the ITT population (LOCF analysis) at endpoint during the double-blind phase.

The primary efficacy parameters for the open-label phase were the HAMD 17 scale and the CGI scale. For the double-blind phase, these parameters were used to evaluate the first time to relapse. Secondary efficacy measures included the HAMD 25 (comprised of the original HAMD 17 plus eight additional items to rate the severity of reverse, negative, or atypical symptoms observed in some depressed subjects), SCL-90, HAM-A, and the PQ.

### HAMD 17: Mean Change from Baseline

The HAMD 17 total score at baseline and the mean change from baseline to each assessment week and endpoint for the open-label phase are presented in Table 13.

**Table 12 HAMD 17: Mean Change from Baseline Score by Week and Treatment Group in the Open-Label Phase (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD 17 Total Score: LOCF |        |        |        |        |                              |
|------------------------|-------------------|-------------------------------------------------------------|--------|--------|--------|--------|------------------------------|
|                        |                   | Week 1                                                      | Week 2 | Week 3 | Week 4 | Week 5 | Week 6/Endpoint <sup>a</sup> |
| Org 33062 20-90 mg/day | 134 (25.2)        | -6.2                                                        | -8.4   | -9.3   | -10.2  | -10.5  | -10.6                        |

<sup>a</sup> Last visit for evaluable data for the subject.

The baseline mean HAMD 17 total score was 25.2. The mean change from baseline to endpoint was a decrease of 10.6 points (LOCF analysis) during the open-label phase.

### PRIMARY EFFICACY PARAMETERS - Double-Blind phase

The primary efficacy parameters for the double-blind phase were comprised of six definitions of relapse.

- A. Return to  $\geq 75\%$  of the (Pre-Treatment) Baseline HAMD 17 Total Score
- B. CGI: Global Improvement Score of “No Change” or “Worse than (Pre-Treatment) Baseline”
- C. Return to  $\geq 75\%$  of the (Pre-Treatment) Baseline HAMD 17 Total Score or Discontinued
- D. CGI: Global Improvement Score of “No Change” or “Worse Than (Pre-Treatment) Baseline” (\$4) or Discontinued
- E. Return to  $\geq 75\%$  of the (Pre-Treatment) Baseline HAMD 17 Total Score or Discontinued Due to Lack of Efficacy
- F. CGI: Global Improvement Score of “No Change” or “Worse Than (Pre-Treatment) Baseline” (\$4) or Discontinued Due to Lack of Efficacy

Each of these relapse definitions was used as a criterion in a survival analysis testing time-to-relapse in the Org 33062 vs. placebo groups. Definition 5 is considered the most important.

Results for the analysis of relapse according to definition 1 are presented in Table 27 and Figure 1.

**Table 27 Return to <sup>≥</sup> 75% of the (Pre-Treatment) Baseline HAMD 17 Total Score by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 7 (20%)                        | 8 (23%)  | 8 (23%)  | 9 (26%)  | 9 (26%)  | 9 (26%)  |
| Placebo (N=33)                | 5 (15%)                        | 12 (36%) | 15 (45%) | 18 (55%) | 18 (55%) | 18 (55%) |

There was a statistically significant difference (p=0.030) between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who returned to  $\geq$  75% of the baseline HAMD 17 total score in the ITT population during the double-blind phase by Week 12.

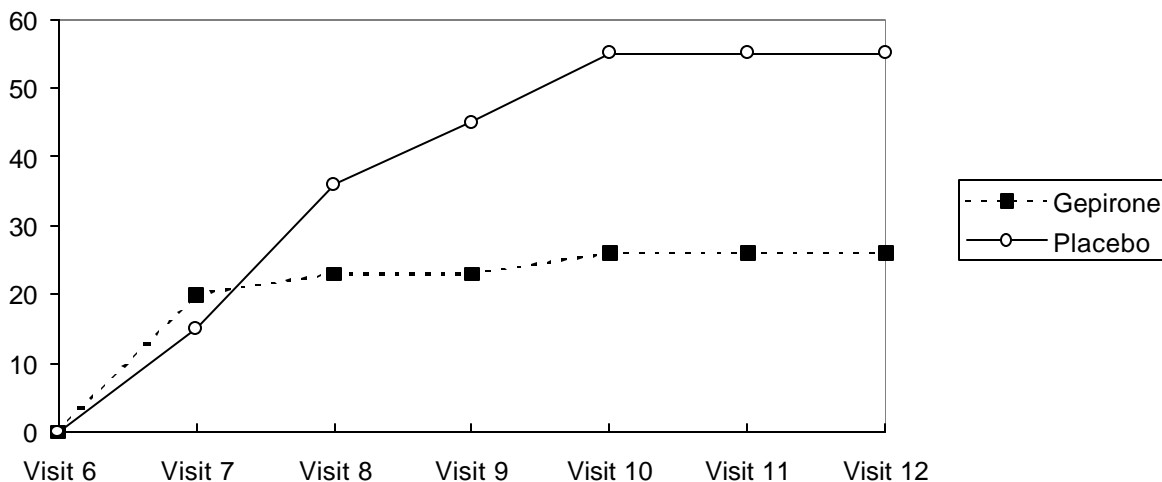


**Figure 1 Percentage of patients relapsing during the double-blind phase by study visit. Relapse is defined as return to  $\geq$ 75% of the pretreatment HAMD 17 total score. Log-rank (p = 0.030).**

Results for the analysis of relapse according to definition 2 are presented in Table 13 and Figure 2.

**Table 13 CGI: Global Improvement Score of “No Change” or “Worse Than (Pre-Treatment) Baseline” (<sup>3</sup>4) by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 9 (26%)                        | 9 (26%)  | 9 (26%)  | 11 (31%) | 11 (31%) | 11 (31%) |
| Placebo (N=33)                | 9 (27%)                        | 16 (48%) | 18 (55%) | 20 (61%) | 20 (61%) | 20 (61%) |

There was a statistically significant difference between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who had a CGI: Global Improvement Score  $\geq 4$  in the ITT population during the double-blind phase by Week 12.

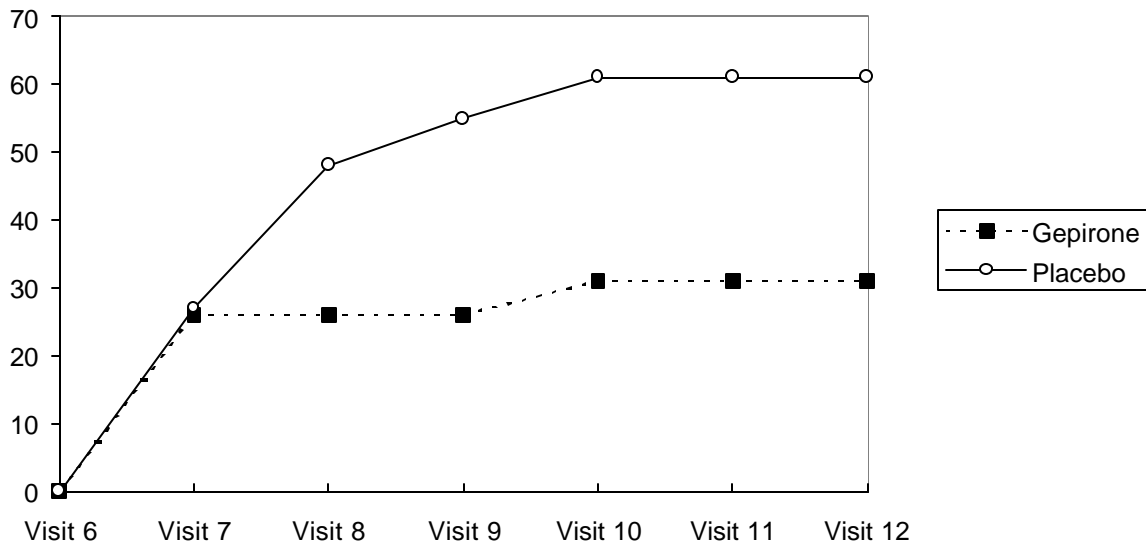


**Figure 2 Percentage of patients relapsing during the double-blind phase by study visit. Relapse is defined as CGI improvement score of no change or worse than pretreatment. Log-rank ( $p = 0.023$ ).**

Results for the definition of relapse according to definition 3 are presented in Table 14 and Figure 3.

**Table 14 Return to <sup>≥</sup> 75% of the (Pre-Treatment) Baseline HAMD 17 Total Score or Discontinued by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 8 (23%)                        | 11 (31%) | 14 (40%) | 15 (43%) | 15 (43%) | 16 (46%) |
| Placebo (N=33)                | 6 (18%)                        | 15 (45%) | 20 (61%) | 23 (70%) | 24 (73%) | 24 (73%) |

Note: Data for this table were derived from Appendix F 7.1.3-3.

There was a statistically significant difference between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who returned to  $\geq 75\%$  of the baseline HAMD 17 total score or discontinued in the ITT population during the double-blind phase by Week 12.

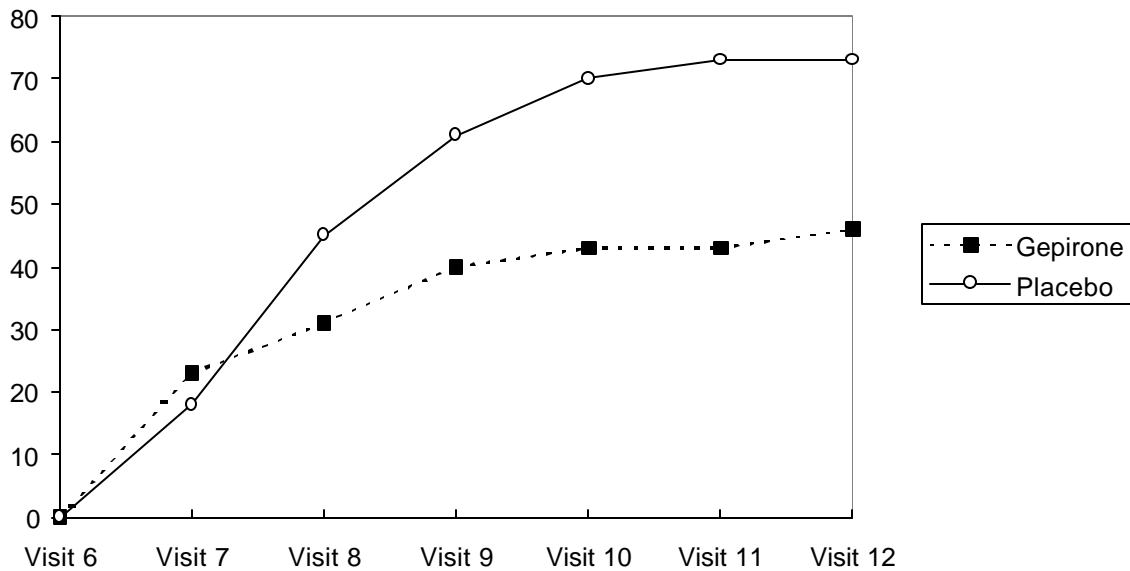


**Figure 3 Percentage of patients relapsing during the double-blind phase by study visit. Relapse is defined as return to  $\geq 75\%$  of the pretreatment HAMD 17 total score, or discontinuation. Log-rank ( $p=0.049$ ).**

Results for the analysis of relapse according to definition 4 are presented in Table 15 and Figure 4.

**Table 15 CGI: Global Improvement Score of “No Change” or “Worse Than (Pre-Treatment) Baseline” (≥4) or Discontinued by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 10 (29%)                       | 13 (37%) | 16 (46%) | 18 (51%) | 18 (51%) | 19 (54%) |
| Placebo (N=33)                | 10 (30%)                       | 19 (58%) | 22 (67%) | 24 (73%) | 24 (73%) | 24 (73%) |

There was no statistically significant difference between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who had a CGI: Global Improvement Score  $\geq 4$  or discontinued in the ITT population during the double-blind phase.

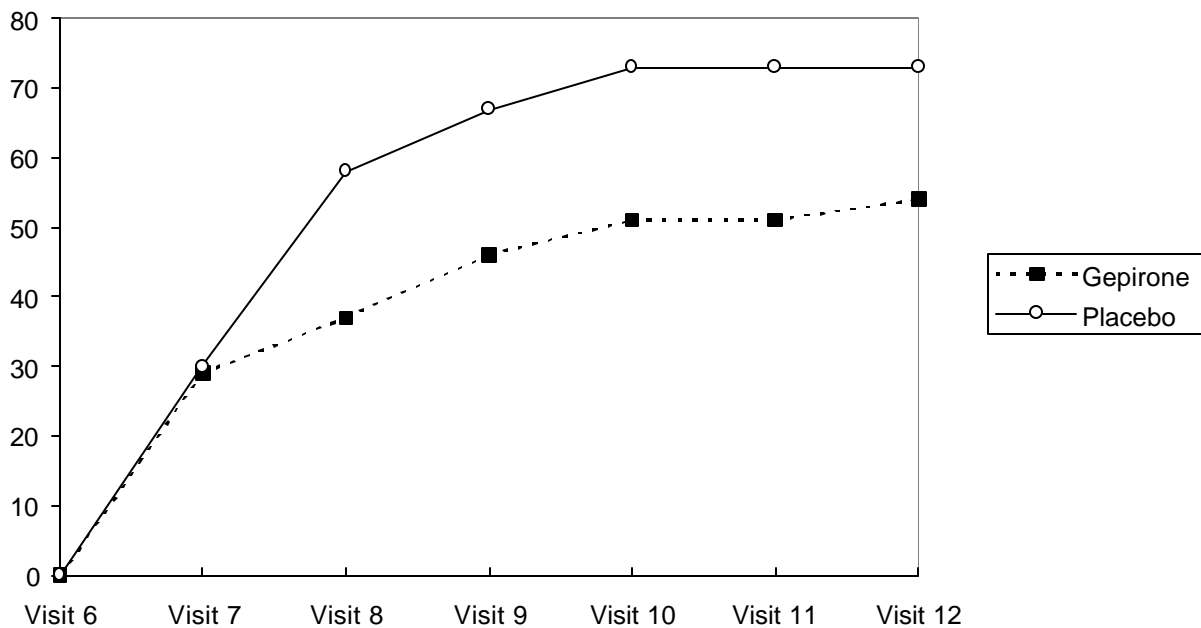


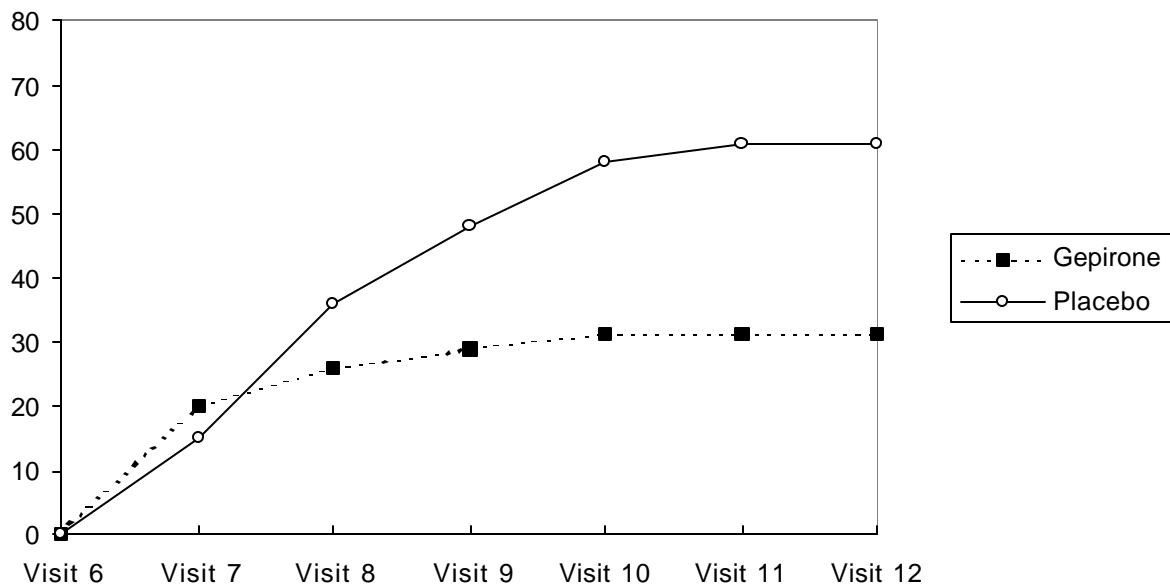
**Figure 4 Percentage of patients relapsing during the double-blind phase by study visit. Relapse is defined as CGI improvement score of no change or worse than pretreatment, or discontinuation. Log-rank ( $p = 0.124$ ).**

Results for the analysis of relapse according to definition 5 are presented in Table 16 and Figure 5.

**Table 16 Return to <sup>≥</sup> 75% of the (Pre-Treatment) Baseline HAMD 17 Total Score or Discontinued Due to Lack of Efficacy by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 7 (20%)                        | 9 (26%)  | 10 (29%) | 11 (31%) | 11 (31%) | 11 (31%) |
| Placebo (N=33)                | 5 (15%)                        | 12 (36%) | 16 (48%) | 19 (58%) | 20 (61%) | 20 (61%) |

There was a statistically significant difference between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who returned to  $\geq 75\%$  of the baseline HAMD 17 total score or discontinued due to lack of efficacy in



the ITT population during the double-blind phase by Week 12.

**Figure 5 Percentage of patients relapsing during the double-blind phase by study visit. Relapse defined as return to  $\geq 75\%$  of the pretreatment HAMD 17 total score, or discontinuation by lack of efficacy. Log-rank ( $p = 0.035$ ).**

Results for the analysis of relapse according to definition 6 are presented in Table 17 and Figure 6.

**Table 17 CGI: Global Improvement Score of “No Change” or “Worse Than (Pre-Treatment) Baseline” ( $\geq 4$ ) or Discontinued Due to Lack of Efficacy by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) of Subjects who Relapsed |          |          |          |          |          |
|-------------------------------|--------------------------------|----------|----------|----------|----------|----------|
|                               | Week 7                         | Week 8   | Week 9   | Week 10  | Week 11  | Week 12  |
| Org 33062 20-90 mg/day (N=35) | 9 (26%)                        | 11 (31%) | 12 (34%) | 14 (40%) | 14 (40%) | 14 (40%) |
| Placebo (N=33)                | 9 (27%)                        | 16 (48%) | 18 (55%) | 20 (61%) | 20 (61%) | 20 (61%) |

There was no statistically significant difference between the Org 33062 20-90 mg/day and the placebo group for the percentage of subjects who had a CGI: Global Improvement Score of  $\geq 4$  or discontinued due to lack of efficacy in the ITT population during the double-blind phase.

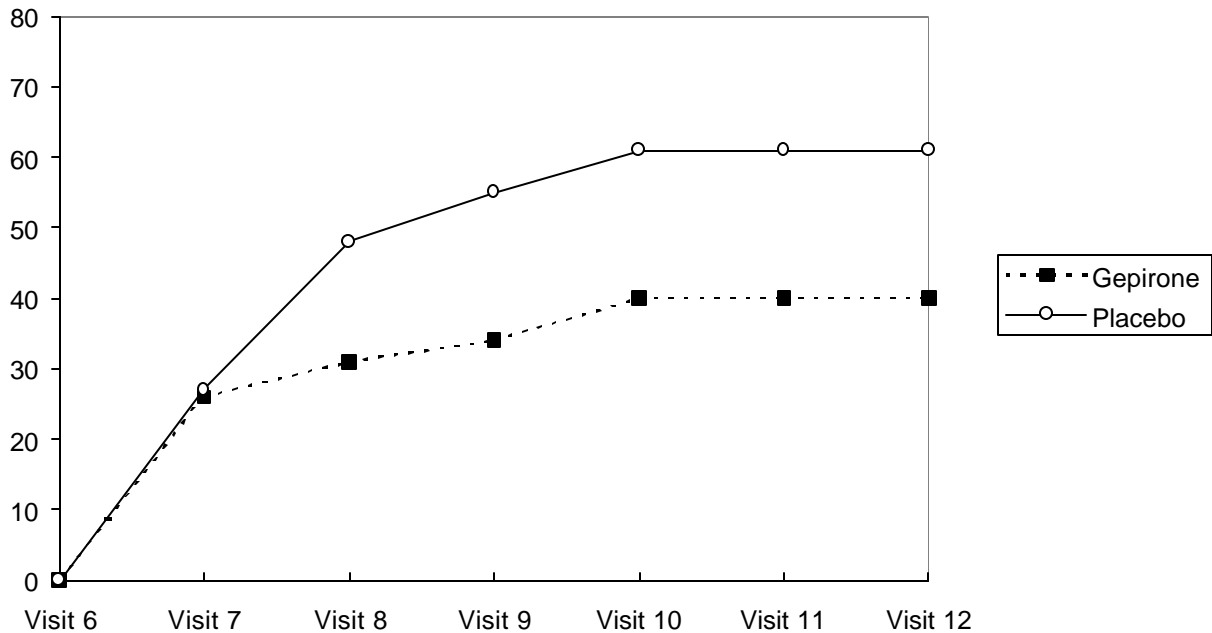


**Figure 6 Percentage of patients relapsing during the double-blind phase by study visit. Relapse is defined as CGI improvement score of no change or worse than pretreatment, or discontinuation by lack of efficacy. Log-rank ( $p = 0.114$ ).**

### HAMD 17: Mean Change from Pre-Treatment Baseline

The HAMD 17 total score at baseline and the mean change from pre-treatment baseline to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) during the double-blind phase are presented in Table 18.

**Table 18 HAMD 17: Mean Change from Baseline Score by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD 17 Total Score: LOCF |        |        |         |         |                               |
|------------------------|-------------------|-------------------------------------------------------------|--------|--------|---------|---------|-------------------------------|
|                        |                   | Week 7                                                      | Week 8 | Week 9 | Week 10 | Week 11 | Week 12/Endpoint <sup>a</sup> |
| Org 33062 20-90 mg/day | 36 (24.8)         | -13.0                                                       | -12.8  | -12.9  | -13.1   | -12.8   | -13.0                         |
| Placebo                | 34 (24.6)         | -11.7                                                       | -9.6   | -9.5   | -9.6    | -9.4    | -9.0                          |

<sup>a</sup> Last visit for evaluable data for the subject.

There were no statistically significant differences between the Org 33062 20-90 mg/day and the placebo group for the HAMD 17 in the ITT population (LOCF analysis) during the double-blind phase at any timepoint.

### CGI: Global Improvement Responders

The number and percentage of subjects “much improved” or “very much improved” for the CGI: Global Improvement at each assessment week by treatment group and study site in the ITT population (LOCF analysis) during the double-blind phase are presented in Table 19.

**Double-Blind Phase (Intent-to-Treat Table 19 CGI: Global Improvement: Number (%) of Subjects “Much Improved” or “Very Much Improved” by Week and Treatment Group in the Population)**

| Treatment Group               | N (%) of Subjects “Much Improved” or “Very Much Improved”: LOCF |          |          |          |          |                               |
|-------------------------------|-----------------------------------------------------------------|----------|----------|----------|----------|-------------------------------|
|                               | Week 7                                                          | Week 8   | Week 9   | Week 10  | Week 11  | Week 12/Endpoint <sup>a</sup> |
| Org 33062 20-90 mg/day (N=36) | 21 (62%)                                                        | 21 (58%) | 19 (53%) | 19 (53%) | 18 (50%) | 20 (56%)                      |
| Placebo (N=33)                | 14 (45%)                                                        | 12 (36%) | 17 (52%) | 16 (48%) | 15 (45%) | 14 (42%)                      |

<sup>a</sup> Last visit for evaluable data for the subject.

There were no statistically significant differences between the Org 33062 20-90 mg/day group and the placebo group for the CGI: Global Improvement Responders in the ITT population (LOCF analysis) during the double-blind phase at any timepoint.

## SECONDARY EFFICACY PARAMETERS - Double-Blind Phase

The secondary efficacy parameters for the double-blind phase included the mean change from baseline to endpoint for the HAMD 25 total score, the HAMD Item 1 (Depressed Mood) score, and the percentage of HAMD 17 Responders.

### HAMD 25: Mean Change from Baseline

The HAMD 25 total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) during the double-blind phase are presented in Table 20.

**Table 20 HAMD 25: Mean Change from Baseline Score by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD 25 Total Score: LOCF |        |        |         |         |                               |
|------------------------|-------------------|-------------------------------------------------------------|--------|--------|---------|---------|-------------------------------|
|                        |                   | Week 7                                                      | Week 8 | Week 9 | Week 10 | Week 11 | Week 12/Endpoint <sup>a</sup> |
| Org 33062 20-90 mg/day | 36 (30.1)         | -15.7                                                       | -15.9  | -16.2  | -16.3   | -15.6   | -16.2*                        |
| Placebo                | 34 (29.9)         | -13.9                                                       | -11.8  | -11.6  | -11.5   | -11.3   | -10.8                         |

<sup>a</sup> Last visit for evaluable data for the subject.

Note: Data for this table were derived from Appendices F 7.2.1-25A and 7.2.1-27A.

\* p-value ≤0.05 vs. placebo.

There was a statistically significant difference between the Org 33062 20-90 mg/day group and the placebo group for the HAMD 25 in the ITT population (LOCF analysis) during the double-blind phase at Week 12 and endpoint (p=0.048).

### HAMD Item 1 (Depressed Mood) & HAMD Factors I (Anxiety/Somatization), V (Retardation) and VI (Sleep Disturbance)

The HAMD Item 1 (Depressed Mood) and factor (Factor I, V, and VI) total score at baseline and the mean change from baseline

to each assessment week and endpoint by treatment group in the ITT population (LOCF analysis) during the double-blind phase are presented in Table 21.

**Table 21 HAMD Item 1 (Depressed Mood): Mean Change from Baseline Score by Week and Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group        | Baseline N (Mean) | Mean Change from Baseline for the HAMD Item 1 Score: LOCF |        |        |         |         |                               |
|------------------------|-------------------|-----------------------------------------------------------|--------|--------|---------|---------|-------------------------------|
|                        |                   | Week 7                                                    | Week 8 | Week 9 | Week 10 | Week 11 | Week 12/Endpoint <sup>a</sup> |
| Org 33062 20-90 mg/day | 36 (2.8)          | -1.5                                                      | -1.6*  | -1.5   | -1.4    | -1.4    | -1.4                          |
| Placebo                | 34 (2.7)          | -1.3                                                      | -0.9   | -1.0   | -1.0    | -1.0    | -0.9                          |

<sup>a</sup> Last visit for evaluable data for the subject.

\* p-value ≤0.05 vs. placebo.

There was a statistically significant difference between the Org 33062 20-90 mg/day group and the placebo group for the HAMD Item 1 in the ITT population (LOCF analysis) during the double-blind phase at Week 8 (p=0.022), but not at endpoint.

### HAMD 17 Responders

The number and percentage of subjects with at least a 50% reduction in HAMD 17 scores from baseline to endpoint by treatment group in the ITT population (LOCF analysis) during the double-blind phase are presented in Table 22.

**Table 22 HAMD 17 Responders: Subjects Displaying 50% Reduction in HAMD 17 Total from Baseline by Treatment Group in the Double-Blind Phase (Intent-to-Treat Population)**

| Treatment Group               | N (%) Responders | p-Value vs. Placebo <sup>a</sup> |
|-------------------------------|------------------|----------------------------------|
| Org 33062 20-90 mg/day (N=36) | 22 (61%)         | 0.058                            |
| Placebo (N=34)                | 13 (38%)         |                                  |

<sup>a</sup>Analyzed using CMH test.

There was a trend for a difference between the Org 33062 20-90 mg/day group and the placebo group for the percentage of HAMD

17 Responders in the ITT population (LOCF analysis) during the double-blind phase at endpoint.

**Double-Blind Phase**

Table 23 summarizes selected primary and secondary efficacy parameters at endpoint by treatment group in the ITT population (LOCF analysis) for the double-blind phase.

**Table 23 Summary of Selected Efficacy Parameters at Endpoint by Treatment Group for the Double-Blind Phase (Intent-to-Treat Population)**

| Parameters                                                                            | Mean Change from Baseline to Endpoint, Relapse, and Percent Responders |                   |
|---------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------|
|                                                                                       | Org<br>20-90<br>mg/day<br>(N=36)                                       | Placebo<br>(N=34) |
| <b>Primary Efficacy Parameters in the Intent-to-Treat Population: LOCF Analysis</b>   |                                                                        |                   |
| <b>Relapse<sup>a</sup></b>                                                            |                                                                        |                   |
| 17<br>≥75% Reduction HAMD                                                             | 9 (26%)*                                                               | 18 (55%)          |
| CGI ≥ 4                                                                               | 11 (31%)*                                                              | 20 (61%)          |
| 17 or Discontinuation<br>≥ 75% Reduction HAMD                                         | 16 (46%)*                                                              | 24 (73%)          |
| CGI ≥ 4 or<br>Discontinuation                                                         | 19 (54%)                                                               | 24 (73%)          |
| 17 or Discontinuation<br>due to Lack of<br>Efficacy<br>≥ 75% Reduction HAMD           | 11 (31%)*                                                              | 20 (61%)          |
| CGI ≥ 4 or<br>Discontinuation due to<br>Lack of Efficacy                              | 14 (40%)                                                               | 20 (61%)          |
| <b>Change from Baseline</b>                                                           |                                                                        |                   |
| HAMD 17 <sup>b</sup>                                                                  | -13.0                                                                  | -9.0              |
| CGI: Global Improvement <sup>c</sup><br>Responders                                    | 56%                                                                    | 42%               |
| <b>Secondary Efficacy Parameters in the Intent-to-Treat Population: LOCF Analysis</b> |                                                                        |                   |
| HAMD 25 <sup>b</sup>                                                                  | -16.2*                                                                 | -10.8             |
| HAMD Item 1 <sup>b</sup>                                                              | -1.4                                                                   | -0.9              |
| HAMD 17 Responders <sup>c</sup>                                                       | 61%                                                                    | 38%               |

- \* p-value  $\leq 0.05$  vs. placebo.
- <sup>a</sup> Survival analysis, log-rank test.
- <sup>b</sup> Anova
- <sup>c</sup> CMH test.

Of the 134 subjects who entered the open-label phase, 70 subjects were considered responders and entered the double-blind phase. Subjects receiving Org 33062 20-90 mg/day had a statistically significant lower incidence of relapse according to four of the six definitions (including #5 pre-specified) of relapse in the ITT population (LOCF analysis) at endpoint during the double-blind phase. In addition, the HAMD 25 change from baseline to endpoint was significantly higher in the Org 33062 group than in the placebo group.

#### Conclusion

Positive findings in four of six relapse indices (including definition 5 pre-specified) and change from baseline on the HAMD 25 tends to support the efficacy of Org 33062 in the prevention of relapse in this population of depressed outpatients. This study is positive as per the sponsor's analysis above and is confirmed by the FDA statistical analysis (see stat review.)

### **Study 03A7C-001B**

A Double-Blind Multicenter Trial of Two Dose Ranges of Org 33062 and Placebo in the Treatment of Depressed Outpatients

#### **Study Period (Years)**

August 7, 1987 (first dose of study drug) to July 26, 1990 (last dose of study drug)

#### **Methodology**

The short-term phase was an 8-week, double-blind, randomized, parallel group, multicenter comparison of the safety and

efficacy of two dose ranges of Org 33062 and placebo in the treatment of outpatients who met RDC for a major depressive disorder. Subjects participated in a 4-day to 14-day baseline phase. Subjects who had moderate to severe depression [ $\geq 20$  on the Hamilton Depression Scale 25-item (HAMD 25), amended from  $\geq 20$  on the first 17 items] and met the entry criteria were randomly assigned to one of three treatment groups: Org 33062 5 to 45 mg/day, Org 33062 10 to 90 mg/day, or placebo. A dose of up to 60 mg/day was allowable in the Org 33062 5 to 45 mg/day group for subjects that tolerated the drug but had not responded. A dose of up to 120 mg/day was allowable in the Org 33062 10 to 90 mg/day group for subjects that tolerated the drug but had not responded.

The long-term phase was a 44-week, double-blind, parallel group, multicenter comparison of two dose ranges of Org 33062 and placebo in the treatment of depressed outpatients who responded to treatment during the short-term phase. Subjects continued the same treatment regimen used in the short-term phase.

## **STUDY DESIGN**

### **Short-Term Phase**

This was an 8-week, double-blind, randomized, parallel group, multicenter comparison of the safety and efficacy of two dose ranges of Org 33062 and placebo in the treatment of outpatients who met RDC criteria for a major depressive disorder. Subjects were to participate in a 4- to 14-day baseline phase to ensure that all eligibility criteria were fulfilled and that all relevant baseline data were recorded. Subjects who had moderate to severe depression ( $\geq 20$  on the HAMD 25, amended from  $\geq 20$  on the first 17 items of the HAMD) were to be randomly assigned to one of three treatment groups: Org 33062 5 to 45 mg/day, Org 33062 10 to 90 mg/day, or placebo. The daily doses were amended to 5 to 60 mg and 10 to 120 mg, respectively, for subjects that tolerated the drug but had not responded. Subjects were to receive one to 12 capsules/day. The dose was to be individualized for each subject.

Sufficient subjects were to be randomized at each of three sites to achieve a minimum of 360 subjects (amended from 120) in the Intent-to-Treat (ITT) population. The anticipated enrolment period was 12 to 18 months (amended from nine to 12 months).

### Long-Term Phase

This was a 44-week, double-blind, parallel group, multicenter comparison of the safety and efficacy of Org 33062 and placebo in the treatment of depressed outpatients who responded to treatment in the 8-week short-term phase, i.e., a CGI improvement rating of at least minimally improved at the end of Week 8. Subjects were to continue with the same treatment regimen used in the short-term phase. The dosing regimen could have been adjusted at any time in order to achieve an optimal therapeutic response. The duration of double-blind therapy in the long-term phase was up to 44 weeks for a total (short-term and long-term combined) double-blind treatment phase of 52 weeks.

### Number of Subjects (total for each treatment)

A total of 360 subjects were to be recruited but due to premature termination by BMS, a total of 211 subjects were randomized at three study centers into the short-term phase. Subjects per treatment group included in each data set were:

| Data Set                        | Org 33062 (mg/day) |       |                |       | Placebo             |       |       | Total |
|---------------------------------|--------------------|-------|----------------|-------|---------------------|-------|-------|-------|
|                                 | 5 to 45            |       | 10 to 90       |       | Cole H <sup>a</sup> |       |       |       |
|                                 | C <sup>b</sup>     | Total | C <sup>b</sup> | Total | C <sup>b</sup>      | Total | Total |       |
| Randomized                      | 10                 | 31    | 10             | 30    | 9                   | 31    | 30    | 211   |
|                                 | 30                 | 71    | 30             | 70    |                     | 70    |       |       |
| All-Subjects-Treated Population | 10                 | 31    | 10             | 30    | 9                   | 31    | 30    | 211   |
|                                 | 30                 | 71    | 30             | 70    |                     | 70    |       |       |
| Intent-to-Treat Population      | 9                  | 31    | 10             | 28    | 9                   | 30    | 30    | 206   |
|                                 | 30                 | 70    | 29             | 67    |                     | 69    |       |       |
| Evaluable Population            | 7                  | 30    | 7              | 23    | 9                   | 29    | 27    | 188   |
|                                 | 29                 | 66    | 27             | 57    |                     | 65    |       |       |

<sup>a</sup> Haggerty (2485)

<sup>b</sup> Carman (2593)

<sup>c</sup> Cole (2483)

In the long-term phase, 75 subjects were enrolled: 29 in the Org 33062 5 to 45 mg/day group, 23 in the Org 33062 10 to 90 mg/day group, and 23 in the placebo group.

## DOSING

Table 24 illustrates the recommended dosing regimen for the short-term phase.

**Table 24 Dosing Regimen**

| Day | Recommended Titration <sup>a</sup> | RX           | Org 33062 5 to 45 mg <sup>a</sup> |                 | Org 33062 10 to 90 mg <sup>a</sup> |                 | Placebo |
|-----|------------------------------------|--------------|-----------------------------------|-----------------|------------------------------------|-----------------|---------|
|     | Schedule capsules/day              |              | mg/capsule                        | mg/day          | mg/capsule                         | mg/day          | mg/day  |
| 1   | 1                                  | 1 hs         | 5                                 | 5               | 10                                 | 10              | 0       |
| 3   | 2                                  | 1 am<br>1 hs | 5                                 | 10              | 10                                 | 20              | 0       |
| 6   | 3                                  | 1 am<br>2 hs | 5                                 | 15              | 10                                 | 30              | 0       |
| 9   | 4                                  | 2 am<br>2 hs | 5                                 | 20              | 10                                 | 40              | 0       |
| 12  | 5                                  | 2 am<br>3 hs | 5                                 | 25              | 10                                 | 50              | 0       |
| 14  | 6                                  | 3 am<br>3 hs | 5                                 | 30              | 10                                 | 60              | 0       |
| 16  | 7                                  | 3 am<br>4 hs | 5                                 | 35              | 10                                 | 70              | 0       |
| 18  | 8                                  | 4 am<br>4 hs | 5                                 | 40              | 10                                 | 80              | 0       |
| 20  | 9 <sup>a</sup>                     | 4 am<br>5 hs | 5                                 | 45 <sup>a</sup> | 10                                 | 90 <sup>a</sup> | 0       |

<sup>a</sup> With permission of the sponsor (or after Amendment 5, upon notification of the study monitor) the dose could be increased to 12 capsules/day (i.e., 5 to 60 mg/day and 10 to 120 mg/day, respectively).

## Diagnosis and Criteria for Inclusion

Short-Term Phase: Outpatients meeting RDC for a major depressive disorder who had a score of  $\geq 20$  on the HAMD 25 at baseline.

Long-Term Phase: Subjects who completed the short-term phase with a final Clinical Global Impression (CGI): Global Improvement score of at least "minimally improved."

### **Inclusion Criteria (Short-Term Phase)**

- The following criteria allowed subjects to enter the baseline phase:
- Male or female outpatients who were >18 years of age. Female subjects were postmenopausal, surgically sterile, or using an adequate method of contraception (or condom by consort). Subjects in this last category were given a pregnancy test before entering the study. If the subject became pregnant during the trial, all treatment was to be stopped and the subject followed.
- Subjects who met RDC criteria for a major depressive disorder (MDD) of at least four weeks duration of the following subtypes:
  - single episode
  - recurrent episodes
- Subjects who had  $\geq 20$  on the HAMD 25 at the end of baseline (amended from a score of  $\geq 20$  on the first 17 items).
- Subjects who gave written informed consent prior to entering the study.

### **Duration of Treatment**

Subjects received eight weeks of double-blind treatment in the short-term phase. Those subjects responding to treatment were eligible for additional 44 weeks of double-blind treatment in the long-term phase.

### **Criteria for Evaluation**

Efficacy Evaluations: Efficacy outcome measures were the HAMD 17, HAMD 25, CGI, Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAM-A), Symptom Checklist 90-Item Version (SCL-90), and the Comprehensive Psychopathologic Rating Scale (CPRS).

Primary efficacy parameters were the change from baseline on the HAMD 17 and the CGI Global Improvement Responders. All other efficacy parameters were considered secondary parameters.

For the short-term phase, the HAMD 17, HAMD 25, and CGI were completed at baseline and Weeks 1, 2, 3, 4, 6, and 8, or early termination. The MADRS and CPRS were completed at baseline and Weeks 1, 4, and 8, or early termination. The HAM-A and SCL-90 were completed at baseline and at Weeks 2, 4, and 8, or early termination. For the long-term phase, the CGI was completed at Weeks 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 52, or early termination. The HAMD, MADRS, HAM-A, and SCL-90 were completed at Weeks 10, 26, and 52, or early termination.

## **Statistical Methods**

Demographic and other subject characterization, duration of exposure to study medication, medication compliance, and dosing information were summarized by treatment group.

For the short-term phase, the primary efficacy variables were the HAMD 17 change from baseline score and the proportion of responders based on the CGI Global Improvement score, with the endpoint as the primary time point. Other efficacy variables included HAMD 25 total score, HAMD Item 1, proportion of responders based on HAMD 17 total score, MADRS, HAMA and CPRS.. For all analyses of continuous variables, an ANOVA was carried out with treatment as factor. Comparisons between each Org 33062 treatment group versus placebo were performed in two ways: without adjusting for multiple comparisons, and with adjustment using Dunnett's multiple comparison procedure. For categorical variables, analyses were performed using the CMH test. In addition, the Org 33062 treatment groups were combined and compared to placebo. All statistical tests were two-sided and considered statistically significant if the overall p-value  $\leq 0.05$ .

For the long-term phase, descriptive statistics at each visit were provided for the HAMD 17 change from baseline score, the proportion of responders based on the CGI Global Improvement score, and the proportion of responders based on the HAMD 17 total score. No statistical tests were performed.

The incidence of adverse events were summarized by treatment group. Similarly, changes in selected laboratory parameters, vital sign measurements, ECGs and physical examinations were also summarized. Statistical comparisons between treatment groups were presented for the number (%) of subjects with notable shifts in laboratory, vital signs or ECG measurements using the CMH test.

#### HAMD 17

The change from baseline in HAMD 17 total score was considered to be a primary efficacy parameter. Post-baseline HAMD 17 total scores were not computed if more than two items were missing. If one or two items were missing, or if the assessment was obtained at baseline, then the HAMD 17 total score was computed in the following manner:

$$\frac{\text{Total for non-missing items} \times \text{Total number of items (17)}}{\text{Number of non-missing items}}$$

## RESULTS

### Investigators

Jonathan O. Cole, M.D. (2483)  
John J. Haggerty, M.D. (2485)  
John Carman, M.D. (2593)

### Study Sites

2483: McLean Hospital, 115 Mill Street, Belmont, MA 02178  
2485: School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514  
2593: Carman Research, 4000 Cumberland Pkwy., Bldg. 100, Suite A, Atlanta, GA 30339

### PROTOCOL AMENDMENTS

There were five amendments to the protocol.

Amendment No. 1 (dated April 13, 1987) specified that the visits at Weeks 5 and 7 were optional, that the HAM-A and SCL-90 were to be performed at baseline and Week 8 (or early termination) only, that the CPRS would be added as an efficacy scale, that the study would involve three sites to enroll 42 participants each and modified the statistical analysis

section accordingly, that the laboratory values for T3, T4, and TSH would be obtained at baseline only, that the exclusion criteria would be modified to allow a 7-day washout and to remove the criteria regarding a HAMD of two on the suicide issue, and that the protocol number would be changed to 03A7C-001-B.

Amendment No. 2 (dated September 22, 1987) applied to the sites of Jonathan Cole (Site 2483), Sidney *Lerfald* (Site 2484), and John Haggerty (Site 2485). This amendment specified that the HAM-A and SCL-90 would be included at Weeks 2 and 4, that the MADRS would be included at baseline and at Weeks 1, 4, and 8, that subjects who had received any psychotropic drugs with a long biological half-life should have had a 14-day washout period, that the CPRS would be analyzed with the categorical data, that the starting dose regimen would change from one capsule for two days BID, for two days to one capsule HS for two days, that the Dose Regimen section would be reworded to place less emphasis on reaching the maximum dose and more emphasis on reaching the optimal therapeutic dose, and that the 21-day drug treatment requirement for the standard efficacy analyses would be eliminated.

Amendment No. 3 (dated November 2, 1987) applied to the sites of Jonathan Cole (2483), and John Haggerty (2485). This amendment changed the inclusion criteria to require  $\geq 20$  on the HAMD 25 (amended from  $\geq 20$  on the first 17 items of the HAMD).

Amendment No. 4 (dated January 6, 1988) replaced the study site of Sidney Lerfald (Site 2484), to that of John Carman (Site 2593). In addition, [REDACTED] <sup>(b) (6)</sup> was replaced by [REDACTED] <sup>(b) (6)</sup> as a study monitor.

Amendment No. 5 (dated November 30, 1988) applied to the sites of Jonathan Cole (Site 2483), John Haggerty (Site 2485), and John Carman (Site 2593). This amendment presented a fully revised protocol that incorporated all the changes made in previous amendments. In addition, this amendment specified that the new protocol would conform to the new BMS' standard

wording, that the enrollment period would increase from nine to 12 months to 12 to 18 months, that the number of participants would be increased from 42 per site to 120 per site, that the name of the clinical monitor would be removed from the cover page and that references to specific BMS personnel would be removed, that the dose range of Org 33062 would be changed to reflect the one capsule HS for two days initial dosing, that the Statistics section would be revised, and that the Exclusion Criteria would be modified to reflect DSM-III-R criteria.

## **Demographic Data**

In the short-term phase, (59%) subjects were female and (94%) Caucasian with a mean age of 42.4 ±10.4 years

Tables 10 (short-term phase) presents the summary of baseline demographics and other baseline characteristics by treatment group and study sites for the All-Subjects-Treated population and Table 11 (long-term phase) presents the summary of baseline demographics and other baseline characteristics by treatment group for the All-Subjects-Enrolled population.

**Table 10      Demographic and Other Baseline  
Characteristics by Treatment Group and Study Site in  
the Short-Term Phase (All-Subjects-Treated Population)**

| Parameter                                    | Org 33062 mg/day |                | Placebo         | Total           |
|----------------------------------------------|------------------|----------------|-----------------|-----------------|
|                                              | 5 to 45          | 10 to 90       |                 |                 |
| All Sites Combined                           | (N=71)           | (N=70)         | (N=70)          | (N=211)         |
| Age (years):<br>Mean $\pm$ SD                | 42.9 $\pm$ 10.2  | 40.1 $\pm$ 9.6 | 44.1 $\pm$ 11.2 | 42.4 $\pm$ 10.4 |
| Weight (lbs) <sup>a</sup> :<br>Mean $\pm$ SD | 161 $\pm$ 35.6   | 174 $\pm$ 41.6 | 170 $\pm$ 40.6  | 168 $\pm$ 39.5  |
| Race:                                        |                  |                |                 |                 |
| Black                                        | 2 (3%)           | 7 (10%)        | 3 (4%)          | 12 (6%)         |
| Oriental                                     | 0 (0%)           | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| White                                        | 69 (97%)         | 63 (90%)       | 67 (96%)        | 199 (94%)       |
| Other                                        | 0 (0%)           | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| Gender:                                      |                  |                |                 |                 |
| Female                                       | 39 (55%)         | 39 (56%)       | 46 (66%)        | 124 (59%)       |
| Male                                         | 32 (45%)         | 31 (44%)       | 24 (34%)        | 87 (41%)        |
| Prior Psychotropic Therapy:                  |                  |                |                 |                 |
| No                                           | 27 (38%)         | 18 (26%)       | 22 (31%)        | 67 (32%)        |
| Yes                                          | 40 (56%)         | 47 (67%)       | 44 (63%)        | 131 (62%)       |
| Missing                                      | 4 (6%)           | 5 (7%)         | 4 (6%)          | 13 (6%)         |
| Site 2593 (Carman)                           | (N = 30)         | (N = 30)       | (N = 30)        | (N = 90)        |
| Age (years):<br>Mean $\pm$ SD                | 40.1 $\pm$ 9.1   | 38.1 $\pm$ 7.5 | 42.7 $\pm$ 11.7 | 40.3 $\pm$ 9.7  |
| Weight (lbs) <sup>a</sup> :<br>Mean $\pm$ SD | 152 $\pm$ 31.5   | 164 $\pm$ 35.4 | 167 $\pm$ 39.3  | 161 $\pm$ 35.5  |
| Race:                                        |                  |                |                 |                 |
| Black                                        | 1 (3%)           | 5 (17%)        | 1 (3%)          | 7 (8%)          |
| Oriental                                     | 0 (0%)           | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| White                                        | 29 (97%)         | 25 (83%)       | 29 (97%)        | 83 (92%)        |
| Other                                        | 0 (0%)           | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| Gender:                                      |                  |                |                 |                 |
| Female                                       | 15 (50%)         | 17 (57%)       | 19 (63%)        | 51 (57%)        |
| Male                                         | 15 (50%)         | 13 (43%)       | 11 (37%)        | 39 (43%)        |
| Prior Psychotropic Therapy:                  |                  |                |                 |                 |
| No                                           | 14 (47%)         | 10 (33%)       | 10 (33%)        | 34 (38%)        |
| Yes                                          | 16 (53%)         | 20 (67%)       | 20 (67%)        | 56 (62%)        |
| Missing                                      | 0 (0%)           | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| Site 2483 (Cole)                             | (N = 10)         | (N = 10)       | (N = 9)         | (N = 29)        |

|                                            |                 |                |                 |                 |
|--------------------------------------------|-----------------|----------------|-----------------|-----------------|
| Age (years):<br>Mean $\pm$ SD              | 41.2 $\pm$ 11.6 | 44.5 $\pm$ 7.8 | 44.3 $\pm$ 11.1 | 43.3 $\pm$ 10.0 |
| Weight (lbs) <sup>a</sup><br>Mean $\pm$ SD | 177 $\pm$ 29.0  | 158 $\pm$ 28.4 | 181 $\pm$ 38.3  | 171 $\pm$ 32.1  |
| Race:                                      |                 |                |                 |                 |
| Black                                      | 0 (0%)          | 2 (20%)        | 0 (0%)          | 2 (7%)          |
| Oriental                                   | 0 (0%)          | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| White                                      | 10 (100%)       | 8 (80%)        | 9 (100%)        | 27 (93%)        |
| Other                                      | 0 (0%)          | 0 (0%)         | 0 (0%)          | 0 (0%)          |
| Gender:                                    |                 |                |                 |                 |
| Female                                     | 3 (30%)         | 3 (30%)        | 5 (56%)         | 11 (38%)        |
| Male                                       | 7 (70%)         | 7 (70%)        | 4 (44%)         | 18 (62%)        |
| Prior<br>Psychotropic<br>Therapy:          |                 |                |                 |                 |
| No                                         | 4 (40%)         | 2 (20%)        | 1 (11%)         | 7 (24%)         |
| Yes                                        | 5 (50%)         | 6 (60%)        | 6 (67%)         | 17 (59%)        |
| Missing                                    | 1 (10%)         | 2 (20%)        | 2 (22%)         | 5 (17%)         |

**Table 10 Demographic and Other Baseline Characteristics by Treatment Group and Study Site in the Short-Term Phase (All-Subjects-Treated Population) (Continued)**

|                                          | Org 33062 mg/day |             | Placebo     | Total       |
|------------------------------------------|------------------|-------------|-------------|-------------|
|                                          | 5 to 45          | 10 to 90    |             |             |
| All Sites Combined                       | (N=71)           | (N=70)      | (N=70)      | (N=211)     |
| Site 2485 (Haggerty)                     | (N=31)           | (N=30)      | (N=31)      | (N=92)      |
| Age (years):<br>Mean ± SD                | 46.1 ± 10.0      | 40.7 ± 11.5 | 45.5 ± 11.0 | 44.1 ± 11.0 |
| Weight (lbs) <sup>a</sup> :<br>Mean ± SD | 164 ± 39.8       | 191 ± 46.2  | 171 ± 43.2  | 174 ± 44.3  |
| Race:                                    |                  |             |             |             |
| Black                                    | 1 (3%)           | 0 (0%)      | 2 (6%)      | 3 (3%)      |
| Oriental                                 | 0 (0%)           | 0 (0%)      | 0 (0%)      | 0 (0%)      |
| White                                    | 30 (97%)         | 30 (100%)   | 29 (94%)    | 89 (97%)    |
| Other                                    | 0 (0%)           | 0 (0%)      | 0 (0%)      | 0 (0%)      |
| Gender:                                  |                  |             |             |             |
| Female                                   | 21 (68%)         | 19 (63%)    | 22 (71%)    | 62 (67%)    |
| Male                                     | 10 (32%)         | 11 (37%)    | 9 (29%)     | 30 (33%)    |
| Prior Psychotropic Therapy:              |                  |             |             |             |
| No                                       | 9 (29%)          | 6 (20%)     | 11 (35%)    | 26 (28%)    |
| Yes                                      | 19 (61%)         | 21 (70%)    | 18 (58%)    | 58 (63%)    |
| Missing                                  | 3 (10%)          | 3 (10%)     | 2 (6%)      | 8 (9%)      |

<sup>a</sup>All subjects did not have a baseline weight measurement. See Appendices F 6.6-1 and 6.6-5 for N for the Weight variable for each treatment group.

There were no important demographic or other baseline characteristic differences among the treatment groups in the short-term phase in the All-Subjects-Treated population, except the placebo group had a slightly greater percentage (66%) of female subjects than the Org 33062 5 to 45 mg/day (55%) or the Org 33062 10 to 90 mg/day group (56%). Of the 211 subjects in the All-Subjects-Treated population, 59% were female and 94% were Caucasian. The mean age of all subjects was 42.4 " 10.4 years.

**Table 11 Demographic and Other Baseline Characteristics by Treatment Group in the Long-Term Phase (All-Subjects-Enrolled Population)**

| Parameter                   | Org 33062 mg/day |                 | Placebo (N=23) | Total (N=75) |
|-----------------------------|------------------|-----------------|----------------|--------------|
|                             | 5 to 45 (N=29)   | 10 to 90 (N=23) |                |              |
| Age (years):<br>Mean ± SD   | 41.8 ± 10.4      | 44.5 ± 7.3      | 42.6 ± 10.3    | 42.9 ± 9.5   |
| Weight (lbs):<br>Mean ± SD  | 167 ± 39.6       | 176 ± 41.3      | 156 ± 38.6     | 166 ± 40.2   |
| Race:                       |                  |                 |                |              |
| Black                       | 1 (3%)           | 3 (13%)         | 1 (4%)         | 5 (7%)       |
| Oriental                    | 0 (0%)           | 0 (0%)          | 0 (0%)         | 0 (0%)       |
| White                       | 28 (97%)         | 20 (87%)        | 22 (96%)       | 70 (93%)     |
| Other                       | 0 (0%)           | 0 (0%)          | 0 (0%)         | 0 (0%)       |
| Gender:                     |                  |                 |                |              |
| Female                      | 17 (59%)         | 10 (43%)        | 16 (70%)       | 43 (57%)     |
| Male                        | 12 (41%)         | 13 (57%)        | 7 (30%)        | 32 (43%)     |
| Prior Psychotropic Therapy: |                  |                 |                |              |
| Yes                         | 15 (52%)         | 17 (74%)        | 12 (52%)       | 44 (59%)     |
| No                          | 13 (45%)         | 5 (22%)         | 8 (35%)        | 26 (35%)     |
| Missing                     | 1 (3%)           | 1 (4%)          | 3 (13%)        | 5 (7%)       |

There were no important demographic or other baseline characteristic differences among the treatment groups in the long-term phase in the All-Subjects-Enrolled population, except that the placebo group had a greater percentage of female subjects (70%) than did the Org 33062 5 to 45 mg/day (59%) or the Org 33062 10 to 90 mg/day group (43%). Of the 75 subjects enrolled, 57% were female and 93% were Caucasian. The mean age of all subjects was 42.9 " 9.5 years.

## **DISPOSITION**

### **Short-Term Phase**

The disposition of subjects by treatment group and study site for the short-term phase is presented in Table 40. The table displays the number of subjects who discontinued by week and

the number of subjects who completed the short-term phase, as well as the ASR, AST, ITT and evaluable populations.

