SYNOPSIS

Name of Sponsor: Medivation, Inc. (Medivation is now a wholly owned subsidiary of Pfizer Inc.)

Name of Finished Product: dimebon (latrepirdine)

Name of Active Ingredient: dimebon dihydrochloride (latrepirdine) (2,3,4,5-tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4,3-b]indole dihydrochloride)

Title of Study: CONCERT PLUS: An Open-Label Extension of the CONCERT Protocol (DIM18) Evaluating Dimebon (Latrepirdine) in Patients with Alzheimer's Disease

Protocol Number: DIM18EXT

Investigators: International, Multicenter

Study Center(s): 105 sites worldwide

Publication (Reference): NA

Phase of Development: 3

Study Period (Years):

First Subject Enrolled: 25 APR 2010

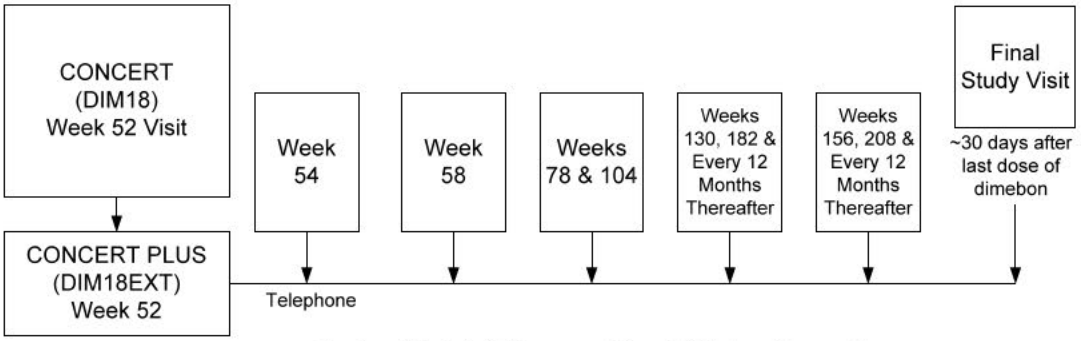
Last Subject Completed: 20 APR 2012

Study Objectives

Primary Objective:

- To evaluate the long-term safety and tolerability of dimebon (latrepirdine) in Alzheimer's disease (AD) patients who have completed 52 weeks of blinded treatment in the DIM18 (CONCERT) protocol.

Study Schematic:



Treatment Period: Until commercial availability in each respective country or until study termination as per Protocol Section 9.8.

Methods: This study was an open-label extension study evaluating one dose and regimen of oral dimebon (10 mg three times per day [TID] for 1 week followed by 20 mg TID thereafter), administered to patients with AD who completed 52 weeks of blinded treatment in the DIM18 (CONCERT) study. Seven hundred ninety-two patients completed 52 weeks of blinded treatment in the DIM18 study, of whom 672 participated in this DIM18EXT (CONCERT-PLUS) extension study after providing informed consent. Because the blinded 52-week DIM18 study was ongoing at the time that patients enrolled in the DIM18EXT study, all patients enrolled in the DIM18EXT study received dimebon 10 mg TID for the first 7 days, after which treatment with the maintenance dose of dimebon 20 mg TID was initiated. Patients then received dimebon 20 mg TID until the sponsor, Medivation, terminated this study on 17 January 2012, due to lack of efficacy in the blinded, placebo-controlled Phase 3 DIM18 study. Following the negative DIM18 study results, Medivation decided to discontinue the development program for dimebon. Investigators and patients were informed of the negative DIM18 study results and the decision to discontinue dimebon development, and advised DIM18EXT patients to discontinue dimebon treatment and to return for a 30-day safety follow-up visit. There were 520 patients ongoing in the DIM18EXT study when these decisions were communicated to investigators and study patients.

All serious adverse events continued to be entered into the safety database and events were followed until resolution whenever possible or until it was confirmed with the Principal Investigator that no additional follow-up information could be obtained.

Patients, Investigators, and members of Medivation's staff overseeing the conduct of the DIM18EXT study remained blinded to the original DIM18 individual subject treatment assignment at the time of the patient's enrollment into DIM18EXT order to maintain the blind for the DIM18 study until that study was formally unblinded. The last assessment performed in the DIM18 study at the Week 52 visit prior to initiation of open-label dimebon treatment served as the baseline reference for subsequent DIM18EXT assessments for safety. Throughout the DIM18EXT study, safety and tolerability were assessed by recording of adverse events and conducting safety laboratory evaluations. Central laboratories were utilized for laboratory safety assessments. Physical examinations, including vital signs and weight, were not performed routinely during the study, but were to be performed at any study visit as appropriate for evaluation of signs and symptoms assessed as possible adverse events. Study visits were conducted at intervals shown in the study schematic provided above, and unscheduled visits could be preformed at any time during the study whenever necessary to evaluate and/or conduct follow-up on an adverse event as deemed necessary by the investigator or subject.

