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A MULTI-CENTER CARDIAC SAFETY STUDY OF SUBJECTS WHO PARTICIPATED IN ORGANON SPONSORED PHASE 1 AND PHASE 2 COMPLETED AND DISCONTINUED TRIALS WITH ORG 24448 (PROTOCOLS: 22601; 22602; 22603; 153001; 153002; 153003; 153004; 29402; III.04.0311) (PROTOCOL NO. P153006)

Other Study Information:	This was a multicenter follow-up study of all subjects in previous Organon studies with SCH 900460 (Org 24448) to evaluate cardiac safety. No treatment was to be administered during this study.
Name of Sponsor:	Organon, a division of Schering-Plough
Included Protocol:	P05719 (P153006)
Development Phase of Study:	Not applicable
Study Initiation Date:	25 MAR 2008

Study Completion Date:	05 JAN 2009
Sponsor's Responsible Medical Officer:	PPD [redacted]
Sponsor's Contact Person:	PPD [redacted]

GCP Compliance:	This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.
Date of the Report:	29 OCT 2009
Doc ID:	4396309

2 SYNOPSIS

Title of Study:	A MULTI-CENTER CARDIAC SAFETY STUDY OF SUBJECTS WHO PARTICIPATED IN ORGANON SPONSORED PHASE 1 AND PHASE 2 COMPLETED AND DISCONTINUED TRIALS WITH ORG 24448 (PROTOCOLS: 22601; 22602; 22603; 153001; 153002; 153003; 153004; 29402; III.04.0311) (PROTOCOL NO. P153006)	
Investigators:	Multicenter	
Study Centers:	Multicenter	
Publications:	None	
Studied Period:	25 MAR 2008 to 05 JAN 2009	**Clinical Phase:** Not applicable

Objectives:

- To provide safety follow-up evaluations to subjects who received SCH 900460 (also known as and hereafter referred to as Org 24448).
- To provide a summary of cardiac status in subjects who participated in previous Organon-sponsored Org 24448 studies.

Methodology: Study P05719 (also known as and hereafter referred to as P153006) was a multicenter, follow-up study to evaluate cardiac safety of all subjects in previous Organon Org 24448 studies. The study was conducted in three phases: screening, evaluation, and follow-up.

The evaluation period was to consist of three visits: Post-Treatment (PT) Visit 1, PT Visit 2, and PT Visit 3. PT Visit 1 was to be the first point of assessment in this study for all subjects. For each subject, all evaluations were to be completed. After completion and availability of results, this visit was to be concluded with a cardiologist evaluation. PT Visit 2 was to be the second visit for subjects who participated in an Org 24448 study on 09 JUL 2006 or thereafter and were off treatment less than 1 year at PT Visit 1. These subjects were to be assessed at PT Visit 1 and PT Visit 2. Subjects who discontinued treatment prior to 09 JUL 2006 or were off treatment for more than 1 year at their first assessment were to be assessed at PT Visit 1 only. Subjects who had an abnormal result on PT Visit 1 or PT Visit 2 were to proceed immediately to PT Visit 3, which was to include a cardiac magnetic resonance imaging (MRI) and serology.

The safety evaluation included documentation of any adverse events (AEs), assessment of standard laboratory parameters, serological testing, physical examinations, and vital signs. Specific cardiac safety evaluations included electrocardiograms (ECGs), echocardiograms (ECHOs), chest radiograph, and cardiac magnetic resonance imaging (MRI) (only for those subjects in whom preceding tests indicated a cardiac finding similar or related to the findings in animals exposed to Org 24448 or to ECHO findings that were inconclusive). In addition, each subject underwent an evaluation by a cardiologist.

Number of Subjects: The goal of this study was to obtain pertinent safety information from all subjects previously treated with Org 24448 and at least 40% of those treated with placebo in previous studies. The study was to be descriptive and was not designed or powered to provide statistical comparisons.

Diagnosis and Criteria for Inclusion: Subjects who participated in a previous Organon-sponsored Org 24448 study.

Test Product, Dose, Mode of Administration, Batch No: Not applicable. No treatment was administered in this study.

Duration of Treatment: Not applicable. No treatment was administered in this study.

Reference Therapy, Dose, Mode of Administration, Batch No: Not applicable. No treatment was administered in this study.