**Table 40      Disposition of Subjects in the Short-Term  
Phase by Study Site and Treatment Group**

| Treatment Group                         | All Sites Combined |            |            |             | Site 2593 (Carman) |            |            |            | Site 2483 (Cole) |           |           |            | Site 2485 (Haggerty) |            |            |            |
|-----------------------------------------|--------------------|------------|------------|-------------|--------------------|------------|------------|------------|------------------|-----------|-----------|------------|----------------------|------------|------------|------------|
|                                         | Org 33062 mg/day   |            | Placebo    | Total       | Org 33062 mg/day   |            | Placebo    | Total      | Org 33062 mg/day |           | Placebo   | Total      | Org 33062 mg/day     |            | Placebo    | Total      |
|                                         | 5 to 45            | 10 to 90   |            |             | 5 to 45            | 10 to 90   |            |            | 5 to 45          | 10 to 90  |           |            | 5 to 45              | 10 to 90   |            |            |
| Randomized Subjects                     | 71                 | 70         | 70         | 211         | 30                 | 30         | 30         | 90         | 10               | 10        | 9         | 29         | 31                   | 30         | 31         | 92         |
| All-Subjects-Treated Population         | 71 (100%)          | 70 (100%)  | 70 (100%)  | 211 (100%)  | 30 (100%)          | 30 (100%)  | 30 (100%)  | 90 (100%)  | 10 (100%)        | 10 (100%) | 9 (100%)  | 29 (100%)  | 31 (100%)            | 30 (100%)  | 31 (100%)  | 92 (100%)  |
| Intent-to-Treat Population <sup>a</sup> | 70 (98.6%)         | 67 (95.7%) | 69 (98.6%) | 206 (97.6%) | 30 (100%)          | 29 (96.7%) | 30 (100%)  | 89 (98.9%) | 9 (90.0%)        | 10 (100%) | 9 (100%)  | 28 (96.6%) | 31 (100%)            | 28 (93.3%) | 30 (96.8%) | 89 (96.7%) |
| Evaluable Population <sup>b</sup>       | 66 (93.0%)         | 57 (81.4%) | 65 (92.9%) | 188 (89.1%) | 29 (96.7%)         | 27 (90.0%) | 27 (90.0%) | 83 (92.2%) | 7 (70.0%)        | 7 (70.0%) | 9 (100%)  | 23 (79.3%) | 30 (96.8%)           | 23 (76.7%) | 29 (93.5%) | 82 (89.1%) |
| Discontinued Treatment by:              |                    |            |            |             |                    |            |            |            |                  |           |           |            |                      |            |            |            |
| Week 1                                  | 5 (7.0%)           | 9 (12.9%)  | 4 (5.7%)   | 18 (8.5%)   | 1 (3.3%)           | 2 (6.7%)   | 3 (10.0%)  | 6 (6.7%)   | 3 (30.0%)        | 3 (30.0%) | 0 (0.0%)  | 6 (20.7%)  | 1 (3.2%)             | 4 (13.3%)  | 1 (3.2%)   | 6 (6.5%)   |
| Week 2                                  | 2 (2.8%)           | 8 (11.4%)  | 4 (5.7%)   | 14 (6.6%)   | 2 (6.7%)           | 2 (6.7%)   | 2 (6.7%)   | 6 (6.7%)   | 0 (0.0%)         | 0 (0.0%)  | 1 (11.1%) | 1 (3.4%)   | 0 (0.0%)             | 6 (20.0%)  | 1 (3.2%)   | 7 (7.6%)   |
| Week 3                                  | 3 (4.2%)           | 3 (4.3%)   | 4 (5.7%)   | 10 (4.7%)   | 2 (6.7%)           | 2 (6.7%)   | 3 (10.0%)  | 7 (7.8%)   | 0 (0.0%)         | 0 (0.0%)  | 1 (11.1%) | 1 (3.4%)   | 1 (3.2%)             | 1 (3.3%)   | 0 (0.0%)   | 2 (2.2%)   |

|                     |                 |                  |                   |                   |                  |                  |                  |                   |                  |                  |                  |                  |                 |                  |                  |                 |
|---------------------|-----------------|------------------|-------------------|-------------------|------------------|------------------|------------------|-------------------|------------------|------------------|------------------|------------------|-----------------|------------------|------------------|-----------------|
| Week 4              | 7<br>(9.9<br>%) | 6<br>(8.6<br>%)  | 7<br>(10.<br>0%)  | 20<br>(9.5<br>%)  | 6<br>(20.0<br>%) | 4<br>(13.<br>3%) | 4<br>(13.3<br>%) | 14<br>(15.<br>6%) | 0<br>(0.0<br>%)  | 1<br>(10.<br>0%) | 1<br>(11.<br>1%) | 2<br>(6.9<br>%)  | 1<br>(3.2<br>%) | 1<br>(3.3<br>%)  | 2<br>(6.5%<br>)  | 4<br>(4.3<br>%) |
| Week 5              | 6<br>(8.5<br>%) | 8<br>(11.<br>4%) | 11<br>(15.<br>7%) | 25<br>(11.<br>9%) | 3<br>(10.0<br>%) | 4<br>(13.<br>3%) | 4<br>(13.3<br>%) | 11<br>(12.<br>2%) | 0<br>(0.0<br>%)  | 1<br>(10.<br>0%) | 4<br>(44.<br>4%) | 5<br>(17.<br>2%) | 3<br>(9.7<br>%) | 3<br>(10.<br>0%) | 3<br>(9.7%<br>)  | 9<br>(9.8<br>%) |
| Week 6              | 7<br>(9.9<br>%) | 3<br>(4.3<br>%)  | 7<br>(10.<br>0%)  | 17<br>(8.1<br>%)  | 3<br>(10.0<br>%) | 3<br>(10.<br>0%) | 2<br>(6.7%<br>)  | 8<br>(8.9<br>%)   | 1<br>(10.<br>0%) | 0<br>(0.0<br>%)  | 0<br>(0.0<br>%)  | 1<br>(3.4<br>%)  | 3<br>(9.7<br>%) | 0<br>(0.0<br>%)  | 5<br>(16.1<br>%) | 8<br>(8.7<br>%) |
| Week 7              | 0<br>(0.0<br>%) | 1<br>(1.4<br>%)  | 1<br>(1.4<br>%)   | 2<br>(1.0<br>%)   | 0<br>(0.0%<br>)  | 0<br>(0.0<br>%)  | 1<br>(3.3%<br>)  | 1<br>(1.1<br>%)   | 0<br>(0.0<br>%)  | 0<br>(0.0<br>%)  | 0<br>(0.0<br>%)  | 0<br>(0.0<br>%)  | 0<br>(0.0<br>%) | 1<br>(3.3<br>%)  | 0<br>(0.0%<br>)  | 1<br>(1.1<br>%) |
| Total               | 30              | 38               | 38                | 106               | 17               | 17               | 19               | 53                | 4                | 5                | 7                | 16               | 9               | 16               | 12               | 37              |
| Discontin-<br>ed    | (42.<br>3%)     | (54.<br>3%)      | (54.<br>3%)       | (50.<br>2%)       | (56.7<br>%)      | (56.<br>7%)      | (63.3<br>%)      | (58.<br>9%)       | (40.<br>0%)      | (50.<br>0%)      | (77.<br>8%)      | (55.<br>2%)      | (29.<br>0%)     | (53.<br>3%)      | (38.7<br>%)      | (40.<br>2%)     |
| Completed           | 41              | 32               | 32                | 105               | 13               | 13               | 11               | 37                | 6                | 5                | 2                | 13               | 22              | 14               | 19               | 55              |
| Short-Term<br>Phase | (57.<br>8%)     | (45.<br>7%)      | (45.<br>7%)       | (49.<br>8%)       | (43.3<br>%)      | (43.<br>3%)      | (36.7<br>%)      | (41.<br>1%)       | (60.<br>0%)      | (50.<br>0%)      | (22.<br>2%)      | (44.<br>8%)      | (71.<br>0%)     | (46.<br>7%)      | (61.3<br>%)      | (59.<br>8%)     |

<sup>a</sup>Subjects who ingested at least one dose of study medication and had at least one post-baseline efficacy evaluation.

<sup>b</sup>Subjects who had a minimum of two weeks of documented exposure to study medication.

Of a planned total of 360 subjects, a total of 211 subjects were randomized into three treatment groups in the short-term phase: 71 subjects to Org 33062 5 to 45 mg/day, 70 subjects to Org 33062 10 to 90 mg/day, and 70 subjects to placebo. All subjects randomized received at least one dose of study medication and are included in the All-Subjects-Treated population. A total of 105 (49.8%) randomized subjects completed the short-term phase: 41 (57.7%) subjects in the Org 33062 5 to 45 mg/day group, 32 (45.7) subjects in the Org 33062 10 to 90 mg/day group, and 32 (45.7%) subjects in the placebo group.

A total of 90 (42.7%) subjects (30 to Org 33062 5 to 45 mg/day, 30 to Org 33062 10 to 90 mg/day, and 30 to placebo) were randomized at Site 2593 (Carman), 29 (13.7%) subjects (10 to Org 33062 5 to 45 mg/day, 10 to Org 33062 10 to 90 mg/day, and nine to placebo) were randomized at Site 2483 (Cole), and 92 (43.6%) subjects (31 to Org 33062 5 to 45 mg/day, 30 to Org 33062 10 to 90 mg/day, and 31 to placebo) were randomized at Site 2485 (Haggerty).

### **Long-Term Phase**

The disposition of subjects who entered the long-term phase by treatment group are presented in Table 41.

**Table 41 Disposition of Subjects in the Long-Term Phase by Treatment Group**

|                                  | All Sites Combined |                 |               |               |
|----------------------------------|--------------------|-----------------|---------------|---------------|
| Treatment Group                  | Org 33062 mg/day   |                 | Placebo       | Total         |
|                                  | 5 to 45 mg/day     | 10 to 90 mg/day |               |               |
| All-Subjects-Enrolled Population | 29<br>(100%)       | 23<br>(100%)    | 23<br>(100%)  | 75<br>(100%)  |
| Total Discontinued               | 25<br>(86.2%)      | 21<br>(91.3%)   | 19<br>(82.6%) | 65<br>(86.7%) |
| Completed Long-Term Phase        | 4<br>(13.8%)       | 2<br>(8.7%)     | 4<br>(17.4%)  | 10<br>(13.3%) |

A total of 75 subjects enrolled in the long-term phase (29 Org 33062 5 to 45 mg/day subjects, 23 Org 33062 10 to 90 mg/day subjects, and 23 placebo subjects). A total of 10 (13.3%) subjects completed the long-term phase: four (13.8%) Org 33062 5 to 45 mg/day subjects, two (8.7%) Org 33062 10 to 90 mg/day subjects, and four (17.4%) placebo subjects. A total of 65 (86.7%) subjects discontinued the long-term phase.

#### **DISCONTINUATIONS**

The number and percentage of subjects who discontinued from the study are presented by treatment group, study site, and reason for discontinuation in Table 42 for the short-term phase (All-Subjects-Treated population) and by treatment group and reason for discontinuation in Table 43 for the long-term phase (All-Subjects-Enrolled population).

**Table 43 Number (%) of Subjects who Discontinued from the Short-Term Phase by Treatment Group, Study Site, and Reason for Discontinuation (All-Subjects-Treated Population)**

| Reason for Discontinuation | Org 33062 mg/day           |                         | Placebo                   | Total          |
|----------------------------|----------------------------|-------------------------|---------------------------|----------------|
|                            | 5 to 45                    | 10 to 90                |                           |                |
| All Sites Combined         | (N = 71)                   | (N = 70)                | (N = 70)                  | (N = 211)      |
| Adverse Event              | 17<br>(23.9%) <sup>b</sup> | 28 (40.0%) <sup>c</sup> | 8<br>(11.4%) <sup>d</sup> | 53 (25.1%)     |
| Death                      | 0 (0.0%)                   | 0 (0.0%)                | 0 (0.0%)                  | 0 (0.0%)       |
| Lack of Efficacy           | 8 (11.3%)                  | 5 (7.1%)                | 21<br>(30.0%)             | 34 (16.1%)     |
| Lost to Follow-Up          | 1 (1.4%)                   | 2 (2.9%)                | 6 (8.6%)                  | 9 (4.3%)       |
| Other <sup>a</sup>         | 4 (5.6%)                   | 3 (4.3%)                | 3 (4.3%)                  | 10 (4.7%)      |
| Total Discontinued         | 30 (42.3%)                 | 38 (54.3%)              | 38<br>(54.3%)             | 106<br>(50.2%) |
| Site 2593 (Carman)         | (N = 30)                   | (N = 30)                | (N = 30)                  | (N = 90)       |
| Adverse Event              | 11 (36.7%)                 | 15 (50.0%)              | 5 (16.7%)                 | 31 (34.4%)     |
| Death                      | 0 (0.0%)                   | 0 (0.0%)                | 0 (0.0%)                  | 0 (0.0%)       |
| Lack of Efficacy           | 4 (13.3%)                  | 1 (3.3%)                | 9 (30.0%)                 | 14 (15.6%)     |
| Lost to Follow-Up          | 1 (3.3%)                   | 1 (3.3%)                | 4 (13.3%)                 | 6 (6.7%)       |
| Other <sup>a</sup>         | 1 (3.3%)                   | 0 (0.0%)                | 1 (3.3%)                  | 2 (2.2%)       |
| Total Discontinued         | 17 (56.7%)                 | 17 (56.7%)              | 19<br>(63.3%)             | 53 (58.9%)     |
| Site 2483 (Cole)           | (N = 10)                   | (N = 10)                | (N = 9)                   | (N = 29)       |
| Adverse Event              | 3 (30.0%)                  | 3 (30.0%)               | 1 (11.1%)                 | 7 (24.1%)      |
| Death                      | 0 (0.0%)                   | 0 (0.0%)                | 0 (0.0%)                  | 0 (0.0%)       |
| Lack of Efficacy           | 0 (0.0%)                   | 2 (20.0%)               | 6 (66.7%)                 | 8 (27.6%)      |
| Lost to Follow-Up          | 0 (0.0%)                   | 0 (0.0%)                | 0 (0.0%)                  | 0 (0.0%)       |
| Other <sup>a</sup>         | 1 (10.0%)                  | 0 (0.0%)                | 0 (0.0%)                  | 1 (3.4%)       |
| Total Discontinued         | 4 (40.0%)                  | 5 (50.0%)               | 7 (77.8%)                 | 16 (55.2%)     |
| Site 2485 (Haggerty)       | (N = 31)                   | (N = 30)                | (N = 31)                  | (N = 92)       |
| Adverse Event              | 3 (9.7%)                   | 10 (33.3%)              | 2 (6.5%)                  | 15 (16.3%)     |
| Death                      | 0 (0.0%)                   | 0 (0.0%)                | 0 (0.0%)                  | 0 (0.0%)       |
| Lack of Efficacy           | 4 (12.9%)                  | 2 (6.7%)                | 6 (19.4%)                 | 12 (13.0%)     |

|                    |           |            |            |            |
|--------------------|-----------|------------|------------|------------|
| Lost to Follow-Up  | 0 (0.0%)  | 1 (3.3%)   | 2 (6.5%)   | 3 (3.3%)   |
| Other <sup>a</sup> | 2 (6.5%)  | 3 (10.0%)  | 2 (6.5%)   | 7 (7.6%)   |
| Total Discontinued | 9 (29.0%) | 16 (53.3%) | 12 (38.7%) | 37 (40.2%) |

<sup>a</sup>Other includes at least one subject with one of the following reasons for discontinuation: patient withdrew consent, patient unreliability, data handling discontinuation, or other known cause.

<sup>b</sup>This number does not include Subject (b) (6) and Subject (b) (6) who discontinued due to AE, because the subjects' final dispositions were listed as "Lack of Efficacy" on th End-of-Study CRF.

<sup>c</sup>The correct number of discontinuations due to AE is 27. This number includes Subject (b) (6) who is also counted (correctly) as a discontinuation from the long-term phase of the study on Table 9.

<sup>d</sup>This number does not include Subject (b) (6) who discontinued due to AE, because the subject's final disposition was listed as "Lack of Efficacy" on th End-of-Study CRF.

A total of 106 (50.2%) subjects discontinued the short-term phase, including 30 (42.3%) Org 33062 5 to 45 mg/day, 38 (54.3%) Org 33062 10 to 90 mg/day, and 38 (54.3%) placebo subjects. The most frequent reason for subjects discontinuing treatment were AE (23.9% Org 33062 5 to 45 mg/day subjects) (40.0% Org 33062 10 to 90 mg/day subjects, compared with 11.4% of placebo subjects), and lack of efficacy (30.0% placebo subjects). No deaths were reported in the short-term phase.

**Table 25 Number (%) of Subjects who Discontinued from the Long-Term Phase by Treatment Group and Reason for Discontinuation (All-Subjects-Enrolled Population)**

| Reason for Discontinuation    | Org 33062 mg/day |                 | Placebo (N=23) | Total (N=75) |
|-------------------------------|------------------|-----------------|----------------|--------------|
|                               | 5 to 45 (N=29)   | 10 to 90 (N=23) |                |              |
| Adverse Event                 | 6 (20.7%)        | 4 (17.4%)       | 2 (8.7%)       | 12 (16.0%)   |
| Death                         | 0 (0.0%)         | 0 (0.0%)        | 0 (0.0%)       | 0 (0.0%)     |
| Lack of Efficacy              | 0 (0.0%)         | 1 (4.3%)        | 3 (13.0%)      | 4 (5.3%)     |
| Lost to Follow-Up             | 0 (0.0%)         | 1 (4.3%)        | 0 (0.0%)       | 1 (1.3%)     |
| Data Handling Discontinuation | 8 (27.6%)        | 4 (17.4%)       | 9 (39.1%)      | 21 (28.0%)   |
| Patient Withdrew Consent      | 2 (6.9%)         | 5 (21.7%)       | 2 (8.7%)       | 9 (12.0%)    |
| Other Known Cause             | 6 (20.7%)        | 5 (21.7%)       | 2 (8.7%)       | 13 (17.3%)   |
| Other <sup>a</sup>            | 3 (10.3%)        | 1 (4.3%)        | 1 (4.3%)       | 5 (6.7%)     |
| Total Discontinued            | 25 (86.2%)       | 21 (91.3%)      | 19 (82.6%)     | 65 (86.7%)   |

<sup>a</sup> Other includes at least one subject with one of the following reasons for discontinuation: improvement, factors related to study design, or patient unreliability.

Notes re: discontinued due to AE: Counts of subjects who discontinued due to AEs on Tables 8 & (and corresponding appendices) are based on reasons indicated on the End-of-Study CRF. Counts of subjects who discontinued due to AEs on Table 23 are based on the AE CRF. The discrepancy in counts are for the following subjects: Subj. (b) (6) is counted on Tables 8 & 9 as discontinuing due to AE in both short and long-term phases. Subjects (b) (6) are listed on Table 23 as discontinued due to AEs, but are counted on Tables 8 & 9 as discontinued due to lack of efficacy.

A total of 65 (86.7%) subjects discontinued from the long-term phase, including 25 (86.2%) Org 33062 5 to 45 mg/day, 21 (91.3%) Org 33062 10 to 90 mg/day, and 19 (82.6%) placebo

subjects. The most frequent reason subjects discontinued treatment was data handling discontinuation for the Org 33062 5 to 45 mg/day group (eight or 27.6%), patient withdrew consent for the Org 33062 10 to 90 mg/day group (five or 21.7%), and data handling discontinuation for the placebo group (nine or 39.1%). More Org 5 to 45 mg/day subjects (20.7%) and Org 10 to 90 mg/day subjects (17.4%) than placebo subjects (8.7%) discontinued due to an AE. No deaths were reported during the long-term phase.

#### **CONCOMITANT MEDICATIONS**

A summary of concomitant medications taken by at least 10% of subjects in any treatment group during the study (short-term and long-term phases combined) is presented by therapeutic classification and treatment group for the All-Subjects-Treated population in Table 12.

**Table 12 Concomitant Medications Taken by at Least 10% of Subjects in Any Treatment Group by Therapeutic Classification and Treatment Group (All-Subjects-Treated Population; Combined Short-Term and Long-Term)**

| Therapeutic Classification Medication Category | Org 33062 mg/day        |                          |                                  | Placebo (N=70)<br>N (%) |
|------------------------------------------------|-------------------------|--------------------------|----------------------------------|-------------------------|
|                                                | 5 to 45 (N=71)<br>N (%) | 10 to 90 (N=70)<br>N (%) | Total Org 33062 (N=141)<br>N (%) |                         |
| Any Concomitant Medication                     | 71 (100%)               | 70 (100%)                | 141 (100%)                       | 70 (100%)               |
| Anti-Infective Agents                          | 13 (18.3%)              | 12 (17.1%)               | 25 (17.7%)                       | 20 (28.6%)              |
| Antibiotics                                    | 7 (9.9%)                | 7 (10.0%)                | 14 (9.9%)                        | 15 (21.4%)              |
| Central Nervous System Agents                  | 48 (67.6%)              | 59 (84.3%)               | 107 (75.9%)                      | 51 (72.9%)              |
| Analgesics and Antipyretics                    | 44 (62.0%)              | 52 (74.3%)               | 96 (68.1%)                       | 46 (65.7%)              |
| Nonsteroidal Anti-inflammatory Agents          | 37 (52.1%)              | 7 (9.9%)                 | 79 (56.0%)                       | 33 (47.1%)              |
| Opiate Agonists                                | 15 (21.1%)              | 42 (60.0%)               | 13 (9.2%)                        | 7 (10.0%)               |
| Other Analgesics and Antipyretics              | 21 (29.6%)              | 6 (8.6%)                 | 33 (23.4%)                       | 19 (27.1%)              |
| Anxiolytics, Sedatives and Hypnotics           | 21 (29.6%)              | 18 (25.7%)               | 48 (34.0%)                       | 20 (28.6%)              |
| Other Anxiolytics, Sedatives and Hypnotics     |                         | 46 (25.7%)               | 46 (32.6%)                       | 20 (28.6%)              |
|                                                |                         | 27 (38.6%)               |                                  |                         |
|                                                |                         | 25 (35.7%)               |                                  |                         |

|                                          |               |                   |               |               |
|------------------------------------------|---------------|-------------------|---------------|---------------|
| Respiratory Drugs                        | 29<br>(40.8%) | 22<br>(31.4%)     | 51<br>(36.2%) | 27<br>(38.6%) |
| Antihistamines                           | 7 (9.9%)      | )                 | 13<br>(9.2%)  | 11<br>(15.7%) |
| Cough/Cold<br>Combination<br>Products    | 15<br>(21.1%) | 6<br>(8.6%)       | 28<br>(19.9%) | 18<br>(25.7%) |
| Decongestants                            | 8<br>(11.3%)  | 13<br>(18.6%)     | 15<br>(10.6%) | 3 (4.3%)      |
|                                          |               | 7<br>(10.0%)      |               |               |
| Gastrointestinal<br>Drugs                | 17<br>(23.9%) | 8<br>(11.4%)      | 25<br>(17.7%) | 12<br>(17.1%) |
| Antacids and<br>Adsorbents               | 5 (7.0%)      | )<br>7<br>(10.0%) | 12<br>(8.5%)  | 3 (4.3%)      |
| Hormones and<br>Synthetic<br>Substitutes | 13<br>(18.3%) | 13<br>(18.6%)     | 26<br>(18.4%) | 17<br>(24.3%) |
| Estrogens                                | 9<br>(12.7%)  | )<br>5<br>(7.1%)  | 14<br>(9.9%)  | 13<br>(18.6%) |
| Vitamins and<br>Minerals                 | 11<br>(15.5%) | 13<br>(18.6%)     | 24<br>(17.0%) | 14<br>(20.0%) |
| Multivitamin<br>Preparations             | 9<br>(12.7%)  | )<br>8<br>(11.4%) | 17<br>(12.1%) | 7<br>(10.0%)  |

All subjects in all treatment groups took one or more concomitant medications during the study. The most common concomitant medications taken by subjects in all groups were central nervous system agents, which were taken by more Org 33062 10 to 90 mg/day subjects (84.3%) than Org 33062 5 to 45 mg/day (67.6%) or placebo subjects (72.9%). In this category, analgesics and antipyretics were most often used (62.0% Org 33062 5 to 45 mg/day, 74.3% Org 33062 10 to 90 mg/day, and 65.7% placebo subjects). Subjects most frequently received ibuprofen (21.1% Org 33062 5 to 45 mg/day, 25.7% Org 33062 10 to 90 mg/day, 20.0% placebo), acetamenophen (19.7% Org 33062 5 to 45 mg/day, 22.9% Org 33062 10 to 90 mg/day, 20.0% placebo), and aspirin (32.4% Org 33062 5 to 45

mg/day, 28.6% Org 33062 10 to 90 mg/day, 22.9% placebo). Other medications used by at least 10% of Org 33062 subjects in any treatment group included chloral hydrate (28.2% Org 33062 5 to 45 mg/day, 35.7% Org 33062 10 to 90 mg/day, 28.6% placebo) and multivitamins (12.7% Org 33062 5 to 45 mg/day, 11.4% Org 33062 10 to 90 mg/day, 10.0% placebo).

#### **EXTENT OF EXPOSURE**

A summary of the duration of exposure to study medication by study site and treatment group (combined short-term and long-term phases in the ITT population) is presented in Table 44.

**Table 44 Duration of Exposure to Study Drug by Treatment Group and Study Site (Intent-to-Treat Population; Combined Short-Term and Long-Term)**

| Duration<br>(Days)      | Org 33062 mg/day |             | Placebo        |
|-------------------------|------------------|-------------|----------------|
|                         | 5 to 45          | 10 to 90    |                |
| All Sites<br>Combined   | (N=70)           | (N=67)      | (N=69)         |
| Mean ± SD               | 92.2 ± 90.0      | 78.9 ± 86.1 | 76.7 ±<br>85.2 |
| Median                  | 57.0             | 55.0        | 56.0           |
| Range                   | 1-385            | 1-372       | 5-366          |
| Site 2593<br>(Carman)   | (N=30)           | (N=29)      | (N=30)         |
| Mean ± SD               | 74.9 ± 63.4      | 100 ± 108   | 97.2 ± 118     |
| Median                  | 56.0             | 56.0        | 42.5           |
| Range                   | 8-213            | 1-372       | 5-366          |
| Site 2483<br>(Cole)     | (N=9)            | (N=10)      | (N=9)          |
| Mean ± SD               | 97.6 ± 123       | 69.5 ± 69.8 | 40.2 ± 16.7    |
| Median                  | 56.0             | 49.5        | 43.0           |
| Range                   | 1-385            | 1-178       | 15-63          |
| Site 2485<br>(Haggerty) | (N=31)           | (N=28)      | (N=30)         |
| Mean ± SD               | 107 ± 101        | 60.2 ± 59.1 | 67.2 ± 46.1    |
| Median                  | 63.0             | 54.0        | 57.0           |
| Range                   | 10-359           | 6-281       | 13-280         |

For all sites combined, the mean duration of exposure (days) for subjects in the ITT population was slightly greater for the Org 33062 5 to 45 mg/day group (92.2 days) than the Org 33062 10 to 90 (78.9 days) or the placebo group (76.7 days).

### Medication Compliance

A summary of medication compliance (combined short-term and long-term phases) by treatment group in the All-Subjects-Treated population is shown in Table 45.

**Table 45 Overall Compliance to Study Medication by Treatment Group (All-Subjects-Treated Population; Combined Short-Term and Long-Term)**

| Overall Compliance | Org 33062 mg/day |                 | Placebo (N=70) |
|--------------------|------------------|-----------------|----------------|
|                    | 5 to 45 (N=71)   | 10 to 90 (N=70) |                |
| <70%               | 6 (8%)           | 1 (1%)          | 8 (11%)        |
| 70% - <80%         | 1 (1%)           | 1 (1%)          | 1 (1%)         |
| 80% - <90%         | 4 (6%)           | 5 (7%)          | 9 (13%)        |
| 90% - <100%        | 33 (46%)         | 29 (41%)        | 25 (36%)       |
| 100%               | 5 (7%)           | 12 (17%)        | 6 (9%)         |
| 100% - <120%       | 18 (25%)         | 16 (23%)        | 19 (27%)       |
| ≥120%              | 1 (1%)           | 4 (6%)          | 0 (0%)         |

More Org 33062 5 to 45 mg/day (92%) and Org 33062 10 to 90 mg/day (99%) than placebo (89%) subjects took  $\geq 70\%$  of their scheduled doses. There were no important differences among treatment groups in compliance rates to study medication during the study.

#### **MEDICATION DOSES**

The average daily dose for each subject was calculated from the total of capsules taken by that subject at each dosing interval. Summary statistics were calculated for the maximum modal dose (the most frequently taken dose) by treatment group, for the duration of the entire study (short and long-term phases). The maximum modal dose by treatment group and study site in the ITT population is presented in Table 46.

**Table 46 Maximum Modal Dose by Org 33062 Treatment Group and Study Site (Intent-to-Treat Population; for Duration of Entire Study Combined Short-Term and Long-Term)**

|                         | Org 33062 mg/day                 |                                   |                   |
|-------------------------|----------------------------------|-----------------------------------|-------------------|
|                         | 5 to 45 <sup>a</sup><br>(mg/day) | 10 to 90 <sup>b</sup><br>(mg/day) | Total<br>(mg/day) |
| All Sites<br>Combined   | (N=70)                           | (N=67)                            | (N=137)           |
| Mean ± SD               | 28.1 ± 14.8                      | 42.1 ± 29.2                       | 34.9 ± 24.0       |
| Median                  | 25.0                             | 40.0                              | 30.0              |
| Range                   | 5.0 - 60.0                       | 10.0 - 120                        | 5.0 - 120         |
| Site 2593<br>(Carman)   | (N=30)                           | (N=29)                            | (N=59)            |
| Mean ± SD               | 31.8 ± 15.3                      | 57.2 ± 31.4                       | 44.3 ± 27.5       |
| Median                  | 30.0                             | 60.0                              | 40.0              |
| Range                   | 5.0-60.0                         | 10.0-120                          | 5.0-120           |
| Site 2483<br>(Cole)     | (N=9)                            | (N=10)                            | (N=19)            |
| Mean ± SD               | 28.9 ± 21.2                      | 33.0 ± 29.8                       | 31.1 ± 25.5       |
| Median                  | 40.0                             | 20.0                              | 20.0              |
| Range                   | 5.0 - 60.0                       | 10.0 - 90.0                       | 5.0 - 90.0        |
| Site 2485<br>(Haggerty) | (N=31)                           | (N=28)                            | (N=59)            |
| Mean ± SD               | 24.2 ± 11.3                      | 29.6 ± 18.2                       | 26.8 ± 15.1       |
| Median                  | 25.0                             | 30.0                              | 25.0              |
| Range                   | 5.0 - 45.0                       | 10.0 - 70.0                       | 5.0 - 70.0        |

<sup>a</sup> A dose of up to 60 mg/day was allowable in subjects that tolerated the drug, but had not yet responded.

<sup>b</sup> A dose of up to 120 mg/day was allowable in subjects that tolerated the drug, but had not yet responded.

A dose of up to 60 mg/day was allowable in the Org 33062 5 to 45 mg/day group for subjects who tolerated the study medication, but had not responded. A dose of up to 120 mg/day was allowable in the Org 33062 10 to 90 mg/day group for subjects who tolerated the study medication, but had not responded. The mean maximum modal dose of 28.1 mg/day in the Org 33062 5 to 45 group was 46.8% of the allowable 60 mg/day.

The mean maximum modal dose of 42.1 mg/day in the Org 33062 10 to 90 mg/day group was 35.1% of the allowable 120 mg/day.

There was a difference in the mean maximum modal dose among the study sites in the Org 33062 10 to 90 mg/day treatment group. In the Org 33062 10 to 90 mg/day group, Site 2593 subjects had a mean maximum modal dose of 57.2 mg/day, Site 2483 subjects had a mean maximum modal dose of 33.0 mg/day, and Site 2485 subjects had a mean maximum modal dose of 29.6 mg/day. The mean maximum modal dose in the Org 33062 5 to 45 mg/day group was similar among the study sites.

### **Efficacy results**

#### HAMD 17

The HAMD 17 total score at baseline and the mean change from baseline to each assessment week and endpoint by treatment group and study site in the ITT population (LOCF analysis) are presented in Table 47. A reduction in the total HAMD score generally indicates improvement in the symptoms of depression.

**Table 47 HAMD 17: Mean Change from Baseline Score by Week, Treatment Group, and Study Site in the Short-Term Phase (Intent-to-Treat Population)**

| Treatment Group             | Mean Change from Baseline for the HAMD 17 Total Score: LOCF |        |              |        |               |               |                              |
|-----------------------------|-------------------------------------------------------------|--------|--------------|--------|---------------|---------------|------------------------------|
|                             | Baseline N (Mean)                                           | Week 1 | Week 2       | Week 3 | Week 4        | Week 6        | Week 8/Endpoint <sup>a</sup> |
| <b>All Sites Combined</b>   |                                                             |        |              |        |               |               |                              |
| Org 33062 5 to 45 mg/day    | 70 (23.4)                                                   | -4.1   | -6.9         | -8.2   | -9.2          | <u>-10.2*</u> | <u>-10.0*</u>                |
| Org 33062 10 to 90 mg/day   | 67 (24.4)                                                   | -5.0   | -8.0         | -9.3   | <u>-10.4*</u> | <u>-11.3*</u> | <u>-11.3*</u>                |
| Org 33062 Total             | 137 (23.9)                                                  | -4.7   | -7.5         | -8.8   | <u>-9.9*</u>  | <u>-10.8*</u> | <u>-10.7*</u>                |
| Placebo                     | 69 (24.1)                                                   | -3.3   | -6.0         | -7.1   | -6.3          | -6.6          | -6.4                         |
| <b>Site 2593 (Carman)</b>   |                                                             |        |              |        |               |               |                              |
| Org 33062 5 to 45 mg/day    | 30 (24.7)                                                   | -8.0   | -9.0         | -10.0  | -11.3         | -11.5         | -10.5                        |
| Org 33062 10 to 90 mg/day   | 29 (25.8)                                                   | -6.2   | -9.4         | -10.8  | -10.8         | -10.8         | -10.1                        |
| Org 33062 Total             | 59 (25.2)                                                   | -7.1   | -9.2         | -10.4  | -11.1         | -11.2         | -10.3                        |
| Placebo                     | 30 (26.6)                                                   | -6.9   | -11.0        | -11.3  | -9.8          | -9.5          | -8.5                         |
| <b>Site 2483 (Cole)</b>     |                                                             |        |              |        |               |               |                              |
| Org 33062 5 to 45 mg/day    | 9 (25.1)                                                    | -1.4   | -4.9         | -6.9   | -7.3          | -9.0          | -8.2                         |
| Org 33062 10 to 90 mg/day   | 10 (26.8)                                                   | -6.9   | <u>-9.2*</u> | -10.3  | <u>-12.3*</u> | <u>-13.4*</u> | <u>-13.6*</u>                |
| Org 33062 Total             | 19 (26.0)                                                   | -4.4   | -7.2         | -8.7   | <u>-9.9*</u>  | <u>-11.3*</u> | <u>-11.1*</u>                |
| Placebo                     | 9 (27.2)                                                    | -1.3   | -2.8         | -2.9   | -1.3          | -1.1          | -1.1                         |
| <b>Site 2485 (Haggerty)</b> |                                                             |        |              |        |               |               |                              |
| Org 33062 5 to 45 mg/day    | 31 (21.6)                                                   | -2.9   | -6.9         | -7.5   | -9.1          | -10.0         | -11.3                        |
| Org 33062 10 to 90 mg/day   | 28 (22.2)                                                   | -1.9   | -5.3         | -6.9   | -8.3          | -9.8          | -10.2                        |
| Org 33062 Total             | 59 (21.9)                                                   | -2.4   | -6.1         | -7.3   | -8.7          | -9.9          | -10.8                        |
| Placebo                     | 30                                                          | -1.8   | -4.3         | -7.2   | -7.7          | -9.2          | -9.5                         |

|  |                                                             |  |  |  |  |  |
|--|-------------------------------------------------------------|--|--|--|--|--|
|  | Mean Change from Baseline for the HAMD 17 Total Score: LOCF |  |  |  |  |  |
|  | (20.7)                                                      |  |  |  |  |  |

<sup>a</sup> Last visit for evaluable data for the subject.

\* (underlined) p-value # 0.05 vs. placebo, unadjusted and adjusted for multiple comparisons.

\* p-value # 0.05 vs. placebo, unadjusted for multiple comparisons.

All Sites Combined:

For all sites combined, there were statistically significant differences for the HAMD 17 total scores between the Org 33062 Total group and the placebo group in the ITT population (LOCF analysis) at Week 4 (p=0.006), Week 6 (p=0.002), and Week 8/endpoint (p=0.001). Adjusted p-values for Org 33063 10 to 90 mg/day group versus placebo were statistically significant at Weeks 4, 6, and 8/endpoint (p=0.006, 0.002 and 0.001, respectively). Adjusted p-values for Org 33063 5 to 45 mg/day group versus placebo are significant at Weeks 6 and 8/endpoint (p=0.020 and 0.015, respectively).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

Site 2593 (Carman):

At Site 2593, there were no statistically significant differences for the HAMD 17 total score between the Org 33062 Total group and the placebo group in the ITT (LOCF and OC analyses) and in the Evaluable (LOCF and OC analyses) populations at endpoint.

Site 2483 (Cole):

At Site 2483, there were statistically significant differences for the HAMD 17 total score between the Org 33062 Total group and the placebo group in the ITT population (LOCF analysis) at Week 4 (p=0.009), Week 6 (p=0.006), and Week 8/endpoint (p=0.008). Adjusted and unadjusted p-values for the Org 33062 10 to 90 mg/day group versus placebo comparison are # 0.05 for Weeks 4, 6, and 8/endpoint.

Site 2485 (Haggerty):

At Site 2485, there were no statistically significant differences for the HAMD 17 total score between the Org 33062 Total group and the placebo group in the ITT (LOCF and OC

analyses) and in the Evaluable (LOCF and OC analyses) populations at endpoint.

CGI: Global Improvement Responders

The number and percentage of subjects "much improved" or "very much improved" for the CGI: Global Improvement Responders at each assessment week by treatment group and study site in the ITT population (LOCF analysis) are presented in Table 48.

**Table 48 CGI: Global Improvement Responders: Number (%) of Subjects "Much Improved" or "Very Much Improved" by Week, Treatment Group, and Study Site in the Short-Term Phase (Intent-to-Treat Population)**

| Treatment Group                        | N (%) of Subjects “Much Improved” or “Very Much Improved”:<br>LOCF |             |             |             |                          |                                  |
|----------------------------------------|--------------------------------------------------------------------|-------------|-------------|-------------|--------------------------|----------------------------------|
|                                        | Week 1                                                             | Week 2      | Week 3      | Week 4      | Week 6                   | Week 8/<br>Endpoint <sup>a</sup> |
| <b>All Sites Combined</b>              |                                                                    |             |             |             |                          |                                  |
| Org 33062<br>5 to 45 mg/day<br>(N=70)  | 12<br>(18%)                                                        | 24<br>(35%) | 27<br>(39%) | 34<br>(49%) | 38<br>(54%)*             | 41 (59%)*                        |
| Org 33062<br>10 to 90 mg/day<br>(N=67) | 3 (5%)                                                             | 21<br>(31%) | 28<br>(42%) | 29<br>(43%) | 34<br>(51%) <sup>†</sup> | 37 (55%)*                        |
| Org 33062 Total<br>(N=137)             | 15<br>(12%)                                                        | 45<br>(33%) | 55<br>(40%) | 63<br>(46%) | 72<br>(53%)*             | 78 (57%)*                        |
| Placebo (N=69)                         | 7<br>(11%)                                                         | 23<br>(33%) | 25<br>(36%) | 24<br>(35%) | 26<br>(38%)              | 27 (39%)                         |
| <b>Site 2593 (Carman)</b>              |                                                                    |             |             |             |                          |                                  |
| Org 33062<br>5 to 45 mg/day<br>(N=30)  | 9<br>(30%)                                                         | 13<br>(43%) | 14<br>(47%) | 17<br>(57%) | 18<br>(60%)              | 18 (60%)*                        |
| Org 33062<br>10 to 90 mg/day<br>(N=29) | 2 (7%)                                                             | 13<br>(45%) | 17<br>(59%) | 15<br>(52%) | 16<br>(55%)              | 15 (52%)                         |
| Org 33062 Total<br>(N=59)              | 11<br>(19%)                                                        | 26<br>(44%) | 31<br>(53%) | 32<br>(54%) | 34<br>(58%)              | 33 (56%)*                        |
| Placebo (N=30)                         | 6<br>(21%)                                                         | 13<br>(43%) | 13<br>(43%) | 12<br>(40%) | 12<br>(40%)              | 10 (33%)                         |
| <b>Site 2483 (Cole)</b>                |                                                                    |             |             |             |                          |                                  |
| Org 33062<br>5 to 45 mg/day<br>(N=9)   | 0 (0%)                                                             | 1 (11%)     | 0 (0%)      | 1 (11%)     | 1 (11%)                  | 2 (22%)                          |
| Org 33062<br>10 to 90 mg/day<br>(N=10) | 1<br>(10%)                                                         | 2 (20%)     | 2 (20%)     | 3 (30%)     | 2 (20%)                  | 5 (50%)*                         |
| Org 33062 Total<br>(N=19)              | 1 (6%)                                                             | 3 (16%)     | 2 (11%)     | 4 (21%)     | 3 (16%)                  | 7 (37%)*                         |
| Placebo (N=9)                          | 0 (0%)                                                             | 0 (0%)      | 0 (0%)      | 0 (0%)      | 0 (0%)                   | 0 (0%)                           |
| <b>Site 2485 (Haggerty)</b>            |                                                                    |             |             |             |                          |                                  |
| Org 33062<br>5 to 45 mg/day<br>(N=31)  | 3<br>(11%)                                                         | 10<br>(33%) | 13<br>(42%) | 16<br>(52%) | 19<br>(61%)              | 21 (68%)                         |
| Org 33062<br>10 to 90 mg/day<br>(N=28) | 0 (0%)                                                             | 6 (21%)     | 9 (32%)     | 11<br>(39%) | 16<br>(57%)              | 17 (61%)                         |
| Org 33062 Total<br>(N=59)              | 3 (6%)                                                             | 16<br>(28%) | 22<br>(37%) | 27<br>(46%) | 35<br>(59%)              | 38 (64%)                         |
| Placebo (N=30)                         | 1 (4%)                                                             | 10<br>(33%) | 12<br>(40%) | 12<br>(40%) | 14<br>(47%)              | 17 (57%)                         |

All Sites Combined:

For all sites combined, there were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 Total group and the placebo group in the ITT population (LOCF analysis) at Week 6 ( $p=0.032$ ), and Week 8/endpoint ( $p=0.013$ ). There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 5 to 45 mg/day group and the placebo group in the ITT population (LOCF analysis) at Week 6 ( $p=0.042$ ) and Week 8/endpoint ( $p=0.018$ ). There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 10 to 90 mg/day group and the placebo group in the ITT population (LOCF analysis) at Week 8/endpoint ( $p=0.050$ ).

These results are consistent with the other analyses, including the OC analysis in the ITT population and the LOCF and OC analyses in the Evaluable population.

Site 2593 (Carman):

For Site 2593, there were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 Total group and the placebo group in the ITT population (LOCF analysis) at Week 8/endpoint ( $p=0.040$ ). There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 5 to 45 mg/day group and the placebo group in the ITT population (LOCF analysis) at Week 8/endpoint. The difference in the proportion of CGI responders in the Org 33062 10-90 mg/day vs placebo groups approached significance ( $p - 0.040$ ).

Site 2483 (Cole):

For Site 2483, there were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 Total group and the placebo group in the ITT population (LOCF analysis) at Week 8/endpoint ( $p=0.039$ ). There were statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 10 to 90 mg/day group and the placebo group in the ITT population (LOCF analysis) at Week 8/endpoint.

Site 2485 (Haggerty):

For site 2485, there were no statistically significant differences for the CGI: Global Improvement Responders between the Org 33062 Total group and the placebo group in the ITT population (LOCF and OC analysis) or the Evaluable population (LOCF and OC analysis).

It should be noted that all p-values in the above section are unadjusted for multiple comparisons.

Please see summary table below for additional efficacy measures:

Table 52 Summary of Selected Efficacy Parameters at Endpoint for the Short-Term Phase by Treatment Group and Study Site:  
Intent-to-Treat Population (LOCF Analysis)

| Parameters                                                                     | Mean Change from Baseline to Endpoint and Percent Responders |             |            |           |                              |           |                   |           |                   |             |                   |           |           |           |           |           |
|--------------------------------------------------------------------------------|--------------------------------------------------------------|-------------|------------|-----------|------------------------------|-----------|-------------------|-----------|-------------------|-------------|-------------------|-----------|-----------|-----------|-----------|-----------|
|                                                                                | Org 33062<br>5 to 45 mg/day                                  |             |            |           | Org 33062<br>10 to 90 mg/day |           |                   |           | Total Org 33062   |             |                   |           | Placebo   |           |           |           |
| Primary Efficacy Parameters in the Intent-to-Treat Population: LOCF Analysis   |                                                              |             |            |           |                              |           |                   |           |                   |             |                   |           |           |           |           |           |
|                                                                                | All Sites                                                    | Site 2593   | Site 2483  | Site 2485 | All Sites                    | Site 2593 | Site 2483         | Site 2485 | All Sites         | Site 2593   | Site 2483         | Site 2485 | All Sites | Site 2593 | Site 2483 | Site 2485 |
| HAMD 17                                                                        | -<br><u>10.0*</u>                                            | -10.5       | -8.2       | -11.3     | -<br><u>11.3*</u>            | -10.1     | -<br><u>13.6*</u> | -10.2     | -<br><u>10.7*</u> | -<br>10.3   | -<br><u>11.1*</u> | -<br>10.8 | -6.4      | -8.5      | -1.1      | -9.5      |
| CGI: Global Improvement Responders                                             | <u>59%*</u>                                                  | <u>60%*</u> | 22%        | 68%       | <u>55%*</u>                  | 52%       | <u>50%*</u>       | 61%       | <u>57%*</u>       | <u>56%*</u> | <u>37%*</u>       | 64%       | 39%       | 33%       | 0%        | 57%       |
| Secondary Efficacy Parameters in the Intent-to-Treat Population: LOCF Analysis |                                                              |             |            |           |                              |           |                   |           |                   |             |                   |           |           |           |           |           |
| HAMD 25                                                                        | -<br><u>13.4*</u>                                            | -13.1       | -<br>12.5* | -14.5     | -<br><u>14.4*</u>            | -12.7     | -<br><u>17.4*</u> | -13.0     | -<br><u>13.9*</u> | -<br>12.9   | -<br><u>15.1*</u> | -13.8     | -7.9      | -9.5      | -1.8      | -12.5     |
| HAMD Item 1                                                                    | -1.1*                                                        | -1.4        | -0.9       | -1.2      | <u>-1.3*</u>                 | -1.2      | <u>-1.7*</u>      | -1.1      | <u>-1.3*</u>      | -1.3        | <u>-1.3*</u>      | -1.2      | -0.7      | -0.9      | -0.1      | -1.0      |
| HAMD 17 Responders                                                             | 57%*                                                         | 53%         | 33%        | 68%       | 48%                          | 41%       | 50%               | 54%       | 53%               | 47%         | 42%               | 61%       | 41%       | 40%       | 11%       | 50%       |
| MADRS                                                                          | -<br><u>14.0*</u>                                            | -14.4       | -11.6      | -16.1     | -<br><u>15.2*</u>            | 14.2      | -<br><u>17.6*</u> | -13.7     | -<br><u>14.6*</u> | -<br>14.3   | -<br><u>14.6*</u> | -14.9     | -8.1      | -10.3     | -1.0      | -13.2     |

\* (Underlined) p-value # 0.05 vs. placebo unadjusted and adjusted for multiple comparisons.

\* Unadjusted p-value # 0.05 vs. placebo.

## Primary Efficacy Parameters

### All Sites Combined:

For all sites combined, there were statistically significant differences between the Org 33062 Total group, the Org 33062 5 to 45 mg/day group, and the Org 33062 10 to 90 mg/day group versus the placebo group for the primary efficacy parameters, HAMD 17 and the CGI: Global Improvement Responders, in the ITT population (LOCF analyses) at endpoint.

### Site 2593 (Carman):

At Site 2593, there were no statistically significant differences between the Org 33062 Total group and the placebo group for the primary efficacy parameter, HAMD 17, in the ITT population (LOCF analysis) at endpoint; however, there was a statistically significant difference for the primary efficacy parameter, CGI: Global Improvement Responders, at endpoint for the Org 33062 Total group and the Org 33062 5 to 45 mg/day group.

### Site 2483 (Cole):

At Site 2483, there were statistically significant differences between the Org 33062 Total group and the Org 33062 10 to 90 mg/day group versus the placebo group for the primary efficacy parameters, HAMD 17 and CGI: Global Improvement Responders, in the ITT population (LOCF analysis) at endpoint.

### Site 2485 (Haggerty):

At Site 2485, there were no statistically significant differences between the Org 33062 group and the placebo group for the primary efficacy parameters, HAMD 17 and CGI: Global Improvement Responders in the ITT population (LOCF analysis) at endpoint.

For all sites combined, there were statistically significant differences between the Org 33062 Total group and the placebo group at endpoint for the primary efficacy parameters, HAMD 17 change from baseline and the CGI: Global Improvement Responders, in the ITT population (LOCF analysis). A treatment by center interaction was present for the HAMD 17 total score with one center (2483:Cole) indicating that the Org 33062 Total group was superior to the placebo group (and the other two indicating that there was no difference) and for the CGI: Global Improvement Responders with two centers (2483:Cole; 2593: Carman) indicating that the Org 33062 Total

group was superior to the placebo group (and the remaining center indicating that there was no difference).

## Secondary Efficacy Parameters

### All Sites Combined:

For all sites combined, there were statistically significant differences between the Org 33062 Total group and the placebo group for the secondary efficacy parameters, HAMD 25, HAMD Item 1, and MADRS, in the ITT population (LOCF analyses) at endpoint. For all sites combined, there was no statistically significant difference between the Org 33062 Total group and the placebo group for the secondary efficacy parameter, HAMD 17 Responders, in the ITT population (LOCF analyses) at endpoint. Results for the individual dose groups are presented in Table 22 and Appendix F.

### Site 2593 (Carman):

At Site 2593, there were no statistically significant differences between the Org 33062 Total group and the placebo group for the secondary efficacy parameters, HAMD 25, HAMD Item 1, HAMD 17 Responders, and MADRS, in the ITT population (LOCF analysis) at endpoint.

### Site 2483 (Cole):

At Site 2483, there were statistically significant differences between the Org 33062 total group and the placebo group for the secondary efficacy parameters, HAMD 25, HAMD Item 1, and MADRS, in the ITT population (LOCF analysis) at endpoint.

### Site 2485 (Haggerty):

At Site 2485, there were no statistically significant differences between the Org 33062 Total group and the placebo group for the secondary efficacy parameters, HAMD 25, HAMD Item 1, HAMD 17 Responders, and MADRS, in the ITT population (LOCF analysis) at endpoint.

## Long-Term Phase

Due to the patient selection and the relatively low numbers of subjects in the long-term phase no meaningful analyses could be performed.

## Conclusion

This study (short term) is positive as per the sponsor's analysis above and I consider it a positive study because of this.

Though the sponsor followed their protocols, ICH E9 guidance on modeling multi-center trials was not followed according to the FDA statisticians. They claim a significant Treatment-by-Center interaction in Study 03A7C-001-B was instrumental for observing small P-values in the sponsor's analyses . They conclude *"The treatment effect can be attributed mostly to one, the smallest, center. In addition, this study had the highest dropout rates. Therefore, Study 03A7C-001-B as a whole may not provide support of the efficacy claim."* Please see stat review.

## **Efficacy Summary**

Table 26 provides a summary of key efficacy results in the 14 other sponsor defined adequate and well controlled studies, including 7 placebo-controlled studies and 7 placebo- and active-controlled studies. Results are briefly discussed by study.

**Table 26 Summary of Key Efficacy Results in Other Adequate and Well Controlled Studies by Study and Treatment Group (Intent-to-Treat, LOCF Data Set)**

| Treatment Group (mg/day)          | N   | Mean Dose ± SD mg/day | HAMD 17                        | HAMD 17                                                    | HAMD 17                                 | CGI Responders at Endpoint <sup>a</sup> (%) | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                    |                |       |
|-----------------------------------|-----|-----------------------|--------------------------------|------------------------------------------------------------|-----------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------|-------------|--------------------|----------------|-------|
|                                   |     |                       | Mean Baseline Total Score ± SD | Mean Reduction from Baseline at Endpoint <sup>a</sup> ± SE | Responders at Endpoint <sup>a</sup> (%) |                                             | HAMD 17 Mean Reduction from Baseline                                        | HAMD Item 1 | HAMD 17 Responders | CGI Responders | MADRS |
| <b>Placebo-controlled studies</b> |     |                       |                                |                                                            |                                         |                                             |                                                                             |             |                    |                |       |
| 134002                            |     |                       |                                |                                                            |                                         |                                             |                                                                             |             |                    |                |       |
| Org 33062 ER 20-80 mg/day         | 107 | 68.2 ± 15.5           | 24.0 ± 2.8                     | 10.0 ± 0.7                                                 | 40                                      | 52                                          | NS                                                                          | 2, 3, 6, 8  | NS                 | NS             | NA    |
| Placebo                           | 104 | --                    | 24.1 ± 2.9                     | 9.3 ± 0.7                                                  | 32                                      | 45                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-078 <sup>b</sup>            |     |                       |                                |                                                            |                                         |                                             |                                                                             |             |                    |                |       |
| Org 33062 Total                   | 88  | 40.5 ± 17.4           | 22.3 ± 2.5                     | 7.4 ± 0.7                                                  | 34                                      | 52                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 10-50 mg/day         | 48  | 30.4 ± 8.1            | 22.7 ± 2.9                     | 7.5 ± 0.9                                                  | 33                                      | 50                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 20-100 mg/day        | 40  | 52.6 ± 17.8           | 21.9 ± 1.8                     | 7.5 ± 1.0                                                  | 35                                      | 55                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Placebo                           | 47  | ---                   | 22.9 ± 2.4                     | 6.5 ± 0.9                                                  | 28                                      | 38                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-083                         |     |                       |                                |                                                            |                                         |                                             |                                                                             |             |                    |                |       |
| Org 33062 ER Total                | 73  | 43.9 ± 18.9           | 23.9 ± 3.4                     | 9.4 ± 0.9                                                  | 45                                      | 52                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 10-50 mg/day         | 36  | 30.4 ± 7.0            | 24.8 ± 4.2                     | 9.8 ± 1.3                                                  | 47                                      | 50                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 20-100 mg/day        | 37  | 57.1 ± 17.6           | 23.1 ± 2.0                     | 9.2 ± 1.3                                                  | 43                                      | 54                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Placebo                           | 39  | ---                   | 24.0 ± 3.5                     | 8.9 ± 1.3                                                  | 44                                      | 44                                          | --                                                                          | --          | --                 | --             | --    |

**Table 26 Summary of Key Efficacy Results in Other Adequate and Well Controlled Studies by Study and Treatment Group (Continued) (Intent-to-Treat, LOCF Data Set)**

| Treatment Group (mg/day)  | N  | Mean Dose ± SD mg/day | HAMD 17                        | HAMD 17                                                    | HAMD 17                                 | CGI                                     | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                    |                |       |
|---------------------------|----|-----------------------|--------------------------------|------------------------------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------|-------------|--------------------|----------------|-------|
|                           |    |                       | Mean Baseline Total Score ± SD | Mean Reduction from Baseline at Endpoint <sup>a</sup> ± SE | Responders at Endpoint <sup>a</sup> (%) | Responders at Endpoint <sup>a</sup> (%) | HAMD 17 Mean Reduction from Baseline                                        | HAMD Item 1 | HAMD 17 Responders | CGI Responders | MADRS |
| CN105-057                 |    |                       |                                |                                                            |                                         |                                         |                                                                             |             |                    |                |       |
| Org 33062 ER 2-4 mg/day   | 49 | 3.6 ± 1.7             | 24.3 ± 2.9                     | 8.1 ± 1.0                                                  | 27                                      | 35                                      | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 5-10 mg/day  | 49 | 9.3 ± 4.4             | 23.6 ± 3.0                     | 8.9 ± 1.0                                                  | 39                                      | 47                                      | NS                                                                          | NS          | 1, 2               | 6              | NS    |
| Org 33062 ER 10-20 mg/day | 49 | 19.1 ± 8.2            | 23.9 ± 2.9                     | 7.0 ± 1.0                                                  | 31                                      | 45                                      | NS                                                                          | NS          | 1                  | NS             | NS    |
| Org 33062 ER 20-40 mg/day | 49 | 33.8 ± 16.5           | 23.8 ± 2.8                     | 8.7 ± 1.0                                                  | 41                                      | 51                                      | NS                                                                          | NS          | 4                  | NS             | NS    |
| Placebo                   | 49 | ---                   | 24.3 ± 3.3                     | 9.3 ± 1.0                                                  | 27                                      | 33                                      | --                                                                          | --          | --                 | --             | --    |
| CN105-043                 |    |                       |                                |                                                            |                                         |                                         |                                                                             |             |                    |                |       |
| Org 33062 5-30 mg/day     | 59 | 17.0 ± 4.3            | 19.9 ± 3.8                     | 7.4 ± 1.0                                                  | 47                                      | 54                                      | NS                                                                          | NS          | NS                 | NS             | n/a   |
| Placebo                   | 60 | --                    | 20.3 ± 4.0                     | 8.4 ± 1.0                                                  | 45                                      | 50                                      | --                                                                          | --          | --                 | --             | --    |
| 03A7C-001A-2496           |    |                       |                                |                                                            |                                         |                                         |                                                                             |             |                    |                |       |
| Org 33062 IR Total        | 77 | 35.7 ± 29.0           | 24.4 ± 3.2                     | 7.1 ± 0.9                                                  | 26                                      | 32                                      | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 IR 5-45 mg/day  | 39 | 24.6 ± 17.0           | 24.5 ± 3.2                     | 7.6 ± 1.2                                                  | 31                                      | 36                                      | NS                                                                          | NS          | 3                  | NS             | NS    |
| Org 33062 IR 10-90 mg/day | 38 | 47.1 ± 34.2           | 24.4 ± 3.2                     | 6.7 ± 1.3                                                  | 21                                      | 29                                      | NS                                                                          | NS          | NS                 | NS             | NS    |
| Placebo                   | 41 | --                    | 24.7 ± 3.2                     | 9.8 ± 1.2                                                  | 41                                      | 46                                      | --                                                                          | --          | --                 | --             | --    |
| 03A7C-001-2486            |    |                       |                                |                                                            |                                         |                                         |                                                                             |             |                    |                |       |
| Org 33062 IR Total        | 83 | 27.9 ± 13.5           | 26.1 ± 4.5                     | 8.0 ± 0.8*                                                 | 34                                      | 57                                      | 1-4, 6, 8                                                                   | NS          | NS                 | 6              | NS    |
| Org 33062 IR 5-45 mg/day  | 42 | 22.0 ± 8.6            | 25.9 ± 4.7                     | 7.7 ± 1.1                                                  | 29                                      | 55                                      | 4                                                                           | NS          | NS                 | NS             | NS    |
| Org 33062 IR 10-90 mg/day | 41 | 33.9 ± 15.1           | 26.2 ± 4.4                     | 8.3 ± 1.1*                                                 | 39                                      | 59                                      | 1, 3, 4, 6, 8                                                               | NS          | NS                 | NS             | NS    |
| Placebo                   | 38 | --                    | 24.9 ± 3.8                     | 4.9 ± 1.2                                                  | 26                                      | 39                                      | --                                                                          | --          | --                 | --             | --    |

**Table 26 Summary of Key Efficacy Results in Other Adequate and Well Controlled Studies by Study and Treatment Group (Continued) (Intent-to-Treat, LOCF Data Set)**

| Treatment Group (mg/day)                      | N  | Mean Dose ± SD mg/day | HAMD 17 Mean Baseline Total Score ± SD | HAMD 17 Mean Reduction from Baseline at Endpoint <sup>a</sup> ± SE | HAMD 17 Responders at Endpoint <sup>a</sup> (%) | CGI Responders at Endpoint <sup>a</sup> (%) | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                    |                |       |
|-----------------------------------------------|----|-----------------------|----------------------------------------|--------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------|-------------|--------------------|----------------|-------|
|                                               |    |                       |                                        |                                                                    |                                                 |                                             | HAMD 17 Mean Reduction from Baseline                                        | HAMD Item 1 | HAMD 17 Responders | CGI Responders | MADRS |
| <b>Placebo- and active-controlled studies</b> |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| CN105-052                                     |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 ER 20-60 mg/day                     | 35 | 38.7 ± 13.7           | 25.5 ± 3.2                             | 11.0 ± 1.5                                                         | 49                                              | 60                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Fluoxetine 20-80 mg/day                       | 36 | 23.3 ± 10.2           | 25.2 ± 2.6                             | 11.0 ± 1.5                                                         | 50                                              | 67                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Placebo                                       | 37 | ---                   | 25.2 ± 3.3                             | 10.5 ± 1.4                                                         | 43                                              | 57                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-053                                     |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 ER 10-60 mg/day                     | 15 | 46.4 ± 12.9           | 23.9 ± 3.1                             | 9.7 ± 1.2                                                          | 43                                              | 54                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Imipramine 50-200 mg/day                      | 15 | 145 ± 32.1            | 24.2 ± 2.9                             | 11.5 ± 1.2                                                         | 54                                              | 72**                                        | 2                                                                           | NS          | 4                  | 2-4, 6, 8      | NS    |
| Placebo                                       | 16 | --                    | 24.2 ± 2.9                             | 9.0 ± 1.2                                                          | 38                                              | 39                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-064                                     |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 ER 5-20 mg/day                      | 23 | 11.6 ± 2.6            | 24.2 ± 3.0                             | 7.3 ± 1.8                                                          | 39                                              | 43                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Org 33062 ER 10-40 mg/day                     | 23 | 22.5 ± 7.1            | 24.9 ± 3.6                             | 8.7 ± 1.8                                                          | 43                                              | 52                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Imipramine 50-200 mg/day                      | 19 | 96.7 ± 42.4           | 23.4 ± 3.5                             | 10.8 ± 2.0                                                         | 53                                              | 53                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Placebo                                       | 21 | --                    | 23.8 ± 2.6                             | 9.7 ± 1.9                                                          | 48                                              | 52                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-037                                     |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 IR 2-12 mg/day                      | 65 | 5.8 ± 2.2             | 24.2 ± 3.6                             | 10.7 ± 1.1                                                         | 49                                              | 55                                          | NS                                                                          | 3           | NS                 | NS             | n/a   |
| Org 33062 IR 5-30 mg/day                      | 61 | 13.5 ± 4.5            | 24.8 ± 3.3                             | 9.8 ± 1.1                                                          | 43                                              | 48                                          | NS                                                                          | NS          | NS                 | NS             | n/a   |
| Imipramine 50-300 mg/day                      | 65 | 117 ± 44.4            | 24.5 ± 3.6                             | 13.2 ± 1.1                                                         | 58                                              | 69                                          | NS                                                                          | 8           | NS                 | NS             | n/a   |
| Placebo                                       | 63 | ---                   | 24.4 ± 3.4                             | 10.8 ± 1.1                                                         | 44                                              | 57                                          | --                                                                          | --          | --                 | --             | --    |

**Table 26 Summary of Key Efficacy Results in Other Adequate and Well Controlled Studies by Study and Treatment Group (Continued) (Intent-to-Treat, LOCF Data Set)**

| Treatment Group (mg/day) | N  | Mean Dose ± SD mg/day | HAMD 17 Mean Baseline Total Score ± SD | HAMD 17 Mean Reduction from Baseline at Endpoint <sup>a</sup> ± SE | HAMD 17 Responders at Endpoint <sup>a</sup> (%) | CGI Responders at Endpoint <sup>a</sup> (%) | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                    |                |       |
|--------------------------|----|-----------------------|----------------------------------------|--------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------|-----------------------------------------------------------------------------|-------------|--------------------|----------------|-------|
|                          |    |                       |                                        |                                                                    |                                                 |                                             | HAMD 17 Mean Reduction from Baseline                                        | HAMD Item 1 | HAMD 17 Responders | CGI Responders | MADRS |
| CN105-022                |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 IR 5-30 mg/day | 67 | 15.4 ± 5.1            | 23.7 ± 3.0                             | 8.6 ± 0.8                                                          | 33                                              | 58                                          | 2                                                                           | 2           | NS                 | 2              | n/a   |
| Fluoxetine 20-40 mg/day  | 67 | 28.4 ± 6.6            | 23.9 ± 3.0                             | 12.2 ± 0.8**                                                       | 55**                                            | 81**                                        | 1-4, 6, 8                                                                   | 2-4, 6, 8   | 3, 6, 8            | 3, 4, 6, 8     | n/a   |
| Placebo                  | 69 | ---                   | 23.3 ± 2.5                             | 7.5 ± 0.8                                                          | 30                                              | 45                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-029                |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 IR 5-45 mg/day | 18 | 15.3 ± 5.4            | 24.8 ± 3.2                             | 4.8 ± 1.7                                                          | 11                                              | 6                                           | NS                                                                          | 4, 6        | NS                 | NS             | n/a   |
| Imipramine 25-150 mg/day | 19 | 71.0 ± 27.9           | 24.2 ± 3.7                             | 10.8 ± 1.7                                                         | 47                                              | 53                                          | NS                                                                          | 6           | 3                  | 3              | n/a   |
| Placebo                  | 18 | ---                   | 23.0 ± 2.5                             | 8.3 ± 1.7                                                          | 22                                              | 28                                          | --                                                                          | --          | --                 | --             | --    |
| CN105-028                |    |                       |                                        |                                                                    |                                                 |                                             |                                                                             |             |                    |                |       |
| Org 33062 IR 5-30 mg/day | 68 | 13.4 ± 6.4            | 27.1 ± 4.5                             | 12.2 ± 1.0                                                         | 51                                              | 69                                          | NS                                                                          | NS          | NS                 | NS             | NS    |
| Imipramine 50-300 mg/day | 71 | 118 ± 56.8            | 27.1 ± 4.7                             | 14.1 ± 1.0                                                         | 56                                              | 75                                          | 1-3                                                                         | 1-3         | NS                 | NS             | NS    |
| Placebo                  | 68 | ---                   | 26.4 ± 4.5                             | 12.1 ± 1.1                                                         | 50                                              | 60                                          | --                                                                          | --          | --                 | --             | --    |

Note: Data shown were reproduced from Tables 18-20 and 22 and Post-Text Tables 6-9 and 12 in the Integrated Summary of Efficacy and from Appendix F8.6.1.2.9-3 and F8.6.1.2.1-1 for Protocol 134002 and from Appendix F, Tables 7.2.2-3, 7.2.3-1, and 7.2.4-3 (if applicable), of the clinical study report for all other studies.