Number of Patients (Planned and Analyzed): 672 patients were enrolled.

Diagnosis and Main Criteria for Inclusion:

Patients eligible to participate in DIM18EXT study were those who:

1. Had completed 52 weeks of blinded treatment in the DIM18 study with available Week 52 efficacy assessment data; at a minimum, the Week 52 Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) data must be available;
2. Were willing and able to give informed consent for study participation. If the patient is not competent, a mentally competent legally-acceptable representative must provide informed consent on their behalf, and the patient must provide verbal assent;
3. Had a caregiver who assists the patient, can oversee study drug administration, report adverse events, and provide written informed consent;
4. If female, were either a) of childbearing potential and compliant in using adequate birth control through 30 days after the last dose of study drug, or b) not of childbearing potential. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception (hormone-based, intrauterine device, barrier contraception [e.g., condom or occlusive cap {diaphragm or cervical/vault caps} with spermicidal foam/gel/film/cream/suppository], vasectomized partner, or sexual abstinence) throughout the duration of the study. Women not of childbearing potential may have undergone menopause or permanent sterilization (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation). Menopause is defined as 1 year without menses. If the patient's menopausal status is in question, a follicle-stimulating hormone (FSH) level of > 40 milli-international units per milliliter (mIU/mL) must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented;
5. If male, were either a) of reproductive potential and compliant in using adequate birth control through 30 days after the last dose of study drug, or b) not of reproductive potential. Surgical sterilization must be documented. Adequate birth control for males is defined as a condom and spermicidal gel or foam, or a condom in combination with an acceptable method of contraception for a female partner as specified in inclusion criterion 4, or abstinence throughout the duration of the study;
6. Were capable of complying with study procedures, including being able to swallow the study drug tablets.

Patients ineligible to participate in the DIM18EXT study were those who:

1. Had any major medical illness or unstable medical condition that may interfere with their ability to comply with study procedures and abide by study restrictions, which places the patient at undue risk, or may interfere with the ability to interpret safety information;
2. Were pregnant or breastfeeding females;
3. Planned to use bupropion, clozapine, or non-selective antihistamines such as chlorpheniramine and diphenhydramine, during this extension study;
4. Planned to participate in another study of an investigational product.

Test Product, Dose, and Mode of Administration, Lot Number: The investigational product evaluated in this study was dimebon dihydrochloride (2,3,4,5-tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4,3-b]indole dihydrochloride presented in a tablet formulation containing 20 mg or 5 mg active ingredient. There was to be a minimum of 4 hours between each dose. Study medication could be taken with or without food. No permanent dose adjustments were permitted under the protocol.

All subjects received dimebon 10 mg (as two 5 mg tablets) TID during the first week (Week 52) of the DIM18EXT study, followed by dimebon 20 mg (as one 20 mg tablet) TID for the remainder of the study. Lot [redacted] was used for the 5 mg tablets in this study, and Lots [redacted] were used for the 20 mg tablets in this study.

There was no reference therapy (i.e., no placebo) in this study.

Duration of Treatment: The study was planned to be continued until commercial availability in each patient's respective country, or until study termination by the sponsor, Medivation,

Criteria for Evaluation:

Safety:

The safety of dimebon was to be assessed by the frequency of serious adverse events, the frequency of discontinuation of dimebon treatment due to an adverse event, the frequency and severity of adverse events, as well as the frequency of new laboratory abnormalities. Safety measures included adverse events and clinical laboratory studies.

The following events were to result in the removal of patients from study drug treatment either permanently or until the etiology of the event had been identified and resolved:

- Seizure;
- Creatinine > 265 µmol/L (3.0 mg/dL);
- Any liver function test (Total Bilirubin [Tbili], Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST], or Alkaline Phosphatase) greater than five times the upper limit of normal;
- An absolute neutrophil count of ≤ 750/microliter (µL);
- A platelet concentration of < 75,000/µL;
- Pregnancy;
- Any adverse event that in the judgment of the Investigator and the medical monitor would lead to undue risk to the patient if dosing with study drug continued.