Criteria for Evaluation: The safety evaluation included documentation of any AEs, assessment of standard laboratory parameters, serological testing, physical examinations, and vital signs. Specific cardiac safety evaluations included ECGs, ECHOs, chest radiograph, and cardiac MRI (only for those subjects in whom preceding tests indicated a cardiac finding similar or related to the animal findings or in whom the ECHO was inconclusive). In addition, each subject underwent an evaluation by a cardiologist.

Statistical Methods:

Disposition and Demographics: The number of subjects who were screened, the number of subjects eligible for participation, and those who completed this clinical study were tabulated by treatment group in the lead-in protocol and overall (pooled across treatment groups).Non-participating subjects were listed by treatment group

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(lead-in protocol), study, center, and main reason for lack of participation (eg, declined, lost to follow-up).

For participating subjects, the number and percentage of subjects who discontinued prematurely were tabulated by main reason for discontinuation and treatment group (lead-in protocol). In addition, a summary table showing the number and percentage of subjects remaining at each visit was prepared.

Demographics and baseline characteristics (eg, medical history, current disease conditions) were summarized by treatment group. Summary statistics for continuous variables included mean, median, standard deviation, minimum, and maximum. For categorical variables, frequency counts and percentages were presented. The number of (non-missing) observations was reported. These tables were presented by treatment group and for all treatment groups combined.

All medical history terms as described by the investigator were coded using the Medical Dictionary for Regulatory Activities (MedDRA). For any medical history term as described by the investigator, a MedDRA lowest term was chosen that best matched or approximated the investigator's actual description, adhering to MedDRA rules and conventions. These lowest level terms map to a MedDRA preferred term, which were classified into a single MedDRA high level term and a single MedDRA system-organ class, as defined by the primary path of the MedDRA version used. For medical history, a frequency table of the corresponding MedDRA preferred term was presented by treatment group. Cardiac related medical history was listed by treatment group.

No statistical tests were performed.

Safety: All AEs noted during the study were listed. The number (%) of subjects with at least one AE was presented in a frequency table of MedDRA system-organ class (according to the primary path) and MedDRA preferred term by treatment group.

The measurements of each laboratory parameter were converted to Organon preferred units before summary, unless otherwise specified. The conversion factors were presented.

For each of the vital sign parameters, descriptive statistics were calculated by treatment group and assessment.

Descriptive statistics of quantitative ECG parameters were calculated. Descriptive statistics consisted of number of non-missing observations, mean, standard deviation, median, minimum and maximum and were tabulated by treatment group for all scheduled assessments. Markedly significant ECG values were listed by ECG parameter and treatment group.

A listing of abnormal ECHOs was provided by treatment group (lead-in protocol) and subject.

SUMMARY-CONCLUSIONS:

RESULTS:

Disposition and Demographics: The objective of retrieving 40% of the placebo subjects was not met. Schizophrenic subjects who participated in the lead-in studies were frequently non-responsive when efforts were made to contact them about this safety follow-up study. Particularly for lead-in studies that had been completed several years ago, subjects had often changed their living situations. As a consequence of the difficulty in locating subjects, sites concentrated their efforts on retrieving subjects who had been treated with Org 24448, and the sites felt would benefit from the evaluations being provided as part of the study. This resulted in a much lower location rate for placebo-treated subjects.

Subjects in this study were both healthy volunteers and schizophrenic subjects from the Phase 1 and Phase 2 studies with Org 24448. Subjects participated from all Organon sponsored trials with one exception (Protocol III.04.0311). Subjects included represent exposure to Org 24448 at a maximum dosage of 1000 mg BID and the maximum duration of 28 days.

A total of 127 subjects of the original 310 individuals in studies with Org 24448 were enrolled in Study 153006: 111 subjects previously treated with Org 24448 and 16 previously treated with placebo. For all subjects who participated in a previous Org 24448 study and were treated with Org 24448 in that study, sites made at least three documented attempts to contact subjects to make the study available to them. For all subjects who previously participated in an Org 24448 study and were treated with placebo, sites were encouraged but not required to offer the study to these potential subjects. One site with 16 subjects who received a single dose of Org 24448 refused to participate, and therefore no contact or follow up with these subjects could be made.

During the study, no subjects discontinued due to AEs, two subjects withdrew consent and did not complete scheduled evaluations (subjects did not provide a reason), and no subject was excluded from protocol eligibility.