CGI = Clinical Global Impression; ER = Extended release; HAMD = Hamilton Depression Scale; IR = Immediate release; LOCF = Last observation carried forward; MADRS = Montgomery and Åsberg Depression Rating Scale; n/a = Not analyzed; NS = Not statistically significant (p>0.05)

<sup>a</sup> Last visit with evaluable data for the subject. Values at Week 8 LOCF (or Week 6 for Protocols CN105-078 and CN105-083) are identical to Endpoint values.

\* Indicates significance at p≤0.05, \*\* p≤0.01. P values are derived from a pairwise comparison with placebo using Cochran-Mantel-Haenszel test for the CGI-Responders and from ANOVA for the HAMD 17 change from baseline score.

## **OTHER STUDIES NOT STATISTICALLY SIGNIFICANT**

Study 134002

### **Objectives**

Primary:

To evaluate the therapeutic efficacy of Org 33062 extended release (ER) in comparison with placebo at the endpoint of an eight-week treatment period in subjects with major depressive disorder (diagnosed according to DSM-IV criteria).

Secondary:

To describe the safety profile of eight weeks treatment with Org 33062 ER in comparison with placebo in subjects with major depression, To evaluate the efficacy of Org 33062 ER in reducing anxiety in subjects with major depression, and to evaluate the therapeutic efficacy of Org 33062 ER in patients with atypical depression.

### **Methodology**

This was to be a double-blind, placebo-controlled, parallel group, multicenter, trial of Org 33062 ER in the treatment of moderately to severely depressed outpatients. Each subject was to participate in a 7-day screening (placebo wash-out) period designed to ensure that all eligibility criteria had been met. Subjects who met all eligibility requirements were to be randomized to receive either placebo or Org 33062 ER (20 mg to 80 mg) once per day in the morning. Subjects were to be informed that the purpose of the first week of medication was to determine the medication's acceptability to the subject and that a final determination of suitability for the trial was to be conducted at the next visit. The investigator was to instruct the subject to begin taking tablets the next day. Subjects in the Org 33062 ER group were to take 20 mg Org 33062 ER and one placebo tablet once daily in the morning with food. At Day 4 (not a clinic visit ), the subject was to take two tablets of Org 33062 ER and no placebo tablets. This increase in dose was mandatory. The subject was not to be informed of the day the dose would increase, only that the titration would occur in the first fourteen days of the trial. The dose could be increased to 60 mg qd after seven days and to 80 mg qd after fourteen days. The investigator could titrate the dose between 40 mg and 80 mg qd as needed to

optimize the therapeutic response and tolerance after Visit 2 (Day 14).

The active treatment duration was to be eight weeks, during which subjects were to be monitored for efficacy and safety. Following active treatment, a follow-up assessment was to be conducted one week after the last dose. As per Amendment 2, (April 19, 2000), a 30-day follow-up for SAE inquiry was included in the protocol.

**Number of subjects (total and for each treatment)**

A total of 218 subjects were in the All-Subjects-Treated Group, including 110 in the Org 33062 treatment group and 108 in the placebo treatment group.

**Diagnosis and criteria for inclusion**

Prospective subjects were to meet all of the following criteria to be included in the trial:

be at least 18 and not more than 70 years of age (as per Amendment 2 , [April 19, 2000], amended from 64 years of age).

meet diagnostic criteria for moderate to severe major depressive disorder according to the DSM-IV criteria (296.22, 296.23, 296.32, 296.33 only)

have a total score of 20 or greater on the HAMD-17 at both screening and baseline assessments

have significant daily dysphoria for the past four weeks, and  
provide written informed consent

Test product, dose and mode of administration, batch No. Org 33062 (gepirone HCl) (batch number: 0581393) was administered as ER tablets containing 20 mg of active dose.

Subjects were to be administered 20-80 mg of Org 33062, orally, in the morning after breakfast.

Duration of treatment

Screen period:

Seven days during which subjects were to receive one screening interview followed by two placebo tablets daily until the baseline interview.

Active treatment:

Fifty-six days to allow for scheduling difficulties.

Follow-up:

Seven days after final dose of the Investigational Product (IP).

Thirty days after final dose of the IP (as per Amendment 2 , [April 19, 2000])

Extension:

Forty-four weeks open-label.

Criteria for evaluation

Efficacy was to be assessed using the Hamilton Depression Rating Scale (primary: HAMD-17; secondary: HAMD-17 responders and remitters HAMD-21, HAMD-28, Montgomery-Åsberg Depression Rating Scale (MADRS), HAMD item 1 (depressed mood), the Clinical Global Impression (CGI ), HAMD anxiety/somatization factor (Factor 1), HAMD item 12 (psychic anxiety) and HAMD-25. Rater training on conventions to be used for the HAMD and efficacy measures were to occur at the Investigator's Meeting; rater performance was to be assessed during the trial. Safety evaluations to be completed included the following: symptoms were to be recorded at screening and baseline.

. As per Amendment 1 (June 24, 1999), sexual function was to be assessed by the Derogatis Inventory for Sexual Function - Self-Report (DISF-SR) at baseline and at endpoint.

. Vital signs: Blood pressure, heart rate, and body weight were to be recorded at every visit. Height was to be recorded at the screening visit.

. Physical exams and laboratory evaluations were to be performed at the screening visit and at the endpoint. Urine drug screens were to be performed at the screening visit. ECGs were to be collected at screening and at endpoint.

. Pregnancy testing was to be performed at the screening visit and whenever the investigator felt it was warranted. Birth-control methods for females were to be reviewed monthly.

. One week and one month after treatment was completed, a follow-up interview was to be done to evaluate any after effects of drug treatment. As per Amendment 2 (April 19, 2000), a 30-day follow-up was to be included in the protocol to inquire about SAEs. This follow-up interview was to be deferred for subjects entering the open-label extension. Deferred follow-up interviews were to be administered under protocol 134501.

## Statistical methods

Demographic and other baseline subject characteristics, duration of exposure to trial medication, compliance to trial medication, dosing information, and use of concomitant medication were summarized by treatment group.

The primary efficacy variable was the change from baseline in the HAMD-17 total score, with the endpoint as the primary time point. Secondary efficacy variables included the change from baseline in the HAMD-21, HAMD-25 and HAMD-28 total scores; the number (%) of HAMD-17 responders and remitters, the number (%) of HAMD-25 responders; the CGI-improvement score; change from baseline in HAMD item 1 (depressed mood), HAMD anxiety/somatization factor (Factor 1), HAMD item 12 (psychic anxiety), MADRS and CGI-severity scores. Descriptive statistics by treatment group were provided at each visit for each of the efficacy variables. For all continuous variables analyzed, an ANOVA was carried out with treatment and center as factors. For categorical variables, analyses were performed using the CMH test, adjusting for center. All statistical tests were two-sided and considered statistically significant if the p-value was  $\leq 0.05$ . The incidence of adverse events was summarized by treatment group. Similarly, changes in laboratory parameters, vital sign measurements and ECGs were also summarized. Subjects with clinically significant changes from baseline on these parameters were identified. No statistical comparisons were performed for any of the safety parameters.

## Summary

### Summary of efficacy:

The efficacy evaluation was based on the Intent-to-Treat Group. The primary time-point for treatment comparisons was the endpoint assessment, also referred to as Visit 6/end of trial using the LOCF approach. The primary statistical analysis approach used was LOCF.

The primary efficacy parameter was the change from baseline in the (re-calculated) HAMD-17 total score based on the LOCF analysis of the Intent-to-Treat Group. At each visit, there was no statistically significant difference in the change from baseline in HAMD-17 total score based on the LOCF analysis for the Intent-to-Treat Group. Results of analyses for the secondary efficacy parameters have shown that at each visit, there was no statistically significant difference between the Org 33062 and placebo treatment groups in the number (%) of

HAMD-17 responders and remitters based on the LOCF analysis for the Intent-to-Treat Group. However, results based on the OC analysis have shown that a statistically significant difference in the number (%) of HAMD-17 responders at Visit 6 ( $p = 0.044$ ); and a marginally significant difference ( $0.05 < p = 0.10$ ), in favor of Org 33062, at Visits 3 and 4. At each visit, there was no statistically significant difference in the change from baseline in HAMD-21 and HAMD-28 total scores based on the LOCF analysis for the Intent-to-Treat Group. A marginally significant difference ( $0.05 < p = 0.10$ ), in favor of Org 33062, was observed at Visit 2 in the change from baseline in the HAMD-28 total score. Results based on the OC analysis have shown that a statistically significant difference between the 2 treatment groups in the change from baseline in the HAMD-28 total score was observed at Visit 2 ( $p = 0.020$ ).

A statistically significant difference between the 2 treatment groups in the HAMD item 1 (depressed mood) score was noted at Visits 2, 3, 5, and 6/end of trial ( $p = 0.050$ ) based on the LOCF analysis for the Intent-to-Treat Group; and a marginally significant difference ( $0.05 < p = 0.10$ ), in favor of Org 33062, was observed in the change from baseline in the HAMD item 1 (depressed mood) score at Visit 1. At Visit 6/end of trial, the statistically significant ( $p = 0.036$ ) difference between the 2 treatment groups was 0.29 points, in favor of Org 33062.

At each visit, there was no statistically significant difference between the Org 33062 and placebo treatment groups in the number (%) of CGI responders. However, a marginally significant difference ( $0.05 < p = 0.10$ ), in favor of Org 33062, was observed in the percentage of CGI responders at Visits 3 and 4 based on the LOCF analysis for the Intent-to-Treat Group. Results based on the OC analysis have shown that a statistically significant difference between the 2 treatment groups was observed at Visits 3 ( $p = 0.043$ ) and Visit 4 ( $p = 0.027$ ).

A statistically significant difference between the Org 33062 and placebo treatment groups was observed in the change from baseline in the CGI severity at Visit 2 ( $p = 0.040$ ; 0.17 points difference in favor of Org 33062) based on the LOCF analysis for the Intent-to-Treat Group. A statistically significant difference between the 2 treatment groups in the CGI improvement score was noted at Visit 2 ( $p = 0.023$ ; - 0.26 points difference in favor of Org 33062) and Visit 4 ( $p =$

0.013; - 0.37 points difference in favor of Org 33062); and a marginally significant difference (0.05 p=0.10), in favor of Org 33062, was observed at Visits 1 and 3 based on the LOCF analysis for the Intent-to-Treat Group.

At each visit, there was no statistically significant difference in the change from baseline in HAMD anxiety/somatization factor (Factor I) based on the LOCF analysis for the Intent-to-Treat Group. However, a statistically significant difference between the 2 treatment groups was observed in the change from baseline in HAMD item 12 (psychic anxiety) at Visit 1 (p = 0.030; 0.21 points difference in favor of Org 33062) based on the LOCF analysis for the Intent-to-Treat Group.

At each visit, there was no statistically significant difference between the Org 33062 and placebo treatment groups in the number (%) of HAMD-25 responders based on the LOCF analysis for the Intent-to-Treat Group. A marginally significant difference (0.05 p =0.10), in favor of Org 33062, was observed in the number (%) of HAMD-25 responders at Visits 3, 4 and 6/end of trial. At Visit 6/end of trial, the difference between the 2 treatment groups in the number (%) of HAMD-25 responders was 13.1%, in favor of Org 33062. Results based on the OC analysis have shown that a statistically significant difference between the 2 treatment groups was observed at Visit 3 (p = 0.027), Visit 4 (p = 0.033), and Visit 6 (p = 0.011). At each visit, there was no statistically significant difference in the change from baseline in HAMD-25 total score based on the LOCF analysis for the Intent-to-Treat Group. A marginally significant difference (0.05 p =0.10), in favor of Org 33062, was observed in the change from baseline in the HAMD-25 total score at Visits 2 and 4 based on the OC analysis for the Intent-to-Treat Group. For the primary and several secondary efficacy parameters, a high placebo response was observed.

This study is similar to 134001 but is not very supportive in nature.

#### Study CN105-078

This was a 2-center, double-blind study of 2 dose ranges of Org 33062 ER (10-50 mg/day [low dose] and 20-100 mg/day [high dose]) in the treatment of MDD. By protocol, the primary efficacy analysis was a comparison of the pooled Org 33062-treated group with placebo, whereas the secondary analysis

compared each individual Org 33062 treatment group with placebo.

The study was prematurely terminated by BMS. Consequently, only 146 (81%) subjects entered the double-blind treatment phase.

The mean dose was 30.4 mg/day in the Org 33062 low-dose group and 52.6 mg/day in the Org 33062 high-dose group. Results of the ITT/LOCF analysis of the two primary efficacy parameters showed no significant drug-placebo differences.

Results of the ITT/OC analysis showed statistically significant differences in favor of the high-dose Org 33062 and total Org 33062 treatment groups over placebo based on the change from baseline in HAMD 17 total score (Week 4). High-dose Org 33062 afforded statistically significant improvement based on the percentage of CGI responders (Week 4), as well.

The study was terminated by BMS when further development of the drug was halted. Please see statistical review and comments on this study.

#### Study CN105-083

This was a 2-center, double-blind study of 2 dose ranges of Org 33062 ER (10-50 mg/day [low dose] and 20-100 mg/day [high dose]) in the treatment of MDD. By protocol, the primary efficacy analysis was a comparison of the pooled Org 33062-treated groups with placebo, whereas the secondary analysis compared each individual Org 33062 treatment group with placebo.

The study was prematurely terminated by BMS. Consequently, only 117 (65%) subjects entered the double-blind treatment phase.

The mean dose was 30.4 mg/day in the Org 33062 low-dose group and 57.1 mg/day in the Org 33062 high-dose group. Results of the ITT/LOCF analysis showed no statistically significant differences between any Org 33062 group and the placebo group for the primary efficacy variables. Results of the ITT/OC analysis were consistent with these findings.

The sponsor feels the inability of this study to demonstrate antidepressant efficacy is likely to have been caused by two factors. First, the study did not reach its intended sample size. Secondly, the discontinuation rate in the first 2 weeks of the study was relatively high. Since the LOCF analysis was

used, results of those early discontinuations were carried forward, thereby lessening the treatment effect. Please see statistical review and comments on this study.

#### Study CN105-057

This was a 3-center, double-blind study of 4 dose ranges of Org 33062 ER (2-4 mg/day, 5-10 mg/day, 10-20 mg/day, and 20-40 mg/day) and placebo in the treatment of subjects with MDD.

Results of the ITT/LOCF analysis showed a statistically significant difference for the 5-10 mg/day Org 33062 group based on the percentage of CGI responders (Week 6). Otherwise, no statistically significant differences were observed between any Org 33062 group and the placebo group for the primary efficacy parameters measured. Results of the ITT/OC analysis were consistent with these findings.

The sponsor feels that several factors may have contributed to the inability of the study to demonstrate the antidepressant efficacy of Org 33062, including the high placebo response, disparate numbers of subjects by center, and differences in discontinuation rates by treatment group.

#### Study CN105-043

This was a 2-center, double-blind, placebo-controlled study of Org 33062 IR 5-30 mg/day in the treatment of subjects diagnosed with MDD with atypical symptoms.

Results of the ITT/LOCF analysis showed no statistically significant differences between Org 33062 and placebo for either primary efficacy parameter. Results of the ITT/OC analysis were consistent with these findings.

The sponsor feels that two factors may have contributed to the inability of this study to demonstrate drug-placebo

differences. First, the mean dose of Org 33062 was 17.0 mg/day, which is lower than the mean dose in other studies in which Org 33062 was shown to be effective. Secondly, the placebo response rate was high: 50% of placebo-treated subjects were CGI responders at Week 8/Endpoint.

#### Study 03A7C-001A-2496

This was a single-center, double-blind comparison of 2 dose ranges of Org 33062 IR (5-45 mg/day [low dose] and 10-90 mg/day [high dose]) in the treatment of MDD. By protocol, the

primary efficacy analysis was a comparison of each Org 33062 dose group with placebo, whereas the secondary analysis compared the total Org 33062 treatment group with placebo.

The mean dose was 24.6 mg/day in the Org 33062 low-dose and 47.1 mg/day in the Org 33062 high-dose group. Results of the ITT/LOCF analysis showed no statistically significant differences between Org 33062 and placebo for either primary efficacy parameter. Results of the ITT/OC analysis were consistent with these findings.

The sponsor feels that two factors may have contributed to the inability of this study to demonstrate the efficacy of Org 33062. The first is the high discontinuation rate in the Org 33062 treatment groups compared with the placebo group. This was particularly apparent in the high-dose Org 33062 treatment group, where the completion rate was as low as 28.6%. Secondly, the placebo response rate was high: 41% of placebo-treated subjects were CGI responders at Week 8/Endpoint.

#### Study 03A7C-001A-2486

This was a single-center, double-blind comparison of 2 dose ranges of Org 33062 IR (5-45 mg/day [low dose] and 10-90 mg/day [high dose]) and placebo in the treatment of MDD. By protocol, the primary efficacy analysis was a comparison of each Org 33062 dose group with placebo, whereas the secondary analysis compared the total Org 33062 treatment group with placebo.

Based on the ITT/LOCF analysis, the total Org 33062 treatment group showed statistically significant greater improvement than placebo for the change from baseline in the HAMD 17 total score (Weeks 1 - 4, 6, and 8/Endpoint). There was also a statistically significant difference in favor of the total Org 33062 group in CGI responders at Week 6 and a marginally significant difference at Week 8/Endpoint ( $0.05 < p \leq 0.10$ ).

Subjects treated with high-dose Org 33062 (mean dose 33.9 mg/day) experienced statistically significant greater improvement than subjects treated with placebo, as measured by the change from baseline in HAMD 17 total score (Weeks 1, 3, 4, 6, and 8/Endpoint). In addition, there was a marginally significant difference in the percentage of CGI responders in favor of the high-dose Org 33062 treatment group at Weeks 3, 4, 6, and 8/Endpoint ( $0.05 < p \leq 0.10$ ).

Low-dose Org 33062 (mean dose 22.0 mg/day) showed statistically significant superiority based on the change from baseline in HAMD 17 total score at Week 4. There was a marginally significant difference in favor of the Org 33062 treatment group based on the change from baseline in HAMD 17 total score at Weeks 2, 3, 4, 6, and 8/Endpoint and the percentage of CGI responders at Week 6 ( $0.05 < p \leq 0.10$ ).

There were inconsistencies between the results of LOCF and OC analyses for the ITT population. In the OC analysis, for example, the change from baseline in HAMD 17 total score showed statistically significant differences for the high-dose group and the total Org 33062 group at Week 1 but not at Week 8/Endpoint.

The sponsor suggests that the discrepancy between the LOCF and OC analyses may be explained by the very high discontinuation rate in this study. Overall, only 31.5% of the subjects completed the study. Although a high percentage of the placebo-treated subjects discontinued due to lack of efficacy (37.2%), most of them discontinued by Weeks 3 and 4.

#### Study CN105-053

This was a 2-center, double-blind study of Org 33062 ER 10-60 mg/day (amended from 10-40 mg/day), imipramine 50-200 mg/day, and placebo in subjects with MDD.

The mean dose of Org 33062 was 50.5 mg/day. Results of the ITT/LOCF analysis showed no statistically significant differences between the Org 33062 group and the placebo group for either primary efficacy parameter. Comparison of the imipramine group and the placebo group showed statistically significant differences in favor of the imipramine group for only 1 of the 2 primary efficacy parameters (percentage of CGI responders [Weeks 2 through 8/Endpoint]). Results of the ITT/OC analysis yielded similar findings.

The sponsor suggests that several factors may have contributed to the inability of the study to demonstrate the antidepressant efficacy of Org 33062. Enrollment in this study was terminated early by BMS. Only 39% of the subjects were enrolled at 1 center. Additionally the sponsor points out that disparate discontinuation rates and a high placebo response led to equivocal results, even for the comparative agent.

## Study CN105-052

This was a 2-center, double-blind comparison of Org 33062 ER 20-60 mg/day, fluoxetine 20 mg/day, and placebo in subjects with MDD. Results of the ITT/LOCF analysis showed no statistically significant differences between Org 33062 and placebo or between fluoxetine and placebo for either primary efficacy parameter. Results of the ITT/OC analysis were consistent with these findings.

The mean dose of Org 33062 ER during the acute treatment phase was 38.7 mg/day, yet the study did not show antidepressant efficacy for Org 33062 ER.

The sponsor suggests that two factors are likely to have contributed to the failure of the study. First, the study was prematurely terminated by BMS. As a result, only 111 of the 240 planned subjects entered the study. Secondly, the placebo response rate was high: 57% of the placebo treated subjects were CGI responders at Week 8/Endpoint. The inability to show drug-placebo differences for the active control group (fluoxetine) make this a failed study.

## Study CN105-064

This was a single-center, double-blind comparison of 2 daily dose ranges of Org 33062 ER (5-20 mg/day and 10-40 mg/day), imipramine 50-200 mg/day, and placebo in subjects with MDD.

The mean dose of Org 33062 was 11.6 mg/day in the low-dose group and 22.5 mg/day in the Org 33062 high-dose group. Results of the ITT/LOCF analysis showed no statistically significant differences between either dose group of Org 33062 and placebo or between imipramine and placebo for either primary efficacy parameter. Results of the ITT/OC analysis were consistent with these findings.

The sponsor suggests that several factors may have contributed to the inability of the study to demonstrate the antidepressant efficacy of Org 33062. First, the projected sample size of 300 subjects (75 in each treatment group) was not achieved. The study was prematurely terminated by BMS; as a result, only 93 subjects were randomized to treatment groups. Secondly, the placebo response rate was high: 52% of placebo-treated subjects were CGI responders at Week 8/Endpoint. Third, the Org 33062 dose level may have been

inadequate. Both mean doses were generally lower than the doses used in studies that demonstrated the antidepressant efficacy of Org 33062. Finally, the discontinuation rates in all active treatment groups (Org 33062 and imipramine) were much higher than that in the placebo group. In the active treatment groups, the discontinuation rates ranged from 43.5% to 60.0%, whereas in the placebo group only 17.4% of the subjects discontinued. Moreover, none of the subjects in the placebo group discontinued due to lack of efficacy.

#### Study CN105-037

This was a single-center, double-blind comparison of 2 daily dose ranges of Org 33062 IR (2-12 mg/day [low dose] and 5-30 mg/day [high dose]), imipramine 50-300 mg/day, and placebo.

The mean dose was 5.8 mg/day in the Org 33062 low-dose group and 13.5 mg/day in the Org 33062 high-dose group. Results of the ITT/LOCF analysis showed no statistically significant differences between either Org 33062 dose group and placebo or between imipramine for either primary efficacy parameter. Results of the ITT/OC analysis generally was consistent with these findings. However, imipramine was statistically significantly superior to placebo based on the percentage of CGI responders (Weeks 4 and 6).

The sponsor suggests that two factors may have contributed to the inability to demonstrate antidepressant efficacy of Org 33062 in this study. First, the mean dose in both Org 33062 dose groups was lower than the doses used in studies that demonstrated the antidepressant efficacy of Org 33062. Secondly, the placebo response rate was high: 56% of placebo-treated subjects were CGI responders at Week 8/Endpoint.

#### Study CN105-022

This was a 2-center, double-blind comparison of Org 33062 IR 5-45 mg/day, fluoxetine 20-40 mg/day, and placebo in the treatment of MDD or bipolar disorder, depressed.

The mean dose of Org 33062 was 15.4 mg/day. Results of the ITT/LOCF analysis showed evidence of the antidepressant efficacy of Org 33062 only at early time points. Org 33062 was statistically significantly superior to placebo based on the change from baseline in HAMD 17 total score (Week 2) and percentage of CGI responders (Week 2). Fluoxetine was statistically significantly superior to placebo based on the change from baseline in HAMD 17 total score (Weeks 2, 3, 4, 6, 8/Endpoint) and percentage of CGI responders (Weeks 2 through

8/Endpoint). Results for the ITT/OC analysis were consistent with these findings.

The sponsor suggests that the inability to demonstrate antidepressant activity for Org 33062 in this study may have been due to inadequate dosing. The mean dose of Org 33062 was lower than that in studies that demonstrated the antidepressant efficacy of Org 33062.

#### Study CN105-029

This was a 2-center, double-blind study of Org 33062 IR 5-45 mg/day, imipramine 25-225 mg/day, and placebo in the treatment of MDD or bipolar disorder, depressed.

The mean dose of Org 33062 was 15.3 mg/day. Results of the ITT/LOCF analysis showed no statistically significant differences between Org 33062 and placebo for either primary efficacy parameter. A statistically significant difference in favor of imipramine over placebo was apparent based on the percentage of CGI responders (Week 3). Results of the ITT/OC analysis were consistent with these findings.

The sponsor suggests that two factors may have contributed to the failure of the study to show drug-placebo differences. The first factor is the small sample size of the study. The projected sample size of 240 subjects was not achieved. The study was prematurely terminated by BMS. As a result, only 57 patients were enrolled in the study with only 18-20 subjects per treatment group. Thus, the study was underpowered to detect statistically significant differences. The second factor is the doses of active drugs employed. The maximum allowed daily dose of Org 33062 was 45 mg/day and of imipramine, 225 mg/day. Overall, the mean doses were much lower than the maximum allowable dose. It is possible, therefore, that the study failed to show drug-placebo differences due to inadequate dosing, as well as the small sample size of the study.

#### Study CN105-028

This was a 3-center, double-blind comparison of Org 33062 IR 5-30 mg/day, imipramine 50-300 mg/day, and placebo in the treatment of MDD or bipolar disorder, depressed.

The mean dose of Org 33062 was 13.4 mg/day. Results of the ITT/LOCF analysis showed no statistically significant differences between Org 33062 and placebo for either primary efficacy parameter. Imipramine was statistically significantly superior to placebo based on the change from baseline in HAMD

17 total score (Weeks 1, 2, 3). Results of the ITT/OC analysis were consistent with these findings.

The sponsor suggests that two factors may have contributed to the failure of the study to demonstrate antidepressant efficacy for Org 33062 in this study. First, the mean dose of Org 33062 was considerably lower than that used in studies that demonstrated the antidepressant efficacy of Org 33062. Secondly, the placebo response rate was high: 60% of placebo-treated subjects were CGI responders at Week 8/Endpoint. Such a high response rate would tend to obscure evidence of response in the other treatment groups. This is evident in the findings that no drug-placebo differences were observed for the imipramine group at Week 8/Endpoint.

#### **D. Efficacy Conclusions**

This 4 pivotal studies in my opinion are positive as per the sponsor's analyses above and is confirmed by the FDA statistical analysis (see stat review.) The statistical reviewers conclude 3 of the studies are positive and one(001B) supportive due to ICH guidelines. Among other studies 134002, CN105-078 and CN105-083 which were not statistically significant tend to detract from the positive studies. See appendix for summaries.

The statistical review concludes with these points among others that I have selected:

"The Mixed Model Repeated Measures (MMRM) approach confirmed the findings of Studies 134001 and 03A7A-003. In addition, the MMRM results for Study 03A7C-001-B are similar to the sponsor's in that one study drives the overall statistical significance."

"The reviewers' statistical methods differed from the sponsor's. Based on their approach, they also concluded that three of the studies (134001, 03A7A-003 and 03A7A-002) demonstrated statistical significance for the designated primary efficacy parameter(s) at the pre-defined endpoint (Table2 Stat Review). In addition, their Meta analysis, which used the combined data of the 4 studies, showed all Gepirone doses statistically significantly superior to placebo (Table 3 Stat Review)."

The efficacy results of the positive and well controlled studies are listed in the table below.

**Table 26 Summary of Key Efficacy Results in Proof-of-Efficacy Studies by Study and Treatment Group (Intent-to-Treat, LOCF Data Set)**

| Treatment Group                         | N   | Mean Dose<br>± SD<br>mg/day | HAMD 17<br>Mean<br>Baseline<br>Score ± SD | HAMD 17<br>Mean<br>Reduction<br>from<br>Baseline at<br>Endpoint <sup>a</sup><br>± SE | CGI<br>Responders<br>at Endpoint <sup>a</sup><br>(%) | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                       |                   |       |
|-----------------------------------------|-----|-----------------------------|-------------------------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|-------------|-----------------------|-------------------|-------|
|                                         |     |                             |                                           |                                                                                      |                                                      | HAMD 17<br>Mean<br>Reduction<br>from Baseline                               | HAMD Item 1 | HAMD 17<br>Responders | CGI<br>Responders | MADRS |
| 134001                                  |     |                             |                                           |                                                                                      |                                                      |                                                                             |             |                       |                   |       |
| Org 33062 ER 20-80 mg/day               | 101 | 70.3 ± 14.9                 | 22.7 ± 2.5                                | 9.0 ± 0.8*                                                                           | 44                                                   | 3, 8                                                                        | 3, 4, 8     | 3, 4                  | NS                | n/a   |
| Placebo                                 | 103 | --                          | 22.8 ± 2.5                                | 6.8 ± 0.8                                                                            | 36                                                   | --                                                                          | --          | --                    | --                | --    |
| 03A7A-003                               |     |                             |                                           |                                                                                      |                                                      |                                                                             |             |                       |                   |       |
| Org 33062 IR 10-90 mg/day               | 30  | 40.6 ± 21.3                 | 13.8 ± 3.6                                | 6.7 ± 1.0**                                                                          | 57**                                                 | 2, 5, 7, 8                                                                  | 5, 7, 8     | 3, 4, 5, 6, 7, 8      | 5, 8              | 8     |
| Placebo                                 | 30  | --                          | 13.7 ± 4.0                                | 2.7 ± 1.0                                                                            | 23                                                   | --                                                                          | --          | --                    | --                | --    |
| 03A7A-003 (Subset of subjects with MDD) |     |                             |                                           |                                                                                      |                                                      |                                                                             |             |                       |                   |       |
| Org 33062 IR 10-90 mg/day               | 23  | NC                          | 14.0 ± 3.8                                | 7.7 ± 1.2**                                                                          | 65**                                                 | 2, 3, 4, 5, 7, 8                                                            | n/a         | n/a                   | 3, 4, 5, 7, 8     | n/a   |
| Placebo                                 | 16  | --                          | 14.7 ± 4.1                                | 2.6 ± 1.4                                                                            | 19                                                   | --                                                                          | --          | --                    | --                | --    |
| 03A7C-001B                              |     |                             |                                           |                                                                                      |                                                      |                                                                             |             |                       |                   |       |
| Org 33062 IR Total                      | 137 | 27.2 ± 17.6                 | 23.9 ± 4.7                                | 10.7 ± 0.7**                                                                         | 57*                                                  | 4, 6, 8                                                                     | 6, 8        | NS                    | 6, 8              | 8     |
| Org 33062 IR 5-45 mg/day                | 70  | 21.4 ± 10.1                 | 23.4 ± 4.9                                | 10.0 ± 1.0*                                                                          | 59*                                                  | 6, 8                                                                        | 8           | 8                     | 6, 8              | 8     |
| Org 33062 IR 10-90 mg/day               | 67  | 33.3 ± 21.4                 | 24.4 ± 4.5                                | 11.3 ± 1.0**                                                                         | 55*                                                  | 4, 6, 8                                                                     | 6, 8        | NS                    | 8                 | 8     |
| Placebo                                 | 69  | ---                         | 24.1 ± 4.8                                | 6.4 ± 1.1                                                                            | 39                                                   | --                                                                          | --          | --                    | --                | --    |

**Table 23 Summary of Key Efficacy Results in Proof-of-Efficacy Studies by Study and Treatment Group (Continued) (Intent-to-Treat, LOCF Data Set)**

| Treatment Group           | N  | Mean Dose<br>± SD<br>mg/day | HAMD 17<br>Mean<br>Baseline<br>Score ± SD | HAMD 17<br>Mean<br>Reduction<br>from Baseline<br>at Endpoint <sup>a</sup><br>± SE | CGI<br>Responders<br>at Endpoint <sup>a</sup><br>(%) | Week in Which Org 33062 was Statistically Significantly Better than Placebo |             |                       |                   |       |
|---------------------------|----|-----------------------------|-------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|-------------|-----------------------|-------------------|-------|
|                           |    |                             |                                           |                                                                                   |                                                      | HAMD 17<br>Mean<br>Reduction<br>from Baseline                               | HAMD Item 1 | HAMD 17<br>Responders | CGI<br>Responders | MADRS |
| 03A7A-002 <sup>b</sup>    |    |                             |                                           |                                                                                   |                                                      |                                                                             |             |                       |                   |       |
| Org 33062 IR 10-90 mg/day | 36 | 39.9 ± 20.3                 | 24.8 ± 4.5                                | 13.0 ± 1.5                                                                        | 56                                                   | NS                                                                          | 8           | NS                    | NS                | NM    |
| Placebo                   | 34 | ---                         | 24.6 ± 4.0                                | 9.0 ± 1.6                                                                         | 42                                                   | --                                                                          | --          | --                    | --                | --    |

Note: Data shown were reproduced from Tables 15, 16, and 21 and Post-Text Tables 6 – 9 and 12 in the Integrated Summary of Efficacy.

CGI = Clinical Global Impression; ER = Extended release; HAMD = Hamilton Depression Scale; IR = Immediate release; LOCF = Last observation carried forward; MADRS = Montgomery and Åsberg Depression Rating Scale; MDD = Major depressive disorder; n/a = Not analyzed; NC = Not calculated; NM = Not measured; NS = Not statistically significant (p>0.05)

<sup>a</sup> Last visit with evaluable data for the subject. Values at Week 8 LOCF are identical to Endpoint values.

<sup>b</sup> Refers to subjects who participated in double-blind phase of the study; results for the primary efficacy parameter in this study (cumulative proportion of relapse) not presented in table, but discussed in the text

\* Indicates significance at p≤0.05, \*\* p≤0.01. P values are derived from a pairwise comparison with placebo using Cochran-Mantel-Haenszel test for the CGI Responders and from ANOVA for the HAMD 17 change from baseline score. For the HAMD 17 change from baseline, underlined values are significant by Dunnett's test adjusting for multiple comparisons.

## **VII. Integrated Review of Safety**

This section is being completed by the division's safety team.

## **VIII. Dosing, Regimen, and Administration Issues**

Efficacy can be demonstrated statistically only in higher dose populations above 40 mg/day. The sponsor explains the lack of efficacy in many of the negative studies with remarks that indicate the dosing was not adequate (<40mg/day). See dosing table in appendix.

## **IX. Use in Special Populations**

### **A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

Data from 17 of the 18 adequate and well controlled studies with similar design were pooled to allow analysis of efficacy by subjects' age, gender, race, and severity of depression at baseline. One study (Protocol 03A7A-002, the relapse prevention study, with 36 subjects treated with Org 33062) was omitted from this pooled analysis because of a difference in design.

Subpopulations then were compared with respect to key efficacy findings: change from baseline in HAMD 17 total score, discontinuation rates, percentage of HAMD responders, and percentage of CGI responders at Endpoint.

### **Gender**

Table 57 provides a summary of the number of subjects by gender and treatment group in the pooled Org 33062 studies.

**Table 57 Number (%) of Subjects during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Gender and Treatment Group (Pooled Analysis, Intent-to-Treat)**

| Gender | Org 33062 |      | Imipramine |      | Fluoxetine |      | Placebo |      | Total <sup>a</sup> |      |
|--------|-----------|------|------------|------|------------|------|---------|------|--------------------|------|
|        | n         | %    | n          | %    | n          | %    | n       | %    | n                  | %    |
| Female | 839       | 61.6 | 155        | 68.0 | 66         | 64.7 | 554     | 60.8 | 1614               | 62.0 |
| Male   | 523       | 38.4 | 73         | 32.0 | 36         | 35.3 | 357     | 39.2 | 989                | 38.0 |
| All    | 1362      | 52.3 | 228        | 8.8  | 102        | 3.9  | 911     | 35.0 | 2603               | 100  |

Note: Data shown were obtained from Appendix B.12 of the Integrated Summary of Efficacy.

<sup>a</sup> The gender of 7 subjects, 5 randomized to receive Org 33062, 1 randomized to receive fluoxetine, and

1 randomized to receive placebo, was unknown. These subjects were not included in the analysis.

A total of 1362 subjects included in the pooled analysis were treated with Org 33062; 61.6% were females. The percentages of females were similar across treatment groups, ranging from 60.8% to 68.0% of subjects. The overall ratio of females to males treated with Org 33062 was similar to that observed in many of the 17 individual studies.

Table 58 provides a summary of the modal dose and mean dose of Org 33062 by subjects' gender. Both the modal dose and mean dose were somewhat lower in women than in men.

**Table 58 Modal Dose and Mean Dose for Subjects Treated with Org 33062 during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Gender (Pooled Analysis, Intent-to-Treat)**

| Gender  | N   | Modal Dose ± SD<br>mg/day | Mean Dose ± SD<br>mg/day |
|---------|-----|---------------------------|--------------------------|
| Females | 839 | 31.9 ± 24.7               | 28.2 ± 20.6              |
| Males   | 523 | 38.8 ± 27.6               | 33.0 ± 22.1              |

Note: Data shown were obtained from Appendix B.13 of the Integrated Summary of Efficacy.

Table 59 provides a summary of results of key efficacy findings by subjects' gender and treatment group.

**Table 59 Key Efficacy Findings at Endpoint during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Gender and Treatment Group (Pooled Analysis, Intent-to-Treat, LOCF Data Set)**

| Parameter                                |                      | Female               |                       |                      |                    |                   | Male                 |                      |                      |                    |                  |
|------------------------------------------|----------------------|----------------------|-----------------------|----------------------|--------------------|-------------------|----------------------|----------------------|----------------------|--------------------|------------------|
|                                          |                      | Org 33062<br>(N=839) | Imipramine<br>(N=155) | Fluoxetine<br>(N=66) | Placebo<br>(N=554) | Total<br>(N=1614) | Org 33062<br>(N=523) | Imipramine<br>(N=73) | Fluoxetine<br>(N=36) | Placebo<br>(N=357) | Total<br>(N=989) |
| HAMD 17 Mean<br>Baseline Score           | n                    | 839                  | 155                   | 66                   | 554                |                   | 523                  | 73                   | 36                   | 357                |                  |
|                                          | Mean                 | 23.96                | 25.3                  | 24.35                | 23.72              |                   | 23.48                | 24.78                | 24.35                | 23.21              |                  |
|                                          | SD                   | 3.89                 | 4.26                  | 2.7                  | 3.89               |                   | 4.13                 | 3.59                 | 3.38                 | 4.22               |                  |
|                                          | p value <sup>a</sup> | 0.274                |                       |                      |                    |                   | 0.347                |                      |                      |                    |                  |
| HAMD 17 Mean<br>Reduction at<br>Endpoint | n                    | 835                  | 155                   | 66                   | 552                |                   | 522                  | 73                   | 36                   | 356                |                  |
|                                          | Mean                 | 9.1                  | 12.24                 | 12.62                | 8.77               |                   | 9.03                 | 13.25                | 10.3                 | 8.18               |                  |
|                                          | SD                   | 7.6                  | 8.24                  | 7.13                 | 7.66               |                   | 7.47                 | 7.52                 | 6.67                 | 7.84               |                  |
|                                          | p value <sup>a</sup> | 0.425                |                       |                      |                    |                   | 0.105                |                      |                      |                    |                  |
| Discontinuation<br>Rate                  | n                    | 368                  | 65                    | 18                   | 234                | 685               | 246                  | 28                   | 12                   | 158                | 444              |
|                                          | %                    | 43.9                 | 41.9                  | 27.3                 | 42.2               | 42.4              | 47.0                 | 38.4                 | 33.3                 | 44.3               | 44.9             |
|                                          | p value <sup>a</sup> | 0.549                |                       |                      |                    |                   | 0.417                |                      |                      |                    |                  |
| HAMD 17<br>Responders                    | n                    | 340                  | 84                    | 39                   | 205                | 668               | 213                  | 42                   | 15                   | 122                | 392              |
|                                          | %                    | 40.5                 | 54.2                  | 59.1                 | 37.0               | 41.4              | 40.7                 | 57.5                 | 41.7                 | 34.2               | 39.6             |
|                                          | p value <sup>a</sup> | 0.181                |                       |                      |                    |                   | 0.05                 |                      |                      |                    |                  |
| CGI Responders                           | n                    | 426                  | 103                   | 53                   | 252                | 834               | 264                  | 54                   | 24                   | 145                | 487              |
|                                          | %                    | 50.8                 | 66.5                  | 80.3                 | 45.5               | 51.7              | 50.5                 | 74.0                 | 66.7                 | 40.6               | 49.2             |
|                                          | p value <sup>a</sup> | 0.05                 |                       |                      |                    |                   | 0.004                |                      |                      |                    |                  |

Note: Data shown were obtained from Appendix B.14 of the Integrated Summary of Efficacy.

CGI = Clinical Global Impression; HAMD = Hamilton Depression Scale; LOCF = Last observation carried forward

<sup>a</sup> p value represents comparison between Org 33062 and placebo.

Among Org 33062-treated subjects, there were no meaningful differences between female and male subjects in key efficacy findings. This same finding was apparent among placebo-treated subjects.

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

**Age**

The following subpopulations were established by the sponsor based on subjects' age:

- Non-elderly subjects (<65 years: 18-<65)
- Elderly subjects (≥65 years: 65- <75, ≥75).

Table 54 provides a summary of the number of subjects by age group and treatment group in the pooled Org 33062 studies.

**Table 54 Number (%) of Subjects during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Age Group and Treatment Group (Pooled Analysis, Intent-to-Treat)**

| Age (years) | Org 33062 |      | Imipramine |      | Fluoxetine |      | Placebo |      | Total <sup>a</sup> |      |
|-------------|-----------|------|------------|------|------------|------|---------|------|--------------------|------|
|             | n         | %    | n          | %    | n          | %    | n       | %    | n                  | %    |
| 18 - < 65   | 1335      | 97.9 | 222        | 97.4 | 101        | 98.1 | 893     | 97.9 | 2551               | 97.9 |
| ≥65         | 29        | 2.1  | 6          | 2.6  | 2          | 1.9  | 19      | 2.1  | 56                 | 2.1  |
| 65 - < 75   | 25        | 1.8  | 5          | 2.2  | 2          | 1.9  | 16      | 1.8  | 48                 | 1.8  |
| ≥75         | 4         | 0.3  | 1          | 0.4  | 0          | 0    | 3       | 0.3  | 8                  | 0.3  |
| Total       | 1364      | 52.3 | 228        | 8.7  | 103        | 4    | 912     | 35   | 2607               | 100  |

Note: Data shown were obtained from Appendix B.9 of the Integrated Summary of Efficacy.

<sup>a</sup>The birth date of 1 subject was unknown and the age of 2 subjects was <18 years. These subjects were all randomized to Org 33062 but not included in the analysis.

A total of 1364 subjects included in the pooled analysis were treated with Org 33062, the majority of whom were 18 to <65 years of age. The sample size of the elderly population treated with Org 33062 (n = 29) was too small to enable meaningful comparisons in terms of dose and outcome of efficacy measures. Nonetheless, summary statistics for the modal dose and mean dose of Org 33062 (Table 55) and the key

efficacy findings (Table 56) are presented by age group and treatment group.

**Table 55      Modal Dose and Mean Dose for Subjects Treated with Org 33062 during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Age Group (Pooled Analysis, Intent-to-Treat)**

| Age (years) | N   | Modal Dose ( $\pm$ SD) mg/day | Mean Dose ( $\pm$ SD) mg/day |
|-------------|-----|-------------------------------|------------------------------|
| 18 - 65     | 133 | 34.7 $\pm$ 26.0               | 30.1 $\pm$ 21.3              |
|             | 5   |                               |                              |
| $\geq$ 65   | 29  | 27.6 $\pm$ 23.1               | 25.6 $\pm$ 20.5              |
| 65 - < 75   | 25  | 25.2 $\pm$ 23.0               | 22.6 $\pm$ 18.5              |
| $\geq$ 75   | 4   | 42.5 $\pm$ 20.6               | 43.9 $\pm$ 26.2              |

**Table 56 Key Efficacy Findings at Endpoint during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Age Group and Treatment Group (Pooled Analysis, Intent-to-Treat, LOCF Data Set)**

| Parameter                          |                      | Non-Elderly Subjects (18 - < 65 years) |                    |                    |                 |                | Elderly Subjects (≥65 years) |                  |                  |                |              |
|------------------------------------|----------------------|----------------------------------------|--------------------|--------------------|-----------------|----------------|------------------------------|------------------|------------------|----------------|--------------|
|                                    |                      | Org 33062 (N=1335)                     | Imipramine (N=222) | Fluoxetine (N=101) | Placebo (N=893) | Total (N=2551) | Org 33062 (N=29)             | Imipramine (N=6) | Fluoxetine (N=2) | Placebo (N=19) | Total (N=56) |
| HAMD 17 Mean Baseline Score        | n                    | 1335                                   | 222                | 101                | 893             |                | 29                           | 6                | 2                | 19             |              |
|                                    | Mean                 | 23.79                                  | 25.11              | 24.42              | 23.5            |                | 22.79                        | 25.83            | 20.5             | 24.47          |              |
|                                    | SD                   | 4.01                                   | 4.07               | 2.9                | 4.04            |                | 2.92                         | 3.76             | 0.71             | 3.39           |              |
|                                    | p value <sup>a</sup> | 0.094                                  |                    |                    |                 |                | 0.074                        |                  |                  |                |              |
| HAMD 17 Mean Reduction at Endpoint | n                    | 1330                                   | 222                | 101                | 890             |                | 29                           | 6                | 2                | 19             |              |
|                                    | Mean                 | 9.15                                   | 12.52              | 11.88              | 8.6             |                | 6.03                         | 13.83            | 8                | 5.68           |              |
|                                    | SD                   | 7.57                                   | 8.04               | 7.04               | 7.7             |                | 6.58                         | 7.47             | 1.41             | 8.57           |              |
|                                    | p value <sup>a</sup> | 0.097                                  |                    |                    |                 |                | 0.874                        |                  |                  |                |              |
| Discontinuation Rate               | n                    | 596                                    | 90                 | 29                 | 388             | 1103           | 17                           | 3                | 1                | 5              | 26           |
|                                    | %                    | 44.6                                   | 40.5               | 28.7               | 43.4            | 43.2           | 58.6                         | 50               | 50               | 26.3           | 46.4         |
|                                    | p value <sup>a</sup> | 0.578                                  |                    |                    |                 |                | 0.028                        |                  |                  |                |              |
| HAMD 17 Responders                 | n                    | 549                                    | 122                | 55                 | 323             | 1049           | 7                            | 4                |                  | 5              | 16           |
|                                    | %                    | 41.1                                   | 55                 | 54.5               | 36.2            | 41.1           | 24.1                         | 66.7             |                  | 26.3           | 28.6         |
|                                    | p value <sup>a</sup> | 0.018                                  |                    |                    |                 |                | 0.865                        |                  |                  |                |              |
| CGI Responders                     | n                    | 682                                    | 153                | 76                 | 390             | 1301           | 10                           | 4                | 2                | 8              | 24           |
|                                    | %                    | 51.1                                   | 68.9               | 75.2               | 43.7            | 51             | 34.5                         | 66.7             | 100              | 42.1           | 42.9         |
|                                    | p value <sup>a</sup> | 0.001                                  |                    |                    |                 |                | 0.594                        |                  |                  |                |              |

Note: Data shown were obtained from Appendix B.11 of the Integrated Summary of Efficacy.

CGI = Clinical Global Impression; HAMD = Hamilton Depression Scale; LOCF = Last observation carried forward

<sup>a</sup>p value represents comparison between Org 33062 and placebo.

Due to the small number of elderly subjects, no conclusions could be drawn with regard to differences between non-elderly and elderly subjects in key efficacy findings.

### Race

The following subpopulations were established based on subjects' race: white, black, Hispanic, Asian, and other. (Note: For subjects of Hispanic origin in the 2 Organon studies [Protocols 134001 and 134002], this information was recorded on the CRF in the "Other" racial category, "comment" field, as "Hispanic".)

Table 60 provides a summary of the number of subjects by racial group and treatment group in the Org 33062 studies.

**Table 60 Number (%) of Subjects during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Race and Treatment Group (Pooled Analysis, Intent-to-Treat)**

| Race     | Org 33062 |      | Imipramine |      | Fluoxetine |      | Placebo |      | Total <sup>a</sup> |      |
|----------|-----------|------|------------|------|------------|------|---------|------|--------------------|------|
|          | n         | %    | n          | %    | n          | %    | n       | %    | n                  | %    |
| White    | 1151      | 84.4 | 191        | 83.8 | 93         | 91.2 | 784     | 86.2 | 2219               | 85.2 |
| Black    | 122       | 9.0  | 18         | 7.9  | 3          | 2.9  | 62      | 6.8  | 205                | 7.9  |
| Hispanic | 61        | 4.5  | 17         | 7.5  | 2          | 2.0  | 45      | 4.9  | 125                | 4.8  |
| Asian    | 7         | 0.5  | 2          | 0.9  | 2          | 2.0  | 11      | 1.2  | 22                 | 0.8  |
| Other    | 22        | 1.6  | 0          | 0    | 2          | 2.0  | 8       | 0.9  | 32                 | 1.2  |
| Total    | 1363      | 52.4 | 228        | 8.8  | 102        | 3.9  | 910     | 35   | 2603               | 100  |

<sup>a</sup> The race of 7 subjects, 4 randomized to Org 33062, 1 randomized to fluoxetine, and 2 randomized to placebo, was unknown.

These subjects were not included in the analysis.

A total of 1363 subjects included in the pooled analysis were treated with Org 33062, 84.4% of whom were white and 9.0% of whom were black. The majority of subjects in all treatment groups (83.8% to 91.2%) were white. Asian and Hispanic subjects represented only 5.0% of the Org 33062-treated subjects and 6.2% of the placebo-treated subjects. For this reason, in the pooled analysis of key efficacy parameters by racial group, white subjects were compared with the combined group of non-white subjects.

Table 61 provides a summary of the modal dose and mean dose of Org 33062 by subjects' race.

**Table 61      Modal Dose and Mean Dose for Subjects Treated with Org 33062 during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Race (Pooled Analysis, Intent-to-Treat)**

| Race     | N        | Modal Dose $\pm$ SD<br>mg/day | Mean Dose $\pm$ SD<br>mg/day |
|----------|----------|-------------------------------|------------------------------|
| White    | 115<br>1 | 35.1 $\pm$ 26.1               | 30.4 $\pm$ 21.4              |
| Black    | 122      | 28.5 $\pm$ 24.2               | 24.9 $\pm$ 19.1              |
| Hispanic | 61       | 34.2 $\pm$ 25.8               | 31.3 $\pm$ 22.8              |
| Asian    | 7        | 39.3 $\pm$ 28.3               | 35.4 $\pm$ 23.0              |
| Other    | 22       | 41.9 $\pm$ 28.4               | 35.1 $\pm$ 23.3              |

Note: Data shown were obtained from Appendix B.16 of the Integrated Summary of Efficacy.

Overall, the modal dose and mean dose of Org 33062 for black subjects were lower than those for subjects in the other racial groups. The modal dose and mean dose for the other subgroups were similar, ranging from 34.2 mg/day to 41.9 mg/day (modal dose) and 30.4 mg/day to 35.4 mg/day (mean dose).

Table 62 provides a summary of key efficacy findings by racial group and treatment group. Table 63 provides a summary of key efficacy findings in black subjects by treatment group.

**Table 62 Key Efficacy Findings at Endpoint during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Race and Treatment Group (Pooled Analysis, Intent-to-Treat, LOCF Data Set)**

| Parameter                                |                      | White                    |                       |                      |                    |                   | Non-White               |                      |                     |                    |                  |
|------------------------------------------|----------------------|--------------------------|-----------------------|----------------------|--------------------|-------------------|-------------------------|----------------------|---------------------|--------------------|------------------|
|                                          |                      | Org<br>33062<br>(N=1151) | Imipramine<br>(N=191) | Fluoxetine<br>(N=93) | Placebo<br>(N=784) | Total<br>(N=2219) | Org<br>33062<br>(N=212) | Imipramine<br>(N=37) | Fluoxetine<br>(N=9) | Placebo<br>(N=126) | Total<br>(N=384) |
| HAMD 17 Mean<br>Baseline Score           | n                    | 1151                     | 191                   | 93                   | 784                |                   | 212                     | 37                   | 9                   | 126                |                  |
|                                          | Mean                 | 23.56                    | 25.19                 | 24.44                | 23.38              |                   | 24.91                   | 24.84                | 23.44               | 24.42              |                  |
|                                          | SD                   | 4                        | 4.18                  | 2.9                  | 4.12               |                   | 3.72                    | 3.32                 | 3.32                | 3.31               |                  |
|                                          | p value <sup>a</sup> | 0.329                    |                       |                      |                    |                   | 0.215                   |                      |                     |                    |                  |
| HAMD 17 Mean<br>Reduction at<br>Endpoint | n                    | 1146                     | 191                   | 93                   | 781                |                   | 212                     | 37                   | 9                   | 126                |                  |
|                                          | Mean                 | 8.92                     | 12.62                 | 11.65                | 8.39               |                   | 9.95                    | 12.24                | 13.33               | 9.49               |                  |
|                                          | SD                   | 7.41                     | 8.24                  | 7.2                  | 7.76               |                   | 8.21                    | 6.82                 | 4.97                | 7.54               |                  |
|                                          | p value <sup>a</sup> | 0.129                    |                       |                      |                    |                   | 0.608                   |                      |                     |                    |                  |
| Discontinuation<br>Rate                  | n                    | 503                      | 71                    | 28                   | 339                | 941               | 111                     | 22                   | 2                   | 52                 | 187              |
|                                          | %                    | 43.7                     | 37.2                  | 30.1                 | 43.2               | 42.4              | 52.4                    | 59.5                 | 22.2                | 41.3               | 48.7             |
|                                          | p value <sup>a</sup> | 0.841                    |                       |                      |                    |                   | 0.049                   |                      |                     |                    |                  |
| HAMD 17<br>Responders                    | n                    | 466                      | 107                   | 47                   | 283                | 903               | 88                      | 19                   | 7                   | 44                 | 158              |
|                                          | %                    | 40.5                     | 56.0                  | 50.5                 | 36.1               | 40.7              | 41.5                    | 51.4                 | 77.8                | 34.9               | 41.1             |
|                                          | p value <sup>a</sup> | 0.05                     |                       |                      |                    |                   | 0.23                    |                      |                     |                    |                  |
| CGI Responders                           | n                    | 584                      | 134                   | 68                   | 339                | 1125              | 107                     | 23                   | 9                   | 58                 | 197              |
|                                          | %                    | 50.7                     | 70.2                  | 73.1                 | 43.2               | 50.7              | 50.5                    | 62.2                 | 100                 | 46.0               | 51.3             |
|                                          | p value <sup>a</sup> | 0.001                    |                       |                      |                    |                   | 0.43                    |                      |                     |                    |                  |

Note: Data shown were obtained from Appendix B.17 of the Integrated Summary of Efficacy.