Patients removed from therapy for any reason continued to be followed for the collection of safety data for 30 days or until resolution or stabilization of any adverse event resulting in study discontinuation, whichever occurred first. If a patient refused further participation in the study, procedures for the Final Study Visit were completed if possible. For patients who refused further clinic study visits, telephone contact were attempted to review for adverse events 30 days after the last dose of study drug.

Statistical Methods: On 22 December 2012, the database management vendor for the DIM18EXT study ceased operations. In the context of the lack of efficacy of dimebon in two Phase 3 efficacy studies (DIM14 and DIM18) and the associated decision to discontinue the clinical development of dimebon, the remaining DIM18EXT case report form data were not entered into the database thereafter. The DIM18EXT Statistical Analysis Plan was not executed. Serious adverse event data only are presented for this study, for which 52-week safety data were analyzed in the preceding double-blind, randomized controlled Phase 3 DIM18 Study.

Summary and Overall Conclusions:

Safety Results:

The database management vendor for the DIM18 and DIM18EXT study ceased operations in December 2011 at which time DIM18EXT case report form receipt at Medivation was incomplete. In the context of the lack of efficacy of dimebon in two Phase 3 efficacy studies (DIM14 and DIM18) and the associated decision to discontinue the clinical development of dimebon, the remaining DIM18EXT case report form data were not entered into a database thereafter. All serious adverse events, however, continued to be entered into a separate safety database and events were followed until resolution whenever possible. Clinical laboratory data were monitored for safety signal detection. Serious adverse event data only are presented for this study.

170 serious adverse events were reported in 103 of the 672 patients (15.3%) enrolled in the DIM18EXT study. Event terms were classified into the following MedDRA System Organ Classes (in descending order of frequency): Nervous system disorders (31 [18.2%]), Infections and infestations (30 [17.6%]), Injury, poisoning and procedural complications (26 [15.3%]), Psychiatric disorders (20 [11.8%]), Reproductive system and breast disorders (1, 0.6%), Respiratory, thoracic and mediastinal disorders (11 [6.5%]), Cardiac disorders (10 [5.9%]), Neoplasm , malignant and unspecified (including cysts and polyps) (9 [5.4%]), Metabolism and nutrition disorders (7 [4.1%]), Gastrointestinal disorders (6 [3.5%]), Vascular disorders (5 [2.9%]), Musculoskeletal and connective tissue disorders (4 [2.4%]), General disorders and administration site disorders (2 [1.2%]), Renal and urinary disorders (3 [1.8%]), Ear and labyrinth disorders (2 [1.2%]), Eye disorders (2 [1.2%]), and Hepatobiliary disorders (1 [0.6%]). Fifteen SAEs accounted for 12 patient deaths during the two years that the DIM18EXT study was ongoing.

The most frequent serious adverse events by MedDRA Preferred Term were: fracture (12 in 10 patients [hip {3}, ankle {2}, femoral neck {2, same (1) patient}, humerus {2}, arm {1}, rib{1}. facial bones {1}]; fall (9 {8 patients]); urinary tract infection (8); syncope (6); aggression (5); pneumonia (5); presyncope (5); pulmonary embolism (5); agitation (4); loss of consciousness (4); confusional state (3); dehydration (3); diverticulitis (3); lower respiratory infection (3); pneumonia aspiration (3); sepsis (3); and transient ischemic attack (3). Two events of overdose [redacted] were reported in 1 patient [redacted] who presented with [redacted]. One "[redacted] dimebon overdose" was reported [redacted] with no associated adverse event. All other serious adverse events (by Preferred Term) were reported no more than twice.

Conclusions:

This report includes serious adverse event data from the 672 patients who were enrolled in the DIM18EXT open-label extension of the DIM18 study evaluating dimebon in patients with Alzheimer's disease. Dimebon was generally well-tolerated in this study. Serious adverse events were reported by 103 of the 672 (15.3%) patients enrolled in this study and twelve patients (1.8%) died during the two years that this study was ongoing. The most frequent serious adverse events (≥ 3 events) reported included falls, fractures, urinary tract infections, syncope, aggression and agitation, pneumonia and lower respiratory tract infections, sepsis and transient ischemic attack. The serious adverse events reported in this study were consistent with those reported in previous dimebon studies and the Dimebon Investigator's Brochure version 7.0 dated 17 JUN 2011, and are consistent with those reported in the Alzheimer's disease literature.

Date of Report: 23 JUL 2012