Of the 127 subjects enrolled in this study, 24 (18.9%) were female and 103 (81.1%) were male. The majority of subjects were White (89, 70.1%) followed by Black or African American (32, 25.2%). The mean age was 44.2 years (range, 19-66 years) and the mean weight was 88.01 kg (range, 49.3-170.1 kg). Of the subjects who

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participated 46 were healthy volunteers from the Phase 1 studies, and 81 were schizophrenic subjects from the Phase 2 studies.

Disposition of Org 24448 Subjects Only (From Previous Studies) (Protocol No. P153006)

Org 24448 Subjects Eligible to Participate	220
Org 24448 Subjects from Non-Participating Site	16
Org 24448 Subjects With Attempts to Contact for Participation in Study 153006	204
Org 24448 Subjects Not Included in Study 153006	93
Org 24448 Subjects Enrolled in Study 153006	111
Org 24448 Subjects Withdrew Consent in Study 153006 Prior to Completion[a]	2
Org 24448 Subjects Completed Study 153006	109

a: Subjects PPD withdrew consent and therefore completed echocardiograms but did not complete all evaluations for which they were eligible. Neither subject provided a reason for withdrawal of consent.

Safety: No subject discontinued Study 153006 due to an AE/serious adverse event (SAE). No subjects died during Study 153006; however, two subjects died prior to Study 153006: Subject PPD (coronary atherosclerosis) and Subject PPD (cardiomegaly with heart failure). Subject PPD gave verbal consent and was scheduled to participate in this study prior to his death. The only data collected for this subject as part of this study comprise an SAE report. Subject PPD died after receiving the notification of the myocarditis findings in the animal study, but prior to returning for testing Study 153006.

Two subjects reported SAEs during Study 153006. One subject was involved in a road traffic accident and experienced four SAEs associated with the event. Another subject reported an SAE related to a psychotic disorder.

In previous studies, five schizophrenic subjects who had taken Org 24448 experienced a cardiac AE/SAE during those studies. The only cardiac disorder that was reported as an SAE in clinical studies with Org 24448 was supraventricular tachycardia in Study 153002; the subject recovered, and both the investigator and sponsor indicated that the SAE was unlikely related to the study medication. The other four cardiac AEs were reported as follows: one subject with a myocardial infarction, one subject with tachycardia, one subject with sinus tachycardia, and one subject with palpitations.

For three additional subjects, cardiac AEs were reported during the course of Study 153006. These AEs were ventricular hypokinesia, left ventricle dysfunction, and dilation ventricular.

No ECG abnormalities were noted during Study 153006 at Visit 1 or Visit 2. Four subjects (all received Org 24448 in the previous studies) had abnormal ECHOs. At Visit 1, four Org 24448 subjects demonstrated a clinically significant finding on chest radiographs (these are not the same subjects who demonstrated an abnormal ECHO); whereas, at Visit 2, no subjects demonstrated a clinically significant finding. Of the four subjects who had cardiac MRI performed, three subjects had no notable deviation, and one subject had notable deviations that were not clinically significant.

Examination by a cardiologist at Visit 1, revealed two subjects with clinically significant findings, and at Visit 2, two subjects (one subject was repeated from Visit 1) with clinically significant findings. At Visit 3, no clinically significant findings were noted during the examination. Overall, no conclusive evidence of myocarditis was found at Visit 3 with the MRIs. One subject was identified for whom myocarditis could not be ruled out without additional testing, which was not performed.

Although abnormally high and low values for vital sign and laboratory parameters were noted, none of the abnormal values were considered clinically significant and no pattern or treatment-related relationship was noted

CONCLUSIONS: Cardiac evaluation of subjects previously exposed to Org 24448 did not reveal any clinically significant trends in the cardiac status of subjects. A small number of cardiac AEs/SAEs occurred, but the AEs in this System/Organ Class varied and in general were not severe or serious in nature. Prior to Study 153006, two subjects died due to cardiac causes that were unrelated to Org 24448 exposure.

There are no clinical data in this or previously conducted Org 24448 studies that support an association between cardiac status or myocarditis and exposure to Org 24448 in previous studies. Although a little fewer than half of the subjects previously exposed to Org 24448 were evaluated, no cases of myocarditis were found and few cardiac AEs were identified.

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The previously mentioned deaths were cardiac associated, but were not directly caused by myocarditis, and evidence of such was not found on autopsy. The subjects in this follow-up study included schizophrenic subjects and healthy volunteers. Although all Org 24448 subjects were not located, subjects representing all dose groups and durations of treatment were located and evaluated with no myocarditis identified.	
Date of the Report: 29 OCT 2009	