CGI = Clinical Global Impression; HAMD = Hamilton Depression Scale; LOCF = Last observation carried forward

<sup>a</sup> p value represents comparison between Org 33062 and placebo.

Among Org 33062-treated subjects, the discontinuation rate was somewhat lower for white subjects than for non-white subjects. This difference was not apparent among placebo-treated subjects. Otherwise, there were no noteworthy differences between white and non-white Org 33062-treated subjects in key efficacy findings.

**Table 63 Key Efficacy Findings at Endpoint for Black Subjects during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Treatment Group (Pooled Analysis, Intent-to-Treat, LOCF Data Set)**

| Parameter                          |                      | Black             |                   |                  |                |               |
|------------------------------------|----------------------|-------------------|-------------------|------------------|----------------|---------------|
|                                    |                      | Org 33062 (N=122) | Imipramine (N=18) | Fluoxetine (N=3) | Placebo (N=62) | Total (N=205) |
| HAMD 17 Mean Baseline Score        | n                    | 122               | 18                | 3                | 62             |               |
|                                    | Mean                 | 24.97             | 24.72             | 21               | 24.72          |               |
|                                    | SD                   | 3.87              | 3.71              | 1                | 3.28           |               |
|                                    | p value <sup>a</sup> | 0.664             |                   |                  |                |               |
| HAMD 17 Mean Reduction at Endpoint | n                    | 122               | 18                | 3                | 62             |               |
|                                    | Mean                 | 9.92              | 12.67             | 13               | 11.09          |               |
|                                    | SD                   | 8.12              | 7.94              | 4.36             | 7.68           |               |
|                                    | p value <sup>a</sup> | 0.351             |                   |                  |                |               |
| Discontinuation Rate               | n                    | 68                | 9                 |                  | 22             | 99            |
|                                    | %                    | 55.7              | 50.0              |                  | 35.5           | 48.3          |
|                                    | p value <sup>a</sup> | 0.009             |                   |                  |                |               |
| HAMD 17 Responders                 | n                    | 52                | 11                | 3                | 24             | 90            |
|                                    | %                    | 42.6              | 61.1              | 100              | 38.7           | 43.9          |
|                                    | p value <sup>a</sup> | 0.61              |                   |                  |                |               |
| CGI Responders                     | n                    | 60                | 9                 | 3                | 32             | 104           |
|                                    | %                    | 49.2              | 50.0              | 100              | 51.6           | 50.7          |
|                                    | p value <sup>a</sup> | 0.755             |                   |                  |                |               |

CGI = Clinical Global Impression; HAMD = Hamilton Depression Scale; LOCF = Last observation carried forward

<sup>a</sup> p value represents comparison between Org 33062 and placebo.

The data indicate that there are no apparent differences in the antidepressant efficacy of Org 33062 between the white and non-white populations.

### Severity of depression

The following subpopulations were established based on subjects' severity of depression at baseline (as measured by HAMD 17 total score):

- Moderate depression - HAMD 17 score at baseline 18 to 24
- Severe depression - HAMD 17 score at baseline  $\geq 25$ .

Table 64 provides a summary of the number of subjects by study and severity of depression (moderate and severe) at baseline in the Org 33062 studies included in the pooled analysis.

**Table 64 Number (%) of Subjects during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Severity of Depression (Moderate and Severe) at Baseline (Pooled Analysis, Intent-to-Treat)**

| Study Number    | Moderate |      | Severe |      | Total <sup>a</sup> |     |
|-----------------|----------|------|--------|------|--------------------|-----|
|                 | n        | %    | n      | %    | n                  | %   |
| 134001          | 160      | 78.4 | 44     | 21.6 | 204                | 7.8 |
| 134002          | 124      | 58.8 | 87     | 41.2 | 211                | 8.1 |
| CN105-078       | 113      | 83.7 | 22     | 16.3 | 135                | 5.2 |
| CN105-083       | 70       | 62.5 | 42     | 37.5 | 112                | 4.3 |
| CN105-052       | 41       | 38.0 | 67     | 62.0 | 108                | 4.1 |
| CN105-053       | 95       | 57.2 | 71     | 42.8 | 166                | 6.4 |
| CN105-064       | 52       | 60.5 | 34     | 39.5 | 86                 | 3.3 |
| CN105-057       | 155      | 63.3 | 90     | 36.7 | 245                | 9.4 |
| CN105-043       | 71       | 59.7 | 16     | 13.4 | 119                | 4.6 |
| CN105-037       | 141      | 55.5 | 113    | 44.5 | 254                | 9.7 |
| CN105-022       | 131      | 64.5 | 72     | 35.5 | 203                | 7.8 |
| CN105-029       | 33       | 60.0 | 22     | 40.0 | 55                 | 2.1 |
| CN105-028       | 73       | 35.3 | 134    | 64.7 | 207                | 7.9 |
| 03A7A-003       | 10       | 16.7 | 0      | 0    | 60                 | 2.3 |
| 03A7C-001A-2496 | 62       | 52.5 | 56     | 47.5 | 118                | 4.5 |
| 03A7C-001B      | 106      | 51.5 | 87     | 42.2 | 206                | 7.9 |
| 03A7C-001A-2486 | 36       | 29.8 | 78     | 64.5 | 121                | 4.6 |
| Total           | 1473     | 56.4 | 1035   | 39.7 | 2610               | 100 |

| Study Number | Moderate |   | Severe |   | Total <sup>a</sup> |   |
|--------------|----------|---|--------|---|--------------------|---|
|              | n        | % | n      | % | n                  | % |

Summary of Efficacy.

<sup>a</sup> A total of 102 subjects had depression that was not moderate or severe, including 32 subjects in Protocol CN105-043, 50 subjects in Protocol 03A7A-003, and 13 subjects in Protocol 03A7C-001B. These subjects were not included in the analysis.

All or nearly all studies contributed to the total samples of subjects with moderate depression and with severe depression. The percentage of subjects in the moderate category contributed by study ranged from 16.7% to 83.7%. The percentage of subjects in the severe category contributed by study ranged from 0% to 64.7%.

Table 65 provides a summary of the modal dose and mean dose of Org 33062 by subjects' severity of depression at baseline.

**Table 65      Modal Dose and Mean Dose for Subjects Treated with Org 33062 during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Severity of Depression (Moderate and Severe) at Baseline (Pooled Analysis, Intent-to-Treat)**

| Severity of Depression | N   | Modal Dose ± SD<br>mg/day | Mean Dose ± SD<br>mg/day |
|------------------------|-----|---------------------------|--------------------------|
| Moderate               | 783 | 36.1 ± 26.7               | 31.6 ± 22.1              |
| Severe                 | 526 | 32.2 ± 25.0               | 27.8 ± 20.2              |

Data shown were obtained from Appendix B.20 of the Integrated Summary of Efficacy.

Table 66 provides a summary of key efficacy findings in subjects with moderate and severe depression at baseline. Among Org 33062-treated subjects, the discontinuation rate was somewhat lower in subjects with depression of moderate severity than in subjects with severe depression. No noteworthy differences were observed between the 2 subpopulations in other efficacy parameters.

**Table 66 Key Efficacy Findings at Endpoint during Short-Term, Double-Blind Treatment in Adequate and Well Controlled Studies by Severity of Depression (Moderate and Severe) at Baseline and Treatment Group (Pooled Analysis, Intent-to-Treat, LOCF Data Set)**

| Parameter                                |                      | Moderate                |                       |                      |                    |                   | Severe                  |                       |                      |                    |                   |
|------------------------------------------|----------------------|-------------------------|-----------------------|----------------------|--------------------|-------------------|-------------------------|-----------------------|----------------------|--------------------|-------------------|
|                                          |                      | Org<br>33062<br>(N=783) | Imipramine<br>(N=113) | Fluoxetine<br>(N=52) | Placebo<br>(N=525) | Total<br>(N=1473) | Org<br>33062<br>(N=526) | Imipramine<br>(N=115) | Fluoxetine<br>(N=51) | Placebo<br>(N=343) | Total<br>(N=1035) |
| HAMD 17 Mean<br>Baseline Score           | N                    | 783                     | 113                   | 52                   | 525                |                   | 526                     | 115                   | 51                   | 343                |                   |
|                                          | Mean                 | 21.87                   | 21.89                 | 21.96                | 21.78              |                   | 27.63                   | 28.31                 | 26.78                | 27.43              |                   |
|                                          | SD                   | 1.51                    | 1.54                  | 1.48                 | 1.59               |                   | 2.62                    | 3.13                  | 1.81                 | 2.47               |                   |
|                                          | p value <sup>a</sup> | 0.303                   |                       |                      |                    |                   | 0.261                   |                       |                      |                    |                   |
| HAMD 17 Mean<br>Reduction at<br>Endpoint | N                    | 779                     | 113                   | 52                   | 523                |                   | 525                     | 115                   | 51                   | 342                |                   |
|                                          | Mean                 | 8.87                    | 10.62                 | 11.65                | 7.75               |                   | 9.81                    | 14.46                 | 11.95                | 10.33              |                   |
|                                          | SD                   | 6.96                    | 6.64                  | 6.27                 | 6.83               |                   | 8.36                    | 8.79                  | 7.73                 | 8.75               |                   |
|                                          | p value <sup>a</sup> | 0.004                   |                       |                      |                    |                   | 0.379                   |                       |                      |                    |                   |
| Discontinuation<br>Rate                  | n                    | 319                     | 49                    | 7                    | 222                | 597               | 272                     | 44                    | 23                   | 155                | 494               |
|                                          | %                    | 40.7                    | 43.4                  | 13.5                 | 42.3               | 40.5              | 51.7                    | 38.3                  | 45.1                 | 45.2               | 47.7              |
|                                          | p value <sup>a</sup> | 0.578                   |                       |                      |                    |                   | 0.06                    |                       |                      |                    |                   |
| HAMD 17<br>Responders                    | n                    | 344                     | 61                    | 30                   | 178                | 613               | 187                     | 65                    | 25                   | 135                | 412               |
|                                          | %                    | 43.9                    | 54.0                  | 57.7                 | 33.9               | 41.6              | 35.6                    | 56.5                  | 49.0                 | 39.4               | 39.8              |
|                                          | p value <sup>a</sup> | 0.001                   |                       |                      |                    |                   | 0.251                   |                       |                      |                    |                   |
| CGI Responders                           | n                    | 420                     | 77                    | 44                   | 227                | 768               | 239                     | 80                    | 34                   | 153                | 506               |
|                                          | %                    | 53.6                    | 68.1                  | 84.6                 | 43.2               | 52.1              | 45.4                    | 69.6                  | 66.7                 | 44.6               | 48.9              |
|                                          | p value <sup>a</sup> | 0.001                   |                       |                      |                    |                   | 0.82                    |                       |                      |                    |                   |

Note: Data shown were obtained from Appendix B.22 of the Integrated Summary of Efficacy.

CGI = Clinical Global Impression; HAMD = Hamilton Depression Scale; LOCF = Last observation carried forward

<sup>a</sup> p value represents comparison between Org 33062 and placebo.

**C. Evaluation of Pediatric Program**

Please see proposed pediatric studies in Phase IV recommendation section. These studies are appropriate.

**D. Comments on Data Available or Needed in Other Populations**

See safety review.

**X. Conclusions and Recommendations**

**A. Conclusions**

I view the four sponsor selected pivotal studies as positive with the statisticians viewing study 001B as only supportive due to ICH guidelines. Some of the other 14 studies were either terminated prematurely (by Bristol Myers) or failed largely due to low drug dose range or high placebo response. Studies 134002, CN105-078 and CN105-083 did not show efficacy.

**B. Recommendations**

I recommend the application be approved assuming appropriate long term safety data in the higher dosing range is provided. OPDRA does not recommend the use of the proposed proprietary name Ariza. Although they initially had no objections to the use of the proprietary name, Ariza (see consult 00-0086) they now believe that there is potential risk of product mix-ups between Arava and Ariza.

## **XI. Appendix**

### **A. Other Relevant Materials**

Between October 1 and 3, 2001, Ms. Barbara M. Frazier, representing the Food and Drug Administration (FDA), met with Dr. Haggerty to review his conduct of a clinical study (protocol #03A7C-001-B) of the investigational drug Gepirone HCl (org 33062) IR Capsules, performed for Organon, Inc. From the FDA evaluation of the inspection report and the documents submitted with that report, The FDA concludes that he adhered to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

A direct communication to me included the following:

"An audit of 12 records was conducted. No major deficiencies were found with the site's conduct of the study or their records.

We note that there were some discrepancies between CRF and the data listing of subjects who discontinued from the study. For example, 6 subjects (# (b)(6) from Gep 5-45 group and # (b)(6) from placebo group) who completed 8- week short-term dosing phase as per CRF were recorded on data listing of subjects discontinued from the short-term phase of study for lack of efficacy. There were also discrepancies in disposition of number of subjects continued into the long-term extension phase: 36 subjects as per data listing versus 20 subjects' records reported by the site.

We also note that different dates were listed for Hamilton Depression score of one subject (# (b)(6)) and also one point discrepancy in CGI-severity score on CRF versus data table listing.

As stated above, there were no major deficiencies found with the conduct of the study at this site. However, it should be noted that there were some discrepancies between CRF and the data listing submitted by the sponsor in the NDA application."

Latest conclusion 1/18/2002:

DSI received a consult request from the Review Division (HFD-120) in July, 2001. Inspection assignment was issued on September 18, 2001 for 3 domestic sites, Drs. Feiger, Haggerty

and Quitkin. The studies were carried out using extended release tablets for protocol #134001 (Feiger) and immediate release capsules for protocols #03A7C-001-B (Haggerty) and #03A7A-003 (Quitkin). The conclusions is below.

"Although some deficiencies were noted in the areas of protocol violations and inadequate record keeping, the data from these sites appear acceptable for use in support of this NDA supplement. Limitation to this inspection was that the investigators' source documents including informed consents, were missing in certain subjects, as stated above. This summary was based on Clinical Investigators' audits of these three sites. Because of some discrepancies between the CRF and the data listing provided by the sponsor, we have expanded our inspection to include sponsor investigation in regards to data handling and is currently ongoing. Should the findings of the sponsor's audit when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly."

| NAME         | CITY        | STATE | ASSIGNED<br>DATE | RECEIVED<br>DATE |     |
|--------------|-------------|-------|------------------|------------------|-----|
| Dr. Feiger   | Wheat Ridge | CO    | 9-18-2001        | 11-07-2001       | VAI |
| Dr. Haggerty | Chapel Hill | NC    | 9-18-2001        | 12-19-2002       | NAI |
| Dr. Quitkin  | New York    | NY    | 9-18-2001        | 01-16-2002       | VAI |

**Key to Classifications**

- NAI = No deviation from regulations. Data acceptable
- VAI = Minor deviations(s) from regulations. Data acceptable
- VAIr= Deviation(s) form regulations, response requested. Data acceptable
- OAI = Significant deviations for regulations. Data unreliable
- Pending = Inspection not completed

**B. Individual More Detailed Study Tables**

Supporting efficacy tables are included in this section.

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**A double-blind, multicenter, randomized, placebo-controlled, efficacy and safety study of Org 33062 ER in subjects with major depressive disorder**

**Study 134001**

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***Investigators***

| Site # | Investigator/Site                                                                                                      |
|--------|------------------------------------------------------------------------------------------------------------------------|
| 01     | Alan D. Feiger, M.D.<br>Feiger Health Research Center<br>3555 Lutheran Parkway<br>Suite 320<br>Wheat Ridge, CO 80033   |
| 02     | Jon F. Heiser, M.D.<br>Pharmacology Research Institute<br>1000 Dove Street, Suite 200<br>Newport Beach, CA 90720-2149  |
| 03     | Ram K. Shrivastava, M.D.<br>Eastside Comprehensive Medical<br>Services<br>133 East 73rd Street<br>New York, NY 10021   |
| 04     | Kenneth J. Weiss, M.D.<br>Delaware Valley Research Associates,<br>Inc.<br>922 Fayette Street<br>Conshohocken, PA 19428 |
| 05     | Ward Smith, M.D.<br>Northwest Research Clinics<br>1849 N. W. Kearny<br>Suite 201<br>Portland, OR 97209                 |

**Original Sponsor**    Organon Inc.

**Study 134001**

**Table 1 Primary efficacy parameter statistical analysis: HAMD 17 reduction from baseline**

| Least squares mean reduction from baseline in HAMD 17 |               |            |       |           |       |           |       |           |       |           |       |           |       |           |
|-------------------------------------------------------|---------------|------------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)       |               |            |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                       | Baseline mean |            | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                       | n             | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                             | 101           | 22.7 (2.5) | 98    | 3.3 (0.5) | 100   | 5.7 (0.6) | 101   | 7.9 (0.7) | 101   | 8.2 (0.7) | 101   | 8.4 (0.8) | 101   | 9.0 (0.8) |
| Placebo                                               | 103           | 22.8 (2.5) | 99    | 2.2 (0.5) | 101   | 4.4 (0.6) | 101   | 5.9 (0.6) | 101   | 6.8 (0.7) | 101   | 6.6 (0.7) | 101   | 6.8 (0.8) |
| p-value for pairwise comparison                       |               |            |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                  | n/a           |            | 0.052 |           | 0.059 |           | 0.013 |           | 0.078 |           | 0.051 |           | 0.018 |           |
| Observed cases analysis (ITT)                         |               |            |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                       | Baseline mean |            | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                       | n             | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                             | 101           | 22.7 (2.5) | 98    | 3.3 (0.5) | 86    | 6.0 (0.6) | 90    | 8.3 (0.7) | 86    | 8.7 (0.7) | 80    | 9.2 (0.9) | 71    | 9.8 (1.0) |
| Placebo                                               | 103           | 22.8 (2.5) | 99    | 2.2 (0.5) | 98    | 4.4 (0.6) | 91    | 6.0 (0.7) | 90    | 6.8 (0.7) | 83    | 6.9 (0.9) | 73    | 6.6 (1.0) |
| p-value for pairwise comparison                       |               |            |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                  | n/a           |            | 0.052 |           | 0.043 |           | 0.007 |           | 0.025 |           | 0.034 |           | 0.008 |           |

n/a = not applicable

## Study 134001

**Table 2 Secondary efficacy parameter statistical analysis: HAMD Item 1 reduction from baseline**

| Least squares mean reduction from baseline in HAMD Item 1 |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------|----------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)           |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                           | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                           | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 101            | 2.7 (0.5) | 98    | 0.4 (0.1) | 100   | 0.7 (0.1) | 101   | 1.0 (0.1) | 101   | 1.0 (0.1) | 101   | 1.1 (0.1) | 101   | 1.2 (0.1) |
| Placebo                                                   | 103            | 2.7 (0.5) | 99    | 0.3 (0.1) | 101   | 0.5 (0.1) | 101   | 0.7 (0.1) | 101   | 0.8 (0.1) | 101   | 0.9 (0.1) | 101   | 0.8 (0.1) |
| p-value for pairwise comparison                           |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a            |           | 0.402 |           | 0.150 |           | 0.007 |           | 0.042 |           | 0.075 |           | 0.005 |           |
| Observed cases analysis (ITT)                             |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                           | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                           | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 101            | 2.7 (0.5) | 98    | 0.4 (0.1) | 86    | 0.7 (0.1) | 90    | 1.1 (0.1) | 86    | 1.1 (0.1) | 80    | 1.2 (0.1) | 71    | 1.3 (0.1) |
| Placebo                                                   | 103            | 2.7 (0.5) | 99    | 0.3 (0.1) | 98    | 0.5 (0.1) | 91    | 0.7 (0.1) | 90    | 0.8 (0.1) | 83    | 1.0 (0.1) | 73    | 0.8 (0.1) |
| p-value for pairwise comparison                           |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a            |           | 0.402 |           | 0.062 |           | 0.008 |           | 0.044 |           | 0.082 |           | 0.009 |           |

n/a = not applicable

## Study 134001

**Table 3 Secondary efficacy parameter statistical analysis: CGI Severity reduction from baseline**

| Least squares mean reduction from baseline in CGI-Severity |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|------------------------------------------------------------|----------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                            | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                            | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                            | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                  | 101            | 4.4 (0.5) | 98    | 0.3 (0.1) | 100   | 0.6 (0.1) | 101   | 0.9 (0.1) | 101   | 1.0 (0.1) | 101   | 1.0 (0.1) | 101   | 1.2 (0.1) |
| Placebo                                                    | 103            | 4.2 (0.4) | 99    | 0.1 (0.1) | 101   | 0.4 (0.1) | 101   | 0.6 (0.1) | 101   | 0.7 (0.1) | 101   | 0.8 (0.1) | 101   | 0.8 (0.1) |
| p-value for pairwise comparison                            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a            |           | 0.012 |           | 0.015 |           | 0.006 |           | 0.009 |           | 0.047 |           | 0.016 |           |
| Observed cases analysis (ITT)                              |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                            | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                            | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                            | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                  | 101            | 4.4 (0.5) | 98    | 0.3 (0.1) | 86    | 0.6 (0.1) | 90    | 0.9 (0.1) | 85    | 1.1 (0.1) | 79    | 1.1 (0.1) | 71    | 1.3 (0.2) |
| Placebo                                                    | 103            | 4.2 (0.4) | 99    | 0.1 (0.1) | 98    | 0.4 (0.1) | 91    | 0.6 (0.1) | 90    | 0.6 (0.1) | 83    | 0.8 (0.1) | 73    | 0.8 (0.2) |
| p-value for pairwise comparison                            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a            |           | 0.012 |           | 0.014 |           | 0.008 |           | 0.003 |           | 0.057 |           | 0.008 |           |

n/a = not applicable

## Study 134001

**Table 4 Secondary efficacy parameter statistical analysis: MADRS reduction from baseline**

| Mean reduction from baseline in MADRS           |                |            |      |           |      |           |      |           |      |            |      |             |      |            |
|-------------------------------------------------|----------------|------------|------|-----------|------|-----------|------|-----------|------|------------|------|-------------|------|------------|
| Last observation carried forward analysis (ITT) |                |            |      |           |      |           |      |           |      |            |      |             |      |            |
| Treatment group                                 | Treatment week |            |      |           |      |           |      |           |      |            |      |             |      |            |
|                                                 | Baseline mean  |            | Wk 1 |           | Wk 2 |           | Wk 3 |           | Wk 4 |            | Wk 6 |             | Wk 8 |            |
|                                                 | n              | X (SD)     | n    | X (SD)    | n    | X (SD)    | n    | X (SD)    | n    | X (SD)     | n    | X (SD)      | n    | X (SD)     |
| Org 33062                                       | 101            | 29.5 (4.6) | 98   | 3.7 (5.8) | 100  | 6.1 (7.2) | 101  | 8.9 (8.2) | 101  | 10.2 (8.0) | 101  | 10.9 (8.8)  | 101  | 12.3 (9.4) |
| Placebo                                         | 103            | 29.9 (4.8) | 99   | 2.7 (4.7) | 101  | 5.1 (6.4) | 101  | 7.6 (8.1) | 101  | 8.8 (8.5)  | 101  | 9.3 (9.8)   | 101  | 9.2 (9.7)  |
| Observed cases analysis (ITT)                   |                |            |      |           |      |           |      |           |      |            |      |             |      |            |
| Treatment group                                 | Treatment week |            |      |           |      |           |      |           |      |            |      |             |      |            |
|                                                 | Baseline mean  |            | Wk 1 |           | Wk 2 |           | Wk 3 |           | Wk 4 |            | Wk 6 |             | Wk 8 |            |
|                                                 | n              | X (SD)     | n    | X (SD)    | n    | X (SD)    | n    | X (SD)    | n    | X (SD)     | n    | X (SD)      | n    | X (SD)     |
| Org 33062                                       | 101            | 29.5 (4.6) | 98   | 3.7 (5.8) | 86   | 6.5 (7.3) | 89   | 9.4 (8.3) | 86   | 11.0 (8.1) | 80   | 11.9 (9.2)  | 71   | 13.4 (9.7) |
| Placebo                                         | 103            | 29.9 (4.8) | 99   | 2.7 (4.7) | 98   | 5.2 (6.5) | 91   | 7.9 (8.3) | 90   | 9.1 (8.5)  | 83   | 10.0 (10.0) | 73   | 9.4 (9.8)  |

Note: Descriptive statistics are provided. The statistical analysis of the MADRS reduction from baseline was not part of the statistical plan for the protocol. Post-hoc analysis reveals a statistically significant effect (p<.05) in favor of Org 33062 at week 8 (and only Week 8) for both the LOCF and OC analyses.

## Study 134001

**Table 5 Secondary efficacy parameter statistical analysis: CGI Responders**

| CGI % Responders                                |                |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|-------------------------------------------------|----------------|----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|
| Last observation carried forward analysis (ITT) |                |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Treatment week |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Wk 1           |    |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N  | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062                                       | 10             | 98 | 10 | 24    | 100 | 24 | 34    | 101 | 34 | 41    | 101 | 41 | 39    | 101 | 39 | 44    | 101 | 44 |
| Placebo                                         | 6              | 99 | 6  | 14    | 101 | 14 | 24    | 101 | 24 | 35    | 101 | 35 | 37    | 101 | 37 | 36    | 101 | 36 |
| p-value for pairwise comparison                 |                |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 vs placebo                            | 0.288          |    |    | 0.067 |     |    | 0.121 |     |    | 0.385 |     |    | 0.772 |     |    | 0.251 |     |    |
| Observed cases analysis (ITT)                   |                |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Treatment week |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Wk 1           |    |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N  | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062                                       | 10             | 98 | 10 | 22    | 86  | 26 | 32    | 90  | 36 | 39    | 85  | 46 | 34    | 79  | 43 | 36    | 71  | 51 |
| Placebo                                         | 6              | 99 | 6  | 14    | 98  | 14 | 23    | 91  | 25 | 32    | 90  | 36 | 32    | 83  | 39 | 27    | 73  | 37 |
| p-value for pairwise comparison                 |                |    |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 vs placebo                            | 0.288          |    |    | 0.055 |     |    | 0.134 |     |    | 0.166 |     |    | 0.563 |     |    | 0.098 |     |    |

## Study 134001

**Table 6 Secondary efficacy parameter statistical analysis: HAMD 17 Responders**

| HAMD-17 % Responders                            |                |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|-------------------------------------------------|----------------|----|---|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|
| Last observation carried forward analysis (ITT) |                |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Treatment week |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Wk 1           |    |   | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N  | % | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062                                       | 9              | 98 | 9 | 21    | 100 | 21 | 34    | 101 | 34 | 39    | 101 | 39 | 39    | 101 | 39 | 44    | 101 | 44 |
| Placebo                                         | 5              | 99 | 5 | 14    | 101 | 14 | 19    | 101 | 19 | 25    | 101 | 25 | 34    | 101 | 34 | 31    | 101 | 31 |
| p-value for pairwise comparison                 |                |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 vs placebo                            | 0.260          |    |   | 0.183 |     |    | 0.017 |     |    | 0.035 |     |    | 0.465 |     |    | 0.059 |     |    |
| Observed cases analysis (ITT)                   |                |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Treatment week |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Wk 1           |    |   | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N  | % | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062                                       | 9              | 98 | 9 | 17    | 86  | 20 | 31    | 90  | 34 | 36    | 86  | 42 | 33    | 80  | 41 | 34    | 71  | 48 |
| Placebo                                         | 5              | 99 | 5 | 14    | 98  | 14 | 18    | 91  | 20 | 22    | 90  | 24 | 30    | 83  | 36 | 21    | 73  | 29 |
| p-value for pairwise comparison                 |                |    |   |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 vs placebo                            | 0.260          |    |   | 0.323 |     |    | 0.027 |     |    | 0.014 |     |    | 0.505 |     |    | 0.019 |     |    |

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**A Double-Blind Trial of Org 33062 vs. Placebo in the Treatment of Outpatients with Atypical Depression**

**Study 03A7A-003**

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**Investigators**

| Site | Investigator                                                                                                |
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**Original Sponsor    Bristol-Myers Squibb**

## Study 03A7A-003

***Table 1 Primary efficacy parameter statistical analysis: HAMD 17 reduction from baseline***

| Least squares mean reduction from baseline in HAMD 17 |                |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-------------------------------------------------------|----------------|------------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)       |                |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                       | Treatment week |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                       | Baseline mean  |            | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5  |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                             | 30             | 13.8 (3.6) | 25    | 2.2 (0.8) | 30    | 4.7 (0.8) | 30    | 4.3 (0.9) | 30    | 4.8 (1.0) | 30    | 6.5 (0.9) | 30    | 5.1 (1.0) | 30    | 6.2 (1.0) | 30    | 6.7 (1.0) |
| Placebo                                               | 30             | 13.7 (4.0) | 22    | 1.3 (0.9) | 29    | 2.1 (0.8) | 30    | 2.2 (0.9) | 30    | 2.8 (1.0) | 30    | 2.7 (0.9) | 30    | 3.5 (1.0) | 30    | 3.2 (1.0) | 30    | 2.7 (1.0) |
| p-value for pairwise comparison                       |                |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                  | n/a            |            | 0.457 |           | 0.036 |           | 0.115 |           | 0.146 |           | 0.004 |           | 0.278 |           | 0.038 |           | 0.009 |           |
| Observed cases analysis (ITT)                         |                |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                       | Treatment week |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                       | Baseline mean  |            | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5  |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                             | 30             | 13.8 (3.6) | 25    | 2.2 (0.8) | 29    | 4.8 (0.9) | 21    | 3.0 (1.0) | 15    | 4.8 (1.5) | 19    | 6.2 (1.1) | 17    | 5.0 (1.4) | 17    | 7.1 (1.3) | 16    | 8.9 (1.4) |
| Placebo                                               | 30             | 13.7 (4.0) | 22    | 1.3 (0.9) | 28    | 2.2 (0.9) | 26    | 2.4 (0.9) | 25    | 2.3 (1.1) | 22    | 3.4 (1.0) | 21    | 4.1 (1.3) | 21    | 3.4 (1.2) | 18    | 3.3 (1.3) |
| p-value for pairwise comparison                       |                |            |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                  | n/a            |            | 0.457 |           | 0.043 |           | 0.656 |           | 0.188 |           | 0.075 |           | 0.617 |           | 0.044 |           | 0.007 |           |

n/a = not applicable

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***Table 2 Secondary efficacy parameter statistical analysis: HAMD Item 1 reduction from baseline***

| Least squares mean reduction from baseline in HAMD Item 1 |               |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------|---------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5  |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                           | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 30            | 2.1 (0.7) | 25    | 0.5 (0.2) | 30    | 0.8 (0.2) | 30    | 1.0 (0.2) | 30    | 1.0 (0.2) | 30    | 1.2 (0.2) | 30    | 1.0 (0.2) | 30    | 1.2 (0.2) | 30    | 1.2 (0.2) |
| Placebo                                                   | 30            | 2.1 (0.6) | 22    | 0.3 (0.2) | 29    | 0.5 (0.2) | 30    | 0.6 (0.2) | 30    | 0.6 (0.2) | 30    | 0.6 (0.2) | 30    | 0.6 (0.2) | 30    | 0.6 (0.2) | 30    | 0.5 (0.2) |
| p-value for pairwise comparison                           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a           |           | 0.394 |           | 0.199 |           | 0.147 |           | 0.165 |           | 0.044 |           | 0.159 |           | 0.038 |           | 0.007 |           |
| Observed cases analysis (ITT)                             |               |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5  |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                           | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 30            | 2.1 (0.7) | 25    | 0.5 (0.2) | 29    | 0.8 (0.2) | 21    | 1.0 (0.2) | 15    | 0.9 (0.3) | 19    | 1.0 (0.2) | 17    | 0.9 (0.3) | 17    | 1.3 (0.3) | 16    | 1.4 (0.3) |
| Placebo                                                   | 30            | 2.1 (0.6) | 22    | 0.3 (0.2) | 28    | 0.5 (0.2) | 26    | 0.5 (0.2) | 25    | 0.5 (0.2) | 22    | 0.8 (0.2) | 21    | 0.7 (0.2) | 21    | 0.7 (0.2) | 18    | 0.6 (0.3) |
| p-value for pairwise comparison                           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a           |           | 0.394 |           | 0.196 |           | 0.185 |           | 0.273 |           | 0.556 |           | 0.564 |           | 0.091 |           | 0.033 |           |

n/a = not applicable

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***Table 3 Secondary efficacy parameter statistical analysis: CGI Severity reduction from baseline***

| Least squares mean reduction from baseline in CGI-Severity |               |           |       |           |       |           |       |           |       |           |        |           |       |           |       |           |       |           |
|------------------------------------------------------------|---------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|--------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)            |               |           |       |           |       |           |       |           |       |           |        |           |       |           |       |           |       |           |
| Treatment group                                            | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5   |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                            | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n      | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                  | 30            | 3.9 (0.5) | 25    | 0.3 (0.1) | 30    | 0.7 (0.2) | 30    | 0.9 (0.2) | 30    | 1.2 (0.2) | 30     | 1.4 (0.2) | 30    | 1.1 (0.2) | 30    | 1.2 (0.2) | 30    | 1.4 (0.2) |
| Placebo                                                    | 30            | 3.9 (0.5) | 22    | 0.2 (0.2) | 29    | 0.4 (0.2) | 30    | 0.4 (0.2) | 30    | 0.4 (0.2) | 30     | 0.3 (0.2) | 30    | 0.6 (0.2) | 30    | 0.5 (0.2) | 30    | 0.4 (0.2) |
| p-value for pairwise comparison                            |               |           |       |           |       |           |       |           |       |           |        |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a           |           | 0.810 |           | 0.273 |           | 0.036 |           | 0.006 |           | <0.001 |           | 0.077 |           | 0.024 |           | 0.002 |           |
| Observed cases analysis (ITT)                              |               |           |       |           |       |           |       |           |       |           |        |           |       |           |       |           |       |           |
| Treatment group                                            | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 5   |           | Wk 6  |           | Wk 7  |           | Wk 8  |           |
|                                                            | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n      | X (SEM)   | n     | X (SEM)   | n     | X SEM     | n     | X (SEM)   |
| Org 33062                                                  | 30            | 3.9 (0.5) | 25    | 0.3 (0.1) | 29    | 0.7 (0.2) | 21    | 0.8 (0.2) | 15    | 1.3 (0.3) | 19     | 1.3 (0.2) | 17    | 1.0 (0.2) | 17    | 1.5 (0.3) | 16    | 1.9 (0.3) |
| Placebo                                                    | 30            | 3.9 (0.5) | 22    | 0.2 (0.2) | 28    | 0.5 (0.2) | 26    | 0.4 (0.2) | 25    | 0.4 (0.2) | 22     | 0.5 (0.2) | 21    | 0.7 (0.2) | 21    | 0.8 (0.2) | 18    | 0.6 (0.3) |
| p-value for pairwise comparison                            |               |           |       |           |       |           |       |           |       |           |        |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a           |           | 0.810 |           | 0.341 |           | 0.129 |           | 0.005 |           | 0.008  |           | 0.260 |           | 0.045 |           | 0.002 |           |

n/a = not applicable

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***Table 4 Secondary efficacy parameter statistical analysis: MADRS reduction from baseline***

| Least squares mean reduction from baseline in MADRS |               |            |                |            |       |            |
|-----------------------------------------------------|---------------|------------|----------------|------------|-------|------------|
| Last observation carried forward analysis (ITT)     |               |            |                |            |       |            |
| Treatment group                                     | Baseline mean |            | Treatment week |            | Wk 8  |            |
|                                                     |               |            | Wk 4           |            |       |            |
|                                                     | n             | X (SD)     | n              | X (SEM)    | n     | X (SEM)    |
| Org 33062                                           | 30            | 22.1 (5.9) | 3              | 11.7 (5.3) | 16    | 12.4 (2.7) |
| Placebo                                             | 30            | 20.3 (7.7) | 2              | 4.0 (6.5)  | 18    | 3.8 (2.5)  |
| p-value for pairwise comparison                     |               |            |                |            |       |            |
| Org 33062 vs placebo                                | n/a           |            | 0.161          |            | 0.026 |            |
| Observed cases analysis (ITT)                       |               |            |                |            |       |            |
| Treatment group                                     | Baseline mean |            | Treatment week |            | Wk 8  |            |
|                                                     |               |            | Wk 4           |            |       |            |
|                                                     | n             | X (SD)     | n              | X (SEM)    | n     | X (SEM)    |
| Org 33062                                           | 30            | 22.1 (5.9) | 1              | 3.0 (8.5)  | 12    | 14.3 (2.9) |
| Placebo                                             | 30            | 20.3 (7.7) | 2              | 4.0 (6.0)  | 13    | 5.8 (2.8)  |
| p-value for pairwise comparison                     |               |            |                |            |       |            |
| Org 33062 vs placebo                                | n/a           |            | 0.623          |            | 0.047 |            |

n/a = not applicable

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***Table 5 Secondary efficacy parameter statistical analysis: CGI Responders***

| CGI % Responders                                |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
|-------------------------------------------------|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|
| Last observation carried forward analysis (ITT) |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment week                                  |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment group                                 | Wk 1  |    |    | Wk 2  |    |    | Wk 3  |    |    | Wk 4  |    |    | Wk 5  |    |    | Wk 6  |    |    | Wk 7  |    |    | Wk 8  |    |    |
|                                                 | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| <i>Org 33062</i>                                | 3     | 25 | 12 | 8     | 30 | 27 | 11    | 30 | 37 | 14    | 30 | 47 | 18    | 30 | 60 | 14    | 30 | 47 | 16    | 30 | 53 | 17    | 30 | 57 |
| Placebo                                         | 2     | 22 | 9  | 7     | 29 | 24 | 7     | 30 | 23 | 8     | 30 | 27 | 8     | 30 | 27 | 11    | 30 | 37 | 9     | 30 | 30 | 7     | 30 | 23 |
| p-value for pairwise comparison                 |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.749 |    |    | 0.825 |    |    | 0.264 |    |    | 0.111 |    |    | 0.010 |    |    | 0.436 |    |    | 0.069 |    |    | 0.009 |    |    |
| Observed case analysis (ITT)                    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment week                                  |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment group                                 | Wk 1  |    |    | Wk 2  |    |    | Wk 3  |    |    | Wk 4  |    |    | Wk 5  |    |    | Wk 6  |    |    | Wk 7  |    |    | Wk 8  |    |    |
|                                                 | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| Org 33062                                       | 3     | 25 | 12 | 8     | 29 | 28 | 7     | 21 | 33 | 9     | 15 | 60 | 12    | 19 | 63 | 8     | 17 | 47 | 12    | 17 | 71 | 12    | 16 | 75 |
| Placebo                                         | 2     | 22 | 9  | 7     | 28 | 25 | 7     | 26 | 27 | 6     | 25 | 24 | 7     | 22 | 32 | 8     | 21 | 38 | 7     | 21 | 33 | 4     | 18 | 22 |
| p-value for pairwise comparison                 |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.749 |    |    | 0.826 |    |    | 0.636 |    |    | 0.025 |    |    | 0.047 |    |    | 0.583 |    |    | 0.024 |    |    | 0.002 |    |    |

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Table 6 Secondary efficacy parameter statistical analysis: HAMD 17 Responders

| HAMD-17 % Responders                            |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
|-------------------------------------------------|-------|----|---|-------|----|----|-------|----|----|-------|----|----|--------|----|----|-------|----|----|-------|----|----|-------|----|----|
| Last observation carried forward analysis (ITT) |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Treatment week                                  |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Treatment group                                 | Wk 1  |    |   | Wk 2  |    |    | Wk 3  |    |    | Wk 4  |    |    | Wk 5   |    |    | Wk 6  |    |    | Wk 7  |    |    | Wk 8  |    |    |
|                                                 | n     | N  | % | n     | N  | %  | n     | N  | %  | n     | N  | %  | n      | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| <i>Org 33062</i>                                | 2     | 25 | 8 | 9     | 30 | 30 | 11    | 30 | 37 | 12    | 30 | 40 | 16     | 30 | 53 | 13    | 30 | 43 | 14    | 30 | 47 | 16    | 30 | 53 |
| Placebo                                         | 1     | 22 | 5 | 4     | 29 | 14 | 2     | 30 | 7  | 5     | 30 | 17 | 3      | 30 | 10 | 5     | 30 | 17 | 6     | 30 | 20 | 5     | 30 | 17 |
| p-value for pairwise comparison                 |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.632 |    |   | 0.137 |    |    | 0.005 |    |    | 0.047 |    |    | <0.001 |    |    | 0.025 |    |    | 0.030 |    |    | 0.003 |    |    |
| Observed cases analysis (ITT)                   |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Treatment week                                  |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Treatment group                                 | Wk 1  |    |   | Wk 2  |    |    | Wk 3  |    |    | Wk 4  |    |    | Wk 5   |    |    | Wk 6  |    |    | Wk 7  |    |    | Wk 8  |    |    |
|                                                 | n     | N  | % | n     | N  | %  | n     | N  | %  | n     | N  | %  | n      | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| Org 33062                                       | 2     | 25 | 8 | 9     | 29 | 31 | 7     | 21 | 33 | 7     | 15 | 47 | 10     | 19 | 53 | 7     | 17 | 41 | 10    | 17 | 59 | 12    | 16 | 75 |
| Placebo                                         | 1     | 22 | 5 | 4     | 28 | 14 | 2     | 26 | 8  | 4     | 25 | 16 | 3      | 22 | 14 | 4     | 21 | 19 | 6     | 21 | 29 | 4     | 18 | 22 |
| p-value for pairwise comparison                 |       |    |   |       |    |    |       |    |    |       |    |    |        |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.632 |    |   | 0.135 |    |    | 0.028 |    |    | 0.038 |    |    | 0.008  |    |    | 0.140 |    |    | 0.064 |    |    | 0.002 |    |    |

**Study 03A7A-002**

**Investigators**

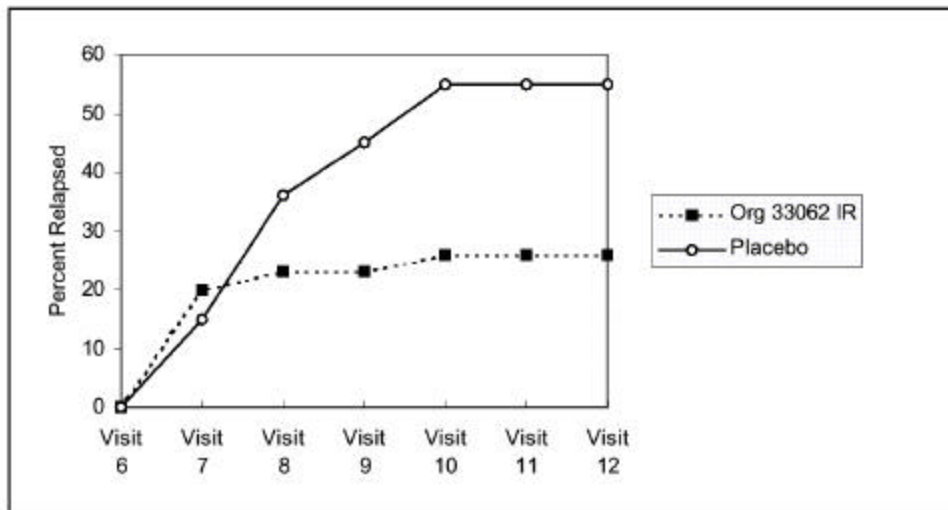
| Site | Investigator                                                    |
|------|-----------------------------------------------------------------|
| 2416 | Jay Amsterdam, M.D.<br>Philadelphia, PA                         |
| 2417 | John J. Schwab, M.D.<br>Elizabeth Lin, Ph.D.<br>Louisville, KY  |
| 2418 | John S. Carmen, M.D.<br>Smyrna, GA                              |
| 2419 | Bradley Evans, M.D.<br>Helen Pettinati, Ph.D.<br>Belle Mead, NJ |
| 2424 | Jeffrey Rausch, M.D.<br>La Jolla, CA                            |

***Original Sponsor Bristol-Myers Squibb***

**Figure 3 Proportion of Patients Relapsing (Definition A) During the Double-Blind Phase by Study Visit (Protocol 03A7A-002)**

Key: Visits 6-12 = Weeks 6-12, respectively; p value applies to the entire distribution of Org 33062-treated subjects versus the entire distribution of placebo-treated subjects during Weeks 6-12

Relapse Defined as Return to  $\geq 75\%$  of the Pretreatment HAMD 17 Total Score  
Comparison of Org 33062 and Placebo  
Intent-to-Treat Group

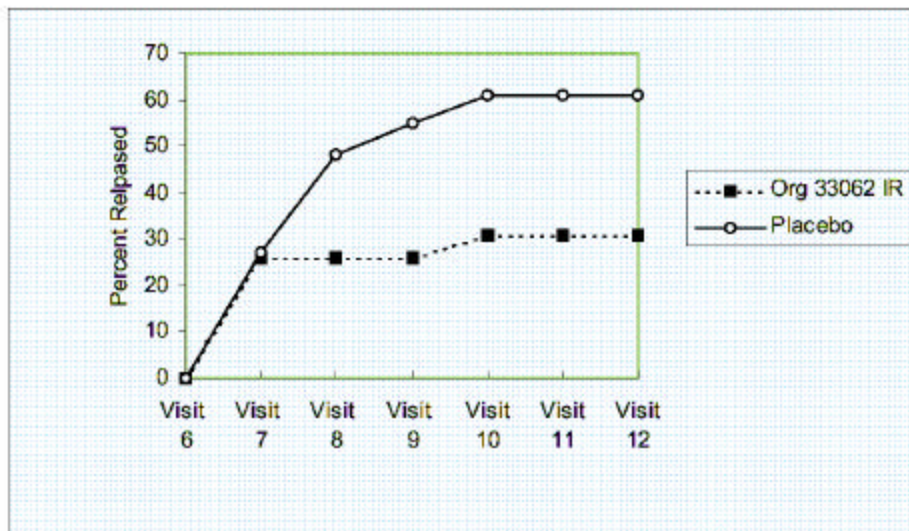


p=0.030 (Log rank)

**Figure 4 Proportion of Patients Relapsing (Definition B) During the Double-Blind Phase by Study Visit (Protocol 03A7A-002)**

**Key:** Visits 6-12 = Weeks 6-12, respectively; p value applies to the entire distribution of Org 33062-treated subjects versus the entire distribution of placebo-treated subjects during Weeks 6-12

Relapse Defined as CGI Improvement Score of No Change or Worse than Pretreatment  
Comparison of Org 33062 and Placebo  
Intent-to-Treat Group

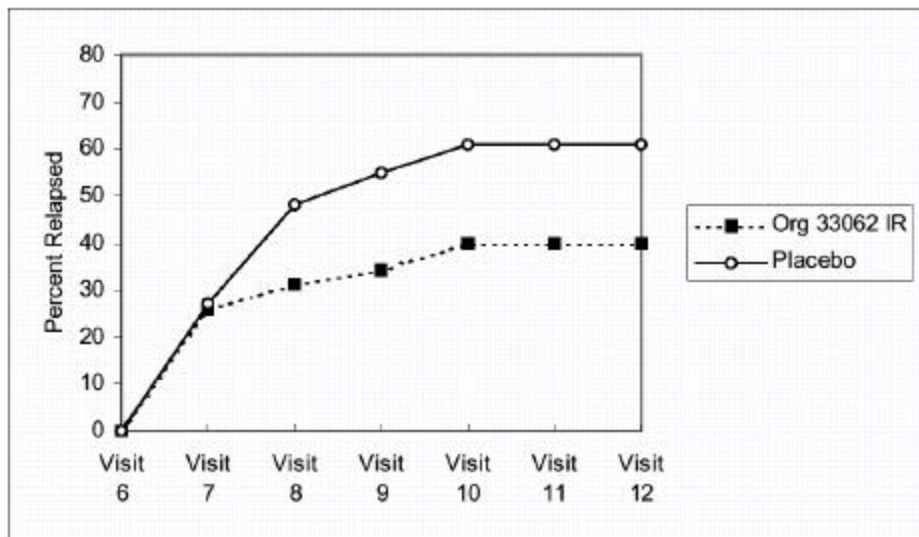


p=0.023 (Log rank)

**Figure 8 Proportion of Patients Relapsing (Definition F) During the Double-Blind Phase by Study Visit (Protocol 03A7A-002)**

Key: Visits 6-12 = Weeks 6-12, respectively; p value applies to the entire distribution of Org 33062-treated subjects versus the entire distribution of placebo-treated subjects during Weeks 6-12

Relapse Defined as CGI Improvement Score of No Change or Worse than Pretreatment or Discontinuation Due to Lack of efficacy  
Comparison of Org 33062 and Placebo  
Intent-to-Treat Group



p = 0.114 (Log rank)

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***Table 1 Primary efficacy parameter statistical analysis: HAMD 17 reduction from baseline***

| Least squares mean reduction from baseline in HAMD 17 |               |            |       |            |       |            |       |            |       |            |       |            |       |            |
|-------------------------------------------------------|---------------|------------|-------|------------|-------|------------|-------|------------|-------|------------|-------|------------|-------|------------|
| Last observation carried forward analysis (ITT)       |               |            |       |            |       |            |       |            |       |            |       |            |       |            |
| Treatment group                                       | Baseline mean |            | Wk 7  |            | Wk 8  |            | Wk 9  |            | Wk 10 |            | Wk 11 |            | Wk 12 |            |
|                                                       | n             | X (SD)     | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062                                             | 36            | 24.8 (4.5) | 34    | 13.0 (1.5) | 36    | 12.8 (1.4) | 36    | 12.9 (1.4) | 36    | 13.1 (1.5) | 36    | 12.8 (1.5) | 36    | 13.1 (1.5) |
| Placebo                                               | 34            | 24.6 (4.0) | 31    | 11.7 (1.5) | 34    | 9.6 (1.4)  | 34    | 9.5 (1.5)  | 34    | 9.6 (1.5)  | 34    | 9.4 (1.5)  | 34    | 9.0 (1.6)  |
| p-value for pairwise comparison                       |               |            |       |            |       |            |       |            |       |            |       |            |       |            |
| Org 33062 vs placebo                                  | n/a           |            | 0.532 |            | 0.103 |            | 0.111 |            | 0.107 |            | 0.125 |            | 0.070 |            |
| Observed cases analysis (ITT)                         |               |            |       |            |       |            |       |            |       |            |       |            |       |            |
| Treatment group                                       | Baseline mean |            | Wk 7  |            | Wk 8  |            | Wk 9  |            | Wk 10 |            | Wk 11 |            | Wk 12 |            |
|                                                       | n             | X (SD)     | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062                                             | 36            | 24.8 (4.5) | 34    | 13.0 (1.5) | 30    | 14.6 (1.4) | 26    | 15.0 (1.6) | 21    | 16.0 (1.6) | 11    | 15.3 (1.9) | 11    | 16.5 (2.3) |
| Placebo                                               | 34            | 24.6 (4.0) | 31    | 11.7 (1.5) | 29    | 10.6 (1.4) | 24    | 10.8 (1.6) | 18    | 13.4 (1.8) | 6     | 12.2 (2.5) | 6     | 10.8 (3.1) |
| p-value for pairwise comparison                       |               |            |       |            |       |            |       |            |       |            |       |            |       |            |
| Org 33062 vs placebo                                  | n/a           |            | 0.532 |            | 0.049 |            | 0.067 |            | 0.293 |            | 0.337 |            | 0.156 |            |

n/a = not applicable

Note: This table contains data on subjects enrolled to the double blind phase of this relapse prevention trial. Baseline values are taken from the pre-treatment baseline visit prior to the start of the open-label phase.

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***Table 2 Secondary efficacy parameter statistical analysis: HAMD Item 1 reduction from baseline***

| Least squares mean reduction from baseline in HAMD Item 1 |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------|---------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean |           | Wk 7  |           | Wk 8  |           | Wk 9  |           | Wk 10 |           | Wk 11 |           | Wk 12 |           |
|                                                           | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 36            | 2.8 (0.6) | 34    | 1.5 (0.2) | 36    | 1.6 (0.2) | 36    | 1.5 (0.2) | 36    | 1.4 (0.2) | 36    | 1.4 (0.2) | 36    | 1.4 (0.2) |
| Placebo                                                   | 34            | 2.7 (0.7) | 31    | 1.3 (0.2) | 34    | 0.9 (0.2) | 34    | 1.0 (0.2) | 34    | 1.0 (0.2) | 34    | 1.0 (0.2) | 34    | 0.9 (0.2) |
| p-value for pairwise comparison                           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a           |           | 0.450 |           | 0.022 |           | 0.166 |           | 0.185 |           | 0.251 |           | 0.148 |           |
| Observed cases analysis (ITT)                             |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                           | Baseline mean |           | Wk 7  |           | Wk 8  |           | Wk 9  |           | Wk 10 |           | Wk 11 |           | Wk 12 |           |
|                                                           | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                 | 36            | 2.8 (0.6) | 34    | 1.5 (0.2) | 30    | 1.8 (0.2) | 26    | 1.7 (0.3) | 21    | 1.9 (0.3) | 11    | 1.6 (0.4) | 11    | 2.0 (0.4) |
| Placebo                                                   | 34            | 2.7 (0.7) | 31    | 1.3 (0.2) | 29    | 0.9 (0.2) | 24    | 1.1 (0.3) | 18    | 1.3 (0.3) | 6     | 0.8 (0.5) | 6     | 1.3 (0.5) |
| p-value for pairwise comparison                           |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                      | n/a           |           | 0.450 |           | 0.005 |           | 0.107 |           | 0.225 |           | 0.224 |           | 0.328 |           |

n/a = not applicable

Note: This table contains data on subjects enrolled to the double blind phase of this relapse prevention trial. Baseline values are taken from the pre-treatment baseline visit prior to the start of the open-label phase.

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***Table 3 Secondary efficacy parameter statistical analysis: CGI Severity reduction from baseline***

| Least squares mean reduction from baseline in CGI-Severity |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|------------------------------------------------------------|----------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment Group                                            | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                            | Baseline mean  |           | Wk 7  |           | Wk 8  |           | Wk 9  |           | Wk 10 |           | Wk 11 |           | Wk 12 |           |
|                                                            | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                  | 36             | 4.3 (0.6) | 34    | 1.5 (0.2) | 36    | 1.6 (0.2) | 36    | 1.5 (0.2) | 36    | 1.5 (0.2) | 36    | 1.4 (0.2) | 36    | 1.6 (0.2) |
| Placebo                                                    | 33             | 4.2 (0.5) | 31    | 1.3 (0.2) | 33    | 1.0 (0.2) | 33    | 1.1 (0.2) | 33    | 1.1 (0.2) | 33    | 1.1 (0.2) | 33    | 1.0 (0.2) |
| p-value for pairwise comparison                            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a            |           | 0.471 |           | 0.034 |           | 0.189 |           | 0.161 |           | 0.313 |           | 0.106 |           |
| Observed cases analysis (ITT)                              |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                            | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                            | Baseline mean  |           | Wk 7  |           | Wk 8  |           | Wk 9  |           | Wk 10 |           | Wk 11 |           | Wk 12 |           |
|                                                            | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062                                                  | 36             | 4.3 (0.6) | 34    | 1.5 (0.2) | 30    | 1.8 (0.2) | 27    | 1.7 (0.3) | 21    | 2.0 (0.3) | 11    | 1.9 (0.3) | 11    | 2.5 (0.4) |
| Placebo                                                    | 33             | 4.2 (0.5) | 31    | 1.3 (0.2) | 28    | 1.2 (0.2) | 23    | 1.3 (0.3) | 18    | 1.4 (0.3) | 6     | 1.7 (0.5) | 6     | 1.2 (0.6) |
| p-value for pairwise comparison                            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 vs placebo                                       | n/a            |           | 0.471 |           | 0.051 |           | 0.409 |           | 0.188 |           | 0.671 |           | 0.063 |           |

n/a = not applicable

Note: This table contains data on subjects enrolled to the double blind phase of this relapse prevention trial.

Baseline values are taken from the pre-treatment baseline visit prior to the start of the open-label phase.

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***Table 4 Secondary efficacy parameter statistical analysis: CGI Responders***

| CGI % Responders                                |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
|-------------------------------------------------|----------------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|-----|
| Last observation carried forward analysis (ITT) |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
| Treatment group                                 | Treatment week |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
|                                                 | Wk 7           |    |    | Wk 8  |    |    | Wk 9  |    |    | Wk 10 |    |    | Wk 11 |    |    | Wk 12 |    |     |
|                                                 | n              | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %   |
| Org 33062                                       | 21             | 34 | 62 | 21    | 36 | 58 | 19    | 36 | 53 | 19    | 36 | 53 | 18    | 36 | 50 | 20    | 36 | 56  |
| Placebo                                         | 14             | 31 | 45 | 12    | 33 | 36 | 17    | 33 | 52 | 16    | 33 | 48 | 15    | 33 | 45 | 14    | 33 | 42  |
| p-value for pairwise comparison                 |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
| Org 33062 vs placebo                            | 0.183          |    |    | 0.070 |    |    | 0.917 |    |    | 0.724 |    |    | 0.708 |    |    | 0.279 |    |     |
| Observed cases analysis (ITT)                   |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
| Treatment group                                 | Treatment week |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
|                                                 | Wk 7           |    |    | Wk 8  |    |    | Wk 9  |    |    | Wk 10 |    |    | Wk 11 |    |    | Wk 12 |    |     |
|                                                 | n              | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %   |
| Org 33062                                       | 21             | 34 | 62 | 20    | 30 | 67 | 19    | 27 | 70 | 16    | 21 | 76 | 8     | 11 | 73 | 11    | 11 | 100 |
| Placebo                                         | 14             | 31 | 45 | 11    | 28 | 39 | 12    | 23 | 52 | 9     | 18 | 50 | 2     | 6  | 33 | 2     | 6  | 33  |
| p-value for pairwise comparison                 |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |     |
| Org 33062 vs placebo                            | 0.183          |    |    | 0.038 |    |    | 0.191 |    |    | 0.093 |    |    | 0.126 |    |    | 0.003 |    |     |

Note: This table contains data on subjects enrolled to the double blind phase of this relapse prevention trial.

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***Table 5 Secondary efficacy parameter statistical analysis: HAMD-17 Responders***

| HAMD-17 % Responders                            |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
|-------------------------------------------------|----------------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|-------|----|----|
| Last observation carried forward analysis (ITT) |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment group                                 | Treatment week |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
|                                                 | Wk 7           |    |    | Wk 8  |    |    | Wk 9  |    |    | Wk 10 |    |    | Wk 11 |    |    | Wk 12 |    |    |
|                                                 | n              | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| Org 33062                                       | 20             | 34 | 59 | 21    | 36 | 58 | 22    | 36 | 61 | 23    | 36 | 64 | 23    | 36 | 64 | 22    | 36 | 61 |
| Placebo                                         | 12             | 31 | 39 | 14    | 34 | 41 | 14    | 34 | 41 | 15    | 34 | 44 | 14    | 34 | 41 | 13    | 34 | 38 |
| p-value for pairwise comparison                 |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.108          |    |    | 0.154 |    |    | 0.098 |    |    | 0.099 |    |    | 0.059 |    |    | 0.058 |    |    |
| Observed cases analysis (ITT)                   |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Treatment Group                                 | Treatment week |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
|                                                 | Wk 7           |    |    | Wk 8  |    |    | Wk 9  |    |    | Wk 10 |    |    | Wk 11 |    |    | Wk 12 |    |    |
|                                                 | n              | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  | n     | N  | %  |
| Org 33062                                       | 20             | 34 | 59 | 20    | 30 | 67 | 20    | 26 | 77 | 17    | 21 | 81 | 10    | 11 | 91 | 9     | 11 | 82 |
| Placebo                                         | 12             | 31 | 39 | 13    | 29 | 45 | 10    | 24 | 42 | 11    | 18 | 61 | 2     | 6  | 33 | 2     | 6  | 33 |
| p-value for pairwise comparison                 |                |    |    |       |    |    |       |    |    |       |    |    |       |    |    |       |    |    |
| Org 33062 vs placebo                            | 0.108          |    |    | 0.094 |    |    | 0.012 |    |    | 0.175 |    |    | 0.016 |    |    | 0.052 |    |    |

Note : This table contains data on subjects enrolled to the double blind phase of this relapse prevention trial. Baseline values for determining HAMD 17 Responder status are taken from the pre-treatment baseline visit prior to the start of the open-label phase.

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**A Double-Blind Multicenter Trial of Two Dose Ranges of Org 33062 and Placebo in the Treatment of Depressed Outpatients**

**Study 03A7C-001B**

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**Investigators:**

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Study 03A7C-001B

**Table 1 Primary efficacy parameter statistical analysis: HAMD 17 reduction from baseline**

| Least squares mean reduction from baseline in HAMD 17                 |                |            |       |           |       |           |       |            |       |            |       |            |       |            |
|-----------------------------------------------------------------------|----------------|------------|-------|-----------|-------|-----------|-------|------------|-------|------------|-------|------------|-------|------------|
| Last observation carried forward analysis (ITT)                       |                |            |       |           |       |           |       |            |       |            |       |            |       |            |
| Treatment group                                                       | Treatment week |            |       |           |       |           |       |            |       |            |       |            |       |            |
|                                                                       | Baseline mean  |            | Wk 1  |           | Wk 2  |           | Wk 3  |            | Wk 4  |            | Wk 6  |            | Wk 8  |            |
|                                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062 Total                                                       | 137            | 23.9 (4.7) | 127   | 4.7 (0.6) | 136   | 7.5 (0.7) | 137   | 8.8 (0.7)  | 137   | 9.9 (0.7)  | 137   | 10.8 (0.8) | 137   | 10.7 (0.7) |
| Org 33062 5-45                                                        | 70             | 23.4 (4.9) | 65    | 4.1 (0.8) | 69    | 6.9 (0.9) | 70    | 8.2 (1.0)  | 70    | 9.2 (1.1)  | 70    | 10.2 (1.1) | 70    | 10.0 (1.0) |
| Org 33062 10-90                                                       | 67             | 24.4 (4.5) | 62    | 5.0 (0.8) | 67    | 8.0 (0.9) | 67    | 9.3 (1.0)  | 67    | 10.4 (1.1) | 67    | 11.3 (1.1) | 67    | 11.3 (1.0) |
| Placebo                                                               | 69             | 24.1 (4.8) | 64    | 3.3 (0.8) | 69    | 6.0 (0.9) | 69    | 7.1 (1.0)  | 69    | 6.3 (1.1)  | 69    | 6.6 (1.1)  | 69    | 6.4 (1.0)  |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |                |            |       |           |       |           |       |            |       |            |       |            |       |            |
| Org 33062 Total vs placebo                                            | n/a            |            | 0.190 |           | 0.207 |           | 0.194 |            | 0.006 |            | 0.002 |            | 0.001 |            |
| Org 33062 5-45 vs placebo                                             | n/a            |            | 0.515 |           | 0.509 |           | 0.490 |            | 0.053 |            | 0.020 |            | 0.015 |            |
| Org 33062 10-90 vs placebo                                            | n/a            |            | 0.152 |           | 0.143 |           | 0.131 |            | 0.006 |            | 0.002 |            | 0.001 |            |
| Observed cases analysis (ITT)                                         |                |            |       |           |       |           |       |            |       |            |       |            |       |            |
| Treatment group                                                       | Treatment week |            |       |           |       |           |       |            |       |            |       |            |       |            |
|                                                                       | Baseline mean  |            | Wk 1  |           | Wk 2  |           | Wk 3  |            | Wk 4  |            | Wk 6  |            | Wk 8  |            |
|                                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062 Total                                                       | 137            | 23.9 (4.7) | 127   | 4.7 (0.6) | 116   | 8.1 (0.8) | 101   | 10.0 (0.8) | 110   | 10.9 (0.9) | 95    | 12.5 (9)   | 60    | 13.1 (0.8) |
| Org 33062 5-45                                                        | 70             | 23.4 (4.9) | 65    | 4.1 (0.8) | 62    | 7.3 (1.0) | 53    | 8.5 (1.2)  | 61    | 10.1 (1.2) | 50    | 11.7 (1.2) | 35    | 12.4 (1.1) |
| Org 33062 10-90                                                       | 67             | 24.4 (4.5) | 62    | 5.0 (0.8) | 54    | 9.3 (1.2) | 48    | 11.6 (1.2) | 49    | 11.9 (1.3) | 45    | 13.5 (1.3) | 25    | 14.5 (1.2) |
| Placebo                                                               | 69             | 24.1 (4.8) | 64    | 3.3 (0.8) | 58    | 5.9 (1.1) | 59    | 8.5 (1.1)  | 57    | 7.6 (1.2)  | 50    | 8.2 (1.2)  | 33    | 11.1 (1.1) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |                |            |       |           |       |           |       |            |       |            |       |            |       |            |
| Org 33062 Total vs placebo                                            | n/a            |            | 0.190 |           | 0.107 |           | 0.294 |            | 0.027 |            | 0.005 |            | 0.145 |            |

|                            |     |       |       |       |       |       |       |
|----------------------------|-----|-------|-------|-------|-------|-------|-------|
| Org 33062 5-45 vs placebo  | n/a | 0.515 | 0.377 | 0.985 | 0.143 | 0.043 | 0.412 |
| Org 33062 10-90 vs placebo | n/a | 0.152 | 0.039 | 0.064 | 0.016 | 0.004 | 0.045 |

n/a = not applicable

### Study 03A7C-001B

***Table 2 Secondary efficacy parameter statistical analysis: HAMD Item 1 reduction from baseline***

| Least squares mean reduction from baseline in HAMD Item 1             |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------------------|---------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Last observation carried forward analysis (ITT)                       |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                                       | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                                       | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062 Total                                                       | 137           | 2.6 (0.7) | 127   | 0.6 (0.1) | 136   | 0.9 (0.1) | 137   | 1.0 (0.1) | 137   | 1.0 (0.1) | 137   | 1.2 (0.1) | 137   | 1.3 (0.1) |
| Org 33062 5-45                                                        | 70            | 2.6 (0.7) | 65    | 0.5 (0.1) | 69    | 0.8 (0.1) | 70    | 0.9 (0.2) | 70    | 0.8 (0.2) | 70    | 1.0 (0.2) | 70    | 1.1 (0.2) |
| Org 33062 10-90                                                       | 67            | 2.7 (0.6) | 62    | 0.6 (0.1) | 67    | 0.9 (0.1) | 67    | 1.1 (0.2) | 67    | 1.2 (0.2) | 67    | 1.3 (0.2) | 67    | 1.3 (0.2) |
| Placebo                                                               | 69            | 2.8 (0.8) | 64    | 0.4 (0.1) | 69    | 0.8 (0.1) | 69    | 0.9 (0.2) | 69    | 0.8 (0.2) | 69    | 0.8 (0.2) | 69    | 0.7 (0.2) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 Total vs placebo                                            | n/a           |           | 0.451 |           | 0.661 |           | 0.511 |           | 0.268 |           | 0.046 |           | 0.004 |           |
| Org 33062 5-45 vs placebo                                             | n/a           |           | 0.588 |           | 0.925 |           | 0.900 |           | 0.960 |           | 0.270 |           | 0.041 |           |
| Org 33062 10-90 vs placebo                                            | n/a           |           | 0.502 |           | 0.534 |           | 0.320 |           | 0.056 |           | 0.020 |           | 0.004 |           |
| Observed cases analysis (ITT)                                         |               |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                                       | Baseline mean |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                                       | n             | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062 Total                                                       | 137           | 2.6 (0.7) | 127   | 0.6 (0.1) | 116   | 0.9 (0.1) | 101   | 1.2 (0.1) | 110   | 1.2 (0.1) | 95    | 1.4 (0.1) | 60    | 1.5 (0.1) |
| Org 33062 5-45                                                        | 70            | 2.6 (0.7) | 65    | 0.5 (0.1) | 62    | 0.9 (0.2) | 53    | 1.0 (0.2) | 61    | 0.9 (0.2) | 50    | 1.2 (0.2) | 35    | 1.4 (0.2) |
| Org 33062 10-90                                                       | 67            | 2.7 (0.6) | 62    | 0.6 (0.1) | 54    | 1.0 (0.2) | 48    | 1.3 (0.2) | 49    | 1.5 (0.2) | 45    | 1.5 (0.2) | 25    | 1.6 (0.2) |

|                                                                       |     |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------------------|-----|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Placebo                                                               | 69  | 2.8 (0.8) | 64    | 0.4 (0.1) | 58    | 0.8 (0.2) | 59    | 1.0 (0.2) | 57    | 1.0 (0.2) | 50    | 1.0 (0.2) | 33    | 1.1 (0.2) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |     |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 Total vs placebo                                            | n/a |           | 0.451 |           | 0.613 |           | 0.517 |           | 0.412 |           | 0.073 |           | 0.096 |           |
| Org 33062 5-45 vs placebo                                             | n/a |           | 0.588 |           | 0.849 |           | 0.957 |           | 0.712 |           | 0.263 |           | 0.216 |           |
| Org 33062 10-90 vs placebo                                            | n/a |           | 0.502 |           | 0.427 |           | 0.236 |           | 0.056 |           | 0.041 |           | 0.096 |           |

n/a = not applicable

### Study 03A7C-001B

**Table 3 Secondary efficacy parameter statistical analysis: CGI Severity reduction from baseline**

|                                                                       |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|-----------------------------------------------------------------------|----------------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Least squares mean reduction from baseline in CGI-Severity            |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Last observation carried forward analysis (ITT)                       |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                                       | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                                       | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |
|                                                                       | n              | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
| Org 33062 Total                                                       | 137            | 4.2 (0.4) | 127   | 0.3 (0.1) | 136   | 0.6 (0.1) | 137   | 0.8 (0.1) | 137   | 0.9 (0.1) | 137   | 1.0 (0.1) | 137   | 1.1 (0.1) |
| Org 33062 5-45                                                        | 70             | 4.2 (0.4) | 65    | 0.3 (0.1) | 69    | 0.5 (0.1) | 70    | 0.7 (0.1) | 70    | 0.9 (0.1) | 70    | 0.9 (0.1) | 70    | 1.1 (0.1) |
| Org 33062 10-90                                                       | 67             | 4.2 (0.4) | 62    | 0.3 (0.1) | 67    | 0.6 (0.1) | 67    | 0.8 (0.1) | 67    | 1.0 (0.1) | 67    | 1.1 (0.1) | 67    | 1.1 (0.1) |
| Placebo                                                               | 69             | 4.3 (0.5) | 64    | 0.3 (0.1) | 69    | 0.6 (0.1) | 69    | 0.7 (0.1) | 69    | 0.7 (0.1) | 69    | 0.7 (0.1) | 69    | 0.6 (0.1) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 Total vs placebo                                            | n/a            |           | 0.799 |           | 0.862 |           | 0.551 |           | 0.268 |           | 0.049 |           | 0.005 |           |
| Org 33062 5-45 vs placebo                                             | n/a            |           | 0.851 |           | 0.837 |           | 0.929 |           | 0.518 |           | 0.191 |           | 0.015 |           |
| Org 33062 10-90 vs placebo                                            | n/a            |           | 0.927 |           | 0.656 |           | 0.371 |           | 0.223 |           | 0.038 |           | 0.016 |           |
| Observed cases analysis (ITT)                                         |                |           |       |           |       |           |       |           |       |           |       |           |       |           |
|                                                                       | Treatment week |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Treatment group                                                       | Baseline mean  |           | Wk 1  |           | Wk 2  |           | Wk 3  |           | Wk 4  |           | Wk 6  |           | Wk 8  |           |

|                                                                       | n   | X (SD)    | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   | n     | X (SEM)   |
|-----------------------------------------------------------------------|-----|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|-------|-----------|
| Org 33062 Total                                                       | 137 | 4.2 (0.4) | 127   | 0.3 (0.1) | 116   | 0.7 (0.1) | 102   | 0.9 (0.1) | 109   | 1.0 (0.1) | 95    | 1.2 (0.1) | 60    | 1.6 (0.1) |
| Org 33062 5-45                                                        | 70  | 4.2 (0.4) | 65    | 0.3 (0.1) | 62    | 0.6 (0.1) | 53    | 0.7 (0.2) | 61    | 0.9 (0.2) | 50    | 1.0 (0.2) | 35    | 1.6 (0.2) |
| Org 33062 10-90                                                       | 67  | 4.2 (0.4) | 62    | 0.3 (0.1) | 54    | 0.8 (0.2) | 49    | 1.1 (0.2) | 48    | 1.2 (0.2) | 45    | 1.3 (0.2) | 25    | 1.6 (0.2) |
| Placebo                                                               | 69  | 4.3 (0.5) | 64    | 0.3 (0.1) | 58    | 0.6 (0.1) | 59    | 0.8 (0.2) | 57    | 0.9 (0.2) | 50    | 0.8 (0.2) | 32    | 1.3 (0.2) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |     |           |       |           |       |           |       |           |       |           |       |           |       |           |
| Org 33062 Total vs placebo                                            | n/a |           | 0.799 |           | 0.662 |           | 0.612 |           | 0.504 |           | 0.110 |           | 0.121 |           |
| Org 33062 5-45 vs placebo                                             | n/a |           | 0.851 |           | 0.933 |           | 0.820 |           | 0.884 |           | 0.388 |           | 0.158 |           |
| Org 33062 10-90 vs placebo                                            | n/a |           | 0.927 |           | 0.311 |           | 0.248 |           | 0.248 |           | 0.047 |           | 0.184 |           |

n/a = not applicable

### Study 03A7C-001B

**Table 4 Secondary efficacy parameter statistical analysis: MADRS reduction from baseline**

| Mean reduction from baseline in MADRS                                 |                |            |       |           |       |            |       |            |
|-----------------------------------------------------------------------|----------------|------------|-------|-----------|-------|------------|-------|------------|
| Last observation carried forward analysis (ITT)                       |                |            |       |           |       |            |       |            |
| Treatment group                                                       | Treatment week |            |       |           |       |            |       |            |
|                                                                       | Baseline mean  |            | Wk 1  |           | Wk 4  |            | Wk 8  |            |
|                                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062 Total                                                       | 135            | 32.2 (6.2) | 125   | 5.0 (0.9) | 133   | 11.7 (1.2) | 135   | 14.6 (1.2) |
| Org 33062 5-45                                                        | 69             | 31.8 (6.3) | 64    | 3.7 (1.2) | 68    | 11.2 (1.7) | 69    | 14.0 (1.7) |
| Org 33062 10-90                                                       | 66             | 32.7 (6.1) | 61    | 6.0 (1.2) | 65    | 12.1 (1.6) | 66    | 15.2 (1.7) |
| Placebo                                                               | 69             | 33.1 (7.8) | 64    | 5.1 (1.2) | 69    | 9.1 (1.6)  | 69    | 8.1 (1.7)  |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |                |            |       |           |       |            |       |            |
| Org 33062 Total vs placebo                                            | n/a            |            | 0.931 |           | 0.184 |            | 0.002 |            |
| Org 33062 5-45 vs placebo                                             | n/a            |            | 0.397 |           | 0.360 |            | 0.013 |            |
| Org 33062 10-90 vs placebo                                            | n/a            |            | 0.577 |           | 0.184 |            | 0.003 |            |

| Observed cases analysis (ITT)                                         |                |            |       |           |       |            |       |            |
|-----------------------------------------------------------------------|----------------|------------|-------|-----------|-------|------------|-------|------------|
| Treatment group                                                       | Treatment week |            |       |           |       |            |       |            |
|                                                                       | Baseline mean  |            | Wk 1  |           | Wk 4  |            | Wk 8  |            |
|                                                                       | n              | X (SD)     | n     | X (SEM)   | n     | X (SEM)    | n     | X (SEM)    |
| Org 33062 Total                                                       | 135            | 32.2 (6.2) | 125   | 5.0 (0.9) | 99    | 14.5 (1.5) | 52    | 18.7 (1.5) |
| Org 33062 5-45                                                        | 69             | 31.8 (6.3) | 64    | 3.7 (1.2) | 55    | 13.1 (1.9) | 29    | 17.9 (2.0) |
| Org 33062 10-90                                                       | 66             | 32.7 (6.1) | 61    | 6.0 (1.2) | 44    | 16.7 (2.3) | 23    | 19.9 (2.3) |
| Placebo                                                               | 69             | 33.1 (7.8) | 64    | 5.1 (1.2) | 54    | 11.2 (1.9) | 30    | 15.8 (2.0) |
| p-value for pairwise comparison (unadjusted for multiple comparisons) |                |            |       |           |       |            |       |            |
| Org 33062 Total vs placebo                                            | n/a            |            | 0.931 |           | 0.175 |            | 0.239 |            |
| Org 33062 5-45 vs placebo                                             | n/a            |            | 0.397 |           | 0.500 |            | 0.460 |            |
| Org 33062 10-90 vs placebo                                            | n/a            |            | 0.577 |           | 0.070 |            | 0.178 |            |

n/a = not applicable

### Study 03A7C-001B

**Table 5 Secondary efficacy parameter statistical analysis: CGI Responders**

| CGI % Responders                                |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|-------------------------------------------------|----------------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|
| Last observation carried forward analysis (ITT) |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Treatment week |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Wk 1           |     |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062 Total                                 | 15             | 127 | 12 | 45    | 136 | 33 | 55    | 137 | 40 | 63    | 137 | 46 | 72    | 137 | 53 | 78    | 137 | 57 |
| Org 33062 5-45                                  | 12             | 65  | 18 | 24    | 69  | 35 | 27    | 70  | 39 | 34    | 70  | 49 | 38    | 70  | 54 | 41    | 70  | 59 |
| Org 33062 10-90                                 | 3              | 62  | 5  | 21    | 67  | 31 | 28    | 67  | 42 | 29    | 67  | 43 | 34    | 67  | 51 | 37    | 67  | 55 |
| Placebo                                         | 7              | 64  | 11 | 23    | 69  | 33 | 25    | 69  | 36 | 24    | 69  | 35 | 26    | 69  | 38 | 27    | 69  | 39 |
| p-value for pairwise comparison                 |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 Total vs placebo                      | 0.904          |     |    | 0.988 |     |    | 0.547 |     |    | 0.110 |     |    | 0.032 |     |    | 0.013 |     |    |

|                                 |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
|---------------------------------|----------------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|----|----|-------|----|----|
| Org 33062 5-45 vs placebo       | 0.248          |     |    | 0.859 |     |    | 0.772 |     |    | 0.091 |     |    | 0.042 |    |    | 0.018 |    |    |
| Org 33062 10-90 vs placebo      | 0.178          |     |    | 0.825 |     |    | 0.461 |     |    | 0.285 |     |    | 0.096 |    |    | 0.050 |    |    |
| Observed cases analysis (ITT)   |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
|                                 | Treatment week |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
| Treatment group                 | Wk 1           |     |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |    |    | Wk 8  |    |    |
|                                 | n              | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N  | %  | n     | N  | %  |
| Org 33062 Total                 | 15             | 127 | 12 | 43    | 116 | 37 | 50    | 102 | 49 | 59    | 109 | 54 | 62    | 95 | 65 | 53    | 71 | 75 |
| Org 33062 5-45                  | 12             | 65  | 18 | 23    | 62  | 37 | 22    | 53  | 42 | 32    | 61  | 52 | 30    | 50 | 60 | 29    | 40 | 73 |
| Org 33062 10-90                 | 3              | 62  | 5  | 20    | 54  | 37 | 28    | 49  | 57 | 27    | 48  | 56 | 32    | 45 | 71 | 24    | 31 | 77 |
| Placebo                         | 7              | 64  | 11 | 22    | 58  | 38 | 24    | 59  | 41 | 24    | 57  | 42 | 24    | 50 | 48 | 19    | 32 | 59 |
| p-value for pairwise comparison |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
| Org 33062 Total vs placebo      | 0.904          |     |    | 0.845 |     |    | 0.328 |     |    | 0.175 |     |    | 0.026 |    |    | 0.082 |    |    |
| Org 33062 5-45 vs placebo       | 0.248          |     |    | 0.892 |     |    | 0.905 |     |    | 0.313 |     |    | 0.168 |    |    | 0.124 |    |    |
| Org 33062 10-90 vs placebo      | 0.178          |     |    | 0.815 |     |    | 0.116 |     |    | 0.187 |     |    | 0.015 |    |    | 0.171 |    |    |

### Study 03A7C-001B

**Table 6 Secondary efficacy parameter statistical analysis: HAMD 17 Responders**

|                                                 |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|-------------------------------------------------|----------------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|
| HAMD-17 % Responders                            |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Last observation carried forward analysis (ITT) |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
|                                                 | Treatment week |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Treatment group                                 | Wk 1           |     |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |     |    | Wk 8  |     |    |
|                                                 | n              | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  |
| Org 33062 Total                                 | 14             | 127 | 11 | 38    | 136 | 28 | 52    | 137 | 38 | 62    | 137 | 45 | 70    | 137 | 51 | 72    | 137 | 53 |
| Org 33062 5-45                                  | 9              | 65  | 14 | 19    | 69  | 28 | 26    | 70  | 37 | 32    | 70  | 46 | 39    | 70  | 56 | 40    | 70  | 57 |
| Org 33062 10-90                                 | 5              | 62  | 8  | 19    | 67  | 28 | 26    | 67  | 39 | 30    | 67  | 45 | 31    | 67  | 46 | 32    | 67  | 48 |
| Placebo                                         | 8              | 64  | 13 | 14    | 69  | 20 | 24    | 69  | 35 | 24    | 69  | 35 | 27    | 69  | 39 | 28    | 69  | 41 |
| p-value for pairwise comparison                 |                |     |    |       |     |    |       |     |    |       |     |    |       |     |    |       |     |    |
| Org 33062 Total vs placebo                      | 0.691          |     |    | 0.207 |     |    | 0.629 |     |    | 0.144 |     |    | 0.105 |     |    | 0.099 |     |    |

|                                 |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
|---------------------------------|----------------|-----|----|-------|-----|----|-------|-----|----|-------|-----|----|-------|----|----|-------|----|----|
| Org 33062 5-45 vs placebo       | 0.895          |     |    | 0.285 |     |    | 0.761 |     |    | 0.177 |     |    | 0.052 |    |    | 0.049 |    |    |
| Org 33062 10-90 vs placebo      | 0.351          |     |    | 0.246 |     |    | 0.610 |     |    | 0.237 |     |    | 0.395 |    |    | 0.386 |    |    |
| Observed cases analysis (ITT)   |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
|                                 | Treatment week |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
| Treatment group                 | Wk 1           |     |    | Wk 2  |     |    | Wk 3  |     |    | Wk 4  |     |    | Wk 6  |    |    | Wk 8  |    |    |
|                                 | n              | N   | %  | n     | N   | %  | n     | N   | %  | n     | N   | %  | n     | N  | %  | n     | N  | %  |
| Org 33062 Total                 | 14             | 127 | 11 | 35    | 116 | 30 | 46    | 101 | 46 | 57    | 110 | 52 | 57    | 95 | 60 | 47    | 71 | 66 |
| Org 33062 5-45                  | 9              | 65  | 14 | 18    | 62  | 29 | 21    | 53  | 40 | 30    | 61  | 49 | 31    | 50 | 62 | 26    | 40 | 65 |
| Org 33062 10-90                 | 5              | 62  | 8  | 17    | 54  | 31 | 25    | 48  | 52 | 27    | 49  | 55 | 26    | 45 | 58 | 21    | 31 | 68 |
| Placebo                         | 8              | 64  | 13 | 13    | 58  | 22 | 23    | 59  | 39 | 23    | 57  | 40 | 25    | 50 | 50 | 19    | 33 | 58 |
| p-value for pairwise comparison |                |     |    |       |     |    |       |     |    |       |     |    |       |    |    |       |    |    |
| Org 33062 Total vs placebo      | 0.691          |     |    | 0.295 |     |    | 0.446 |     |    | 0.195 |     |    | 0.240 |    |    | 0.221 |    |    |
| Org 33062 5-45 vs placebo       | 0.895          |     |    | 0.395 |     |    | 0.932 |     |    | 0.395 |     |    | 0.221 |    |    | 0.356 |    |    |
| Org 33062 10-90 vs placebo      | 0.351          |     |    | 0.310 |     |    | 0.229 |     |    | 0.158 |     |    | 0.431 |    |    | 0.259 |    |    |

**Table 21 Maximum Modal Dose and Mean Dose of Org 33062 in Proof-of-Efficacy Studies by Study and Treatment Group (Intent-to-Treat)**

| Study Number           | Treatment Group                        | N   | Maximum Modal Dose <sup>a</sup> in mg/day |      |        |          | Mean Dose <sup>a</sup> in mg/day |      |        |             |
|------------------------|----------------------------------------|-----|-------------------------------------------|------|--------|----------|----------------------------------|------|--------|-------------|
|                        |                                        |     | Mean                                      | SD   | Median | Min-Max  | Mean                             | SD   | Median | Min-Max     |
| 134001                 | Org 33062 ER 20-80 mg/day              | 101 | 68.3                                      | 16.1 | 80.0   | 40 - 80  | 70.3                             | 14.9 | 80.0   | 40.0 - 80.0 |
| 03A7A-003              | Org 33062 IR 10-90 mg/day <sup>b</sup> | 30  | 47.0                                      | 29.1 | 35.0   | 10 - 110 | 40.6                             | 21.3 | 35.6   | 10 - 87.1   |
| 03A7C-001B             | Total Org 33062 IR                     | 137 | 33.3                                      | 24.7 | 25.0   | 0 - 120  | 27.2                             | 17.6 | 22.1   | 1.3 - 87.0  |
|                        | Org 33062 IR 5-45 mg/day <sup>c</sup>  | 70  | 26.7                                      | 15.1 | 25.0   | 0 - 60   | 21.4                             | 10.1 | 19.3   | 1.3 - 45.9  |
|                        | Org 33062 IR 10-90 mg/day <sup>b</sup> | 67  | 40.1                                      | 30.5 | 40.0   | 0 - 120  | 33.3                             | 21.4 | 29.6   | 3.0 - 87.0  |
| 03A7A-002 <sup>d</sup> | Org 33062 IR 10-90 mg/day              | 36  | 42.2                                      | 22.7 | 40.0   | 0 - 90   | 39.9                             | 20.3 | 40.0   | 9.0 - 86.1  |

Note: Data shown were those based on short-term, double-blind treatment and were obtained from Appendix F8.3-8 of the clinical study report and Appendix B.5 of the Integrated

Summary of Efficacy for Protocol 134001 and from Appendix F, Tables 6.10-5 and 6.10-7, of the clinical study report for all other studies.

ER = Extended release; IR = Immediate release

<sup>a</sup>The mean of the maximum modal dose and the mean dose were calculated for the duration of short-term, double-blind treatment. The maximum modal dose was defined

as the dose most frequently prescribed. In a case of a tie, the highest modal dose was selected.

<sup>b</sup>The dose could be increased up to 120 mg/day.

<sup>c</sup>The dose could be increased up to 60 mg/day.

<sup>d</sup>Refers to subjects who participated in double-blind phase of the study

**Table 22 Maximum Modal Dose and Mean Dose of Org 33062 in Other Adequate and Well Controlled Studies by Study and Treatment Group (Intent-to-Treat)**

| Study Number                                  | Treatment Group                        | N   | Maximum Modal Dose <sup>a</sup> in mg/day |        |          | Mean Dose <sup>a</sup> in mg/day |        |             |
|-----------------------------------------------|----------------------------------------|-----|-------------------------------------------|--------|----------|----------------------------------|--------|-------------|
|                                               |                                        |     | Mean ± SD                                 | Median | Min-Max  | Mean ± SD                        | Median | Min-Max     |
| <b>Placebo-controlled studies</b>             |                                        |     |                                           |        |          |                                  |        |             |
| 134002                                        | Org 33062 ER 20-80 mg/day              | 107 | 64.7 ± 17.5                               | 80.0   | 40 - 80  | 68.2 ± 15.5                      | 80.0   | 40.0 - 80.0 |
| CN105-078                                     | Total Org 33062 ER                     | 88  | 49.0 ± 23.1                               | 50.0   | 0 - 100  | 40.5 ± 17.4                      | 36.6   | 13.3 - 81.0 |
|                                               | Org 33062 ER 10-50 mg/day              | 48  | 36.0 ± 11.4                               | 30.0   | 10 - 50  | 30.4 ± 8.1                       | 29.3   | 13.3 - 42.4 |
|                                               | Org 33062 ER 20-100 mg/day             | 40  | 64.5 ± 24.2                               | 60.0   | 0 - 100  | 52.6 ± 17.8                      | 55.5   | 15.0 - 81.0 |
| CN105-083                                     | Total Org 33062 ER                     | 73  | 50.7 ± 24.6                               | 40.0   | 10 - 100 | 43.9 ± 18.9                      | 36.9   | 10.0 - 81.4 |
|                                               | Org 33062 ER 10-50 mg/day              | 36  | 35.0 ± 10.6                               | 35.0   | 10 - 50  | 30.4 ± 7.0                       | 29.8   | 10.0 - 41.0 |
|                                               | Org 33062 ER 20-100 mg/day             | 37  | 65.9 ± 24.9                               | 60.0   | 20 - 100 | 57.1 ± 17.6                      | 59.1   | 18.1 - 81.4 |
| CN105-057                                     | Org 33062 ER 2-4 mg/day                | 49  | 4.1 ± 2.0                                 | 4.0    | 2 - 8    | 3.6 ± 1.7                        | 3.2    | 1.5 - 7.4   |
|                                               | Org 33062 ER 5-10 mg/day               | 49  | 10.5 ± 5.0                                | 10.0   | 5 - 20   | 9.3 ± 4.4                        | 8.1    | 3.6 - 19.8  |
|                                               | Org 33062 ER 10-20 mg/day              | 49  | 21.8 ± 9.7                                | 20.0   | 10 - 40  | 19.1 ± 8.2                       | 16.3   | 9.0 - 36.8  |
| CN105-043                                     | Org 33062 ER 20-40 mg/day              | 49  | 37.6 ± 21.5                               | 40.0   | 20 - 80  | 33.8 ± 16.5                      | 29.7   | 17.8 - 73.6 |
|                                               | Org 33062 IR 5-30                      | 59  | 18.8 ± 7.0                                | 15.0   | 5 - 30   | 17.0 ± 4.3                       | 17.7   | 4.5 - 23.8  |
|                                               | Total Org 33062 IR                     | 77  | 35.7 ± 29.0                               | 30.0   | 0 - 120  | 29.7 ± 17.9                      | 25.5   | 3.3 - 71.1  |
| 03A7C-001A-2496                               | Org 33062 IR 5-45mg/day <sup>b</sup>   | 39  | 24.6 ± 17.0                               | 20.0   | 0 - 60   | 22.0 ± 10.4                      | 21.2   | 4.3 - 46.6  |
|                                               | Org 33062 IR 10-90 mg/day <sup>c</sup> | 38  | 47.1 ± 34.2                               | 45.0   | 0 - 120  | 37.6 ± 20.6                      | 37.8   | 3.3 - 71.1  |
| 03A7C-001A-2486                               | Total Org 33062 IR                     | 83  | 33.6 ± 19.9                               | 30.0   | 5 - 100  | 27.9 ± 13.5                      | 25.1   | 5.0 - 73.5  |
|                                               | Org 33062 IR 5-45 mg/day <sup>b</sup>  | 42  | 26.7 ± 12.9                               | 25.0   | 5 - 50   | 22.0 ± 8.6                       | 21.1   | 5.0 - 37.2  |
|                                               | Org 33062 IR 10-90 mg/day <sup>c</sup> | 41  | 40.7 ± 23.3                               | 40.0   | 10 - 100 | 33.9 ± 15.1                      | 33.3   | 10.9 - 73.5 |
| <b>Placebo- and active-controlled studies</b> |                                        |     |                                           |        |          |                                  |        |             |
| Study Number                                  | Treatment Group                        | N   | Mean ± SD                                 | Median | Min-Max  | Mean ± SD                        | Median | Min-Max     |
| CN105-052                                     | Org 33062 ER 20-60 mg/day              | 35  | 42.6 ± 17.4                               | 40.0   | 10 - 60  | 38.7 ± 13.7                      | 44.0   | 11.7 - 56.1 |
| CN105-053                                     | Org 33062 ER 10-60 mg/day              | 56  | 50.5 ± 14.7                               | 60.0   | 20 - 60  | 46.4 ± 12.9                      | 53.3   | 19.3 - 59.2 |
| CN105-064                                     | Org 33062 ER 5-20 mg/day               | 23  | 13.0 ± 5.2                                | 10.0   | 5 - 20   | 11.6 ± 2.6                       | 12.3   | 7.0 - 15.3  |
|                                               | Org 33062 ER 10-40 mg/day              | 23  | 26.1 ± 10.8                               | 20.0   | 10 - 40  | 22.5 ± 7.1                       | 22.3   | 7.8 - 35.9  |
| CN105-037                                     | Org 33062 IR 2-12 mg/day               | 65  | 6.8 ± 3.3                                 | 6.0    | 0 - 12   | 5.8 ± 2.2                        | 5.8    | 1.4 - 9.8   |
|                                               | Org 33062 IR 5-30 mg/day               | 61  | 15.1 ± 6.4                                | 15.0   | 5 - 30   | 13.5 ± 4.5                       | 13.6   | 3.1 - 22.5  |
| CN105-022                                     | Org 33062 IR 5-30 mg/day               | 67  | 18.1 ± 8.0                                | 20.0   | 5 - 30   | 15.4 ± 5.1                       | 15.2   | 3.8 - 24.5  |
| CN105-029                                     | Org 33062 IR 5-45 mg/day               | 18  | 18.1 ± 8.9                                | 17.5   | 5 - 30   | 15.3 ± 5.4                       | 16.0   | 6.0 - 22.7  |
| CN105-028                                     | Org 33062 IR 5-30 mg/day               | 68  | 15.6 ± 8.9                                | 15.0   | 0 - 30   | 13.4 ± 6.4                       | 12.6   | 3.8 - 26.7  |

Note: Data shown were those based on short-term, double-blind treatment and were obtained from Appendix F8.3-8 of the clinical study report and Appendix B.6 of the Integrated Summary of Efficacy for Protocol 134002 and from Appendix F, Tables 6.10-5 and 6.10-7, of the clinical study report for all other studies.

ER = Extended release; IR = Immediate release

<sup>a</sup> The mean of the maximum modal dose and the mean dose were calculated for the duration of short-term, double-blind treatment. The maximum modal dose was defined as the dose most frequently prescribed. In a case of a tie, the highest modal dose was selected.

<sup>b</sup> The dose could be increased up to 60 mg/day.

<sup>c</sup> The dose could be increased up to 120 mg/day.

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

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Earl Hearst  
2/20/02 07:54:33 AM  
MEDICAL OFFICER

Thomas Laughren  
3/3/02 06:52:02 PM  
MEDICAL OFFICER

I do not agree that this application is approvable;  
see memo to file for more detailed comments  
in support of my recommendation for a nonapproval  
action.--TPL

Review and Evaluation of Clinical Data  
Safety Team Leader Review of NDA

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**NDA:** 21-164

**Drug:** Ariza (gepirone)

**Route:** oral

**Indication:** depression

**Sponsor:** Organon

**Action Date:** 3-18-02

**Date Review Completed:** 2-28-02

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## 1 Background

Bristol-Myers Squibb (BMS) originally developed gepirone. During the clinical development program, it was first studied in an immediate-release (IR) formulation primarily in anxiety disorders and major depression. After BMS reviewed the safety data for the IR formulation, they developed the extended-release (ER) formulation to reduce the incidence of what the sponsor identified as “troublesome” adverse experiences such as dizziness, nausea, and insomnia. Clinical trials that employed the ER formulation were designed primarily as double-blind, randomized, controlled trials for the treatment of depression.

In 1992, BMS discontinued all work on gepirone ER (GER) and, as a result, discontinued the ongoing phase-III trials in major depression “due to other priorities”. In 1993, Fabre-Kramer Pharmaceuticals, Inc., Houston, Texas, acquired rights to GER and completed a series of phase-I trials in special populations. In May 1998, Organon Inc. signed an agreement with Fabre-Kramer Pharmaceuticals, Inc., granting Organon rights to further develop and market gepirone. An NDA (NDA 21-164) for the use of GER in depression was submitted to the Food and Drug Administration by Organon Inc. on October 1, 1999. The Agency issued a refuse-to-file (RTF) action letter dated 11-30-99 and requested more studies to satisfy the efficacy requirements for filing of the NDA.

On 5/18/01, Organon submitted a new NDA for GER, seeking an indication for the treatment of depression. This current submission includes a two-part ISS. The “original” ISS includes the safety data from the earlier development program. The second part, referred to as the “updated” ISS, largely covers the newer safety data generated by Organon alone, but some sections pool safety information from the Organon studies with that from the BMS studies.

Safety reviewer Tarek Hammad, MD, PhD primarily reviewed the gepirone safety experience with the exception of the analysis of the exposure data that was performed by safety reviewer Gerard Boehm MD, MPH.

## 2 Exposure

Exposure in the gepirone development program does not meet the ICH guidelines for number of patients chronically exposed to an efficacious dose of a new drug (300 patients

for six months, 100 patients for one year). The exact specification of an efficacious dose is somewhat uncertain for GER because the pivotal trials involved randomization to a dose range. However, the mean modal dose in two positive studies was 28 mg and 35 mg per day. Hence one would expect to see substantial chronic exposure around 30-40 mg per day. The following tables constructed by Dr. Boehm show the exposure to gepirone at 24 weeks and 48 weeks by modal dose.

Table 1. Exposure by modal dose in phase II/III gepirone trials for those with at least **168** days of exposure

| Exposure                                                     | Number of Subjects by Modal Dose |         |         |       |       |
|--------------------------------------------------------------|----------------------------------|---------|---------|-------|-------|
|                                                              | 0-19mg                           | 20-39mg | 40-79mg | ≥80mg | Total |
| Gepirone Original ISS, All Phase II/III except ER depression | 106                              | 85      | 26      | 2     | 219   |
| Gepirone ER Depression trials, through 4 month safety update | 22                               | 18      | 53      | 43    | 136   |
| Total                                                        | 128                              | 103     | 79      | 45    | 355   |

Table 2. Exposure by modal dose in phase II/III gepirone trials for those with at least **336** days of exposure

| Exposure                                                     | Number of Subjects by Modal Dose |         |         |       |       |
|--------------------------------------------------------------|----------------------------------|---------|---------|-------|-------|
|                                                              | 0-19mg                           | 20-39mg | 40-79mg | ≥80mg | Total |
| Gepirone Original ISS, All Phase II/III except ER depression | 49                               | 40      | 12      | 0     | 101   |
| Gepirone ER Depression trials, through 4 month safety update | 10                               | 5       | 10      | 13    | 38    |
| Total                                                        | 59                               | 45      | 22      | 13    | 139   |

As can be seen above, only 124 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 6 months and only 35 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 1 year. Even when exposure to a sub-therapeutic modal dose was included, the exposure was still deficient by ICH standards (227 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 6 months and 80 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 1 year).

### 3 Limitations of the sponsor's safety analysis

The review of the gepirone safety database was made challenging by the way the sponsor organized and presented the safety data. The following issues complicated the assessment of gepirone ER's safety:

- ◇ Although Organon is seeking approval for the ER formulation of gepirone, most of the analyses in the ISS combine the ER and IR data, comparing them to the combined placebo.
- ◇ The incidence of events occurring in the GER group in the controlled depression trials was compared to the incidence of events occurring in a pool of placebo patients from gepirone ER and IR trials.
- ◇ The “updated” ISS pooled safety information from Organon GER studies and BMS GER studies inconsistently, making it difficult to synthesize a comprehensive impression of the overall safety of GER.

Additionally, the sponsor did not include an adequate review of the medical literature related to gepirone. The PDF document submitted with the NDA (called “litsearch”) included only a printout of 286 Medline references. The sponsor did not provide text commenting on any findings in the papers that might have added to the fund of knowledge regarding the safety of gepirone.

## 4 Significant Safety Findings

### 4.1 Dizziness

In phase II/III controlled depression trials of the GER formulation (short-term phase and long-term phase combined), dizziness was reported in 34.1% (249/731) of GER patients compared to 12.7% (60/472) of placebo patients; this difference was statistically significant (RR 2.7; 95% CI [2.1-3.5]). In this same population, dizziness led to discontinuation in 2.3% (17/731) GER patients compared with 0.4% (2/472) placebo patients; this difference was also statistically significant (RR 5.5; 95% CI [1.3-23.6]). Of the patients in Organon's two phase III depression trials who reported dizziness as an AE, the dizziness was rated as severe by 10.2% (10/98) of gepirone patients compared to 4.3% (1/23) of the placebo patients.

In some cases, dizziness may have been a premonitory sign of syncope or a symptom of postural hypotension. Table 3 below shows the incidence of syncope and postural hypotension in phase II/III controlled depression trials of the GER formulation.

Table 3. Incidence of reported syncope or postural hypotension in controlled phase II/III trials of GER in depression

| Treatment group      | Placebo<br>N=769<br>(%) | GER<br>N=519<br>(%) |
|----------------------|-------------------------|---------------------|
| Syncope              | 3<br>(0.4)              | 6<br>(1.2)          |
| Postural hypotension | 3<br>(0.4)              | 5<br>(1.0)          |

In general, these events did not occur frequently; however, there was a 2.5-3 times excess in the GER group compared to the placebo group. Some of this excess may be explained by the tendency of GER to cause some amount of orthostatic change. For the Organon controlled trials in depression, Dr. Hammad calculated the incidences and risk ratio for orthostatic change in the GER and placebo groups. About 4% (8/212) of the GER patients compared with 0.5% (1/214) of the placebo patients developed a clinically significant orthostatic change in diastolic blood pressure (defined as a drop of  $\geq 10$  mmHg sustained for three minutes). The risk ratio was 8.1 with 95% CI 1.0-64.0, p-value=0.02 (Fisher exact test, Epi Info). Again, these changes were not measured commonly; however, the studies were not designed to measure orthostatic vital signs at the time of maximal drug concentration (Tmax). The observation of the significantly elevated risk ratio supports the potential for gepirone to induce orthostatic hypotension.

## 4.2 Neutropenia

Although the combined gepirone risk was not statistically different from placebo (1.4% [26/1849] vs. 1.2% [14/1176]), the risk of observing a clinically significant decrease in absolute neutrophil count (ANC  $< 1.5 \times 10^3/\text{mm}^3$ ) was significantly greater (risk ratio 2.9, 1.7-5.0) in the GER treatment (14/527, 2.7%) group than in the gepirone IR (GIR) (12/1322, 0.9%) treatment group. Dr. Hammad investigated this finding further and displays the patients with clinically significant (CS) decreases of ANC in FDA Table 29 of his review.

In order to get a sense of the persistence of the decreased ANC and determine whether it was associated with a low total WBC, I examined the line listings of abnormal hematology values in Appendix J12 of the updated ISS. Table 4 below displays the number of GER patients in the BMS controlled phase II/III trials with treatment emergent (TE) CS low ANC who had associated CS low total WBC count, those whose ANC fell below 1000, and those whose low ANC was present at the last blood draw (either new or persistent). No patients had an ANC fall below 500.

Table 4. Patients in BMS controlled phase II/III trials with treatment emergent clinically significantly low ANC

| Treatment group  | # pts with ANC >1500 (%) | # pts with ANC >1500 and WBC <3000 (%) | # pts with ANC <1500 on last available blood draw (%) | # pts with ANC 500-1000 (%) | # pts with ANC 500-1000 on last available blood draw (%) |
|------------------|--------------------------|----------------------------------------|-------------------------------------------------------|-----------------------------|----------------------------------------------------------|
| GER (N=527)      | 14 (2.7)                 | 1 (0.2)                                | 6 (1.1)                                               | 3 <sup>^</sup> (0.6)        | 1 (0.2)                                                  |
| GIR (N=1322)     | 12 (0.9)                 | 3 (0.2)                                | 8 (0.6)                                               | 1 (0.1)                     | 1 (0.1)                                                  |
| Placebo (N=1176) | 14 (1.2)                 | 2 (0.2)                                | 5 (0.4)                                               | 3 (0.3)                     | 2 (0.2)                                                  |

<sup>^</sup> The sponsor also identified patient (b) (6) as having a CS TE low ANC, but this patient is listed in Appendix J12 as having an abnormally low baseline ANC; as such, I did not include this patient in my count.

While the overall finding of an excess of low ANC in the GER group compared to the GIR and placebo groups is unexplained, the observation of similar frequencies of concurrent low total WBC and low ANC in each treatment group is reassuring. Similarly, of the 14 patients in the GER and placebo groups with a CS TE low ANC, the same proportion fell below 1000 (21%, [3/14]).

When I looked for evidence of clinical manifestations of a low ANC in the controlled BMS studies, I did not find any evidence of an excess of serious infections in the GER group. However, there was some excess of common preferred terms related to infections in the GER group (see table 5 below)

Table 5. Incidence of infection-related preferred terms in BMS controlled phase II/III trials

| Treatment group     | Infection    | Fever       | Pharyngitis | Rhinitis    | Sinusitis   |
|---------------------|--------------|-------------|-------------|-------------|-------------|
| GER<br>(N=603)      | 86<br>(14.3) | 22<br>(3.6) | 50<br>(8.3) | 35<br>(5.8) | 29<br>(4.8) |
| Placebo<br>(N=1342) | 121<br>(9.0) | 27<br>(2.0) | 52<br>(3.9) | 38<br>(2.8) | 21<br>(1.6) |

Although the Organon phase III controlled depression trials enrolled many fewer GER patients than the BMS trials, it should be noted that there was no excess of CS TE low ANC values in the GER group in these trials (GER 0.5% [1/212] vs. placebo 0.5% [1/214]). No patients participating in these trials reported a serious adverse event related to infection. For the common AEs shown in table X above, only infection (11.3% [24/212] vs. 7.5% [16/214]) and rhinitis (3.8% [8/212] vs. 2.3% [5/214]) were reported at least 50% more frequently in the GER group as the placebo group.

Overall, it does not appear that the excess of CS TE low ANC in the controlled BMS trials of GER was related to leukopenia or clinically serious adverse events.

### 4.3 *Hyperbilirubinemia*

The most frequently observed CS change in a clinical chemistry parameter was elevation of total bilirubin (TB), defined as  $\geq 1.5$  ULN equivalent to 1.5 mg/dL. This lab abnormality occurred in approximately 1.4% (25/1849) of the combined GIR/GER formulation group compared to 0.5% (6/1176) of the placebo group. The risk ratio comparing GIR/GER to placebo was statistically significant (RR = 2.65, [1.41-4.97]); however, there was no difference in risk between the two gepirone formulations [RR = 0.98], sponsor's table 36, original ISS). A summary of all subjects who experienced CS elevations in TB is presented in sponsor's table 39 (original ISS). Seven ER and 18 IR subjects had a post-baseline TB  $\geq 1.5$  ULN. The majority (21/25) of subjects in each treatment group experienced only single episodes of CS increase in serum TB concentrations.

In order to get a sense of the whether the elevated TB was associated with elevated transaminases (TA), I examined the line listings of abnormal clinical chemistry values in

Appendix J10 of the updated ISS. Table 6 below displays the number of GER patients in the BMS controlled phase II/III trials with TE CS high TB who had associated CS high TA, those whose TB rose above 2.0 mg/dl, and those whose high TB was present at the last blood draw (either new or persistent). No patients had a TB>2.0 mg/dl associated with an elevated TA > 3X ULN.

Table 6. Patients in BMS controlled phase II/III trials with treatment emergent clinically significantly high TB

| Treatment group  | # pts with TB $\geq 1.5$ mg/dl (%) | # pts with TB $\geq 1.5$ mg/dl and TA* > 3X ULN (%) | # pts TB >1.5 mg/dl on last available blood draw (%) | # pts with TB $\geq 2.0$ mg/dl (%) | # pts with TB $\geq 2.0$ mg/dl on last available blood draw (%) |
|------------------|------------------------------------|-----------------------------------------------------|------------------------------------------------------|------------------------------------|-----------------------------------------------------------------|
| GER (N=527)      | 7 (1.3)                            | 0 (0.0)                                             | 4 (0.8)                                              | 2 (0.4)                            | 2 (0.4)                                                         |
| GIR (N=1322)     | 18 (1.4)                           | 0 (0.0)                                             | 9 (0.7)                                              | 5 (0.4)                            | 4 (0.3)                                                         |
| Placebo (N=1176) | 6 (0.5)                            | 0 (0.0)                                             | 2 (0.2)                                              | 2 (0.2)                            | 0 (0.0)                                                         |

\*SGOT and/or SGPT

About one-third of patients with a CS elevated TB had a measurement in excess of 2.0 mg/dl and about one half of patients had either a new or persistently elevated TB at the end of the study; however, none of the bilirubin elevations observed were associated with an elevation of transaminases.

When I looked for evidence of clinical manifestations related to elevated TB in the controlled BMS data, I did not find any evidence of an excess of hepatitis in the gepirone group (GER 0% [0/637] v. GIR 0.1% [1/1342] v. placebo 0.1% [1/1342]). However, there was a slight excess of the preferred term “liver function test abnormal” in the GER group (GER 0.6% [4/637] v. GIR 0.2% [4/1342] v. placebo 0.3% [4/1342]).

Although the Organon phase III controlled depression trials enrolled many fewer GER patients than the BMS trials, it should be noted that there was no excess of CS TE elevated TB values in the GER group in these trials (GER 0.5% [1/213] vs. placebo 0.5% [1/215]). Furthermore, there were no reports of hepatitis and only one report of “liver function test abnormal” in the GER group (GER 0.5% [1/212] v. placebo 0.0% [0/214]).

It is not clear why some patients had isolated elevations of bilirubin, some as high as 7 mg/dl. However, these elevations did not tend to be persistent, and were not associated with a clinical syndrome of hepatotoxicity.

#### 4.4 Suicide

During the gepirone development program, no deaths were attributed to suicide. However, some patients experienced suicidal ideation and there were a small number of suicide attempts. The incidence of suicidal ideation and suicide attempt is shown in the table below.

Table 7. Incidence of reported syncope or postural hypotension in controlled phase II/III trials of gepirone in depression

| Treatment group   | Placebo<br>N=769<br>(%) | GIR<br>N=835<br>(%) | GER<br>N=519<br>(%) |
|-------------------|-------------------------|---------------------|---------------------|
| Suicidal ideation | 4<br>(0.5)              | 3<br>(0.4)          | 8<br>(1.5)          |
| Suicide attempt   | 1<br>(0.1)              | 2<br>(0.2)          | 3<br>(0.6)          |

For both suicidal ideation and suicide attempt, there was an excess of risk in the GER group compared to the GIR and placebo groups. In trials of antidepressants, it is common to see differential dropout between treatment groups, due in part to lack of efficacy in the placebo group. Hence, use of number of patients in the denominator does not result in the best estimate of the rate of an adverse event. This differential in person-time exposure may explain the excess risk of suicidal ideation and suicide attempt in the GER group. As such, we will ask the sponsor to calculate the rate of suicidal ideation and suicide attempt using person-time exposure in the denominator.

#### 4.5 Allergic Reaction

In one of the open label multicenter trials of GIR in depression (CN105-050), a 26 year old male patient ( (b) (6) ) discontinued from GIR on day 17 for “hepatic cytolysis with toxidermia”. Over the two months **prior** to initiating the study drug, the patient complained of a range of gastrointestinal symptoms (including abdominal pain, constipation, diarrhea, and anorexia), as well as mood symptoms (including depression, anxiety, memory impairment, and mental dulling); he also lost 10 kg. However, at baseline he had normal LFTs (see table below). By day 7 of treatment, the patient was titrated to 20 mg/day of GIR. On day 13 the patient experienced a fever of 38.8C and was treated with 500 mg of acetaminophen. On day 14 the patient was discharged from the hospital but returned for lab tests on day 15. On that day the patient’s LFTs were grossly elevated (see table below); gepirone was discontinued on day 17. The following day the patient was admitted to the hospital with fever and hepatosplenomegaly. Over the next two days the patient developed a generalized erythroderma with pruritis, edema, and purpura, as well as painful posterior cervical and axillary adenopathy. A skin biopsy confirmed a diagnosis of “toxidermia”. Concurrently, the patient had an elevated WBC to 13.6 associated with a mild eosinophilia (700 up from 200 at baseline [nl range 75-300]) and a basophilia (200 up from 0 at baseline [nl range 25-70]). Following treatment with dexamethasone, the patient recovered.

Although the patient’s history prior to starting GIR suggested a pre-existing gastrointestinal illness, his baseline LFTs were normal. Other than gepirone, the only other drugs the patient was exposed to were chloral hydrate and hydroxyzine. The patient received one dose of acetaminophen for the fever that preceded the discovery of the LFT abnormalities, but the small dose could not account for the hepatosplenomegaly and

severely abnormal transaminases. The associated full body rash and painful lymphadenopathy add to the picture of this severe allergic reaction that appears to be most closely related to gepirone.

Table 8. Chronology of liver function tests for patient (b) (6)

|                                | SGPT<br>(<25 U/L) | SGOT<br>(<25 U/L) | GGT<br>(5-38 U/L) | Alkaline<br>Phosphatase<br>(73-207 U/L) | Total Bilirubin<br>(0-17 µmol/L) | Conjugated<br>Bilirubin<br>(0-3 µmol/L) |
|--------------------------------|-------------------|-------------------|-------------------|-----------------------------------------|----------------------------------|-----------------------------------------|
| Screening                      | 5                 | 6                 | 12                | 71                                      | 8                                | 0                                       |
| Day 15                         | 2160              | 948               | 91                | 176                                     | 10                               | 3                                       |
| Day 17 – gepirone discontinued |                   |                   |                   |                                         |                                  |                                         |
| Day 23                         | 582               | 234               |                   |                                         |                                  |                                         |
| Day 25                         | 917               | 589               |                   |                                         |                                  |                                         |
| Day 28                         |                   |                   |                   |                                         | 265                              | 193                                     |
| Day 32                         |                   |                   |                   | 911                                     |                                  |                                         |
| Day 33                         | 152               | 50                |                   |                                         |                                  |                                         |
| Day 34                         |                   |                   | 412               |                                         |                                  |                                         |
| Day 44                         |                   |                   | 152               | 248                                     | 46                               | 27                                      |
| Day 91                         | 18                | 19                | 54                | 57                                      | 6                                | 2                                       |

The following table displays the incidence of adverse events from BMS GER controlled phase II/III trials that might be associated with an allergic reaction.

Table 9. . Incidence of hypersensitivity/allergic reaction related preferred terms in BMS controlled phase II/III trials

| Treatment group     | Allergic<br>Reaction | Arthralgia  | Myalgia     | Rash        |
|---------------------|----------------------|-------------|-------------|-------------|
| Placebo<br>(N=1342) | 43<br>(3.2)          | 47<br>(3.5) | 47<br>(3.5) | 39<br>(2.8) |
| GER<br>(N=603)      | 30<br>(5.0)          | 45<br>(7.5) | 47<br>(7.8) | 19<br>(3.2) |

On review of the verbatim terms mapped to the preferred term “allergic reaction”, a subset were related to seasonal allergic rhinitis. Similarly, the group of verbatim terms mapped to the preferred term “rash” included terms that were not specifically related to a potential allergic reaction.

In the two Organon controlled trials in depression, there was no excess of arthralgia or myalgia in the GER group as seen above (arthralgia: GER 1.9% [4/212] v. placebo 2.8% [6/214]; myalgia: GER 3.8% [8/212] v. placebo 5.1% [11/214] ).

The serious adverse event described in this section raises my concern that the sponsor has not adequately explored the potential for gepirone to cause allergic or hypersensitivity reactions. My efforts to detect other AEs potentially suggestive of allergic reactions identified an excess of arthralgia and myalgia in the BMS GER group compared to the placebo group.

In order to more thoroughly identify patients whose symptoms may have represented an allergic reaction or hypersensitivity syndrome, we will ask the sponsor to develop a case definition for allergic reaction/hypersensitivity syndrome, taking into account multiple symptoms that may be part of such a syndrome. Using this case definition, the sponsor can identify patients whose AE profile fits that of a hypersensitivity syndrome. This investigation should also include an assessment of eosinophilia in the controlled clinical trials, including mean change from baseline and outlier analyses.

## **5 Conclusions**

There is no safety issue that would preclude gepirone from being marketed if it is shown to have therapeutic efficacy in its intended indication.

The most common adverse event, frequently leading to discontinuation, appears to be dizziness, affecting about one third of treated patients. The AE profile and orthostatic vital sign data suggests that GER may have ability to cause postural hypotension. As few elderly patients were exposed to GER in the clinical trials, there is no way to know what the impact of this AE will be. Hence, caution should be used when titrating the gepirone dose in older patients, especially because serum levels are increased 50-80% in the elderly.

The finding of an excess of low ANC values in GER patients does not appear to be associated with clinically serious infections.

The finding of an excess of isolated hyperbilirubinemia in GER patients does not appear to be associated with clinically significant hepatotoxicity.

The risk of suicidal ideation and suicidal gesture in GER patients exceeds that in placebo patients two-threefold. Rates of these events should be calculated using person-time exposure in the denominator to adjust for differential discontinuation between active and placebo treatment.

At least one patient suffered a severe systemic hypersensitivity reaction that was temporally related to GER therapy. The sponsor needs to do additional analyses to determine the frequency and severity of gepirone-related allergic reaction/hypersensitivity syndrome.

Long-term exposure to GER at efficacious doses is inadequate by ICH standards. Once an adequate level of exposure is reached, the safety database will have to be reviewed again to look for the emergence of new safety signals, and to follow-up on signals identified in this round of review.

## **6 Requests for Action Letter**

In his review, Dr. Hammad provided a detailed list of issues for the sponsor to follow-up. The requests that follow below relate only to issues I identified in this memo that Dr. Hammad did not address in his review:

- ◇ The sponsor should go back to the list of 286 references they supplied in their “litsearch” file and review the papers for new information pertinent to the safe use of gepirone. This information should be summarized and pertinent references provided.
- ◇ The sponsor should calculate the rate of suicidal ideation and suicide attempt using person-time exposure in the denominator.
- ◇ In order to more thoroughly identify patients whose symptoms may have represented an allergic reaction or hypersensitivity syndrome, the sponsor should develop a case definition for allergic reaction/hypersensitivity syndrome, taking into account the multiple symptoms that may be part of such a syndrome. Using this case definition, the sponsor should identify patients whose AE profile fits that of an allergic reaction/ hypersensitivity syndrome. This investigation should also include an assessment of eosinophilia in the controlled clinical trials, including mean change from baseline and outlier analyses.
- ◇ In Dr. Hammad’s review, he describes patient (b) (6) in ongoing study 28709 who had elevated hepatic enzymes. After three months on blinded treatment, the subject’s normal pretreatment AST, ALT, and alkaline phosphatase values increased to 52, 93, and 151, respectively. Seven days after stopping study drug, the values were 148, 393, and 485. There was no information about bilirubin values, diagnostic work-up, or outcome of this event. Should this patient turn out to have been on GER treatment, follow-up on this event will be needed.

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/s/

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Judith Racoosin  
3/1/02 10:25:57 AM  
MEDICAL OFFICER

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**

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**SAFETY REVIEW OF NDA**

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**Brand Name:** Ariza  
**Generic Name:** Gepirone hydrochloride  
**Sponsor:** Organon Inc.  
**Indication:** Depression  
**NDA Number:** 21-164  
**Original Receipt Date:** 5/18/2001  
**Safety Reviewer:** Tarek A Hammad, MD, PhD, MSc, MS

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**Review completed:** 2/26/2002

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## Glossary

This section provides an explanation of some of the terminology used in this review.

Organon data: the term refers to safety data from studies conducted by Organon.

BMS data: the term refers to safety data from studies conducted by previous sponsors (Bristol-Myers Squibb and Fabre-Kramer Pharmaceuticals) of gepirone.

Updated ISS: the term refers to the part of the ISS that largely covers the safety data generated by Organon. However, some sections of this ISS contain pooled safety information from both “Organon data” and “BMS data”. This part is referred to as “updated ISS” by Organon in their submission.

Original ISS: the term refers to the part of the ISS that covers the safety data from earlier development program conducted by previous sponsors (Bristol-Myers Squibb and Fabre-Kramer Pharmaceuticals) of gepirone. This part is referred to as “addendum I ISS” by Organon in their submission.

The sponsor: the term refers to Organon, Inc.

FDA table: the term refers to tables generated by this FDA reviewer.

Gepirone IR: Gepirone immediate-release formulation.

Gepirone ER: Gepirone extended-release formulation.

Subject: the term refers to any participant in a clinical trial regardless of drug development phase (may be healthy volunteer or patient)

## **1 Safety (Executive Summary Section)**

### **1.1 Adequacy of safety testing**

The sponsor does not fulfill the ICH guidelines for long-term exposure data (300 individuals exposed to an effective dose for 6 months and 100 individuals exposed to an effective dose for 1 year). The pivotal trials suggest that the minimum effective gepirone dose is 40 mg/day. The review found that the exposure to gepirone was deficient at this minimum effective dose. Specifically, only 124 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 6 months and only 35 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 1 year. Even when exposure to a sub-therapeutic modal dose was included, the exposure was still deficient by ICH standards (227 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 6 months and 80 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 1 year).

### **1.2 Serious adverse events**

Three deaths have been reported in the gepirone development program. Only one death occurred in a patient taking gepirone.

A total of 15/958 (1.6%) and 46/2063 (2.2%) subjects in the gepirone ER and IR development programs, respectively, experienced a serious adverse event (AE) compared to 16/1408 (1.1%) placebo patients. There are no statistically significant differences between the various active treatment groups and placebo for serious adverse events due to low numbers of observations.

Serious adverse events that occurred infrequently, but had at least double the risk in the combined IR and ER gepirone group in comparison with the placebo group are: accidental injury, psychosis, depression, suicide attempt, syncope, breast neoplasm, hernia, leukopenia, migraine, overdose, psychotic depression and thinking abnormal. These data reflect both formulations in all studied indications; hence they do not allow separate assessment of the risk of these SAEs in the sub-population of interest (depressed patients).

### **1.3 Common adverse events**

The sponsor pooled their phase II/III AEs data (Organon data) and previously generated data (BMS data) for the gepirone ER formulation. The pooled population includes 849 subjects treated with gepirone ER and 1,556 subjects treated with placebo. With the exception of headache (46.6% in BMS data and 29.2% in Organon data) and dizziness (29.0% in BMS data and 46.2% in Organon data), there are few substantive differences between the two series for the incidence of adverse events. The adverse events with an incidence of 5% or more and a risk in the gepirone group twice or more the risk in the placebo group includes dizziness, nausea, insomnia, paresthesia, and vomiting.

## **1.4 Relationship of adverse events to known animal toxicity**

Not applicable.

## **1.5 Drug-drug interaction potential**

Gepirone is primarily metabolized by CYP450-3A4. Co-administration of a potent inhibitor of CYP450-3A4, ketoconazole, with gepirone ER in healthy volunteers resulted in marked inhibition of metabolism of gepirone ER and in some increase in the incidence and severity of central nervous and gastrointestinal adverse experiences.

The sponsor also examined the concomitant medication database to identify subjects treated with drugs for chronic diseases. This search revealed that subjects taking drugs like B-blockers and ACE inhibitors amounted to only 1 to 3 % of the population. Concomitant use of anti-diabetic agents was likewise limited to 1 to 1.5% of the population. Because of the low incidence of use of chronic drugs in this otherwise healthy population, the sponsor did not undertake an intensive analysis of drug-drug interactions.

## **1.6 Exposure in trials versus probable marketing exposure**

The sponsor is proposing the long-term use of gepirone in a patient population with a chronic illness. The exposure time to drug is not sufficient.

## **1.7 Effect of trial exclusions on safety profile versus expected marketed population**

In general, trial exclusions usually affect drug safety profile. The inclusion of a relatively "healthy" population of subjects with minimum co-morbidity inevitably underestimates the AEs profile in the real life subject population. Furthermore, as described in section 1.5 above, the sponsor did not investigate potential drug-drug interactions that may occur in subjects with comorbidities. Although these are generic issues, they are always important to bear in mind when considering the use of a newly marketed drug in patients with comorbidities and concomitant medications.

## **1.8 Recommended warnings**

The following statement is suggested under "PRECAUTIONS"

(b) (4)



This reviewer's comments on the proposed labeling describing the safety profile (see section 2.6.2) may substantially change from that included herein because it will have to be rewritten to reflect the issues under section "1.10 Unresolved safety issues".

## **1.9 Relationship of safety to other drugs available for indication**

The relationship of safety of gepirone to active controls (total 529 subjects) was not assessed directly, but each one was compared to placebo. Overall, the AE profile of gepirone did not seem different from the active controls (antidepressants and anxiolytics), although no trials or analyses were designed specifically to make such comparisons.

## **1.10 Unresolved safety issues**

The sponsor implied in various parts of the ISS that the safety profile of the two formulations of gepirone (ER and IR) is similar or that the ER has a better one. Although this is true for some adverse events, it is not necessarily true for all of them. In most analyses in the ISS, the sponsor combines the ER and IR data, comparing them to the combined placebo. This approach diminished this reviewer's ability to fully characterize the safety of the ER formulation, which is the one intended for marketing.

In addition, the data organization precludes the ability to pool the old (BMS) and new (Organon) ER development program data for the purpose of this reviewer's own analyses. Furthermore, in parts of the ISS where the sponsor pooled these data together, the risk of gepirone-related AEs in depressed subjects was compared to the risk of AEs from the pooled placebo data for the entire development program regardless of indication, obscuring the interpretation of these comparisons. We asked the sponsor to submit new tables showing the adverse events in the phase II/III controlled depression trials for the IR and ER formulations separately, each compared to its own placebo.

The investigation of possible causes for one of the most common side effect, dizziness, was not sufficient. This AE is of particular importance to subjects operating heavy machinery or driving. The sponsor should more completely characterize the dizziness addressing, for example, the following questions: 1) How often does it occur? 2) How long does it last? 3) Does the frequency or severity of the episodes change over time? 4) Are there any risk factors for dizziness, such as comorbidities or concomitant medications?.

The criterion for "clinically significant" change in the QTc was defined in absolute terms, as the increase, from baseline, of QTc interval to  $\geq 480$ . However, outliers were not expressed as proportions of subjects with prolongation of  $\geq 30$  msec and  $\geq 60$  msec from baseline, which would be desired, as well. Further analysis of the sponsor's data is required to describe these proportions.

The sponsor used treatment-related AEs (as determined by investigator attribution) in the dose-response analysis. This analysis should be redone using all reported treatment-emergent AEs, regardless of the investigator's "drug-relatedness" attribution.

## 2 Integrated Review of Safety (Clinical Review Section)

This document reviews the safety profile for the use of gepirone ER (NDA 21-164, submitted 5/18/2001) in patients with depression.

### 2.1 *Brief statement of conclusions*

- The sponsor's development program does not meet the ICH guidelines for long-term exposure. Additional exposure out to six-month and one-year is required.
- The adverse events presentation should to be restructured to reflect:
  - The adverse event consequences of the effective dose (40 mg or more per day).
  - The appropriate comparisons of the gepirone ER and IR treatment groups to the corresponding placebo groups.
  - The separate and pooled depiction of short-term and long-term safety data.
- The QTc data should be reanalyzed to compare the incidence of QTc prolongation of  $\geq 30$  msec and  $\geq 60$  msec between treatment groups.
- The estimates of specific AEs leading to dropout are expected to be underestimated because 18% of the subjects who dropped out, as identified from the End of Study CRF page, did not specify the adverse experience resulting in dropout.
- The sponsor used treatment-related AEs (as determined by investigator attribution) in the dose-response analysis. This analysis should be redone using all reported treatment-emergent AEs, regardless of the investigator's "drug-relatedness" attribution.
- This reviewer's comments on the proposed labeling describing the safety profile may substantially change from that included herein because it will have to be rewritten to reflect the previous suggestions to data presentation.
- There are no safety issues in the present submission that would preclude approval.

### 2.2 *Background about gepirone development program*

Bristol-Myers Squibb (BMS) originally developed gepirone. During the clinical development program, it was first studied in an immediate-release (IR) formulation primarily in anxiety disorders, major depression, and in other indications such as obsessive-compulsive disorder and substance abuse. After BMS reviewed the safety data for the IR formulation, they developed the extended-release (ER) formulation to reduce the incidence of what the sponsor identified as "troublesome" adverse experiences such as dizziness, nausea, and insomnia. Clinical trials that employed the ER formulation were designed primarily as double-blind, randomized, controlled trials for the treatment of depression.

In 1992, BMS discontinued all work on gepirone ER and, as a result, discontinued the ongoing phase-III trials in Major Depression "due to other priorities". No other reason was given for this discontinuation. In 1993, Fabre-Kramer Pharmaceuticals, Inc.,

Houston, Texas, acquired rights to gepirone ER and completed a series of phase-I trials in special populations. In May 1998, Organon Inc. signed an agreement with Fabre-Kramer Pharmaceuticals, Inc., granting Organon rights to further develop and market gepirone. An NDA (NDA 21-164) for the use of gepirone ER in depression was submitted to the Food and Drug Administration by Organon Inc. on October 1, 1999. The Agency issued a refuse-to-file (RTF) action letter dated 11-30-99 and requested more studies to satisfy the efficacy requirements for filing of the NDA.

During the February 2, 2000 meeting that was held to discuss the reasons behind the RTF action, the Agency concurred with the sponsor's (Organon, Inc) proposal for an Integrated Summary of Safety (ISS) supplement that contained the new data generated by the Organon development program. The proposal specified that integration of safety data for the supplement would be limited to an analysis of the combined adverse event data from depression trials 134001 and 134002 (Organon trials) and to a combined analysis of the adverse events from all phase II/III ER trials. The incidence of AEs from the latter analysis would be used for development of the product labeling.

In the NDA submission currently under consideration (5/18/2001), Organon included a two-part ISS. The first part largely covers the safety data generated by Organon (referred to as "updated ISS" by the Organon in their current submission). However, some sections of this ISS pooled safety information from both Organon's studies and studies conducted by previous sponsors (Bristol-Myers Squibb and Fabre-Kramer Pharmaceuticals). In this review, when referring to the studies conducted by Organon, I will use the term "Organon data", and when referring to the ISS itself, I will use the term "updated ISS".

The second part of the submitted ISS covers the safety data from the earlier development program (referred to as "addendum-I ISS" in the current submission) conducted by previous sponsors (Bristol-Myers Squibb and Fabre-Kramer Pharmaceuticals). In this review, when referring to the studies conducted by previous sponsors, I will use the term "BMS data", and when referring to the ISS itself, I will use the term "original ISS". It is helpful to keep in mind that gepirone ER studies were conducted both by BMS and Organon.

More details about the data sources, number of trials, and indications are under the section "2.4.3 ISS POPULATION".

## **2.3 Description of subject exposure**

DNDP safety reviewer Gerard Boehm, MD, MPH reviewed this section.

### **2.3.1 METHODS**

In addition to reviewing the sponsor's ISS exposure presentation, Dr. Boehm used the sponsor's data sets to conduct additional exposure analyses. The sponsor's *updated ISS* presentation included both the number of persons exposed and the person years (PY) of exposure. The sponsor's *original ISS* exposure presentation included the number of subjects exposed but not the PY (Appendix A, *original ISS*). I calculated PY for the phase II/III trials in the *original ISS* using the sponsor's data set, DOSE\_OLD. To calculate exposure time for the *original ISS* study subsets (ex. controlled trials,

depression RCTs), Dr. Boehm merged the DOSE\_OLD data set with the MASTER data set to be able to identify each subject's study number. After cross checking the number of subjects exposed in the data set with the information from Appendix A, Dr. Boehm calculated PY by treatment using the study groupings described in the sponsor's table 1 (pp. 4-5, original ISS).

The sponsor's 4-month safety update included a table that updated exposure information for depression trials using the gepirone ER formulation (the only new trials ongoing). The sponsor did not submit a data set for exposure in the four-month safety update and therefore these data do not appear in any of the exposure analyses below.

### 2.3.2 OVERALL EXPOSURE

The sponsor provided safety data for 3,631 subjects exposed to gepirone through the four-month safety update. There were 3,331 subjects exposed in the *original* and *updated* ISS reports and 300 additional subjects included in the 4-month safety update. The exposed subjects included in the four-month safety update had limited safety data reported, specifically line listings only about deaths, serious adverse events, and discontinuations.

#### 2.3.2.1 BMS data

The sponsor reported that 3,021 subjects were exposed to gepirone in the *original* ISS. Of those, 2,496 were exposed during phase II/III trials for a total of 519 PY. The following FDA table (1) summarizes the exposure data in the phase II/III trials (persons, person years) included in the *original* ISS.

FDA table (1): Exposure in Phase II/III trials (subjects, person years) Included in the *Original* ISS

| Exposure       | Number of Subjects | Person years |
|----------------|--------------------|--------------|
| Placebo        | 1,308*             | 253 PY       |
| Gepirone IR    | 1,859              | 383 PY       |
| Gepirone ER    | 637                | 136 PY       |
| Total gepirone | 2,496              | 519 PY       |

\*Thirty four subjects were exposed to both gepirone and placebo during study 037A7A-002 and are not counted among the placebo group in this summary (Appendix A1, original ISS).

#### 2.3.2.2 Organon data

The sponsor's *updated* ISS included 310 additional gepirone subjects, all exposed to the ER preparation. Two hundred twelve subjects were exposed in two phase-III trials (27 PY, p.39 updated ISS) and 98 were exposed during phase I trials (0.5 PY, Appendix A.3 updated ISS).

#### 2.3.2.3 Four-month safety update

The four-month safety update included 300 additional subjects and the person time exposure increased by approximately 100 person years compared to the *original* and *updated* ISS reports.

### 2.3.3 EXPOSURE IN PHASE II/III CONTROLLED TRIALS

#### 2.3.3.1 BMS data

The sponsor reported that 2,160 subjects were exposed to gepirone during phase II/III controlled trials in the *original ISS* and Dr Boehm calculated 417 PY. The following FDA table (2) summarizes the exposure in the phase II/III controlled trials (persons, person years) included in the *original ISS*.

FDA table (2): Exposure in Phase II/III controlled trials (persons, person years) Included in the *original ISS*

| Exposure       | Number of Subjects | Person years |
|----------------|--------------------|--------------|
| Placebo        | 1,308*             | 253 PY       |
| Gepirone IR    | 1,557              | 288 PY       |
| Gepirone ER    | 603                | 129 PY       |
| Total gepirone | 2,160              | 417 PY       |

\*Thirty four subjects were exposed to both gepirone and placebo during study 037A7A-002 and are not counted among the placebo group in this summary (Appendix A1, original ISS).

#### 2.3.3.2 Organon data

The sponsor reported that 212 subjects were exposed to gepirone (all ER, 27 PYs) in the 2 controlled trials included in the *updated ISS*. Two hundred and fourteen subjects were exposed to placebo (28 PY) in these 2 trials (sponsor's Table 5, p. 39 updated ISS).

### 2.3.4 EXPOSURE IN PHASE II/III CONTROLLED DEPRESSION TRIALS

#### 2.3.4.1 BMS data

In the *original ISS*, the sponsors identified 1,354 gepirone-exposed subjects during phase II/III depression controlled trials with a total of 301 PY. The following FDA table (3) summarizes the exposure in the phase II/III controlled depression trials (persons, person years) included in the *original ISS*.

FDA table (3): Exposure in Phase II/III controlled depression trials (persons, person years) Summarized in the *original ISS*

| Exposure       | Number of Subjects | Person years |
|----------------|--------------------|--------------|
| Placebo        | 735*               | 174 PY       |
| Gepirone IR    | 835                | 186 PY       |
| Gepirone ER    | 519                | 115 PY       |
| Total gepirone | 1,354              | 301 PY       |

\*Thirty four subjects were exposed to both gepirone and placebo during study 037A7A-002 and are not counted among the placebo group in this summary (Appendix A1, original ISS).

### 2.3.4.2 Organon data

The two controlled trials included in the *updated ISS* were both depression RCTs (212 subjects exposed to gepirone for 27 PY, 214 exposed to placebo for 28 PY, sponsor's table 5, p.39, updated ISS).

### 2.3.5 EXPOSURE BY DURATION

Using the data sets supplied with the gepirone NDA, Dr Boehm examined the number of subjects exposed in phase II/III trials by duration. The following FDA table (4) provides a summary for exposure by duration for the phase II/III trials (Appendix A.17, *original ISS*, and Appendix A.6, *updated ISS*).

FDA table (4): Summary of Exposure by duration for Phase II/III gepirone Trials

| Exposure                   | Number of Subjects | Median Days of Exposure | Maximum Days of Exposure |
|----------------------------|--------------------|-------------------------|--------------------------|
| Original ISS, All gepirone | 2,496              | 48                      | 724                      |
| Gepirone IR                | 1,859              | 45                      | 724                      |
| Gepirone ER                | 637                | 56                      | 371                      |
| Updated ISS*               | 212                | 55                      | 69                       |

\* Gepirone ER

In the *original ISS*, most of the gepirone subjects (89% 2216/2496) were exposed for less than 6 months. There were 280 subjects exposed for  $\geq 180$  days and 76 subjects exposed for  $\geq 365$  days. To further clarify the long-term exposure Dr Boehm counted the number of subjects exposed at least 50 and 51 weeks. Using the sponsor's DOSE OLD data set, Dr Boehm found that 93 subjects were exposed for at least 51 weeks and 15 additional subjects were exposed for at least 50 weeks (108 total). Seventy-four of the seventy-six subjects exposed for at least a year were in gepirone IR trials. In trials summarized in the *updated ISS*, the longest exposure was 69 days.

### 2.3.6 EXPOSURE BY DOSE

Exploring exposure by dose in the gepirone development program is somewhat complicated by trial design issues. The sponsor's trials generally randomized subjects to dose ranges of gepirone and subjects were titrated to a dose within their assigned range. Since subjects were not randomized to a fixed dose, the sponsor used subjects' modal dose (dose taken most frequently during the study) for dose related analyses.

To explore the PY exposure at different dosages, Dr Boehm used the sponsor's data sets to calculate person time at selected modal dose ranges by summing the person time for each modal dose. This is not the most accurate summary of the exposure by dose because this approach attributes all the person time for an individual subject to their modal dose rather than the specific doses taken during the study. Unfortunately, the submitted data sets did not allow for a summary of the person time for each dose.

The sponsor's 4-month safety update included exposure from phase II/III depression trials for the ER preparation. To arrive at an estimate of the total updated exposure by modal dose, Dr Boehm calculated the exposure for the IR preparation and the ER non-

depression exposure from phase II/III trials (unchanged from original ISS). Dr Boehm added that to the updated Phase II/III ER depression exposure from the 4-month safety update. That information is summarized in the following FDA table (5).

FDA table (5): Exposure by modal dose in phase II/III gepirone trials through the four-month safety update

| Exposure                                                     | Subjects (PY) by Modal Dose |              |              |             |               |
|--------------------------------------------------------------|-----------------------------|--------------|--------------|-------------|---------------|
|                                                              | 0-19mg                      | 20-39mg      | 40-79mg      | ≥80mg       | Total         |
| Gepirone Original ISS, All Phase II/III except ER depression | 996<br>(186)                | 558<br>(135) | 338<br>(66)  | 51<br>(9)   | 1943<br>(396) |
| Gepirone ER Depression trials, through 4 month safety update | 125<br>(32)                 | 179<br>(33)  | 474<br>(106) | 287<br>(78) | 1065<br>(249) |
| Total                                                        | 1121<br>(218)               | 737<br>(168) | 812<br>(172) | 338<br>(87) | 3008<br>(645) |

### 2.3.7 EXPOSURE BY DOSE AND DURATION

The following FDA tables (6 & 7) depict the number of subjects exposed by modal dose at 168 days (roughly 6 months) and 336 days (roughly 1 year) through the 4-month safety update.

FDA table (6): Exposure by modal dose in phase II/III gepirone trials for those with at least 168 days of exposure

| Exposure                                                     | Number of Subjects by Modal Dose |         |         |       |       |
|--------------------------------------------------------------|----------------------------------|---------|---------|-------|-------|
|                                                              | 0-19mg                           | 20-39mg | 40-79mg | ≥80mg | Total |
| Gepirone Original ISS, All Phase II/III except ER depression | 106                              | 85      | 26      | 2     | 219   |
| Gepirone ER Depression trials, through 4 month safety update | 22                               | 18      | 53      | 43    | 136   |
| Total                                                        | 128                              | 103     | 79      | 45    | 355   |

FDA table (7): Exposure by modal dose in phase II/III gepirone trials for those with at least 336 days of exposure

| Exposure                                                     | Number of Subjects by Modal Dose |         |         |       |       |
|--------------------------------------------------------------|----------------------------------|---------|---------|-------|-------|
|                                                              | 0-19mg                           | 20-39mg | 40-79mg | ≥80mg | Total |
| Gepirone Original ISS, All Phase II/III except ER depression | 49                               | 40      | 12      | 0     | 101   |

|                                                              |    |    |    |    |     |
|--------------------------------------------------------------|----|----|----|----|-----|
| Gepirone ER Depression trials, through 4 month safety update | 10 | 5  | 10 | 13 | 38  |
| Total                                                        | 59 | 45 | 22 | 13 | 139 |

As shown above, the sponsor does not fulfill the ICH guidelines for long-term exposure data (300 individuals exposed to an effective dose for 6 months and 100 individuals exposed to an effective dose for 1 year). The pivotal trials suggest that the minimum effective gepirone dose is 40 mg/day. The review found that the exposure to gepirone was deficient at this minimum effective dose. Specifically, only 124 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 6 months and only 35 subjects were exposed to a modal dose  $\geq 40$  mg for roughly 1 year. Even when exposure to a sub-therapeutic modal dose was included, the exposure was still deficient by ICH standards (227 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 6 months and 80 subjects were exposed to a modal dose  $\geq 20$  mg for roughly 1 year).

### 2.3.8 EXPOSURE BY SEX

Dr Boehm used the sponsor's data sets to examine dose by sex in the gepirone phase II/III trials reported in the *original* and *updated* ISS reports. The following FDA table (8) summarizes the exposure providing both the number of subjects and person time stratified by sex.

FDA table (8) Exposure by sex in phase II/III gepirone trials

| Exposure                 | Sex                  |                    |
|--------------------------|----------------------|--------------------|
|                          | Female subjects (PY) | Male subjects (PY) |
| Gepirone IR <sup>†</sup> | 1064 (237)           | 789 (145)          |
| Gepirone ER <sup>†</sup> | 407 (93)             | 225 (42)           |
| Gepirone ER*             | 137 (17)             | 75 (10)            |

<sup>†</sup>original ISS- gender missing for 11 subjects

\*updated ISS

There appears to be adequate distribution of subjects by sex in the gepirone development program.

## 2.4 Methods of safety review and specific findings of safety review

### 2.4.1 MATERIALS USED IN THIS REVIEW

| Source       | Submission date | Material                                  |
|--------------|-----------------|-------------------------------------------|
| Organon, Inc | 9/30/1999       | Original ISS section of the NDA           |
|              | 5/18/2001       | Updated ISS section of the NDA            |
|              | 5/18/2001       | Data sets: AESPIII, AES_OLD, and DOSE OLD |
|              | 9/18/2001       | 120 days Safety update                    |
|              | 10/11/2001      | Additional tables requested by reviewer   |

|  |            |                                         |
|--|------------|-----------------------------------------|
|  | 11/13/2001 | Additional tables requested by reviewer |
|--|------------|-----------------------------------------|

## 2.4.2 BACKGROUND

### 2.4.2.1 Non-clinical toxicology

The summary of the toxicokinetics of gepirone and its metabolites is in Section 1.5 of the supplement to the Nonclinical Pharmacology and Toxicology Summary of the NDA for gepirone, which is located in Appendix I.

In acute studies, high oral doses of gepirone caused hypoactivity and tonic clonic convulsions in rodents and tremor, ataxia, emesis, salivation and increased respiratory rate in dogs.

In oral subchronic and chronic toxicology studies, rats showed a dose-related hypoactivity and decreased body weight gain.

In oral subchronic and chronic toxicology studies in dogs, clinical signs included 1) a dose-related increase in hypoactivity, tremors, and respiration rate and 2) a dose-related decrease in body weight gain.

Two segment-I studies were conducted to explore the effects of gepirone at doses ranging from 5 – 150 mg/kg/day. Orally administered gepirone did not affect fertility or general reproduction in rats at 5 or 27 mg/kg/day, but caused maternal toxicity at 64 and 150 mg/kg/day. These doses were also associated with increases in empty implantation sites, decreased implantation index, decreased lactational index, and increased number of stillbirth.

In rat and rabbit embryo-fetal (segment II) development studies, gepirone was not teratogenic or embryotoxic. In a rat peri- and postnatal development (segment III) study, gepirone did not induce any adverse effects on pregnancy, labor, delivery, or physical or behavioral development of the offspring. However, there was a dose-related decrease in offspring viability during the first four days after birth, lower birth weights, and decreased body weight gains during lactation.

Gepirone was not mutagenic in the Ames *Salmonella typhimurium* assay, the E. Coli WP2 uvrA assay, or the CHO/HGPRT forward mutation assay. Gepirone was not genotoxic in the hepatocyte primary culture/DNA repair assay (UDS test). Gepirone was neither clastogenic in a rat *in vivo* cytogenetic assay (micronucleus test) or in the Chinese Hamster Ovary cytogenetic assay (chromosomal aberration test).

Gepirone was not carcinogenic in mice or rats in 2-year dietary carcinogenicity studies.

### 2.4.3 ISS POPULATION

The ISS population includes every participant who received at least one dose of study medication in any Organon or BMS study. The sponsor pooled and analyzed the results of 22 Phase I trials conducted in 579 healthy subjects and 36 Phase II/III trials (8 conducted with the ER formulation and 28 with the IR formulation) conducted in 4,333

subjects. Of these 58 trials, 53 were sponsored and conducted by BMS and five Phase-I trials were sponsored and conducted by Fabre-Kramer Pharmaceuticals.

Subsequently, the ISS was updated with safety results obtained from two completed Organon Phase III, randomized, double-blind, placebo-controlled, 8-week clinical trials in subjects with major depressive disorder and three Phase I trials. Organon still has four ongoing trials. All serious adverse events that occurred in these four trials prior to December 1, 2000 are included in the safety analyses presented in the ISS. FDA table (9) presents the distribution of all study participants in the whole gepirone development program.

FDA table (9): Distribution of study participants in both the BMS and Organon trials (Source: sponsor's table 1, page 2, updated ISS. Details of all trials are provided in sponsor's table 2 , page 15, updated ISS).

| Phase               | Gepirone     |              |              | Active Controls | Placebo      | Total Subjects |
|---------------------|--------------|--------------|--------------|-----------------|--------------|----------------|
|                     | ER           | IR           | ER&IR        |                 |              |                |
| <b>BMS</b>          |              |              |              |                 |              |                |
| Phase I             | 321          | 204          | 525          | 0               | 54           | 579            |
| Phase II/III        | 637          | 1,859        | 2,496        | 529             | 1,308        | 4,333          |
| Totals              | 958          | 2,063        | 3,021        | 529             | 1,362        | 4,912          |
| <b>Organon</b>      |              |              |              |                 |              |                |
| Phase I             | 98           | 0            | 98           | 0               | 0            | 98             |
| Phase II/III        | 212          | 0            | 212          | 0               | 214          | 426            |
| Totals              | 310          | 0            | 310          | 0               | 214          | 524            |
| <b>Grand Totals</b> | <b>1,268</b> | <b>2,063</b> | <b>3,331</b> | <b>529</b>      | <b>1,576</b> | <b>5,436</b>   |

Appendices A.1, A.2 & A.3 (original ISS) present the number of study participants by various indications and treatment groups. Appendix A.2 shows that the safety analysis population of the BMS **controlled depression trials** included 519 ER, 835 IR and 735 placebo<sup>1</sup> subjects.

All the completed ER and most of the completed IR controlled trials in depression were conducted in the USA. I reviewed the summary of all study designs (sponsor's table 2, page 15, updated ISS) and, in more depth, the individual controlled trials in depression. All trials had a flexible dosing with dose titration. The following trials were terminated prematurely when BMS ceased its gepirone development program: CN105-003, CN105-004, CN105-018, CN105-022, CN105-023, CN105-028, CN105-029, CN105-036, CN105-043, CN105-052, CN105-053, CN105-055, CN105-057, CN105-064, CN105-071, CN105-078, CN105-083, and 03A7C-001B.

I listed in the following FDA table (10) all the controlled phase II/III controlled clinical trials in depression for both gepirone IR and ER formulations. The table contains the short-term and long-term phases of trials. In most trials, subjects responding to treatment received an additional period of double-blind treatment in the long-term phase under the same trial number.

<sup>1</sup> Includes placebo patients from both IR and ER trials.

FDA table (10): List of phase II/III controlled clinical trials in depression for gepirone IR and ER formulations.

| Short-term         |                      | Long-term    |                | Sponsor |
|--------------------|----------------------|--------------|----------------|---------|
| Trial number       | Duration (wks)       | Trial number | Duration (wks) |         |
| <u>Gepirone ER</u> |                      |              |                |         |
| CN105-052          | 8                    | same         | 42             | BMS     |
| CN105-053          | 8                    | same         | 44             | BMS     |
| CN105-057          | 8                    | same         | 42             | BMS     |
| CN105-064          | 8                    | same         | 44             | BMS     |
| CN105-078          | 6                    | same         | 20             | BMS     |
| CN105-083          | 6                    | same         | 20             | BMS     |
| 134001             | 8                    | 134501       | 42 OL          | Organon |
| 134002             | 8                    | 134501       | 42 OL          | Organon |
| <u>Gepirone IR</u> |                      |              |                |         |
| 03A7A-002          | 6 (after 6 weeks OL) | None         |                | BMS     |
| 03A7A-003          | 8                    | None         |                | BMS     |
| 03A7C-001-A-2486   | 8                    | None         |                | BMS     |
| 03A7C-001-A        | 8                    | None         |                | BMS     |
| 03A7C-001-B        | 8                    | same         | 44             | BMS     |
| CN105-022          | 8                    | same         | 44             | BMS     |
| CN105-028          | 8                    | same         | 44             | BMS     |
| CN105-029          | 8                    | same         | 44             | BMS     |
| CN105-037          | 8                    | same         | 44             | BMS     |
| CN105-043          | 8                    | same         | 44             | BMS     |

OL = open label

### 2.4.3.1 Demographics

#### 2.4.3.1.1 BMS data

In all Phase II/III trials, a total of 2496 subjects were exposed to gepirone, 1308 subjects to placebo, 346 to antidepressant comparators, and 183 to anxiolytic comparators (sponsor's table 10, page 45, original ISS). The average age was between 39 and 41 across treatment groups with 95 – 98% younger than 65. The age range was 18-84 years. One subject was recorded as one year old which is most likely a mistake in the data entry. Fifty-seven to 67% of the subjects were female; 80 – 86% of the subjects were Caucasian and 7–11% of the subjects were Black. For the groups treated with anxiolytics, race was missing for 40% of the subjects.

In the controlled gepirone ER trials in depression, 519 subjects were exposed to gepirone, 258 to placebo, and 110 to either fluoxetine or imipramine (sponsor's table 11, page 47, original ISS). Mean age in all treatment groups was between 39 and 40 years with 96 to 99% of the subjects less than 65 years of age. Mean weight varied between 76 and 78 kg; 83 to 91% of the subjects were Caucasian and 2 to 8% of the subjects were Black.

#### 2.4.3.1.2 Organon data

In the two completed phase III depression trials conducted by Organon (sponsor's table 7, page 41, updated ISS), a total of 212 subjects were exposed to gepirone ER and 214 subjects were exposed to placebo. The average age was approximately 39 years in both treatment groups with 98 to 99% in both treatment groups less than 65 years of age. The age range was 18-69 years. Fifty-eight to 65% of the subjects were female; 80% of the participants were Caucasian and 7% to 11% in each treatment group were Black or other.

#### **2.4.4 REVIEW OF SPONSOR'S SURVEILLANCE AND CODING OF AE: AE CATEGORIZATION AND PREFERRED TERMS**

The sponsor mapped AEs to the fifth edition (1995) of COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) according to the dictionary presented in sponsor's Appendices I.5 (updated ISS) and J.5 (original ISS).

The sponsor defined adverse experiences as "any event, irrespective of causality, that had a significant negative impact on the health or well-being of a subject. Adverse experiences included any side effect, injury, inter-current illness, toxicity, or sensitivity reaction."

I reviewed the appendices referenced above (I.5 and J.5) and found the AE verbatim terms mapped to appropriate preferred terms. I focused in particular on some of the most common adverse event. I was concerned about the potential relationship between accidental injury and dizziness, which is one of the most common adverse events. Examining the data sets (AESPIII & AES\_OLD) provided by the sponsor did not reveal any pattern of specific type or cluster of injury. Furthermore, the AEs coded as dizziness were mainly reported either as "dizziness" or "lightheadedness" with no other details provided.

#### **2.4.5 REVIEW OF SPONSOR'S APPROACH TO EVALUATING SAFETY OF GEPIRONE**

All AEs that occurred between the start of drug administration and within seven days (30 days for serious AE) of the termination of dosing were reportedly collected and analyzed. All serious adverse events that occurred in ongoing Organon trials prior to December 1, 2000 (cut-off date) are included in the safety analyses of the ISS.

Subjects who withdrew prematurely from clinical trials due to adverse experiences were identified from several sources. These included the following:

1. The subject was reported as having withdrawn from study drug in the last Bristol-Myers Squibb IND Annual Report dated May 29, 1992 or was reported in the Fabre-Kramer [REDACTED] (b) (4); or
2. The subject was reported to have discontinued study drug due to an adverse experience on an "end of study" case report form page. The subject was included regardless of whether the adverse experience was a primary, secondary, or tertiary reason for discontinuation; or
3. The subject had any adverse experience where the action was to permanently discontinue treatment on an adverse experience case report form (CRF) page.

Subjects who experienced serious adverse experiences were identified from several sources. These included the following:

1. The subject was reported as having a serious adverse experience in the last Bristol-Myers Squibb IND Annual Report dated May 29, 1992 or was reported in the Fabre-Kramer [REDACTED] (b) (4); or

2. The subject was reported as having a serious adverse experience on an end of study CRF page.

#### **2.4.6 CRF AUDIT FINDINGS**

The sponsor counted adverse experiences in individual subjects with multiple reports of a single COSTART preferred term only once in the statistical tabulation of preferred term incidence. The sponsor provided CRFs for subjects with serious AEs, AEs leading to dropout, and death. I cross-checked 20-30 CRFs against the corresponding CRT focusing on the Gepirone ER trials in depression. I used the three largest US trials (# 134001, 134002, and CN105-057) and reviewed files containing information about AEs (AES.xpt, 30 records), concomitant medications (CONMED.xpt, 20 records) and vital signs (VITALS.xpt, 20 records). The degree of discrepancy for various files was as follows: AEs (1/29, one AE is missing and one CRF is not provided), concomitant medications (0/20), and vital signs (0/19, one CRF is not provided).

#### **2.4.7 DEATHS**

##### **2.4.7.1 BMS data**

In the BMS data (original ISS) three deaths were reported. Only one death occurred in the gepirone treatment group. Subject (b) (6) died on (b) (6) of an aortic dissection approximately 40 days after his last dose of gepirone IR. The subject had been treated with gepirone IR for approximately 35 days ((b) (6)) and had been treated for eight years for hypertension with furosemide and metoprolol. Additional details on all the death cases are in the subject narratives presented in Appendix J.15 (original ISS).

##### **2.4.7.2 Organon data**

There were no deaths reported in the Organon data (updated ISS).

##### **2.4.7.3 Four-month safety update**

There were no deaths reported up to and including June 18, 2001.

#### **2.4.8 SERIOUS ADVERSE EVENTS**

This section reflects data from all study participants in all controlled and uncontrolled clinical trials in phase-I and phase-II/III.

The sponsor did not provide the definition of serious adverse events (SAE) in the ISS or in the study reports. However, the definition of SAE was listed in the investigational plans of various clinical trials and included: "death (during the study or within 30 days after the last dose of study medication), immediately life-threatening AEs, cancer, congenital abnormalities, permanent disability, symptomatic overdose, and any event that required hospitalization during or shortly after treatment. Other AEs that could be considered serious included myocardial infarction, cerebrovascular accidents, seizure,

severe rash, any serious laboratory abnormality, and any unusual, potentially serious or usually severe effects.”

### 2.4.8.1 BMS data

A total of 81 of 4912 subjects (1.6%) experienced a serious adverse event while participating in gepirone clinical trials. Listings of all serious adverse experiences by subject and event are presented in Appendices J.8 and J.9 (original ISS), respectively, and are attached to this review. The following FDA table (11) summarizes the number and percent of subjects that developed serious AEs in various treatment groups (source: Appendix C.58, original ISS).

FDA table (11): Number and percent of subjects that developed serious AEs in various treatment groups.

| Gep ER           | Gep IR            | GepER+GepIR       | Anti depressants | Anxiolytics     | Placebo           |
|------------------|-------------------|-------------------|------------------|-----------------|-------------------|
| 15/958<br>(1.6%) | 46/2063<br>(2.2%) | 61/3021<br>(2.0%) | 4/346<br>(1.2%)  | 0/183<br>(0.0%) | 16/1408<br>(1.1%) |

Only the combined gepirone IR & ER treatment group showed a significantly greater risk of any serious adverse experience compared to placebo (risk ratio=1.78, confidence interval 1.03 to 3.07). The sponsor is attributing this difference in part to the fact that exposure in subject years in the combined gepirone treatment group (519 person years) was twice that in the placebo group (253 person years) and in part to the higher incidence in the gepirone IR treatment group compared to the gepirone ER treatment group. However, these data reflect all studied indications and does not allow separate assessment of the sub-population of interest (depressed patients).

There are no statistically significant differences between the various active treatment groups and placebo for serious adverse experiences due to low numbers of observations. However, serious adverse events that occurred infrequently, but had at least double the risk in the combined IR and ER gepirone group in comparison with the placebo group include the following: accidental injury, psychosis, depression, suicide attempt, syncope, breast neoplasm, hernia, leukopenia, migraine, overdose, psychotic depression and thinking abnormal (Appendix C.58, original ISS). I summarized these serious AEs in the following FDA table (12).

FDA table (12): Summary of serious adverse experiences (with RR >=2) among all study participants (Source: Appendix C.58, original ISS).

| Adverse Experience | Gep ER<br>N(%) | Gep IR<br>N(%) | ER+IR<br>N(%) | Placebo<br>N(%) | Gep vs PI<br>ratio (C.I.) | ER vs IR<br>ratio (C.I.) |
|--------------------|----------------|----------------|---------------|-----------------|---------------------------|--------------------------|
| NUMBER OF SUBJECTS | 958            | 2063           | 3021          | 1408            |                           |                          |
| ACCIDENTAL INJURY  | 2<br>(0.2%)    | 3<br>(0.1%)    | 5<br>(0.2%)   | 1<br>(0.1%)     | 2.33<br>(0.27, 19.93)     | 1.44<br>(0.24, 8.58)     |
| PSYCHOSIS          | 0<br>(0.0%)    | 7<br>(0.3%)    | 7<br>(0.2%)   | 1<br>(0.1%)     | 3.26<br>(0.40, 26.49)     | 0.14<br>(0.01, 2.51)     |
| DEPRESSION         | 2<br>(0.2%)    | 3<br>(0.1%)    | 5<br>(0.2%)   | 0<br>(0.0%)     | 5.13<br>(0.28, 92.69)     | 1.44<br>(0.24, 8.58)     |
| SUICIDE ATTEMPT    | 2<br>(0.2%)    | 1<br>(0.0%)    | 3<br>(0.1%)   | 0<br>(0.0%)     | 3.26<br>(0.17, 63.14)     | 4.31<br>(0.39, 47.44)    |
| SYNCOPE            | 2<br>(0.2%)    | 1<br>(0.0%)    | 3<br>(0.1%)   | 0<br>(0.0%)     | 3.26<br>(0.17, 63.14)     | 4.31<br>(0.39, 47.44)    |
| BREAST NEOPLASM    | 0<br>(0.0%)    | 2<br>(0.1%)    | 2<br>(0.1%)   | 0<br>(0.0%)     | 2.33<br>(0.11, 48.53)     | 0.43<br>(0.02, 8.96)     |
| HERNIA             | 0<br>(0.0%)    | 2<br>(0.1%)    | 2<br>(0.1%)   | 0<br>(0.0%)     | 2.33<br>(0.11, 48.53)     | 0.43<br>(0.02, 8.96)     |
| LEUKOPENIA         | 1<br>(0.1%)    | 1<br>(0.0%)    | 2<br>(0.1%)   | 0<br>(0.0%)     | 2.33<br>(0.11, 48.53)     | 2.15<br>(0.13, 34.39)    |
| MIGRAINE           | 0<br>(0.0%)    | 2<br>(0.1%)    | 2<br>(0.1%)   | 0<br>(0.0%)     | 2.33<br>(0.11, 48.53)     | 0.43<br>(0.02, 8.96)     |

|                      |             |             |             |             |                       |                       |
|----------------------|-------------|-------------|-------------|-------------|-----------------------|-----------------------|
| OVERDOSE             | 1<br>(0.1%) | 1<br>(0.0%) | 2<br>(0.1%) | 0<br>(0.0%) | 2.33<br>(0.11, 48.53) | 2.15<br>(0.13, 34.39) |
| PSYCHOTIC DEPRESSION | 1<br>(0.1%) | 1<br>(0.0%) | 2<br>(0.1%) | 0<br>(0.0%) | 2.33<br>(0.11, 48.53) | 2.15<br>(0.13, 34.39) |
| THINKING ABNORMAL    | 1<br>(0.1%) | 1<br>(0.0%) | 2<br>(0.1%) | 0<br>(0.0%) | 2.33<br>(0.11, 48.53) | 2.15<br>(0.13, 34.39) |

I reviewed the data in Appendix J.9 (original ISS) about subjects reported to have experienced serious accidental injury in the gepirone group. Most subjects (4/5) were injured in motor vehicle accidents. The sponsor did not provide information indicating if the injured subject was a passenger or a driver. The sponsor did not explore the role of dizziness induced by gepirone in causing the accidents.

Regarding the two cases of breast neoplasm in the gepirone IR group, one is benign [# (b) (6)] and one is ductal carcinoma [# (b) (6)].

There were no reported rare unexpected serious adverse events such as hepatic failure, renal failure, aplastic anemia, serious skin reactions, or rhabdomyolysis.

### 2.4.8.2 Organon data

In the two completed Organon trials (134001 and 134002), there were 3 SAEs. One subject treated with gepirone ER was hospitalized for polypoid chronic cystitis and two subjects treated with placebo were hospitalized for accidental injury. There were no reports of rare unexpected serious adverse events such as hepatic failure, renal failure, aplastic anemia, serious skin reactions, or rhabdomyolysis.

All serious adverse events that occurred in ongoing Organon trials prior to December 1, 2000 (cut-off date) are reportedly included in the safety analyses of the updated ISS. Reports have been obtained from subjects participating in two ongoing trials. Six subjects reported serious adverse events in the first study (134501), which is an open-label long-term extension study to trials 134001 and 134002. This setting does not allow a comparison with a control. These events are:

- Subject (b) (6) attempted suicide during the extension by overdosing on an unknown quantity of gepirone ER and another unknown drug. The subject was hospitalized and recovered from the event. After hospital discharge the subject was lost to follow-up.
- Subject (b) (6) experienced an episode of psychotic depression and discontinued from the trial. The event was considered serious by the investigator because it led to disability/incapacity.
- Subject (b) (6) was hospitalized for renal calculi.
- Subject (b) (6) was hospitalized for acute appendicitis.
- Subject (b) (6) was brought to the hospital for worsening major depressive disorder along with suicidal ideation. The subject was not admitted, but was treated as an outpatient.

- Subject (b) (6) developed a positive urine pregnancy test. On notification of the result, she reported that she had stopped taking the study medication prior to the positive result and that she had a tubal ligation in the previous year. She requested that the test results be forwarded to her gynecologist, and stated that she would follow up with him. The subject has been lost to follow-up and her outcome remains unknown.

In the second ongoing study (28709), which is a placebo-controlled relapse prevention trial, ten (10) subjects have been reported to have a serious adverse experience. The trial is still blinded and currently ongoing in a number of countries in Europe. The serious adverse events reported in this still blinded trial include: tendon rupture (subject (b) (6)); convulsion grand mal (subject (b) (6)); aggravated or psychotic depression (subjects (b) (6)); dyspepsia, dysphagia, and chest pain (subject (b) (6)), skeletal pain (subject (b) (6)), and aggravated depression and elevated hepatic enzymes (subject (b) (6)). The elevated hepatic enzymes for subject (b) (6) were AST, ALT, and alkaline phosphatase. The subject's pretreatment values were normal, increased on treatment to 52, 93, & 151, seven days after stopping study drug were 148, 393, & 485. The sponsor provided no information about bilirubin results, diagnostic workup or outcome of this event. Seven out of the ten subjects discontinued treatment with study medication due to the serious adverse event, two continued treatment, and the status of one is unknown.

#### **2.4.8.3 Four-month safety update**

The cut-off date for this report is June 18, 2001. The sponsor reported that it has nine ongoing trials, in which twelve subjects reported serious AEs in seven blinded trials and 18 subjects reported serious AEs in two open-labeled trials (eight subjects in trial number 134501 and ten subjects in trial number 28709<sup>2</sup>). Only line listings of these subjects are provided. The WHO preferred terms for these events are:

- Treatment blinded: accidental injury, depression aggravated (n=6), abdominal pain, bone disorder.

- Open label on gepirone: renal calculus, depression psychotic, intestinal obstruction, suicide attempts (n=2), pregnancy unintended, gastro-intestinal disorder, depression (n=5), generalized seizure, panic attack, depression psychotic (n=2), thrombosis profunda cruris, AP, SGOT & SGPT increased (n=2) (no information is available on the magnitude of abnormality), psychosom (pain due to depression).

#### **2.4.8.4 Data provided from sponsor upon request**

The sponsor pooled the safety data derived from both gepirone formulations (ER & IR) and compared it to the pooled placebo data. In some analyses, the sponsor pooled their phase II/III data with BMS data from ER depression trials and compared to placebo data from the entire development program regardless of indication, obscuring the interpretation of these comparisons.

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<sup>2</sup> These events occurred during the open label phase of the relapse prevention trial.

Because of the reasons mentioned above, and upon request (10/24/2001), the sponsor submitted new tables (11/13/2001) showing the adverse events in the phase II/III controlled depression trials for the IR and ER formulations separately, each compared to its own placebo. In the following sections, I used the sponsor's tables that pooled their short ( $\leq 63$  days) and long ( $> 63$  days) term data.

#### 2.4.8.4.1 Gepirone IR formulation

I summarized in the FDA table (13) SAEs in phase II/III controlled depression trials of gepirone IR formulation. Note that the more frequent SAEs are largely the same as the ones reported in the original submission with no unexpected major differences. In this comparison accidental injury risk is not markedly greater among gepirone IR subjects compared to placebo.

FDA table (13): Number of subjects with SAEs in phase II/III controlled depression trials of gepirone IR formulation --short-term phase and long-term phase combined (source table 6a, submission 11/13/2001).

|                                 | Gepirone IR<br>N (%) | Placebo<br>N (%) | Risk Ratio (95% CI)<br>GepironeIR vs. Placebo |
|---------------------------------|----------------------|------------------|-----------------------------------------------|
| Total Number of Subjects        | 737                  | 511              |                                               |
| Number of Subjects with Any SAE | 17 (2.3)             | 3 ( 0.6)         | 3.93 (1.16-13.3)                              |
| Psychosis                       | 5 ( 0.7)             | 0                |                                               |
| Depression                      | 2 ( 0.3)             | 0                |                                               |
| Angina pectoris                 | 1 ( 0.1)             | 0                |                                               |
| Breast carcinoma                | 1 ( 0.1)             | 0                |                                               |
| Breast neoplasm                 | 1 ( 0.1)             | 0                |                                               |
| Convulsion                      | 1 ( 0.1)             | 0                |                                               |
| Kidney pain                     | 1 ( 0.1)             | 0                |                                               |
| Leukopenia                      | 1 ( 0.1)             | 0                |                                               |
| Migraine                        | 1 ( 0.1)             | 0                |                                               |
| Overdose                        | 1 ( 0.1)             | 0                |                                               |
| Pain                            | 1 ( 0.1)             | 0                |                                               |
| Psychotic depression            | 1 ( 0.1)             | 0                |                                               |
| Syncope                         | 1 ( 0.1)             | 0                |                                               |

##### 2.4.8.4.1.1 Selected narratives

33-year-old white female ( (b) (6) ) developed leukopenia (with neutropenia) after 384 days on gepirone IR (modal dose 10 mg). The subject had at least one prior episode of documented leukopenia (WBC =  $3.70 \times 10^3/\text{mL}$ ), which occurred 2 months prior to study entry. The subject had entered the short-term phase of the study with a normal WBC of  $6.37 \times 10^3/\text{mL}$ , with 55% neutrophils, hemoglobin and platelets. At the end of the short-term phase, after 8 weeks of Gepirone therapy, her WBC decreased to  $4.54 \times 10^3/\text{mL}$ , with 53.7% neutrophils. Hemoglobin and platelets were in the normal range. The subject entered the study extension and completed 52 weeks of gepirone therapy. Her week 52 (end of study) hematology results showed WBC of  $2.19 \times 10^3/\text{mL}$ , with 33.3%

neutrophils, normal hemoglobin and low platelets ( $112 \times 10^9/L$ ). Clinically, the subject showed few adverse sequelae from her leukopenia, with only one documented infection (an episode of sinusitis) which began approximately six days before her leukopenia was discovered. The subject was subsequently evaluated by a hematologist who confirmed leukopenia and neutropenia in the subject's peripheral blood smear, but found no significant pathology in the subject's bone marrow sample. The hematologist also suggested that, since the subject's antinuclear antibody was negative but her rheumatoid factor was positive, there was some possibility of collagen-vascular disease. Approximately two months after cessation of gepirone therapy at week 52, the subject's WBC remained low at  $3.50 \times 10^3/mL$ , but her differential returned to normal. There was no further documented follow-up. Concomitant medications included Aspirin, Norethin, Fiorinal, and Anaprox.

A 42-year-old white male ( (b) (6) ) was hospitalized for angina pectoris after 11 days on gepirone IR (modal dose 50 mg). The patient experienced cold sweat, numbness in the lower facial area and nausea. Pretreatment ECG was abnormal showing a possible old infarction and a pattern consistent with ischemia. Four months before the study entry the subject had suffered left arm paresthesia that was thought to be a possible silent myocardial infarction. Baseline and termination ECG showed no change from pretreatment ECG and the available laboratory values (LDH & alk phos) were within normal limits. The patient discontinued due to this SAE.

A 63-year-old white male ( (b) (6) ) hospitalized for loss of consciousness after 45 days on gepirone IR (modal dose 5 mg). The subject "blacked out" and apparently injured himself in falling. The subject baseline ECG tracing was normal. A listing of adverse symptoms experienced within the month prior to starting the study was not available. The subject reported moderate chest pain on days 4, 18, & 23. The subject stopped taking study medication after the "blacking out" incident. The subject had a prior "cerebrovascular accident" with no other details provided in his narrative. Concomitant medications included nitroglycerin and pentoxifylline.

A 52-year-old white female ( (b) (6) ) was hospitalized due to a grand mal seizure after 92 days on gepirone IR (modal dose 4 mg). Serial neurologic evaluations showed no evidence of neurologic deterioration, and EEG testing was normal. The only concomitant medication was chloral hydrate.

All cases coded as "psychosis" in the SAEs listed in the above table were due to "worsening of depression".

#### 2.4.8.4.2 Gepirone ER formulation

I summarized in the FDA table (14) SAEs in phase II/III controlled depression trials of gepirone ER. Note that the more frequent SAEs are largely the same as the ones reported in the original submission with no unexpected major differences. In this analysis accidental injury risk is not markedly greater among gepirone ER subjects compared to placebo.

FDA table (14): Number of subjects with SAEs in phase II/III controlled depression trials of gepirone ER formulation --short-term phase and long-term phase combined (source table 12a, submission 11/13/2001).

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| Gepirone ER | Placebo | Risk Ratio (95% CI) |
|-------------|---------|---------------------|
|-------------|---------|---------------------|

|                                | N (%)     | N (%)    | GepironeER vs. Placebo |
|--------------------------------|-----------|----------|------------------------|
| Total Number of Subjects       | 731       | 472      |                        |
| Number of Subjects with Any AE | 13 ( 1.8) | 3 ( 0.6) | 2.80 (0.80-9.77)       |
| Depression                     | 2 ( 0.3)  | 0        |                        |
| Suicide attempt                | 2 ( 0.3)  | 0        |                        |
| Syncope                        | 2 ( 0.3)  | 0        |                        |
| Accidental injury              | 1 ( 0.1)  | 3 ( 0.6) | 0.22 (0.02-2.06)       |
| Cardiovascular disorder        | 1 ( 0.1)  | 0        |                        |
| Chest pain                     | 1 ( 0.1)  | 0        |                        |
| Cholecystitis                  | 1 ( 0.1)  | 0        |                        |
| Cyst                           | 1 ( 0.1)  | 0        |                        |
| Cystitis                       | 1 ( 0.1)  | 0        |                        |
| Electrocardiogram abnormal     | 1 ( 0.1)  | 0        |                        |
| Leukopenia                     | 1 ( 0.1)  | 0        |                        |
| Psychotic depression           | 1 ( 0.1)  | 0        |                        |
| Thinking abnormal              | 1 ( 0.1)  | 0        |                        |

#### 2.4.8.4.2.1 Selected narratives

A 27-year-old white female ( (b) (6) ) developed leukopenia after 57 days on Gepirone ER (modal dose 40mg). Her baseline adverse symptoms included menstrual irregularity. Her baseline ( (b) (6) ) blood testing was within normal limits with a WBC count of  $4.96 \times 10^3/\mu\text{L}$  and normal percentages of neutrophils (48.4%), lymphocytes (43.3%), monocytes (5.5%), eosinophils (1.6%) and basophils (1.2%). Baseline platelets and hemoglobin were  $289 \times 10^9/\text{L}$  and 13.7 g/dL, respectively, and were maintained within normal limits throughout the study. Absolute neutrophil count was never less than  $1000/\text{mm}^3$ . At the end of study week 6, WBC count was  $2.77 \times 10^3/\mu\text{L}$ . The subject was allowed to continue in the study, and her leukopenia was reported as a non-serious adverse event ( (b) (6) ). The subject entered the long-term phase of the study on ( (b) (6) ), at a dosage of 40-mg gepirone daily. Investigators subsequently reviewed the subject's decreasing WBC values for study week 8 ( $3.9 \times 10^3/\mu\text{L}$ ) and study week 9 ( $3.3 \times 10^3/\mu\text{L}$ ) and decided to discontinue gepirone therapy. Throughout the study, the subject did not have any documented infections, but experienced increased bruising after approximately 8 weeks of gepirone therapy. No concomitant medications were reported other than aspirin (625 gm/day), that started about the same time as gepirone.

A 50-year-old white male ( (b) (6) ) was hospitalized for intentional overdose after 58 days on gepirone ER (modal dose 20 mg). His baseline ECG was interpreted as "within normal limits" with a heart rate of 62 BPM. In his 7<sup>th</sup> week of study participation, the subject attempted suicide by taking 20 gepirone tablets (200 mg total), as well as 5 placebo. Although his admission ECG showed no change from baseline, approximately 2 hours later he developed an incomplete right bundle branch block. The subject was "placed on telemetry and transferred to the hospital's psychiatric floor". There is no record of his subsequent hospital treatment, progress, or exact date of discharge. A few days after this episode the subject was seen for a final study visit, at which time his repeat ECG was interpreted as "within normal limits", with sinus bradycardia at a rate of 54 BPM, and a "return to normal sinus rhythm".

A 63-year-old white female ( (b) (6) ) was hospitalized for syncope preceded by dizziness after 11 days on gepirone ER (modal dose 20 mg). The subject had a history of palpitations of unspecified duration and hypertension of unspecified duration (untreated). On baseline physical examination, the subject was found to have bradycardia with a blood pressure of 100/64 mmHg, but there were no other cardiovascular abnormalities. Her baseline ECG confirmed a sinus bradycardia of 53 bpm, together with nonspecific ST-T wave changes. The subject was taken to a hospital emergency room, where she was found to have a bradycardia of 56 BPM, blood pressure of 140/77 mmHg. She withdrew from the study because of her adverse event. At her final visit, the subject's ECG showed a "marked sinus bradycardia" with a heart rate of 46 BPM.

A 39-year-old white female ( (b) (6) ) was hospitalized for a concussion, loss of consciousness, and possible fractured sternum sustained in a motor vehicle accident in which her car was struck from behind while stopped at a traffic light. The event was incorrectly coded as "syncope".

## 2.4.9 ADVERSE EVENTS LEADING TO DROPOUT

### 2.4.9.1 BMS data

The sponsor's analysis likely underestimates the risk of discontinuation due to **specific** adverse events. The sponsor noted that 761 subjects had "adverse event" identified on the CRF as the reason for discontinuing from a study but 18% (n=138) did not specify the adverse event that led to discontinuation. Therefore, the tables summarizing the events leading to discontinuation (Appendix J6) include only 82% of the events leading to discontinuation for these subjects.

In FDA table (15), I summarized the adverse experience (with RR  $\geq 2$  and incidence of  $\geq 1\%$ ) in the BMS data resulting in premature dropout in all clinical trials (source: sponsor's table 30, page 123 original ISS). Listings of subjects who dropped out due to adverse experiences are provided in Appendices J6. & J.7 (original ISS).

FDA table (15): Summary of adverse experiences with an incidence  $\geq 1\%$  (and a RR of two or more) resulting in premature discontinuation from all clinical trials (source: Appendix J.7, original ISS).

|                 | ER<br>N (%) | IR<br>N (%) | ER & IR<br>N (%) | Placebo<br>N (%) | ER&IR vs. PI<br>ratio (95% CI) | ER vs. IR<br>ratio (95% CI) |
|-----------------|-------------|-------------|------------------|------------------|--------------------------------|-----------------------------|
| No. of Subjects | 958         | 2063        | 3021             | 1362             |                                |                             |
| Dizziness       | 19 ( 2.0)   | 96 ( 4.7)   | 115 ( 3.8)       | 7 ( 0.5)         | 7.41 (3.46- 15.8)              | 0.43 (0.26- 0.69)           |
| Nausea          | 22 ( 2.3)   | 85 ( 4.1)   | 107 ( 3.5)       | 12 ( 0.9)        | 4.02 (2.22- 7.28)              | 0.56 (0.35- 0.89)           |
| Headache        | 15 ( 1.6)   | 63 ( 3.1)   | 78 ( 2.6)        | 17 ( 1.2)        | 2.07 (1.23- 3.48)              | 0.51 (0.29- 0.90)           |
| Somnolence      | 4 ( 0.4)    | 37 ( 1.8)   | 41 ( 1.4)        | 8 ( 0.6)         | 2.31 (1.09- 4.92)              | 0.23 (0.08- 0.65)           |
| Depression      | 10 ( 1.0)   | 23 ( 1.1)   | 33 ( 1.1)        | 7 ( 0.5)         | 2.13 (0.94- 4.79)              | 0.94 (0.45- 1.96)           |
| Vomiting        | 7 ( 0.7)    | 20 ( 1.0)   | 27 ( 0.9)        | 1 (0.1)          | 12.2 (1.66- 89.5)              | 0.75 (0.32- 1.78)           |

The risk ratio for vomiting is significantly high (ratio=12.2), therefore I examined this event more closely. Among subjects dropping out because of vomiting, 29% (6/21) rated the intensity of vomiting as severe. Four discontinuations for vomiting came from one study, 28718, a phase I trial. All four subjects were receiving 80mg at the time, the

highest intended dose. While vomiting led to discontinuation of 27 gepirone subjects, it was reported as a serious adverse event for only a single subject (Appendix J.9, original ISS). No cases of ruptured esophagus were reported.

No discontinuations were due to renal failure, hepatic failure, liver injury or hematologic dyscrasias.

### 2.4.9.2 Combined BMS and Organon data for gepirone ER

In the combined BMS and Organon data (all phase II/III depression trials), the number who withdrew due to adverse experiences were 114 out of 849 (13.4%) for gepirone ER and 116 out of 1556 (7.5%) for all<sup>3</sup> placebo. (Appendix C.29A, updated ISS). I summarized in FDA table (16) adverse events leading to dropout where the incidence is 1% or more and the risk in the gepirone group is twice or more the risk in the placebo group. No discontinuations were due to renal failure, hepatic failure, or hematologic dyscrasias.

FDA table (16): Summary of adverse events [N (%)] leading to dropout in the combined data (Organon + BMS) where the incidence is 1% or more and the risk in the gepirone ER group was twice or more the risk in the placebo group (Source: Appendix C.29A, updated ISS).

| COSTART Preferred Term* | Treatment Group       |                    | Risk Ratio (C.I.)#   |
|-------------------------|-----------------------|--------------------|----------------------|
|                         | Gepirone ER<br>N= 849 | Placebo<br>N= 1556 |                      |
| NAUSEA                  | 22 ( 2.6%)            | 12 ( 0.8%)         | 3.423 (1.685, 6.951) |
| DI ZZI NESS             | 19 ( 2.2%)            | 5 ( 0.3%)          | 7.101 (2.642, 19.09) |
| NERVOUSNESS             | 19 ( 2.2%)            | 10 ( 0.6%)         | 3.539 (1.638, 7.646) |
| DEPRESSI ON             | 13 ( 1.5%)            | 6 ( 0.4%)          | 4.017 (1.521, 10.61) |
| I NSOMNI A              | 13 ( 1.5%)            | 11 ( 0.7%)         | 2.184 (0.974, 4.897) |
| ANXI ETY                | 11 ( 1.3%)            | 7 ( 0.4%)          | 2.905 (1.122, 7.521) |

# Relative risk and 95% confidence intervals for gepirone ER versus Placebo.

It is worthy to note that the dropout data presented in the table are based on the short-term trials (of less than or equal 63 days) and do not reflect the long-term causes of dropout.

### 2.4.9.3 Four-month safety update

One hundred fifteen subjects reportedly dropped out due to an AE in nine ongoing trials. The sponsor can not calculate the discontinuation rates from the data provided at this point because some of the trials are still blinded. The profile of adverse events is similar to what is reported in the other parts of the ISS. One subject (# (b) (6)) in study number 28709 had “severe pancytopenia”. However, no other relevant information is available and the treatment assignment of the subject is unknown because of blinding.

### 2.4.9.4 Data provided from sponsor upon request

See Section 2.4.8.4 for explanation of data source.

In the following sections, I used the sponsor’s tables that pooled the short (<=63 days) and long (>63 days) term data.

<sup>3</sup> regardless of indication

#### 2.4.9.4.1 Gepirone IR formulation

I summarized in the FDA table (17) AEs leading to drop out in phase II/III controlled depression trials of gepirone IR formulation where the incidence is 1% or more and the risk in the gepirone group is twice or more the risk in the placebo group. Note that the more frequent AEs are largely the same as the ones reported in the original submission except that the RR are notably higher for most of the AEs, especially dizziness. In this comparison, risk of vomiting is not markedly greater among gepirone IR subjects compared to placebo.

FDA table (17): Number of subjects with AEs leading to drop out in phase II/III controlled depression trials of gepirone IR formulation - short-term phase and long-term phase combined (source table C2, submission 11/13/2001).

|                                     | GepironeIR<br>N (%) | Placebo<br>N (%) | Risk Ratio (95% CI)<br>GepironeIR vs. Placebo |
|-------------------------------------|---------------------|------------------|-----------------------------------------------|
| Total Number of Subjects            | 737                 | 511              |                                               |
| Subjects Discontinued Due To Any AE | 168(22.8)           | 44( 8.6)         | 2.65 (1.94-3.62)                              |
| Dizziness                           | 42( 5.7)            | 1( 0.2)          | 29.1 (4.02- 211)                              |
| Nausea                              | 38( 5.2)            | 4( 0.8)          | 6.59 (2.37-18.3)                              |
| Headache                            | 23( 3.1)            | 4( 0.8)          | 3.99 (1.39-11.5)                              |
| Somnolence                          | 13( 1.8)            | 2( 0.4)          | 4.51 (1.02-19.9)                              |
| Abdominal pain                      | 10( 1.4)            | 2( 0.4)          | 3.47 (0.76-15.8)                              |
| Sweating                            | 8( 1.1)             | 1( 0.2)          | 5.55 (0.70-44.2)                              |
| Paresthesia                         | 8( 1.1)             | 1( 0.2)          | 5.55 (0.70-44.2)                              |
| Diarrhea                            | 8( 1.1)             | 0                |                                               |

#### 2.4.9.4.2 Gepirone ER formulation

I summarized in the FDA table (18) AEs leading to drop out in phase II/III controlled depression trials of gepirone ER formulation where the incidence is 1% or more and the risk in the gepirone group is twice or more the risk in the placebo group. Note that the more frequent AEs are largely the same as the ones reported in the original submission except that the RR are notably higher for most of the AEs. In this comparison, risk of vomiting is not markedly greater among gepirone ER subjects compared to placebo.

FDA table (18): Number of subjects with AEs leading to drop out, by descending frequency, in phase II/III controlled depression trials of gepirone ER formulation - short-term phase and long-term phase combined (source table F2, submission 11/13/2001).

|                                     | GepironeER<br>N (%) | Placebo<br>N (%) | Risk Ratio (95% CI)<br>GepironeER vs Placebo |
|-------------------------------------|---------------------|------------------|----------------------------------------------|
| Total Number of Subjects            | 731                 | 472              |                                              |
| Subjects Discontinued Due To Any AE | 118(16.1)           | 41 (8.7)         | 1.86(1.33-2.60)                              |

|             |          |         |                 |
|-------------|----------|---------|-----------------|
| Nausea      | 22( 3.0) | 3( 0.6) | 4.74(1.43-15.7) |
| Nervousness | 19( 2.6) | 3( 0.6) | 4.09(1.22-13.7) |
| Dizziness   | 17( 2.3) | 2( 0.4) | 5.49(1.27-23.6) |
| Headache    | 12( 1.6) | 3( 0.6) | 2.58(0.73-9.10) |
| Depression  | 11( 1.5) | 3( 0.6) | 2.37(0.66-8.44) |
| Anxiety     | 10( 1.4) | 2( 0.4) | 3.23(0.71-14.7) |

## 2.4.10 ADVERSE EVENT PROFILE IN GEPIRONE TRIALS

### 2.4.10.1 Single- and Multiple Dose Phase I Trials

The sponsor did not present the combined ER data for BMS and Organon in phase-I.

#### 2.4.10.1.1 BMS data

The data for single-dose trials are presented in Appendix C.2 (original ISS). In the following FDA table (19), I summarized the AEs where the incidence in the combined gepirone (ER &IR) group is 5% or more and the risk is twice or more the risk in the placebo group.

FDA table (19): Summary of adverse events by decreasing frequency in **Phase I** single-dose trials where the incidence is 5% or more and the risk in the gepirone group is twice or more the risk in the placebo group.

| Adverse Experience | Gep-ER<br>N(%) | Gep-IR<br>N(%) | RE+IR<br>N(%) | Placebo<br>N(%) | Gep vs PI<br>ratio(C.I.) |
|--------------------|----------------|----------------|---------------|-----------------|--------------------------|
| NUMBER OF PATIENTS | 139            | 67             | 206           | 18              |                          |
| DIZZINESS          | 7<br>( 5.0%)   | 40<br>(59.7%)  | 47<br>(22.8%) | 2<br>( 11.1%)   | 2.05<br>( 0.54, 7.77)    |
| NAUSEA             | 4<br>( 2.9%)   | 27<br>(40.3%)  | 31<br>(15.0%) | 1<br>( 5.6%)    | 2.71<br>( 0.39,18.70)    |
| SOMNOLENCE         | 2<br>( 1.4%)   | 20<br>(29.9%)  | 22<br>(10.7%) | 0<br>( 0.0%)    |                          |
| VASODILATATION     | 1<br>( 0.7%)   | 11<br>(16.4%)  | 12<br>( 5.8%) | 0<br>( 0.0%)    |                          |

The data for multiple-dose trials are presented in Appendix C.8 (original ISS). In the following FDA table (20), I summarized the AEs where the incidence in the combined gepirone (ER &IR) group is 5% or more and the risk is twice or more the risk in the placebo group.

FDA table (20): Summary of adverse events by decreasing frequency in **Phase I** multiple-dose trials where the incidence is 5% or more and the risk in the gepirone group is twice or more the risk in the placebo group.

| Adverse Experience | Gep-ER<br>N(%) | Gep-IR<br>N(%) | RE+IR<br>N(%)  | Placebo<br>N(%) | Gep vs PI<br>ratio(C.I.) |
|--------------------|----------------|----------------|----------------|-----------------|--------------------------|
| NUMBER OF PATIENTS | 182            | 137            | 319            | 48              |                          |
| DIZZINESS          | 65<br>(35.7%)  | 60<br>(43.8%)  | 125<br>(39.2%) | 4<br>( 8.3%)    | 4.70<br>( 1.82,12.14)    |
| NAUSEA             | 22             | 32             | 54             | 3               | 2.71                     |

(12.1%) (23.4%) (16.9%) (6.3%) (0.88, 8.32)

### 2.4.10.1.2 Organon data

Dizziness (48.6%), headache (35.1%), somnolence (27%), nausea (25.7%), vomiting (17.6%), asthenia (16.2%), and abdominal pain (12.2%) were the most frequently reported adverse experiences in subjects receiving single 40 and 80 mg doses of gepirone ER in the two single dose Phase I trials, 28708 and 28718 (sponsor's table 8, page 43, updated ISS). Vomiting was rated as severe in 11 of 13 subjects (84.6%) reporting the event in these trials. Otherwise, the majority of adverse events were either mild or moderate in severity. It is not clear if the rating of severity was based on the subject or on the physician opinion.

The AEs observed during Study 28717, an open, randomized, multiple dose, two-period crossover study investigating the potential interaction between ketoconazole and gepirone, are detailed in section "2.4.17.2 Drug-Drug Interactions".

### 2.4.10.2 All Phase II/III Clinical Trials

#### 2.4.10.2.1 Organon data

In the following FDA table (21) I summarized adverse events that had a prevalence of at least 2% and twice the risk in the gepirone ER group in comparison to the placebo group (source: sponsor's table 10, page 47, updated ISS).

FDA table (21): Summary of adverse events [N (%)] by decreasing frequency in Phase III trials where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group. \*

| COSTART Preferred Term | Treatment Group       |                   | Risk Ratio (C.I.)§   |
|------------------------|-----------------------|-------------------|----------------------|
|                        | Gepirone ER<br>N= 212 | Placebo<br>N= 214 |                      |
| DI ZZI NESS            | 98 (46.2%)            | 23 (10.7%)        | 7.139 (4.287, 11.89) |
| NAUSEA                 | 60 (28.3%)            | 23 (10.7%)        | 3.278 (1.938, 5.546) |
| I NSOMNI A             | 38 (17.9%)            | 12 (5.6%)         | 3.676 (1.863, 7.256) |
| NERVOUSNESS            | 21 (9.9%)             | 8 (3.7%)          | 2.831 (1.225, 6.543) |
| PARESTHESI A           | 14 (6.6%)             | 6 (2.8%)          | 2.451 (0.924, 6.505) |
| ABDOMI NAL PAI N       | 12 (5.7%)             | 6 (2.8%)          | 2.080 (0.766, 5.648) |
| HYPERTENSI ON          | 9 (4.2%)              | 3 (1.4%)          | 3.118 (0.832, 11.68) |
| WEI GHT GAI N          | 8 (3.8%)              | 2 (0.9%)          | 4.157 (0.872, 19.81) |
| MI GRAI NE             | 7 (3.3%)              | 1 (0.5%)          | 7.273 (0.887, 59.63) |
| PALPI TATI ON          | 6 (2.8%)              | 2 (0.9%)          | 3.087 (0.616, 15.47) |
| ACNE                   | 5 (2.4%)              | 2 (0.9%)          | 2.560 (0.491, 13.34) |

\* Data are derived from Trials 134001 and 134002.

§ Relative risk and 95% confidence intervals for gepirone ER versus placebo.

#### 2.4.10.2.2 Combined BMS and Organon data

The sponsor pooled their phase II/III AEs data (Organon data) and BMS data for the ER formulation. The pooled population includes 849 subjects treated with gepirone ER and 1,556 subjects treated with placebo (sponsor's table 16, page 64, updated ISS). While the gepirone subjects are from depression trials, the placebo subjects are from the entire development program regardless of indication, which obscures interpretation of the sponsor's risk comparisons.

With the exception of headache (46.6% in BMS data and 29.2% in Organon data) and dizziness (29.0% in BMS data and 46.2% in Organon data), there are few substantive

differences between the two series for the incidence of adverse experiences. Therefore, pooling the gepirone data from both sources seems appropriate.

In the following FDA table (22), I summarized Appendix C.24.A. (updated ISS) to reflect the most common adverse experiences (incidence of 2% or more and RR of two or more) in the combined data with statistically significant risk ratios. Note that the adverse events reported in excess of 10% of all subjects receiving gepirone ER, include dizziness (33.3%), nausea (27.9%), and insomnia (20.7%).

FDA table (22): Summary of the combined (Organon + BMS data) adverse events [N (%)] where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group (source: Appendix C.24.A, updated ISS).

| COSTART Preferred Term           | Treatment Group       |                    | Risk Ratio (C.I.)#   |
|----------------------------------|-----------------------|--------------------|----------------------|
|                                  | Gepirone ER<br>N= 849 | Placebo<br>N= 1556 |                      |
| Subjects with Any Adverse Events | 762 (89.8%)           | 1226 (78.8%)       | 2.358 (1.831, 3.036) |
| DIZZINESS                        | 283 (33.3%)           | 191 (12.3%)        | 3.573 (2.902, 4.400) |
| NAUSEA                           | 237 (27.9%)           | 253 (16.3%)        | 1.994 (1.630, 2.440) |
| INSOMNIA                         | 176 (20.7%)           | 179 (11.5%)        | 2.012 (1.602, 2.526) |
| PARESTHESIA                      | 58 (6.8%)             | 45 (2.9%)          | 2.462 (1.652, 3.668) |
| VOMITING                         | 51 (6.0%)             | 48 (3.1%)          | 2.008 (1.341, 3.005) |
| PALPITATION                      | 41 (4.8%)             | 37 (2.4%)          | 2.083 (1.325, 3.275) |
| AGITATION                        | 34 (4.0%)             | 29 (1.9%)          | 2.197 (1.329, 3.631) |
| SINUSITIS                        | 26 (3.1%)             | 16 (1.0%)          | 3.041 (1.622, 5.701) |
| TREMOR                           | 23 (2.7%)             | 21 (1.3%)          | 2.035 (1.120, 3.700) |
| AMBLYOPIA                        | 21 (2.5%)             | 19 (1.2%)          | 2.052 (1.097, 3.838) |
| CONFUSION                        | 17 (2.0%)             | 11 (0.7%)          | 2.870 (1.338, 6.156) |
| HYPERTENSION                     | 17 (2.0%)             | 8 (0.5%)           | 3.954 (1.699, 9.200) |

# Relative risk and 95% confidence intervals for gepirone ER versus Placebo.

#### 2.4.10.2.2.1 Dizziness

Dizziness is one of the most common AEs in the gepirone development program, and is one of the most common AEs leading to dropout. In addition, in the combined ER data (Organon and BMS), dizziness was the second most common AE leading to dropout (risk ratio 7.10).

I examined dizziness more closely since it is a potentially significant risk especially if subjects are driving or operating heavy machinery while taking the drug. Cumulatively, in the Organon ER data (sponsor's table 17, page 68, updated ISS), 38% of subjects had their first occurrence of dizziness within the first 14 days and 50% within the first 28 days of initiating treatment. In the BMS data, the percentages are 34% and 42%, respectively (Appendix C.37 original ISS).

The BMS data from controlled phase II/III clinical trials (summarized in the FDA tables 23 & 24) suggest a dose-response relationship for dizziness (Appendices E.7 for gepirone ER & E.11 for gepirone IR, original ISS).

FDA table (23): Comparison of risk of dizziness across the modal dose of gepirone ER.

| Gepirone ER Daily Dose (mg) |               |               |              |                |                | Risk Ratios (C.I.)§  |                      |                      |                      |  |
|-----------------------------|---------------|---------------|--------------|----------------|----------------|----------------------|----------------------|----------------------|----------------------|--|
| <20                         | 20-39         | 40-80         | >80          | All#           | Placebo        | <20 v P              | 20-39 v P            | 40-80 v P            | >80 v P              |  |
| N=                          | N=            | N=            | N=           | N=             | N=             |                      |                      |                      |                      |  |
| 177                         | 151           | 256           | 19           | 603            | 1342           |                      |                      |                      |                      |  |
| 25<br>(14.1%)               | 36<br>(23.8%) | 95<br>(37.1%) | 6<br>(31.6%) | 162<br>(26.9%) | 155<br>(11.5%) | 1.22<br>(0.83, 1.81) | 2.06<br>(1.50, 2.85) | 3.21<br>(2.58, 3.99) | 2.73<br>(1.39, 5.39) |  |

§ Relative risk and 95% confidence intervals for gepirone ER versus Placebo.

FDA table (24): Comparison of risk of dizziness across the modal dose of gepirone IR.

| Gepirone IR Daily Dose (mg) |                |                |               |                |                | Risk Ratios (C.I.)§  |                      |                      |                      |
|-----------------------------|----------------|----------------|---------------|----------------|----------------|----------------------|----------------------|----------------------|----------------------|
| <20                         | 20-39          | 40-80          | >80           | All#           | Placebo        | <20 v P              | 20-39 v P            | 40-80 v P            | >80 v P              |
| N=                          | N=             | N=             | N=            | N=             | N=             |                      |                      |                      |                      |
| 965                         | 609            | 531            | 55            | 2160           | 1342           |                      |                      |                      |                      |
| 264<br>(27.4%)              | 255<br>(41.9%) | 264<br>(49.7%) | 27<br>(49.1%) | 810<br>(37.5%) | 155<br>(11.5%) | 2.37<br>(1.98, 2.84) | 3.63<br>(3.04, 4.32) | 4.30<br>(3.63, 5.11) | 4.25<br>(3.13, 5.78) |

§ Relative risk and 95% confidence intervals for gepirone ER versus Placebo.

A similar trend was observed for doses up to 60 mg in the Organon data (Appendix E.3, updated ISS).

FDA table (25): Comparison of risk of dizziness across the modal dose of gepirone ER.\*

| Gepirone ER Daily Dose (mg) |               |               |               |               |               | Risk Ratios (C.I.)§ |                        |                        |                        |
|-----------------------------|---------------|---------------|---------------|---------------|---------------|---------------------|------------------------|------------------------|------------------------|
| 20                          | 40            | 60            | 80            | All#          | Placebo       | 20 v P              | 40 v P                 | 60 v P                 | 80 v P                 |
| N=7                         | N=42          | N=47          | N=116         | N=212         | N=214         |                     |                        |                        |                        |
| 0<br>(0.0%)                 | 19<br>(45.2%) | 29<br>(61.7%) | 50<br>(43.1%) | 98<br>(46.2%) | 23<br>(10.7%) | N/A                 | 6.860<br>(3.254,14.46) | 13.38<br>(6.447,27.77) | 6.291<br>(3.566,11.10) |

\* Data are derived from Studies 134001 and 134002.

§ Relative risk and 95% confidence intervals for gepirone ER versus Placebo.

For the gepirone ER studies, patients attaining a modal dose of 80 mg tended to have slightly lower incidences of dizziness. Since patients were titrated to the highest tolerated dose, the lower risk of dizziness at the modal dose of 80 mg may reflect a lack of susceptibility to dizziness in patients reaching that dose (i.e., those patients that were susceptible to gepirone-induced dizziness never made it to 80 mg).

Additionally, severity of the dizziness in both the combined gepirone ER & IR group and the ER only group showed a statistically significant increase in frequency associated with increasing dose. It is important to note in this context that no studies randomized subjects to fixed dose, instead these results are based on analyses using the modal daily dose, which represents the daily dose most frequently prescribed for subjects in the clinical trials.

Examining the “dizziness” events showed that the investigators used the verbatim term “dizziness” (almost 50% of the AEs coded as dizziness) or “lightheadedness” (almost 50% of the AEs coded as dizziness) with no other details provided that would allow one to determine the etiology of these events.

Orthostatic changes were objectively assessed in the Organon data but not the BMS data. Please refer to the section “2.3.22. VITAL SIGNS” for the results of this assessment.

The sponsor presented a evaluation of postural hypotension (sponsor’s table 34, p 132, original ISS) and syncope AEs (sponsor’s table 35, p 134, original ISS) using BMS data and there were no marked differences in risk between treatment groups. The incidence of reported postural hypotension AEs in the combined (IR and ER) gepirone treatment group was [0.3%, (8/2496)] compared favorably with the incidence in the placebo treatment group [0.4%, (5/1342)]. However, postural hypotension AEs are based on subject/physician report in the CRF and may not be corroborated with vital sign data. Postural hypotension was not considered serious in any subject. Only one subject (# (b) (6)) discontinued because of severe orthostatic effects.

The overall incidence of syncope in the combined (IR and ER) gepirone treatment group [0.4%, (10/2496)] was slightly higher than the incidence in the placebo group [0.3%, (4/1342)]. The incidence in the gepirone ER treatment group [0.6%, (4/637)] was twice as high as that in the gepirone IR treatment group [0.3%, (6/1859)]. Three cases of syncope were considered serious, two in the ER group (# (b) (6) ) and one in the IR group (# (b) (6) ); two of these subjects, one in each of the two treatment groups discontinued from therapy due to the syncope. Upon examining Appendix J.3 (original ISS), which lists all AEs by study and subject, no AEs suggesting postural hypotension were listed for subjects # (b) (6) . Subject # (b) (6) had an episode of dizziness ten days before the syncope. Orthostatic effects of the drug were not objectively evaluated in these subjects (as they were part of the BMS program).

#### 2.4.10.2.2 Accidental injury

In the combined Organon and BMS data, the risk of accidental injury in the gepirone ER group is almost twice the placebo group (30/849 [3.5%] & 30/1556 [1.9%], respectively, ratio=1.86, 1.115-3.113). I was concerned about the potential relationship between accidental injury and dizziness, which is one of the most common adverse events. Examining the reported AEs did not reveal any pattern of specific type or cluster of injury. I further used the sponsor's data sets (AESPIII & AES\_OLD) to examine the risk of accidental injury among those suffering from dizziness, which was not different between various groups (2.75% [8/291], 1.96% [16/816], and 3.50% [7/200] in the gepirone ER, gepirone IR, and placebo groups, respectively).

Although dizziness did not appear in the list of serious AEs, accidental injury did (refer to FDA table 12; gepirone [ER+IR] 0.2% vs. placebo 0.1%). The data in Appendix J.9 (original ISS) detailing the serious accidental injury AEs showed that 4/5 in the gepirone group were injured in motor vehicle accidents compared to the one subject in the placebo group. In no case did the sponsor indicate whether the victim was a driver or a passenger.

#### 2.4.10.2.3 Sexual dysfunction

Sponsor's data (table 22, page 83, updated ISS) show that the incidence of sexual dysfunction for subjects taking gepirone ER was rare and not different from placebo (see table below).

FDA Table (25-A): Frequency of AEs related to sexual dysfunction in gepirone ER trials

| Adverse Event            | Combined ER (N=849) | Combined Placebo (N=1556) |
|--------------------------|---------------------|---------------------------|
| Libido decreased         | 7 (0.8%)            | 15 (1.0%)                 |
| Impotence                | 1 (0.1%)            | 6 (0.4%)                  |
| Libido increased         | 1 (0.1%)            | 0 (0.0%)                  |
| Sexual function abnormal | 1 (0.1%)            | 3 (0.2%)                  |
| Abnormal ejaculation     | 0 (0.0%)            | 1 (0.1%)                  |

#### 2.4.10.2.3 Long term adverse experience (> 63 days)

The number of subjects included in the analysis of adverse experiences in the long-term phase is small compared to the number of subjects available in the short-term phase. Note that patients were maintained on their original double-blind randomized treatment in the long-term phase. In all Phase II/III Trials, 1456 of the 2496 (58%) subjects that began treatment with one of the gepirone formulations completed the short-term phase. Seven hundred seventy-six of these subjects entered a long-term phase with 122 (16%) subjects completing the study. In comparison, 827 of the 1308 (63%) placebo subjects completed a short-term phase. Of the 371 subjects treated with placebo who continued long-term treatment, 46 (12%) completed this phase of the studies.

Only 0.5 to 2.70% of the subjects in long-term extensions experienced their first adverse experience of any kind in the long-term extension phases compared to 79 to 90% who experienced their first adverse experience of any kind in the short-term phase. There was no statistically significant increased risk of experiencing any individual adverse experience during long-term treatment with gepirone compared to placebo. (sponsor's table 65, p 264, original ISS). The comparison between long and short term events (sponsor's table 65, p 264, original ISS) shows that many of the common events are more likely to occur on the short term compared to the long term.

I examined Appendix I.3 (original ISS) and the unusual or potentially serious AEs associated with gepirone treatment reported in the long-term phase that were not reported in the short-term phase are one case each (0.1%) of a vestibular disorder and a breast carcinoma.

**2.4.10.2.4 Data provided from sponsor upon request**

See Section 2.4.8.4 for explanation of data source.

In the following sections, I used the sponsor's tables that pooled the short (<=63 days) and long (>63 days) term data.

*2.4.10.2.4.1 Gepirone IR formulation*

I summarized in the FDA table (26) AEs in phase II/III controlled depression trials of gepirone IR formulation where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group. Note that the more frequent AEs are largely the same as the ones reported in the original submission. In this comparison, accidental injury risk is not markedly greater among gepirone IR subjects compared to placebo.

FDA table (26): Number of subjects with AEs in phase II/III controlled depression trials of gepirone IR formulation (short-term phase and long-term phase combined) where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group (source table 3A, submission 11/13/2001).

|                                | GepironeIR<br>N (%) | Placebo<br>N (%) | Risk Ratio (95% CI)<br>GepironeIR vs. Placebo |
|--------------------------------|---------------------|------------------|-----------------------------------------------|
| Total number of subjects       | 737                 | 511              |                                               |
| Number of subjects with any AE | 655(88.9)           | 413(80.8)        | 1.10(1.05-1.16)                               |
| Dizziness                      | 337(45.7)           | 56(11.0)         | 4.17(3.22-5.41)                               |
| Paresthesia                    | 67( 9.1)            | 13( 2.5)         | 3.57(1.99-6.40)                               |

|                   |          |          |                 |
|-------------------|----------|----------|-----------------|
| Tinnitus          | 49( 6.6) | 12( 2.3) | 2.83(1.52-5.27) |
| Anxiety           | 35( 4.7) | 12( 2.3) | 2.02(1.06-3.86) |
| Sweating          | 33( 4.5) | 10( 2.0) | 2.29(1.14-4.60) |
| Thinking abnormal | 28( 3.8) | 6( 1.2)  | 3.24(1.35-7.76) |
| Agitation         | 24( 3.3) | 5( 1.0)  | 3.33(1.28-8.66) |
| Amblyopia         | 21( 2.8) | 6( 1.2)  | 2.43(0.99-5.97) |
| Confusion         | 15( 2.0) | 2( 0.4)  | 5.20(1.19-22.6) |

#### 2.4.10.2.4.2 Gepirone ER formulation

I summarized in the FDA table (27) AEs in phase II/III controlled depression trials of gepirone ER formulation where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group. Note that the more frequent AEs are largely the same as the ones reported in the original submission. In this comparison, accidental injury risk is not markedly greater among gepirone ER subjects compared to placebo.

FDA table (27): Number of subjects with AEs, by descending frequency, in phase II/III controlled depression trials of gepirone ER formulation (short-term phase and long-term phase combined) where the incidence is 2% or more and the risk in the gepirone group is twice or more the risk in the placebo group (source table 9A, submission 11/13/2001).

|                                | GepironeER<br>N (%) | Placebo<br>N (%) | Risk Ratio (95% CI)<br>GepironeER vs. Placebo |
|--------------------------------|---------------------|------------------|-----------------------------------------------|
| Total number of subjects       | 731                 | 472              |                                               |
| Number of subjects with any AE | 653(89.3)           | 386(81.8)        | 1.09(1.04-1.15)                               |
| Dizziness                      | 249(34.1)           | 60(12.7)         | 2.68(2.07-3.46)                               |
| Palpitation                    | 37( 5.1)            | 10( 2.1)         | 2.39(1.20-4.76)                               |
| Chest pain                     | 25( 3.4)            | 8( 1.7)          | 2.02(0.92-4.44)                               |
| Sinusitis                      | 24( 3.3)            | 7( 1.5)          | 2.21(0.96-5.10)                               |
| Depression                     | 22( 3.0)            | 6( 1.3)          | 2.37(0.97-5.80)                               |
| Tremor                         | 21( 2.9)            | 5( 1.1)          | 2.71(1.03-7.14)                               |
| Fever                          | 20( 2.7)            | 6( 1.3)          | 2.15(0.87-5.32)                               |
| Vasodilatation                 | 19( 2.6)            | 5( 1.1)          | 2.45(0.92-6.53)                               |
| Hypertension                   | 17( 2.3)            | 4( 0.8)          | 2.74(0.93-8.11)                               |

### 2.4.11 CLINICAL CHEMISTRY

Evaluations of clinical laboratory parameters, including hematology, chemistry and urinalysis were performed periodically throughout both the short-term and long-term phases of the clinical trials and varied from trial to trial. It is not clear if a central laboratory was responsible for conducting the analyses.

The data in this section incorporate short-term and long-term safety of gepirone as reflected in the laboratory evaluations of subjects in the controlled phase II/III clinical trial population. The subjects continued into the long-term phases of these trials in the same treatment groups to which they were initially randomized.

The sponsor evaluated the mean change from baseline and identified subjects with clinically significant abnormalities. In general, the outlier criteria (Appendix D.1, original & updated ISS) seemed appropriate and are attached to in this review under the original name, "Appendix D1". The sponsor stated that these criteria were developed in conjunction with the FDA. It is worthy to note that protocols did not specify that subjects

fast prior to drawing of blood samples; hence, it is difficult to interpret the results of nutritionally sensitive parameters, e.g. glucose and triglycerides levels.

#### **2.4.11.1 BMS data**

##### **2.4.11.1.1 Analysis of Subjects with Clinically Significant Abnormalities**

Risk ratios and 95% confidence intervals are presented for clinical chemistry data in the sponsor's table 36 (original ISS). By-subject listings of all subjects who experienced clinically significant laboratory abnormalities are presented in Appendices J.10 & J.11 (original ISS). Clinically significant laboratory values are presented by subject and by treatment group in Appendix D.94 (original ISS).

In general, the number of subjects who experienced laboratory values that were considered clinically significant is small. The most frequently observed clinically significant change in a laboratory parameter was "total bilirubin" ( $\geq 1.5$  ULN equivalent to 1.5 mg/dL) occurring 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], sponsor's table 36, original ISS). A summary of all subjects who experienced clinically significant elevations in total bilirubin is presented in sponsor's table 39 (original ISS). Seven ER and 18 IR subjects had a post-baseline total bilirubin  $\geq 1.5$  ULN. The majority (21/25) of subjects in each treatment group experienced only single episodes of clinically significant increase in serum total bilirubin concentrations. The highest abnormal values were all in the IR group; 6 mg/dL (# [REDACTED] (b) (6)), this was the last measurement on record (Appendix J.10, original ISS) but other hepatic function tests were normal and outcome is unknown), 6.7 mg/dL (# [REDACTED] (b) (6)), subsequent measurement was normal [0.6 mg/dL] and other hepatic function tests were normal), and 7.10 mg/dL (# [REDACTED] (b) (6)), this was the last measurement on record but other hepatic function tests were normal and outcome is unknown). Five other subjects (5/25) had total bilirubin levels  $\geq 2$  mg/dL (measurements for patients # [REDACTED] (b) (6) are the last one on record. Measurements for patients # [REDACTED] (b) (6) were subsequently reduced), but serum transaminases were all normal for those subjects.

I examined the subject listings of lab values in Appendix J.10 to detect any pattern suggesting hepatic insult. The explanation for a higher risk of developing hyperbilirubinemia in the gepirone treatment groups is not readily apparent and it was not associated with clinically significant elevations in SGPT, SGOT, or alkaline phosphatase. For subjects with clinically significant elevations of total bilirubin, there was no apparent relationship between the extent of the elevation and gepirone dose.

##### **2.4.11.1.2 Analysis of Mean Change from Baseline**

There were no clinically meaningful statistical differences in the mean change from baseline between the combined gepirone and placebo treated groups in the levels of SGOT (Appendix D.3, original ISS), SGPT (Appendix D.8, original ISS), alkaline phosphatase (Appendix D.18, original ISS), total bilirubin (Appendix D.23, original ISS), and serum sodium (Appendix D.43, original ISS). The differences between the two formulations (IR and ER) were minimal.

Treatment with gepirone resulted in small statistically significant increases in mean and mean change from baseline values for creatinine (Appendix D.28, original ISS) at weeks 1 through 14, and at scattered points thereafter (range of change is 0.03 to 0.08 and – 0.03 to 0.01 in the gepirone and placebo groups, respectively). Only one subject in the gepirone IR treatment group had elevations in serum creatinine that reached the criteria for clinical significance (baseline value 1.6 mg/dL and abnormal value 2.0 mg/dL on days 23, 45, and 53). No diagnosis or work up results given.

Examination of the change of serum albumin (Appendix D.33, original ISS) from baseline revealed statistically significant decrease in the gepirone group compared to the placebo at weeks 20 (-0.26 g/dL, p 0.04) and 52 (-0.27 g/dL, p 0.008) time intervals that are not clinically significant. Only one subject ( (b) (6) ) in gepirone ER group (sponsor's table 41, page 155, original ISS) met the criteria for clinical significance (baseline value 4.9 g/dL and abnormal value 2.7 g/dL at day 44. However, patient continued in the study and serum albumin increased to 4.3 two months later).

Isolated statistically significant differences in change of serum potassium (Appendix D.48, original ISS) from baseline (p < 0.05) were detected between the gepirone and placebo groups at weeks 6, 10 and 38, but the magnitude of the difference is not clinically relevant.

#### **2.4.11.1.3 Analysis of Toxicity Grade Distribution**

The sponsor performed an analysis for each laboratory parameter that had a defined National Cancer Institute toxicity grade (NCI Common Toxicity Criteria, Version 2.0, January 30, 1998). The NCI toxicity grades are defined for each applicable laboratory parameter in Appendix D.1 (original ISS).

When the most severe value for each subject that occurred “anytime” during the trials was examined, the vast majority of values were Grade 1 or less, which represents the mildest abnormality, for SGOT (Appendix D.4, original ISS), SGPT (Appendix D.9, original ISS), alkaline phosphatase (Appendix D.19, original ISS), total bilirubin (Appendix D.24, original ISS), serum creatinine (Appendix D.29, original ISS), serum albumin (Appendix D.34, original ISS), and serum sodium (Appendix D.44, original ISS). None of the subjects had a measurement that met the criteria for Grade 4 during the treatment interval. When the measurements were examined over time intervals, there were no statistically or clinically meaningful significant overall differences due to treatment.

Although 98% of all serum potassium measurements were normal or categorized as Grade 1 (3 or 5.5 mEq/L), Grade 3 (2.5-<3 or > 6-7 mEq/L) or 4 (<2.5 or > 7 mEq/L) abnormality occurred in 7 and 2 subjects, respectively, in the gepirone treatment groups. However, there were no statistically significant differences overall or for any individual treatment group. Clinically significant changes in serum potassium was defined as <3 or > 6 mEq/L. Seven subjects in the gepirone IR group (three low [all 2.9 mEq/L] and four high [range 6.3-9.4 mEq/L]), and one subject in the gepirone ER (6.2 mEq/L) group had a clinically significant change in serum potassium. Data for all subjects represent single occurrences and there was no correlation with increased serum creatinine. Serum potassium levels subsequently became normal except for patients # (b) (6) (2.9 mEq/L), (b) (6) (2.9 mEq/L), and (b) (6) (8.7 mEq/L, no associated serious adverse event reported) where their measurements were the last one on record.

#### 2.4.11.1.4 Analysis of the Relationship between the Gepirone Dose, Formulation, and Mean Change From Baseline

The sponsor conducted another analysis to explore the relationship between dose, formulation, and change from baseline using a two-way analysis of variance. There was no consistent relationship between the gepirone dose or formulation and change from baseline in SGOT (Appendix D.5, original ISS), SGPT (Appendix D.10, original ISS), alkaline phosphatase (Appendix D20, original ISS), total bilirubin (Appendix D.25, original ISS), serum sodium (Appendix D.45, original ISS), and potassium (Appendix D.50, original ISS).

Mean change from baseline in serum creatinine (Appendix D.30, original ISS) appeared be associated with the dose of gepirone, and generally tended toward larger changes at higher doses with a maximum change at endpoint of +0.14 mg/dL for the > 80 mg dose group (FDA table 28). However, only one subject in the gepirone IR treatment group had elevations in serum creatinine that reached the criteria for clinical significance (described above in section 2.4.11.2.2 ).

FDA table (28): Comparison of mean change from baseline to the endpoint in serum creatinine (mg/dl) by dose and formulation over time in all controlled phase II/III trials.

|       | Modal Dose (mg)            |                            |                            |                            | P-Values                     |        |        |
|-------|----------------------------|----------------------------|----------------------------|----------------------------|------------------------------|--------|--------|
|       | Gep: 0-19                  | Gep: 20-39                 | Gep: 40-80                 | Gep: > 80                  | Dose Formulation Interaction |        |        |
| ER    | 0.02 (+/- 0.01)<br>(N=146) | 0.03 (+/- 0.01)<br>(N=126) | 0.06 (+/- 0.01)<br>(N=233) | 0.14 (+/- 0.04)<br>(N= 16) | 0.0001                       | 0.4399 | 0.4352 |
| IR    | 0.03 (+/- 0.01)<br>(N=582) | 0.04 (+/- 0.01)<br>(N=413) | 0.05 (+/- 0.01)<br>(N=267) | 0.10 (+/- 0.02)<br>(N= 36) |                              |        |        |
| ER+IR | 0.03 (+/- 0.01)<br>(N=728) | 0.03 (+/- 0.01)<br>(N=539) | 0.06 (+/- 0.01)<br>(N=500) | 0.12 (+/- 0.02)<br>(N= 52) |                              |        |        |

Analysis of levels of serum albumin (Appendix D.35, original ISS) revealed that only one subject in gepirone ER group (sponsor’s table 41, page 155, original ISS) met the criteria for clinical significance (described above in section 2.4.11.2.2).

#### 2.4.11.2 Organon data

The criteria for clinically significant clinical laboratory abnormalities were reportedly developed in conjunction with the FDA and are presented in Appendix D.1 (updated ISS).

Separate tables of risk ratios and 95% confidence intervals are presented for clinical chemistry data (sponsor’s table 23, updated ISS) and hematology data (sponsor’s table 25, updated ISS). By-subject listings of all subjects who experienced clinically significant laboratory abnormalities are presented in Appendices I.10 through I.12 (updated ISS). There is no substantial difference between gepirone treated groups and placebo in any of the evaluated parameters.

One subject (Subject (b) (6) treated with a modal daily dose of 40 mg

Org 33062 ER) exhibited clinically significant values for both ALT and AST. At baseline, this subject had values for both ALT and AST (68 and 75 U/L, respectively) that were approximately two times the upper limit of normal; at endpoint (Day 14), ALT (476 U/L) and AST (200 U/L) were approximately 13 times and 5 times the upper limit of normal, respectively; no other tests of liver function were abnormal at that time. The subject's highest bilirubin was at baseline (0.6 mg/dL). At a follow-up visit conducted approximately 2 weeks later, off drug, the subject's ALT and AST values were normal (21 and 23 U/L, respectively), and a hepatitis screen was negative. The presence of abnormal liver function tests at baseline suggests that elevation of the subject's ALT and AST values could have been due to a pre-existing condition. This subject discontinued study drug due to nausea two days before her abnormal liver function tests were detected.

## 2.4.12 HEMATOLOGY

Hematology parameters measured included hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, absolute eosinophil count, platelet count, red blood cell count, and white blood cell count. Hematology parameters were evaluated at baseline and periodically until the final study visit.

### 2.4.12.1 BMS data

Results reported in Appendix D.124 (original ISS) indicate that there were no consistent differences between the combined gepirone and placebo groups regarding the number of subjects with clinically significant abnormalities in hematology parameters.

Although the combined gepirone risk was not statistically different from placebo (1.4% [26/1849] vs. 1.2% [14/1176]), the risk of observing a clinically significant decrease in absolute neutrophil count (ANC <  $1.5 \times 10^3/\text{mm}^3$ ) was significantly greater (risk ratio 2.93, 1.70-5.02) in the gepirone ER treatment (14/527, 2.7%) group than in the gepirone IR (12/1322, 0.9%) treatment group. In addition, although not statistically significant (risk ratio 2.51, 0.63-10.0), the risk of observing a clinically significant decrease in hemoglobin was greater in the gepirone ER treatment (2/527, 0.4%) group than in the gepirone IR (2/1322, 0.2%) treatment group. This raises concerns about pooling these data from the two formulations. The sponsor did not provide a direct comparison between each of the ER and IR formulation and its own placebo (sponsor's table 46, page 173, original ISS).

I reviewed the details of subjects with clinically significant abnormalities in Appendix J.12 (original ISS) and sponsor's table 49 (page 180, original ISS). The Appendix presented data about hemoglobin, total WBC, ANC, lymphocyte count, eosinophil count and platelets. I summarized in FDA table (29) subjects that were normal at baseline and developed clinically significant reduction in the absolute neutrophil counts. No subject had ANC less than 500. The data in Appendix J.12 (original ISS) showed that five subjects (all in gepirone IR group) had another hematologic cell line with clinically significant change in addition to the ANC. No subjects on placebo had a comparable combination of reductions in more than one hematologic parameter. The sponsor stated that "there was no indication for any subject as to the etiology for the reduction in ANC." The severity of the decrease in neutrophil counts does not seem to be related to dose. Patients number [REDACTED] <sup>(b) (6)</sup> discontinued because of the AE.

FDA table (29): Summary of subjects treated with gepirone who developed clinically significant change in absolute neutrophil counts ( $<1.5 \times 10^3/\text{mm}^3$ ).

| Subject No.               | Modal Dose (mg/d) | Baseline Value | Day | Abnormal Value(s) | Severity Grade | Other Decrease |
|---------------------------|-------------------|----------------|-----|-------------------|----------------|----------------|
| <b><u>Gepirone ER</u></b> |                   |                |     |                   |                |                |
| (b) (6)                   | 60                | 2.100          | 20  | 1.100             | 2              |                |
|                           | 60                | 9.600          | 23  | 0.800             | 3              |                |
|                           | 40                | 3.919          | 55  | 1.310             | 2              |                |
|                           | 40                | 2.401          | 31  | 1.300             | 2              |                |
|                           |                   |                | 43  | 1.294             | 2              |                |
|                           |                   |                | 57  | 1.489             | 2              |                |
|                           |                   |                | 64  | 1.414             | 2              |                |
|                           | 2                 | 3.869          | 22  | 1.388             | 2              |                |
|                           | 20                | 2.038          | 21  | 1.180             | 2              |                |
|                           |                   |                | 42  | 1.492             | 2              |                |
|                           |                   |                | 56  | 0.678             | 3              |                |
|                           | 20                | 1.962          | 21  | 1.404             | 2              |                |
|                           | 20                | 4.328          | 22  | 1.405             | 2              |                |
|                           | 20                | 5.016          | 29  | 1.428             | 2              |                |
|                           | 30                | 2.200          | 99  | 0.80              | 3              |                |
|                           | 80                | 4.000          | 22  | 1.400             | 2              |                |
|                           | 30                | 4.200          | 22  | 1.300             | 2              |                |
|                           |                   |                | 43  | 1.300             | 2              |                |
|                           | 40                | 2.200          | 23  | 0.900             | 3              |                |
|                           |                   |                | 29  | 1.300.            | 2              |                |
|                           |                   |                | 43  | 1.200             | 2              |                |
|                           | 100               | 4.500          | 41  | 1.300             | 2              |                |
| <b><u>Gepirone IR</u></b> |                   |                |     |                   |                |                |
| (b) (6)                   | 30                | 2.346          | 57  | 1.272             | 2              |                |
|                           | 20                | 3.589          | 153 | 1.331             | 2              | L 0.56         |
|                           | 8                 | 2.168          | 15  | 1.286             | 2              | W 2.89         |
|                           | 10                | 3.504          | 387 | 0.729             | 3              | W 2.19         |
|                           | 60                | 3.59           | 44  | 1.30              | 2              | W 2.70         |
|                           | 30                | 4.69           | 18  | 1.40              | 2              | W 2.80         |
|                           | 10                | 2.592          | 25  | 1.196             | 2              |                |
|                           | 30                | 2.230          | 15  | 1.462             | 2              |                |
|                           | 30                | 1.872          | 22  | 1.485             | 2              |                |
|                           | 30                | 2.288          | 22  | 1.364             | 2              |                |
|                           | 20                | 3.520          | 12  | 1.320             | 2              |                |
|                           | 60                | 1.755          | 60  | 1.150             | 2              |                |
|                           | 10                | 1.788          | 133 | 1.390             | 2              |                |
|                           | 25                | 2.652          | 43  | 1.369             | 2              |                |

L = lymphocyte count (x1000/ul)

W = total WBC (x1000/ul)

D = patient discontinued (not always due to hematologic AE)

S = patient had serious AE

\* Not clear if subjects are from controlled trials, source Appendix J.12.

Regarding absolute lymphocyte count (ALC), although not significantly different from placebo, expression of the data as mean change from baseline revealed statistically significant differences ( $p < 0.05$ ) between the IR & ER formulations at Weeks 2, 6, 7, 9, and 26 due to minor but larger decreases in ALC in the gepirone ER group over the treatment interval (Appendix D.111).

Data in Appendix D.112 (original ISS) show that there was a tendency toward a slight yet statistically significant effect of gepirone modal dose on mean change from baseline for ALC. However, after having closer examination of subjects with clinically significant values (Appendix J.12, original ISS), most of the clinically significant decreases were observed on only a single occasion and generally was the only one of the hematologic

parameters measured that showed a clinically significant decrease. No diagnosis, events related to low ALC, or further work up were reported for these subjects. No information was provided regarding whether these subjects improved on treatment or were discontinued.

For subjects treated with gepirone, there was no relationship between dose and the severity of the clinically significant value.

#### **2.4.12.2 Organon data**

Results reported in Appendix D.14 (updated ISS) indicate that there were no statistically significant or clinically meaningful differences between the gepirone and the placebo groups for changes in hematology parameters during the conduct of the two Phase III clinical trials. The short duration and small number of subjects in this program precludes our ability to estimate the rate of more rare and potentially delayed adverse effects. Definitions of clinically significant laboratory values are found in Appendix D.1 (updated ISS).

#### **2.4.13 URINALYSIS**

The only quantitative urinalysis parameter measured in these trials for which there is a criterion for clinically abnormal values is urine pH.

##### **2.4.13.1 BMS data**

Data were collected on abnormalities in urine protein, glucose, ketones, and blood, specific gravity and pH. Appendix D.138 (original ISS) which report the proportion of subjects with a clinically significant change in urinalysis shows no statistical difference between the combined gepirone and the placebo groups.

##### **2.4.13.2 Organon data**

Results reported in Appendix D.17 (updated ISS) indicate that there were no clinically or statistically significant differences in urinary pH between subjects treated with gepirone ER and placebo

#### **2.4.14 VITAL SIGNS**

This section examines these data for subjects in the controlled phase II/III trial population.

##### **2.4.14.1 BMS data**

Pulse rate and systolic and diastolic blood pressure measurements were collected at each scheduled clinic visit.

Definitions of criteria for determining clinically significant changes in vital signs may be found in Appendix H.17 (original ISS). Because of the small numbers of subjects in each treatment group that demonstrated clinically significant changes in vital sign parameters,

the confidence intervals for the risk ratios are sometimes wide and all included 1.0 in the interval. I reviewed Appendix J.13 (original ISS) that lists vital signs data for subjects with clinically significant abnormalities. Most abnormalities occurred in a single occasion. The clinical importance, if any, of these observations is difficult to determine because of the low incidence rates observed for these parameters in all treatment groups.

Although data were collected in supine, sitting and standing, the sponsor, in discussing vital signs, focused only on pulse rates and blood pressures collected in the sitting position. There were no consistent effects of gepirone throughout the conduct of the clinical trials on mean change from baseline in pulse rate, blood pressure or body temperature.

No orthostatic changes were described as the necessary data were not collected.

#### **2.4.14.2 Organon data**

Heart rate and blood pressure were measured at each assessment visit and included an assessment of orthostatic change by measuring those parameters after the subject was supine for five minutes, and also 1 to 2 and 3 to 4 minutes after the subject arose to a standing position.

##### **2.4.14.2.1 Supine and Standing Changes**

Examination of the data of supine and standing heart rate and blood pressure does not reveal any consistent statistically or clinically significant differences between treatment groups for mean or mean change from baseline at any of the scheduled visits.

##### **2.4.14.2.2 Orthostatic Changes**

The orthostatic change was determined by calculating the standing blood pressure minus the supine blood pressure.

It is worthy to note that dizziness is one of the most common adverse events occurring with gepirone treatment. Therefore, it was important to assess the clinically significant decreases in diastolic blood pressure that might result in dizziness and/or syncope in the development program. I summarized in FDA table (30) the nine subjects that experienced a clinically significant orthostatic change in diastolic blood pressure. The sponsor defined clinically significant change as a change of  $\geq 10$  mm Hg diastolic blood pressure sustained for three minutes. Of these nine subjects, eight were treated with gepirone ER, of which five had a modal dose of 80 mg, one had a modal dose of 60 mg, and two had a modal dose of 40 mg (Appendix H.17, updated ISS).

The sponsor did not provide the corresponding risk rates and statistical evaluation, so I calculated those using the denominators as the total number of subjects in the gepirone (8/212, 3.77%) and the placebo (1/214, 0.47) groups. The risk ratio is 8.08 with 95% CI 1.02-64.01, p-value=0.02 (Fisher exact test, Epi Info). While 98 (46.2%) of gepirone subjects had evidence of dizziness, only 3.77% had objective evidence of orthostatic changes. Additionally, in spite of the higher risk of orthostatic changes among the gepirone subjects, none of the subjects exhibited a diastolic blood pressure lower than 70 mm Hg.

FDA table (30): Identification of subjects with clinically significant orthostatic blood pressure changes by treatment group\* (Source: Appendix H.17, updated ISS).

| Subject No.       | Gender | Dose#<br>(mg/day) | Day | SBP/DBPS<br>Supine | Standing             |                      |
|-------------------|--------|-------------------|-----|--------------------|----------------------|----------------------|
|                   |        |                   |     |                    | SBP/DBPS<br>1 Minute | SBP/DBPS<br>3 Minute |
| Gepirone ER group |        |                   |     |                    |                      |                      |
| (b) (6)           | Male   | 80                | 20  | 110/ 84            | 106/ 70              | 110/ 70              |
|                   | Female | 80                | 27  | 100/ 88            | 112/ 74              | 110/ 72              |
|                   | Female | 60                | 54  | 135/ 90            | 128/ 80              | 110/ 80              |
|                   | Male   | 80                | 6   | 132/ 94            | 124/ 84              | 128/ 84              |
|                   | Male   | 80                | 55  | 160/100            | 130/100              | 140/ 96              |
|                   | Female | 80                | 54  | 110/ 90            | 100/ 70              | 110/ 80              |
|                   | Female | 40                | 26  | 110/ 80            | 110/ 70              | 106/ 70              |
|                   | Female | 40                | 54  | 140/ 90            | 138/ 80              | 128/ 80              |
|                   | Male   | 80                | 14  | 128/ 88            | 130/ 74              | 130/ 74              |
| Placebo group     |        |                   |     |                    |                      |                      |
| (b) (6)           | Male   | 0                 | 10  | 140/102            | 126/ 90              | 132/ 90              |

\* Data are derived from Trials 134001 and 134002.  
 # Modal dose taken throughout the treatment period.  
 § SBP=systolic blood pressure DBP=diastolic blood pressure.  
 \$ Definitions of clinically significant orthostatic changes: decrease  $\geq$  20 mmHg SBP or 10 mmHg DBP.

Only one subject (Subject (b) (6)) was found to have a clinically significant change in systolic blood pressure 1 to 2 minutes after standing at Week 8. This change was a clinically significant decrease to 88 mm Hg (Appendix H.14, updated ISS, systolic blood pressure at baseline 110 mm Hg). The sponsor defined clinically significant decrease in systolic blood pressure as systolic blood pressure < 90 mm Hg and decrease  $\geq$  20 mm Hg. The subject’s modal dose was 80 mg per day.

There were no subjects with clinically significant orthostatic changes in pulse rate. Mean pulse rate was increased by 1 to 6 beats per minute at both measurements over the 8-week study period.

### 2.4.15 ELECTROCARDIOGRAPHIC DATA

This section examines the ECG evaluations of subjects in the controlled phase II/III clinical trial population.

#### 2.4.15.1 BMS data

Electrocardiographic (ECG) evaluations were performed at periodic intervals throughout both the short-term and long-term phases of the clinical trials. The scheduled study visits at which these evaluations were performed varied from study to study. The subjects continued into the long-term phases of these trials in the same treatment groups to which they were initially randomized.

I summarized in the following FDA table (31) the clinically significant ECG changes where the risk is twice or more in the gepirone group compared to placebo (sponsor’s Table 54, p 198, original ISS). The clinical importance, if any, of these observations is difficult to determine because of the low incidence rates observed for these parameters in all treatment groups.

FDA table (31): Summary of the incidence of clinically significant changes in ECG parameters in all controlled phase II/ III trials.

| ECG Parameter       | ER<br>N(%) | IR<br>N(%) | Combined<br>N(%) | Placebo<br>N(%) | Risk Ratio<br>(95% C.I.) |
|---------------------|------------|------------|------------------|-----------------|--------------------------|
| Number of Patients* | 526        | 1367       | 1893             | 1186            |                          |

|                                   |          |           |           |          |                   |
|-----------------------------------|----------|-----------|-----------|----------|-------------------|
| Decreased Heart Rate <sup>1</sup> | 2 ( 0.4) | 13 ( 1.0) | 15 ( 0.8) | 4 ( 0.3) | 2.35 (1.08- 5.12) |
| Increased Heart Rate <sup>2</sup> | 0        | 3 ( 0.2)  | 3 ( 0.2)  | 0        |                   |
| PR Interval >= 240 msec           | 2 ( 0.4) | 11 ( 0.8) | 13 ( 0.7) | 4 ( 0.3) | 2.04 (0.92- 4.49) |
| Myocardial Infarction             | 1 ( 0.2) | 2 ( 0.1)  | 3 ( 0.2)  | 0        |                   |
| Myocardial Ischemia               | 0        | 1 ( 0.1)  | 1 ( 0.1)  | 0        |                   |
| 2 <sup>nd</sup> Degree AV Block   | 0        | 1 ( 0.1)  | 1 ( 0.1)  | 0        |                   |

\* The number of patients represents the number of patients with paired Baseline and any on treatment ECG results.

1 Decreased heart rate defined as < 50 **and** >= 15 bpm decrease from baseline

2 Increased heart rate defined as > 120 **and** >= 15 bpm increase from baseline

The criterion for “clinically significant” change in the QTc was defined in absolute terms, as increase from baseline in QTc interval to >= 480 msec. There was a slight excess of gepirone-treated patients who met this criterion as compared to placebo-treated patients (RR=1.35, CI 0.97-1.88, 2.8% [54/1893] vs. 2.1% [25/1186]) However, changes in QTc were not expressed as proportions of subjects with prolongation of >=30 msec and >=60 msec. Further analysis of the sponsor’s data is required to describe these proportions. Note that there were no PK studies to evaluate drug effect on QTc at Tmax.

There were no consistent effects of gepirone throughout the conduct of the clinical trials on mean change from baseline in heart rate, PR interval, QRS interval or QTc interval.

#### 2.4.15.2 Organon data

A 12-lead electrocardiogram (ECG) was obtained at baseline and at the end of treatment (or subject’s last visit in case of early termination). ECGs were recorded on and stored in ECG units provided by the central ECG recording company ( (b) (4) ) ECGs were transmitted on a daily basis to the central facility for archiving and later analysis by a computerized diagnostic system and review by a cardiologist.

Criteria for evaluation of ECG values for clinical significance are listed in Appendix H.1 (updated ISS). Data were collected for mean values and mean change from baseline for PR interval, QRS interval, QTc interval (QT interval corrected for heart rate using Bazett method, which is appropriate given that gepirone does not affect heart rate), QT interval, and ventricular rate. I summarized these data in FDA table (32).

FDA table (32): Comparison of mean change from baseline to endpoint for ECG parameters (in msec) and heart rate (in bpm) by treatment group.

|              | Org 33062 ER (n=172) |       |        |         |       | Placebo (n=186) |       |        |        |       | p-Value |
|--------------|----------------------|-------|--------|---------|-------|-----------------|-------|--------|--------|-------|---------|
|              | Mean                 | SE    | Median | Min     | Max   | Mean            | SE    | Median | Min    | Max   |         |
| PR interval  | 0.98                 | 0.875 | 0.00   | -24.00  | 42.00 | 0.10            | 0.847 | 0.00   | -36.00 | 36.00 | 0.4732  |
| QRS interval | -1.06                | 0.530 | 0.00   | -28.00  | 44.00 | 0.87            | 0.403 | 0.00   | -20.00 | 20.00 | 0.0041  |
| QTc interval | -0.70                | 1.368 | -2.00  | -62.00  | 55.00 | 1.23            | 1.218 | 2.00   | -47.00 | 46.00 | 0.2929  |
| QT interval  | -14.04               | 2.206 | -12.00 | -108.00 | 60.00 | -5.78           | 1.965 | -4.00  | -76.00 | 76.00 | 0.0055  |
| Heart rate   | 4.42                 | 0.744 | 3.00   | -16.00  | 29.00 | 2.59            | 0.811 | 3.00   | -41.00 | 29.00 | 0.0968  |

For the most part, the data showed that there were no clinically or statistically significant differences between the gepirone and placebo groups for change from baseline to endpoint (Appendix H.2, updated ISS) or in the proportion of subjects with clinically significant values (Appendix H.3, updated ISS).

The only statistically significant differences were in the mean change at endpoint for QRS and QT intervals. Mean change from baseline in the QRS interval was -1.06 (range -28 to 44) in the gepirone ER group and 0.87 (range -20 to 20) in the placebo group. Mean change from baseline in the QT interval was -14 (range -108 to 60) in the gepirone ER group and -5.78 (range -76 to 76) in the placebo group.

It is worthy to note that the criterion used by the sponsor for “clinically significant” change in the QTc was an absolute “increase from baseline in QTc interval to  $\geq 480$  msec”. Appendix H.2 (updated ISS) showed the range of change of QTc interval to be -62 to 55. However, the sponsor’s analysis did not include an analysis of outliers with a relative prolongation of QTc of  $\geq 30$  msec and  $\geq 60$  msec. Further analysis of the sponsor’s data is required to describe these proportions. Note that there were no PK studies to evaluate drug effect on QTc at Tmax.

## 2.4.16 BODY WEIGHT CHANGE

### 2.4.16.1 BMS data

Data in Appendix H.61 (original ISS) show the mean change in body weight compared to baseline in all treatment groups. Statistically significant differences ( $p = 0.0272$ ) were observed at weeks 1 (gepirone,  $0.21 \pm 0.04$  kg; placebo,  $0.06 \pm 0.04$  kg) and 20 (gepirone,  $0.05 \pm 0.21$  kg; placebo,  $0.86 \pm 0.21$  kg) indicating that there were no consistent time dependent effects on body weight compared to placebo.

Clinically significant changes in body weight are reported in the sponsor’s table 61 (page 222, original ISS). The risk of experiencing both clinically significant increases or decreases in body weight in the gepirone treatment group were not statistically significantly different from placebo (risk = 0.97 and 0.90, respectively).

### 2.4.16.2 Organon data

Data in Appendix H.19 (updated ISS) show the mean change in body weight compared to baseline in all treatment groups. At Weeks 1 through 4, 6 and 8 statistically significant differences ( $p < 0.005$ , all within one kilogram) were observed between treatment groups with a pattern of gaining weight in the gepirone ER group.

Clinically significant changes in body weight were defined as either increases or decreases in body weight that exceeded 7% of body weight at baseline. There were 8 subjects, 5 in the gepirone ER group ( $n=212$ ) and 3 in the placebo ( $n=214$ ) group, who experienced a clinically significant increase in body weight compared to baseline at one or more scheduled visits (risk ratio=1.68, 0.41-6.95). In the following FDA table (33) I summarized subjects with clinically significant body weight change (in kilograms) in the gepirone ER group.

FDA table (33): Subjects with clinically significant body weight changes (in kilograms) from baseline (increase of 7% from baseline) by in the gepirone ER group.

| Subject No. | Gender | Modal Dose (mg/day) | Abnormal Values(s) |     |                           |                              |
|-------------|--------|---------------------|--------------------|-----|---------------------------|------------------------------|
|             |        |                     | Baseline Value     | Day | Clin. Sig. Weight Value § | Percent Change From Baseline |
| (b) (6)     | Female | 80                  | 45.4               | 59  | 49.9                      | 9.91                         |
|             | Female | 60                  | 70.9               | 16  | 98.9                      | 39.49                        |
|             | Female | 80                  | 74.4               | 12  | 80.3                      | 7.93                         |
|             | Male   | 80                  | 122                | 55  | 130.2                     | 7.07                         |
|             | Male   | 80                  | 119                | 58  | 127.9                     | 7.84                         |

§ Clinically significant values reported at any time during the trials.

## 2.4.17 REVIEW OF SPECIAL STUDIES

### 2.4.17.1 Withdrawal phenomena/abuse potential

The sponsor conducted one study (# 03A7A-002) with the IR formulation in depression subjects to examine the effect of withdrawal of gepirone.

This was a multicenter, two-phase study of the safety and efficacy of gepirone, in comparison with placebo, in the treatment of subjects with a major depressive disorder. The first phase consisted of a six-week, open-label, gepirone dose-titration period. The second phase consisted of a six-week, double blind, randomized, parallel-group period designed to allow comparison of the relapse rates between subjects who were continued on gepirone and subjects who were switched to placebo after having responded to gepirone in the open-label phase.

Subjects were allowed to titrate the dose of gepirone between 10 to 90 mg daily during the open-label phase to an optimal therapeutic response. When subjects were randomized to the double-blind phase of the trial, they were to start with the same dose (number of capsules/day) that they were taking at the end of the open-label phase. A total of 36 subjects were randomized to gepirone and 34 to placebo in the double-blind phase of the study. The only adverse symptom that may be associated with the abrupt withdrawal of gepirone is headache (gepirone 13.9% [5/36] vs. placebo 23.5% [8/34]). However, it is not clear in general how closely patients were monitored for withdrawal symptoms. Hence, other withdrawal-related symptoms may have not been detected.

In Organon-sponsored controlled trials in depression, the sponsor reports that there was no evidence of withdrawal effects in those subjects who did not continue treatment with gepirone ER compared to those who did not continue placebo. However, patients were only contacted at 7 and/or 30 days following last drug dose; this delayed follow-up period would not be a sensitive approach for detecting withdrawal symptoms.

### 2.4.17.2 Drug-Drug Interactions

Gepirone is primarily metabolized by CYP450-3A4. Interaction study (# 28717) results indicated that co-administration of a potent inhibitor of CYP450-3A4, ketoconazole, with gepirone ER in healthy volunteers resulted in marked inhibition of metabolism of gepirone ER. At the minimum efficacious dose of 40 mg/day, the inhibition of metabolism of gepirone ER resulted in some increase in the incidence and severity of dizziness, nausea, and vomiting. (sponsor's table 29, p 113, updated ISS). I summarized these findings in FDA table (34).

FDA table (34): Incidence [N (%)] of adverse experiences in drug interaction study of gepirone ER and Ketoconazole.

| Adverse experience | Treatment   |              |              |
|--------------------|-------------|--------------|--------------|
|                    | A<br>N = 24 | B1<br>N = 12 | B2<br>N = 12 |
| Dizziness          | 20 (83.3)   | 12 (100)     | 10 (83.3)    |
| Drowsiness         | 9 (37.5)    | 4 (33.3)     | 1 ( 8.3)     |
| Flatulence         | 8 (33.3)    | 0            | 1 ( 8.3)     |
| Headache           | 11 (45.8)   | 5 (41.7)     | 4 (33.3)     |

|                      |           |           |          |
|----------------------|-----------|-----------|----------|
| Nausea               | 16 (66.7) | 11 (91.7) | 7 (58.3) |
| Sensitivity to Light | 4 (16.7)  | 3 (25.0)  | 1 ( 8.3) |
| Stomach Pain         | 3 (12.5)  | 0         | 2 (16.7) |
| Tiredness            | 7 (29.2)  | 1 ( 8.3)  | 4 (33.3) |
| Vomiting             | 4 (16.7)  | 8 (66.7)  | 1 ( 8.3) |

A: 40 mg Org 33062 ER single dose and 5 consecutive doses of 40 mg gepirone ER once daily.

B1: 40 mg Org 33062 ER single dose and 200 mg ketoconazole b.i.d.

B2: 20 mg Org 33062 ER single dose and 200 mg ketoconazole b.i.d.

Dizziness was rated as severe in 14 of 23 subjects (60.9%) reporting the event in this trial (appendices C.3 and C.9, updated ISS). It is not clear if these “severe” events occurred in subjects taking gepirone alone or with concomitant ketoconazole.

The sponsor examined the concomitant medications database to assess the concomitant use of inhibitors of the hepatic drug metabolizing enzymes, CYP450-3A4 and CYP450-2D6 which are involved in the metabolism of gepirone. Of these inhibitors, the most frequently used concomitant medication used was erythromycin with an incidence of use of about 3% across all treatment groups. Based on comparing the two groups of subjects, the overall risk of experiencing any adverse experience or any individual adverse experience was reportedly unchanged in the presence or absence of erythromycin.

The sponsor also examined the concomitant medications database to identify subjects treated with drugs for chronic diseases such as hypertension and diabetes. This search revealed that subjects taking such cardiovascular drugs as B-blockers and ACE inhibitors amounted to only 1 to 3 % of the population. Concomitant use of antidiabetic agents was likewise limited to 1 to 1.5% of the population. Because of the low incidence of use of chronic drugs in this otherwise healthy population, the sponsor did not undertake an intensive analysis of drug-drug interactions.

### 2.4.17.3 Drug-demographic interaction

The number of subjects  $\geq 65$  years of age was quite small amounting to only 3.3% of subjects treated with gepirone and 2.7% in subjects treated with placebo. When exploratory analysis of these data was conducted, the only adverse experience that was markedly different numerically, but not statistically, was a 10-fold increase in the risk of insomnia in gepirone-treated subjects  $\geq 65$  years of age ([11/82], 13.4% gepirone vs [0/36] placebo, RR 10.25, CI 0.62-169.4, Appendix G.1 original ISS), compared to the smaller increase in risk in the younger group ([308/2414], 12.8% gepirone vs [108/1306], 8.3% placebo, RR 1.54, CI 1.25-1.90).

Analysis of treatment-related adverse experiences by gender and race revealed no statistically significant or remarkable differences.

### 2.4.18 DOSE-RESPONSE TRIALS

The gepirone trials summarized in the NDA had flexible-dosing designs and dose-response evaluation is difficult to interpret because of potential misclassification with respect to dose and lack of randomization to a fixed dose. The adverse events are potentially misclassified with respect to dose because the sponsor classified adverse events by the subject’s modal dose, which might not be the dose taken at the time of the

event. Misclassification biases towards the null, potentially reducing the ability to detect a drug effect. Additionally, when flexible dosing designs are used, subjects are not randomized with respect to dose, making comparisons of adverse event risks by dose problematic.

The data that I am presenting here concentrate on the modal daily dose that represents the daily dose most frequently prescribed for subjects in the clinical trials.

#### **2.4.18.1 Organon data**

Dose-response effects based on the modal dose are presented in Appendices E.3 and E.4 (updated ISS). Due to the variability of the data and the fact that relatively few subjects had the modal dose of 20 or 40 mg/day, it is difficult to find consistent dose-response relationships among the data.

#### **2.4.18.2 BMS data**

In this section comparison is made of the relative risk of experiencing any given gepirone treatment-related adverse event compared to placebo across gepirone dosage ranges of < 20, 20 – 39, 40 – 80, and > 80 mg/day. Note that the sponsor is focusing on the “treatment-related” adverse experiences. These are the ones judged by the investigators to be related to study medication. In general, the division believes that it is impossible for an investigator to make a determination as to the “relatedness” of an AE; therefore we will request an additional dose-response analysis of all treatment-emergent AEs..

##### **2.4.18.2.1 Controlled Phase II/III clinical trials**

###### *2.4.18.2.1.1 Combined Gepirone ER & IR*

Data on the risk for all **treatment-related** adverse experiences with an incidence  $\geq 5\%$  as a function of the modal daily dose are listed in Appendix E.11 (original ISS). Data on relative severity for these adverse experiences are in Appendix E.12 (original ISS).

Dizziness, nausea, paresthesia, headache, somnolence, insomnia and nervousness showed a dose-response relationship with a pattern of increase in the risk with increase in the dose compared to placebo. Only the severity of dizziness was overall significantly greater for gepirone than for placebo (overall p-value = 0.05).

###### *2.4.18.2.1.2 Gepirone ER*

Data on the relative risk for treatment-related adverse experience with an overall incidence  $\geq 5\%$  as a function of the modal daily dose are in Appendix E.7 (original ISS) and the distribution of severity by modal daily dose are in Appendix E.8 (original ISS).

Headache, dizziness, nausea, insomnia, nervousness, and constipation showed visually recognizable dose-response relationships. The severity of gepirone ER-related headache, dizziness, nausea, and insomnia is also related to dose (overall p-value = 0.001, 0.034, 0.026 & 0.028, respectively).

#### **2.4.18.2.2 Controlled Gepirone ER trials in depression**

Data on the risk of experiencing each treatment-related adverse experience with an incidence  $\geq 5\%$  as a function of the modal daily dose are in Appendix E.15 (original ISS). Data on the distribution of severity of these adverse experiences as a function of modal daily dose are in Appendix E.16.

There were visually apparent dose-related increases in the risk for experiencing dizziness, headache, nausea and constipation. There was no overall statistically significant difference in severity for any treatment-related adverse experience compared to placebo. This lack of statistical significance is likely related to the smaller sample size in this analysis population, particularly in the placebo group, which was reduced in size from 1308 to 258 in progressing from the controlled phase II/III trials to controlled gepirone ER trials in depression.

#### **2.4.19 HUMAN REPRODUCTION DATA**

No pregnancy exposure was reported for gepirone aside from the two cases of unintended pregnancy reported in sections 2.4.8.2 and 2.4.8.3.

#### **2.4.20 OVERDOSE EXPERIENCE**

Documented cases of overdose of gepirone, either alone or in combination with other drugs, occurred in 3 cases of 1701 subjects treated for depression with gepirone (0.2%). Data analysis of subjects who took an overdose of Org 33062 (200-500 mg = 2.5 to 6 times the upper recommended limit) revealed that symptoms like nausea and vomiting, and drowsiness were usually mild to moderate in intensity. One subject had transient incomplete right bundle branch block on the ECG. More details about this patient are available under section "2.4.8.4.2.1 Selected narratives". Recent experience includes one attempted suicide by taking an unknown overdose of gepirone and an unknown other drug. All subjects who took an overdose of gepirone reportedly recovered.

#### **2.4.21 REVIEW OF SYSTEMS**

This section provides general summaries for deaths, serious AEs and AEs leading to dropout by body system, in addition to pertinent negative findings. More details about specific AEs can be found in the earlier sections of this review.

##### **2.4.21.1 Cardiovascular**

Only one death occurred in the gepirone treatment group. Subject (b) (6) died on (b) (6) of an aortic dissection approximately 40 days after his last dose of gepirone IR. The subject had been treated with gepirone IR for approximately 35 days ( (b) (6) ) and had been treated for eight years for hypertension with furosemide and metoprolol.

Serious AEs reported in this system are syncope, chest pain, angina pectoris, and ECG abnormal.

The only AE leading to dropout reported in this system is palpitation where the RR was 9.21 (CI 1.074, 78.98) compared to placebo. This is based on five cases in the gepirone group (0.6%) and one case in the placebo group (0.1%). I reviewed the terminology used in the CRFs as depicted in the dataset provided with the ISS, AES\_OLD. Upon examining what was coded under “palpitation”, and the majority was reported as “palpitations” without a suggestion of a specific arrhythmia.

The risk ratio of objectively evaluated orthostatic changes is 8.08 in the gepirone ER group compared with placebo (95% CI 1.02-64.01, p-value=0.02). More details are provided in section “2.4.14.2.2 Orthostatic changes”.

There were no rare unexpected AEs such as torsades de pointes or ventricular fibrillation. No evidence was found for QT prolongation.

### **2.4.21.2 Gastrointestinal**

No death in a gepirone group was attributed to this system.

Serious AEs reported in this system are vomiting, SGOT increased, SGPT increased, intestinal obstruction, acute appendicitis, hepatitis and cholecystitis.

The AEs leading to dropout reported in this system are nausea, vomiting, abdominal pain, and diarrhea.

The most frequently observed clinically significant change in a laboratory parameter was isolated cases of elevated “total bilirubin” occurring 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). More details can be found in section “2.4.11.1.1 Analysis of Subjects with Clinically Significant Abnormalities ”.

There were no rare unexpected AEs such as liver necrosis, liver failure, liver transplant, or acute pancreatitis. No subjects are reported with 3x ULN elevation of SGOT and/or SGPT, concomitantly with bilirubin more than 2 mg/dL.

### **2.4.21.3 Genitourinary/renal**

No death in a gepirone group was attributed to this system.

Serious AEs reported in this system are prostate neoplasm, kidney calculus, cystitis, pregnancy unintended and kidney pain.

No AEs leading to dropout were reported in this system.

Mean change from baseline in serum creatinine appeared be associated with the dose of gepirone, and generally tended toward larger changes at higher doses with a maximum change at endpoint of +0.14 mg/dL for the > 80 mg dose group (described above in section 2.4.11.2.4). However, only one subject in the gepirone IR treatment group had elevations in serum creatinine that reached the criteria for clinical significance (described above in section 2.4.11.2.2).

There were no rare unexpected AEs such as renal failure. Lab data did not reveal any concerns related to findings in BUN, or urinalysis.

#### **2.4.21.4 Hematologic**

No death in a gepirone group was attributed to this system.

The only serious AE that is reported in this system is leukopenia, where the patient with leukopenia dropped out. No other AEs leading to dropout were reported in this system.

Twenty-eight subjects treated with gepirone had clinically significant change in the absolute neutrophil counts. More details can be found in section "2.4.12.1 BMS data". Two cases of leukopenia were reported among patients treated with gepirone. More details can be found in section "2.4.8.4 Data provided from sponsor upon request".

There were no rare unexpected AEs such as agranulocytosis, aplastic anemia, bone marrow depression, pancytopenia, thrombotic thrombocytopenia purpura, hemolytic anemia, or disseminated intravascular coagulation.

#### **2.4.21.5 Body as a whole**

No death in a gepirone group was attributed to this system.

Serious AEs reported in this system are accidental injury, breast neoplasm, migraine, overdose, and suicide attempt.

The AEs leading to dropout reported in this system are headache and sweating.

#### **2.4.21.6 Nervous**

No death in a gepirone group was attributed to this system.

Serious AEs reported in this system are psychosis, depression, psychotic depression, thinking abnormal, panic attack, convulsion, and pain.

The AEs leading to dropout reported in this system are dizziness, nervousness, depression, insomnia, anxiety, paresthesia and somnolence.

Dizziness is one of the most common AEs in the gepirone development program, and is one of the most common AEs leading to dropout. Among the combined gepirone ER treated patients, 33% reported dizziness compared with 12% of placebo patients. About 40% of patients reporting dizziness experienced this symptom in the first two weeks of treatment. Gepirone ER treated patients discontinued treatment due to dizziness seven times more frequently than placebo patients did. Furthermore, severity of the dizziness showed a statistically significant increase associated with increasing dose of gepirone. More details can be found in section "2.4.10.2.2.1 Dizziness".

One subject in a gepirone ER open label study was reported in the 120 days safety update to have generalized seizure.

#### **2.4.21.7 Musculoskeletal**

No death in a gepirone group was attributed to this system.

Serious AE reported in this system was hernia.

No AEs leading to dropout were reported in this system.

There were no rare unexpected AEs such as rhabdomyolysis.

#### **2.4.21.8 Special senses**

No death or serious AE in a gepirone group was attributed to this system.

The AEs leading to dropout reported in this system are two cases each of amblyopia and tinnitus (out of 849 subjects). No information is available on the severity and frequency of these AEs.

There were no rare unexpected AEs such as blindness or deafness.

#### **2.4.21.9 Dermatologic**

No death in a gepirone group was attributed to this system. No serious AEs or AEs leading to dropout were reported in this system.

There were no rare unexpected AEs such as Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, or anaphylactoid reactions.

#### **2.4.21.10 Metabolic/endocrine**

No death in a gepirone group was attributed to this system. The only serious AE reported in this system is one case of thyroid disorder. No AEs leading to dropout were reported in this system.

#### **2.4.21.11 Respiratory**

No death in a gepirone group was attributed to this system. No serious AEs or AEs leading to dropout were reported in this system.

There were no rare unexpected AEs such as acute respiratory failure.

### ***2.5 Adequacy of safety testing***

#### **2.5.1 GENERAL FINDINGS**

- The exposure time to drug is not sufficient. The sponsor does not have data required by the ICH guidelines for exposure, which are 300 individuals exposed to an effective dose for 6 months and 100 individuals exposed to an effective dose for 1 year. The

efficacy analysis suggests that the effective gepirone dose is 40 mg/day. Section “2.3.7 Exposure by dose and duration” clearly illustrates that there were only 124 subjects exposed to a modal dose  $\geq 40$  mg for roughly 6 months and only 35 subjects exposed to a modal dose  $\geq 40$  mg for roughly 1 year.

- In general, trial exclusions usually affect drug safety profile. The inclusion of a relatively “healthy” population of subjects with minimum co-morbidity inevitably underestimates the AEs profile in the real life subject population. Furthermore, as described in section 1.5 above, the sponsor did not investigate potential drug-drug interactions that may occur in subjects with comorbidities. Although these are generic issues, they are always important to bear in mind when considering the use of a newly marketed drug in patients with comorbidities and concomitant medications.
- The relationship of safety of gepirone to active controls (total 529 subjects) was not assessed directly, but each one was compared to placebo. Overall, the AEs profile of gepirone did not seem different than the active controls (anti-depressants and anxiolytics) although no trials were designed specifically to make such comparisons.

## **2.5.2 ADDITIONAL ANALYSES AND EXPLORATIONS**

The sponsor should conduct the following analyses:

### **2.5.2.1 Common adverse events**

The investigation of possible causes for the most common side effect, dizziness, was not sufficient. The sponsor should characterize the dizziness over time, for example, how often does it occur, how long does it last, and does the severity change with subsequent episodes. In addition, the sponsor should provide a discussion of the relationship, or lack thereof, between gepirone-associated dizziness, syncope, objectively measured orthostatic changes, and accidental injury.

### **2.5.2.2 Adverse events leading to drop out**

The sponsor noted that 761 subjects had “adverse event” identified on the End of Study CRF page as the reason for discontinuing from a study but 18% (N=138) did not specify the adverse event resulting in discontinuation. The sponsor should try to re-evaluate those adverse events. One approach would be to go to the AE page in the CRF and identify the outcome for each specific AE. This process affords an additional opportunity to determine which AE led to discontinuation for those patients that didn’t have it specified on the end of study page in the CRF.

### **2.5.2.3 Orthostatic changes**

The sponsor did not provide the risk ratios for orthostatic changes and their statistical evaluation so I calculated those from the submitted data. As new data accrue, the sponsor should evaluate the risk ratios for the incidence of orthostatic hypotension.

#### 2.5.2.4 Dose-response analysis

The sponsor should provide a dose response analysis using all reported treatment-emergent AEs. In the current submission, the sponsor used only “treatment-related” AEs as judged by the investigator.

#### 2.5.2.5 QTc analysis

The sponsor should provide a comparison of the frequency of outliers with a change from baseline of  $\geq 30$  msec and of  $\geq 60$  msec in each treatment group (gepirone IR, gepirone ER and placebo).

#### 2.5.2.6 Presentation of safety data

Since the clinical trial data suggest efficacy at doses between 40mg and 80mg/day, the safety data presentation should include analyses that consider two separate groups: 1) those subjects who received a modal dose of 40 mg or more; 2) those subjects who received a modal dose of less than 40 mg (see details below). In all the requested tables, in addition to the event risk ratios, the 95% confidence intervals should be provided. Also the data should be sorted by descending frequency within body system. The data should be presented in a SINGLE FULLY integrated summary of safety (ISS) that contains data from gepirone ER and IR formulations.

##### 2.5.2.6.1 Analyses using subjects receiving a modal dose of 40 mg/day or more of gepirone for the treatment of depression

###### 2.5.2.6.1.1 *Controlled data:*

We request summary tables for serious adverse events, adverse events leading to discontinuation, and overall adverse events for the following groups:

- Pooled short-term data from depression Phase II/III controlled trials using gepirone **IR** and the **IR** comparators (placebo, active) only.
- Pooled long-term data from depression Phase II/III controlled trials using gepirone **IR** and the **IR** comparators (placebo, active) only.
- Pooled short term and long term data from depression Phase II/III controlled trials using gepirone **IR** and the **IR** comparators (placebo, active).
- Pooled short-term data from depression Phase II/III controlled trials using gepirone **ER** and the **ER** comparators (placebo, active) only.
- Pooled long-term data from depression Phase II/III controlled trials using gepirone **ER** and the **ER** comparators (placebo, active) only.
- Pooled short term and long term data from depression Phase II/III controlled trials using gepirone **ER** and the **ER** comparators (placebo, active).
- Pooled data from depression Phase II/III controlled trials comparing gepirone **ER** to gepirone **IR**. The comparison should cover short-term, long-term, and pooled short & long-term data.

#### 2.5.2.6.1.2 *Open label data:*

- Frequencies of serious adverse events, adverse events leading to discontinuation, and overall adverse events should be calculated comparing gepirone **ER** to gepirone **IR**. In addition to the events risk ratios, please calculate the 95% confidence intervals.

#### 2.5.2.6.2 **Analyses using subjects receiving a modal dose less than 40 mg/day of gepirone for treatment of depression**

The safety data from this sub-population will be helpful in detecting adverse events that are not necessarily dependent on the dose.

##### 2.5.2.6.2.1 *Controlled data*

We request summary tables for serious adverse events, adverse events leading to discontinuation, and overall adverse events for the following groups:

- Pooled short-term and long-term data from depression Phase II/III controlled trials using gepirone **IR** and the **IR** comparators (placebo, active) only.
- Pooled short term and long term data from depression Phase II/III controlled trials using gepirone **ER** and the **ER** comparators (placebo, active) only.
- Pooled short term and long term data from depression Phase II/III controlled trials comparing gepirone **ER** to gepirone **IR**.

##### 2.5.2.6.2.2 *Open label data*

Frequencies of serious adverse events, adverse events leading to discontinuation, and overall adverse events should be calculated comparing gepirone **ER** to gepirone **IR**. In addition to the events risk ratios, please calculate the 95% confidence intervals.

## 2.6 **Summary of critical safety findings and limitations of data**

### 2.6.1 **GENERAL FINDINGS**

The sponsor implied in various parts of the ISS that the safety profile of the two formulations of gepirone (ER and IR) is similar or that the ER has a better one. Although this is true for some adverse events, it is not necessarily true for all of them. In most analyses in the ISS, the sponsor combines the ER and IR data, comparing them to the combined placebo. This approach diminished this reviewer's ability to fully characterize the safety of the ER formulation, which is the one intended for marketing.

In addition, the data organization precludes the ability to pool the old (BMS) and new (Organon) ER development program data for the purpose of this reviewer's own analyses. Furthermore, in parts of the ISS where the sponsor pooled these data together, the risk of gepirone-related AEs in depressed subjects was compared to the risk of AEs from the pooled placebo data for the entire development program regardless of indication, obscuring the interpretation of these comparisons.

For the reasons stated above, the division requested the sponsor to present their data separating the gepirone IR and ER formulations and their comparators (placebo, active), for the short-term and the long-term phases of phase II/III controlled depression trials (as described in section 2.5.2.6).

## **2.6.2 COMMENTS ON PROPOSED LABELING**

This reviewer's comments on the proposed labeling describing the safety profile may substantially change from that included herein because it will have to be rewritten to reflect the issues under section "2.5.2 ADDITIONAL ANALYSES AND EXPLORATIONS".

(b) (4)



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

## **INDEX OF ATTACHMENTS**

Sponsor's Appendix D.1 (updated ISS): Definition of clinically significant laboratory values.

Sponsor's Appendix D.1 (original ISS): Definition of significant laboratory values and toxicity grades.

Appendix D.1  
Organon, Inc.  
Definition of Clinically Significant Laboratory Values

The following table lists the criteria used to identify patients with potentially significant changes in laboratory test results.

| PARAMETER                 | LOW                      | HIGH             |
|---------------------------|--------------------------|------------------|
| <b>Hematology</b>         |                          |                  |
| Hemoglobin                | < 10.0 g/dL              |                  |
| Total White Blood Cells   | < 3,000/mm <sup>3</sup>  |                  |
| Absolute Neutrophil Count | < 1,500/mm <sup>3</sup>  |                  |
| Absolute Lymphocyte Count | < 1,000/mm <sup>3</sup>  |                  |
| Platelet Count            | < 75,000/mm <sup>3</sup> |                  |
| <b>Serum Chemistry</b>    |                          |                  |
| AST (SGOT)                |                          | > 3 x ULN        |
| ALT (SGPT)                |                          | > 3 x ULN        |
| GGT                       |                          | > 3 x ULN        |
| Alkaline Phosphatase      |                          | > 3 x ULN        |
| Total Bilirubin           |                          | ≥ 1.5 x ULN      |
| Creatinine                |                          | ≥ 2 mg/dL        |
| Albumin                   | < 3 g/dL                 |                  |
| Calcium                   | < 7.0 mg/dL              | > 12.5 mg/dL     |
| Sodium                    | < 130 mEq/L              | > 155 mEq/L      |
| Potassium                 | < 3.0 mEq/L              | > 6 mEq/L        |
| Phosphorous               | < 2.0 mg/dL              |                  |
| Uric Acid                 |                          | > 10 mg/dL       |
| Glucose                   | < 40 mg/dL               | > 250 mg/dL      |
| Amylase                   |                          | > 2 x ULN        |
| Cholesterol               |                          | > 400 mg/dL      |
| Triglycerides             |                          | > 400 mg/dL      |
| Prothrombin Time          |                          | > 1.5 x ULN      |
| Partial Prothrombin Time  |                          | > 1.5 x ULN      |
| <b>Urinalysis</b>         |                          |                  |
| PH                        | ≤ 4                      | ≥ 9              |
| Specific Gravity          | ≤ 1.001                  |                  |
| Protein                   |                          | 4 <sup>+</sup>   |
| Glucose                   |                          | ≥ 3 <sup>+</sup> |
| Ketones                   |                          | ≥ 3 <sup>+</sup> |
| Blood                     |                          | ≥ 3 <sup>+</sup> |

**Appendix D.1**  
**Definition of Significant Laboratory Values and Toxicity Grades**

|                        | Units | Gender | Normal Range |            | Clinically Significant Values |            | Toxicity Grades* |                 |                 |            |
|------------------------|-------|--------|--------------|------------|-------------------------------|------------|------------------|-----------------|-----------------|------------|
|                        |       |        | Low          | High       | Low                           | High       | 1                | 2               | 3               | 4          |
| <b>SERUM CHEMISTRY</b> |       |        |              |            |                               |            |                  |                 |                 |            |
| SGOT                   | IU/L  | F<br>M | 9<br>10      | 25<br>40   |                               | >3xULN     | >ULN-2.5xULN     | >2.5-5.0xULN    | >5.0-20.0xULN   | >20.0xULN  |
| SGPT                   | IU/L  | F<br>M | 7<br>10      | 30<br>55   |                               | >3xULN     | >ULN-2.5xULN     | >2.5-5.0xULN    | >5.0-20.0xULN   | >20.0xULN  |
| GGT                    | IU/L  | F/M    | 1            | 60         |                               | >3xULN     | >ULN-2.5xULN     | >2.5-5.0xULN    | >5.0-20.0xULN   | >20.0xULN  |
| Alkaline Phosphatase   | IU/L  | F<br>M | 30<br>45     | 100<br>115 |                               | >3xULN     | >ULN-2.5xULN     | >2.5-5.0xULN    | >5.0-20.0xULN   | >20.0xULN  |
| Total Bilirubin        | mg/dL | F/M    | 0            | 1          |                               | ≥1.5ULN    | >ULN1.5xULN      | >1.5-3.0xULN    | >3.0-10.0xULN   | >10.0xULN  |
| Creatinine             | mg/dL | F/M    | 0.6          | 1.5        |                               | ≥2mg/dL    | >ULN1.5xULN      | >1.5-3.0xULN    | >3.0-6.0xULN    | >6.0xULN   |
| Albumin                | g/dL  | F/M    | 3.1          | 4.3        | <3g/dL                        |            | <LLN-3g/dL       | ≥2-<3g/dL       | <2g/dL          |            |
| Calcium hypocalcemia   | mg/dL | F/M    | 8.5          | 10.5       | <7mg/dL                       | >12.5mg/dL | <LLN-8.0mg/dL    | 7.0-<8.0mg/dL   | 6.0-<7.0mg/dL   | <6.0mg/dL  |
| hypercalcemia          |       |        |              |            |                               |            | >ULN-11.5mg/dL   | >11.5-12.5mg/dL | >12.5-13.5mg/dL | >13.5mg/dL |
| Sodium hyponatremia    | mEq/L | F/M    | 135          | 145        | <130mEq/L                     | >155mEq/L  | <LLN-130mEq/L    |                 | 120-<130mEq/L   | <120mEq/L  |
| hypernatremia          |       |        |              |            |                               |            | >ULN-150mEq/L    | >150-155mEq/L   | 155-160mEq/L    | >160mEq/L  |
| Potassium hypokalemia  | mEq/L | F/M    | 3.5          | 5          | <3mEq/L                       | >6mEq/L    | <LLN-3.0mEq/L    |                 | 2.5-<3.0mEq/L   | <2.5mEq/L  |
| hyperkalemia           |       |        |              |            |                               |            | >ULN-5.5mEq/L    | >6.0-7.0mEq/L   | >7.0mEq/L       |            |

NCI Common Toxicity Criteria, Version 2.0 (1/30/98)

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**Appendix D.1**

**Definition of Significant Laboratory Values and Toxicity Grades**

|                                          | Units                             | Gender | Normal Range |            | Clinically Significant Values         |           | Toxicity Grades*                         |                                          |                                          |                                      |
|------------------------------------------|-----------------------------------|--------|--------------|------------|---------------------------------------|-----------|------------------------------------------|------------------------------------------|------------------------------------------|--------------------------------------|
|                                          |                                   |        | Low          | High       | Low                                   | High      | 1                                        | 2                                        | 3                                        | 4                                    |
| Phosphorus                               | mg/dL                             | F/M    | 2.6          | 4.5        | <2mg/dL                               |           | <LLN-2.5mg/dL                            | ≥2.0-2.5mg/dL                            | ≥1.0-<2.0mg/dL                           | <1.0mg/dL                            |
| Uric Acid                                | mg/dL                             | F<br>M | 1.5<br>2.5   | 6.6<br>8.5 |                                       | >10mg/dL  | >ULN-≤10mg/dL                            |                                          |                                          | >10mg/dL                             |
| Glucose<br>hypoglycemia<br>hyperglycemia | mg/dL                             | F/M    | 70           | 110        | <40mg/dL                              | >250mg/dL | <LLN-55mg/dL<br>>ULN-160mg/dL            | 40-<55mg/dL<br>>160-250mg/dL             | 30-<40mg/dL<br>>250-500mg/dL             | <30mg/dL<br>>500mg/dL                |
| Cholesterol                              | mg/dL                             | F/M    | 0            | 240        |                                       | >400mg/dL | >ULN-300mg/dL                            | >300-400mg/dL                            | >400-500mg/dL                            | >500mg/dL                            |
| Triglycerides                            | mg/dL                             | F/M    | 40           | 150        |                                       | >400mg/dL | >ULN-2.5xULN                             | >2.5-5.0xULN                             | >5.0-10xULN                              | >10xULN                              |
| <b>Hematology</b>                        |                                   |        |              |            |                                       |           |                                          |                                          |                                          |                                      |
| Hemoglobin                               | g/dL                              | F<br>M | 12<br>13     | 16<br>18   | <10g/dL                               |           | <LLN-10.0g/dL                            | 8.0-<10.0g/dL                            | 6.5-<8.0g/dL                             | <6.5g/dL                             |
| WBCs                                     | x10 <sup>3</sup> /mm <sup>3</sup> | F/M    | 4.3          | 10.8       | <3x10 <sup>3</sup> /mm <sup>3</sup>   |           | <LLN-3x10 <sup>3</sup> /mm <sup>3</sup>  | ≥2-<3x10 <sup>3</sup> /mm <sup>3</sup>   | ≥1-<2x10 <sup>3</sup> /mm <sup>3</sup>   | <1x10 <sup>3</sup> /mm <sup>3</sup>  |
| Neutrophils(ANC)                         | x10 <sup>3</sup> /mm <sup>3</sup> | F/M    | 2            |            | <1.5x10 <sup>3</sup> /mm <sup>3</sup> |           | ≥1.5-2x10 <sup>3</sup> /mm <sup>3</sup>  | ≥1-<1.5x10 <sup>3</sup> /mm <sup>3</sup> | ≥.5-<1x10 <sup>3</sup> /mm <sup>3</sup>  | <.5x10 <sup>3</sup> /mm <sup>3</sup> |
| Lymphocytes                              | x10 <sup>3</sup> /mm <sup>3</sup> | F/M    | 1            |            | <1x10 <sup>3</sup> /mm <sup>3</sup>   |           | <LLN-1x10 <sup>3</sup> /mm <sup>3</sup>  | ≥.5-<1x10 <sup>3</sup> /mm <sup>3</sup>  | <.5x10 <sup>3</sup> /mm <sup>3</sup>     |                                      |
| Platelets                                | x10 <sup>3</sup> /mm <sup>3</sup> | F/M    | 150          | 350        | <75x10 <sup>3</sup> /mm <sup>3</sup>  |           | <LLN-75x10 <sup>3</sup> /mm <sup>3</sup> | ≥50-<75x10 <sup>3</sup> /mm <sup>3</sup> | ≥10-<50x10 <sup>3</sup> /mm <sup>3</sup> | <10x10 <sup>3</sup> /mm <sup>3</sup> |

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**Appendix D.1**  
**Definition of Significant Laboratory Values and Toxicity Grades**

|                     | Units | Gender | Normal Range |       | Clinically Significant Values |      | Toxicity Grades* |   |   |   |
|---------------------|-------|--------|--------------|-------|-------------------------------|------|------------------|---|---|---|
|                     |       |        | Low          | High  | Low                           | High | 1                | 2 | 3 | 4 |
| <b>Urine</b>        |       |        |              |       |                               |      |                  |   |   |   |
| Urine Blood         |       | F/M    | Neg          |       |                               |      | ≥3+              |   |   |   |
| Urine Ketones       |       | F/M    | Neg          |       |                               |      | ≥3+              |   |   |   |
| Urine Glucose       |       | F/M    | Neg          |       |                               |      | ≥3+              |   |   |   |
| Urine Protein       |       | F/M    | Neg          |       |                               |      | 4+               |   |   |   |
| Urine pH            |       | F/M    | 4.6          | 8     | ≤4.0                          | ≥9.0 |                  |   |   |   |
| U. Specific Gravity |       | F/M    | 1.002        | 1.030 | ≤1.001                        |      |                  |   |   |   |

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MEDICAL OFFICER

Judith Racoosin  
2/26/02 04:32:31 PM  
MEDICAL OFFICER

DEC 18 1999

Evaluation of Clinical Materials for RTF Meeting  
NDA #21-164

**Sponsor:** Organon, Inc.  
**Drug:** Gepirone hydrochloride ER  
**Drug Category:** 5-HT1A agonist  
**Indication:** Major Depressive Disorder  
**Correspondence Date:** September 30, 1999  
**Date Received:** October 1, 1999

In this submission, Organon asserts that 16 adequate and well-controlled studies have been completed, seven of which support the use of gepirone for major depressive disorder. A summary of these studies with results is attached. Of the seven 'supportive' studies, 3 used the ER formulation of gepirone; the others used the IR. The ER formulation was developed to reduce the incidence of side effects of the IR formulation, primarily nausea, dizziness, and insomnia. Neither gepirone ER nor IR has been approved for use in any country. (b) (4)

The drug was originally developed by Bristol-Myers Squibb.

As the IR formulation has not been approved as efficacious, two adequate and well-controlled studies will be necessary for approval of gepirone ER. In the Division's March 20, 1998 meeting with Fabre-Kramer, they were advised that 'since the immediate and extended release are not equivalent as to rate and extent of absorption, we would not normally accept the immediate release study for demonstrating efficacy in the extended release product'. I have concentrated by evaluation of this submission therefore, on the 3 placebo-controlled, double-blind ER studies that the sponsor claims as support for efficacy. These studies evaluated patients with DSM-III-R major depression, with at least a 20 on the HAMD-17 at the end of baseline evaluation. Note that 3 other ER studies were not supportive of the efficacy of gepirone for depression.

1. The attached table shows the number of study participants for the gepirone development program. A total of 603 patients were included in phase II/III placebo-controlled trials of gepirone ER. An additional 34 were included in uncontrolled studies. This number is rather low as per ICH guidelines for the filing of an NDA for a new molecular entity.

2. All 3 of the 'supportive' ER studies were terminated prior to completion of enrollment by Bristol-Myers Squibb when they discontinued development of the drug. The sponsor's claimed positive results are based on the numbers of subjects shown in the table:

| Numbers of Gepirone ER Patients in Claimed Positive Studies |     |            |
|-------------------------------------------------------------|-----|------------|
| Study                                                       | ITT | Completers |
| CN105-053                                                   | 42  | 26         |
| CN105-078                                                   | 88  | 55         |
| CN105-083                                                   | 33  | 14         |
| Total                                                       | 163 | 95         |

A number of other problems exist for these studies. These will be addressed below for each individual study.

3. An interim analysis, unspecified in the protocol, was performed on 2 of the primary ER studies (CN105-078 and -083). It was based on 60% of the projected final sample size or 217 patients total from both studies. The objective of this analysis was 'to determine whether gepirone ER has a discernible effect on the specified efficacy parameters in each of the centers separately, and when data from both studies are combined.'

#### CN105-053

This was a 2-center 8-week study comparing gepirone ER (10-60 mg) with imipramine (50-200 mg) and placebo. The number of patients planned for enrollment was 240 but the study was terminated early by Bristol-Myers Squibb; 170 were randomized and 166 included in the ITT population. In addition 46% of patient discontinued prematurely. These included 60% of the placebo group, 41% of the gepirone group, and 37% of the imipramine group. It is questionable whether an adequate analysis can be done on this study that was terminated early and had a high drop-out rate. The Biometrics reviewer, Dr. Richard Chen, will comment further on this.

In the protocol, it is noted that: 'Data for the centers will be pooled, if appropriate. Justification for pooling will be provided . . .' The company claims positive results for 1 site in the ITT population for the two primary efficacy measures. Minutes from a March 20, 1998 meeting between the Division and Fabre-Kramer Pharmaceuticals indicated that there would be no reason to pool the 2 study sites, though the final decision was left as a matter of review. This site (site #1, administered by Dr. Feiger) randomized 42 subjects to gepirone, 41 to imipramine and 40 to placebo. In the gepirone group, 38% discontinued early, leaving an n of 26 completers. For imipramine, 38% and for placebo 67%. A total of 48% of subjects discontinued the study early from this site.

In the original protocol for this study, seven different efficacy measures are noted with no primary measure identified. This is admitted in the submitted study report: 'The primary efficacy variable was not explicitly identified in the protocol, but was implied by the parameter used in the calculation of sample size.' The report goes on to state that 'the protocol stated a criterion for therapeutic response based on the CGI Global Improvement score.' Hence, this parameter is also considered a primary efficacy variable.

In the results summary submitted by Organon, primary measures are identified as: 1.) mean change from baseline to endpoint for total HAM-D; 2.) percentage of CGI responders (score of 1 or 2). It is unclear when these were chosen.

For both sites, the blind was broken during the study in 4 patients that were included in the ITT population. Two for overdose and 2 for unknown reasons (the latter at site #1). All had discontinued the study for serious AEs. Three patients with significant protocol violations were included in the ITT population, all at site #1. The violations noted are 'patient unreliability'. Two were on placebo and one on imipramine.

#### **CN105-078**

This was a 2-center, 6-week, double-blind study comparing 2 dose ranges of gepirone (10-50 mg and 20-100 mg) and placebo. The plan was to include 180 patients in the ITT population. Bristol-Myers terminated the study early so 146 were randomized and 135 included in the ITT (88 on gepirone and 47 on placebo. A total of 38% discontinued early, 34% in the 10-50 mg group, 51% in the 20-100 mg group, and 31% on placebo. The number of completers on gepirone was 55 and for placebo, 34.

As in protocol CN105-053, no primary efficacy measure was identified in the protocol; 6 efficacy measures are noted. In the protocol, the primary analysis was stated to be a comparison between gepirone (both dose groups pooled) and placebo. A secondary analysis would compare each dose group alone to placebo.

The blind was broken for 2 subjects (both at center #2) included in the ITT population for unknown reasons. This was after completion of the study, though prior to analysis for these 2 patients who discontinued due to serious AEs. In addition, significant protocol violation occurred in an additional 17 patients, 13 on gepirone. All discontinued the study for the violation and all but 2 were included in the ITT population. Violations were usually cited as patient unreliability; one was randomized in error.

The sponsor reports that the results of this study were positive because one (of the two poorly specified) primary measures showed a statistically significant difference between gepirone overall

and placebo, though only in the EE (efficacy evaluable) group and not in the ITT population.

The sponsor attempts to make a case for doing by-center analyses though no treatment x center interaction was observed. There was still no difference between placebo and gepirone for the ITT population at endpoint for either center on the HAMD. At center #2 there was a significant difference ( $p \leq 0.05$ ) in the number of CGI-Improvement responders for the high dose group. It is unclear whether the difference for overall gepirone treatment vs. placebo was found to be significant first.

### **CN105-083**

This protocol for this study is identical to that for CN105-078 above. The total number of patients randomized was 121, with 112 included in the ITT population (36 on 10-50 mg, 37 on 20-100 mg, and 39 on placebo. Discontinuation rates were 38% for each of the gepirone groups and 34% for placebo. At the end of the study therefore, 23 patients remained in the 10-50 mg group and 24 in the 20-100 mg group.

At site #2, (Dr. Cal Cohn), the blind was broken prior to analysis in 3 patients included in the ITT, two on gepirone and one on placebo, for unknown reasons. Four additional patients had significant protocol violations, 3 for patient unreliability and one for randomized in error. Six of these were included in the ITT.

The sponsor claims this as a positive study based on statistically significant improvement on both primary efficacy measures in the Efficacy Evaluable (and not the ITT) population at one of the two study sites (#2, Dr. Cal Cohn). The ITT population at this site included 17 patients on 10-50 mg, 16 on 20-100 mg, and 16 patients on placebo.

As in the study above, no statistically significant treatment x center interaction was observed for the ITT population.

The same problems of early termination by Bristol-Myers, lack of identification of primary efficacy measures, and an unplanned interim analysis exist for this study as for the one above.

In an analysis of the pooled sample from all studies, the sponsor reports that they were unable to document any evidence of efficacy in severely depressed patients (though they report they documented evidence for moderately depressed patients). Severely depressed was defined as baseline scores of  $\geq 25$  on the HAMD 17. Whether this analysis was done correctly is a review issue, but it does bring up a point for possible future studies of gepirone. That is that enough patients with severe enough depressions are

included in samples for an indication of major depressive disorder.

I could not locate the following in the submission: Exposure in patient-years, literature search, adverse event thesaurus, drop-outs due to labs, vital signs, ECGs, CRF Index. Also no studies of withdrawal/abuse potential have been done for the ER formulation, though 2 such studies have been negative for the IR formulation.

### **Recommendations and Conclusions**

A summary of problems with this submission follows:

1. Low exposure rates for the ER formulation and inadequate number of patients treated with gepirone in the 3 studies that are claimed as positive. A total of 163 patients were treated with gepirone in these 3 trials; 95 completed. This is inadequate for the evaluation of a new molecular entity for the treatment of major depression.
2. All 3 of the claimed positive studies were terminated early. In addition, their high drop-out rates make it unlikely that an adequate evaluation of the data can be accomplished.
3. Interim analyses that were not specified in the protocols were performed on 2 of the claimed 3 pivotal studies. This complicates further analyses and calls into question whether administration of the study was altered based on interim results.
4. No primary efficacy measure was clearly specified in any of the three protocols for the pivotal studies. In addition, the blind was broken for some subjects prior to analyses and there were a relatively large number of subjects included in ITT analyses that had violated the protocols.
5. Analyses on 'Efficacy Evaluable' populations are not acceptable. In an ITT population, both (poorly identified) primary efficacy variables were found to be positive only in study CN105-053, and this only at one of two sites.
6. The splitting of centers for analysis in study CN105-083 is probably not warranted, given the lack of statistically significant treatment x center interaction.
7. I was unable to locate the following in the submission: Exposure in patient-years, literature search, adverse event thesaurus, drop-outs due to labs, vital signs, ECGs, CRF Index. Also no studies of withdrawal/abuse potential have been done for the ER formulation.

The sponsor has failed to provide at least 2 adequate and well-controlled studies documenting efficacy for gepirone ER. Based on this and other grounds detailed above, I recommend that the Division refuse to file this NDA. If the sponsor chooses to

pursue development of this drug, it is highly recommended that they submit their plans to the Division for review and discussion.



Susan Molchan, M.D.  
November 15, 1999

12-18-99

See my memo to  
file on this date  
for additional comment  
on 11-30-99 refusal  
to file action.  
→ J. J. J.

cc: NDA #21-164  
HFD-120  
HFD-120/SMolchan  
TLaughren  
PDavid

**Table 4**  
**Distribution of All Study Participants<sup>a</sup> in the Org 33062 Development Program by Treatment Group**

| Study Group                                | ER         | Org 33062<br>IR | Total                  | Antidepressants |            | Anxiolytics |            | Placebo     |
|--------------------------------------------|------------|-----------------|------------------------|-----------------|------------|-------------|------------|-------------|
|                                            |            |                 |                        | Fluoxetine      | Imipramine | Bromazepam  | Diazepam   |             |
| <b>Phase I Clinical Trials</b>             |            |                 |                        |                 |            |             |            |             |
| Single-Dose Trials                         | 139        | 67              | 206                    | 0               | 0          | 0           | 0          | 6           |
| Multiple-Dose Trials                       | 182        | 137             | 319                    | 0               | 0          | 0           | 0          | 48          |
| <b>Phase 1 Subtotal</b>                    | <b>321</b> | <b>204</b>      | <b>525<sup>d</sup></b> | <b>0</b>        | <b>0</b>   | <b>0</b>    | <b>0</b>   | <b>54</b>   |
| <b>Phase II/III Clinical Trials</b>        |            |                 |                        |                 |            |             |            |             |
| <b>Flexible Dose</b>                       |            |                 |                        |                 |            |             |            |             |
| <b>Placebo-Controlled</b>                  |            |                 |                        |                 |            |             |            |             |
| Short-term                                 | 603        | 1557            | 2160                   | 106             | 240        | 73          | 110        | 1308        |
| Long-term <sup>b</sup>                     | (233)      | (409)           | (642)                  | (64)            | (104)      | (10)        | (39)       | (371)       |
| <b>Uncontrolled Studies</b>                |            |                 |                        |                 |            |             |            |             |
| Short-term                                 | 34         | 302             | 336                    | 0               | 0          | 0           | 0          | 0           |
| Long-term <sup>b</sup>                     | (12)       | (122)           | (134)                  | 0               | 0          | 0           | 0          | 0           |
| <b>Phase II – III Subtotal<sup>c</sup></b> | <b>637</b> | <b>1859</b>     | <b>2496</b>            | <b>106</b>      | <b>240</b> | <b>73</b>   | <b>110</b> | <b>1308</b> |
| <b>Grand Total<sup>c</sup></b>             | <b>958</b> | <b>2063</b>     | <b>3021</b>            | <b>106</b>      | <b>240</b> | <b>73</b>   | <b>110</b> | <b>1362</b> |

- a: Includes all study subjects who received at least one dose of study medication. Subjects in crossover study 03A7A-002 were counted only in the treatment group they were first exposed to.
- b: Includes studies with a short-term phase and a long-term extension phase (numbers in parentheses indicate subjects in short-term phase previously counted)
- c: Excludes subjects in long-term extension phase previously counted in short-term phase
- d: One additional patient was treated with Org 33062 IR for 8 days in Study CN105-023 before the study was terminated. No CRF is available, thus the subject does not contribute to the safety database.

Table 2 Overview of Efficacy Results at Endpoint in 16 US Adequate and Well-Controlled Studies by Study

| Study Number<br>(Center/Investigator)    | Formulation | Population and Efficacy Parameter |                                 |                  |                                 |                  | Description of Findings                                                                                                                                                                          |
|------------------------------------------|-------------|-----------------------------------|---------------------------------|------------------|---------------------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                          |             | Intent-to-Treat                   |                                 |                  | Efficacy-Evaluable              |                  |                                                                                                                                                                                                  |
|                                          |             | Relapse                           | Change from Baseline in HAMD 17 | % CGI responders | Change from Baseline in HAMD 17 | % CGI responders |                                                                                                                                                                                                  |
| <b>Studies with Positive Findings</b>    |             |                                   |                                 |                  |                                 |                  |                                                                                                                                                                                                  |
| CN105-053 <sup>a</sup><br>(-0001/Feiger) | ER          | --                                | X                               | X                | X                               | X                | Primary efficacy parameters positive at 1 of 2 centers (-0001/ Feiger)                                                                                                                           |
| 03A7A-003                                | IR          | --                                | X                               | X                | X                               | X                | Primary and secondary efficacy parameters positive                                                                                                                                               |
| 03A7A-002                                | IR          | X <sup>b</sup>                    | --                              | --               | --                              | --               | Primary efficacy parameters positive                                                                                                                                                             |
| 03A7C-001B <sup>a</sup>                  | IR          | --                                | X                               | X                | X                               | X                | Primary efficacy parameters positive for all centers combined and at 1 of 3 centers (-2483/Cole) with small number of subjects; positive efficacy based on CGI at another center (-2593/ Carman) |
| 03A7C-001A-2486                          | IR          | --                                | X                               |                  |                                 |                  | Efficacy parameters positive for total Org 33062 group alone                                                                                                                                     |
| CN105-078 <sup>a</sup>                   | ER          | --                                |                                 |                  |                                 | X                | One primary efficacy parameter positive for EE population for all centers combined                                                                                                               |
| CN105-083 <sup>a</sup><br>(-0002/Cohn)   | ER          | --                                |                                 |                  | X                               | X                | Primary efficacy parameters positive for EE population at 1 of 2 centers (0002/Cohn, Org 33062 high-dose group)                                                                                  |
| CN105-057 <sup>a</sup>                   | ER          | --                                |                                 | X                | --                              | --               | Dose range too low; efficacy at 1 center (-0002/Cohn) in 2 dose groups                                                                                                                           |
| <b>Nonsupportive Studies</b>             |             |                                   |                                 |                  |                                 |                  |                                                                                                                                                                                                  |
| CN105-052 <sup>a</sup>                   | ER          | --                                |                                 |                  | --                              | --               | Terminated with less than half of planned enrollment                                                                                                                                             |
| CN105-064 <sup>a</sup>                   | ER          | --                                |                                 |                  | --                              | --               | Terminated with less than half of planned enrollment                                                                                                                                             |
| CN105-029 <sup>a</sup>                   | IR          | --                                |                                 |                  | --                              | --               | Terminated to divert resources to ER program with less than half of planned enrollment                                                                                                           |
| CN105-022                                | IR          | --                                |                                 |                  | --                              | --               | Dose range too low                                                                                                                                                                               |
| CN105-028                                | IR          | --                                |                                 |                  | --                              | --               | Dose range too low                                                                                                                                                                               |
| CN105-037                                | IR          | --                                |                                 |                  | --                              | --               | Dose range too low                                                                                                                                                                               |
| CN105-043 <sup>a</sup>                   | IR          | --                                |                                 |                  | --                              | --               | Dose range too low                                                                                                                                                                               |
| 03A7C-001A-2496                          | IR          | --                                |                                 |                  | --                              | --               | Failed due to high placebo response                                                                                                                                                              |

X = positive efficacy results; --: Not applicable - parameter either not measured or not analyzed

<sup>a</sup>The study was terminated by BMS prior to completion of enrollment.

<sup>b</sup>A total of 6 definitions of relapse, which were based on the HAMD 17 and CGI, were used. Org 33062 prevented relapse based on 4 of the 6 definitions.