SYNOPSIS

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

Study Number: DIM14

Name of Finished Product: Dimebon (latrepirdine)

Name of Active Ingredient: Dimebon dihydrochloride (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: CONNECTION: A Global, Phase 3, Double-Blind, Placebo-Controlled, Safety and Efficacy Study of Oral Dimebon in Patients with Mild-to-Moderate Alzheimer's Disease

Study Center(s): 72 initiated, with 63 enrolling, in the United States, European Union, Russian Federation, and Chile

Phase of Development: Phase 3

Study Period:

First patient enrolled: 27 May 2008
Last patient completed: 10 December 2009

Objectives:

Co-Primary Objectives:

- To determine the benefit of dimebon (latrepirdine) as compared to placebo on the primary measure of cognition and memory, the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog);
- To determine the benefit of dimebon as compared to placebo on the primary measure of global function, the Clinician's Interview-Based Impression of Change, plus caregiver input (CIBIC-plus).

Secondary Objectives:

- Key Secondary Objective: To determine the benefit of dimebon as compared to placebo on a measure of self-care and daily function, the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL);
- To determine the benefit of dimebon as compared to placebo on a measure of behavior, the Neuropsychiatric Inventory (NPI);
- To determine the safety of treatment with dimebon as compared to placebo;
- To establish the covariates that may impact the variability in pharmacokinetic (PK) parameters;
- To develop a PK model linking dimebon exposure with efficacy and safety outcomes.

Methods:

This study was a global, Phase 3, randomized, double-blind, placebo-controlled, safety and efficacy study of two doses of oral dimebon (5 mg three times a day [TID] and 20 mg TID) administered for 26 weeks to patients with mild-to-moderate Alzheimer's disease (AD). Eligible patients had screening Mini-Mental State Examination (MMSE) scores of 10 through 24 and were not taking approved background antidementia therapies, including cholinesterase inhibitors and memantine. Patients were randomized 1:1:1 into three groups (dimebon 5 mg TID, dimebon 20 mg TID, and placebo). Patients randomized to dimebon 20 mg TID received dimebon 10 mg TID for the first 7 days of therapy, before titration up to dimebon 20 mg TID for the remainder of the treatment period.

Efficacy assessments including the ADAS-cog, ADCS-ADL, NPI, and the MMSE were performed at the Baseline visit and at the Weeks 12 and 26 visits. The CIBIC-plus was performed at the Weeks 12 and 26 visits after severity was established at the Baseline visit using the Clinician's Interview-Based Impression of Severity (CIBIS). The MMSE was also performed at the Weeks 6 and 18 visits.

Throughout the study, safety and tolerability were assessed by recording of adverse events (AEs), monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs).

Pharmacokinetic samples were collected to measure dimebon plasma concentrations just prior to a dose (C_{min}) and then at 1 hour post-dose (C_{1h}) at Baseline and at Weeks 1, 2, 6, 12, 18, and 26. Additional PK samples were collected at Weeks 6 and 18 (prior to discharge from the clinic) and Week 12 (at 2 and 3 hours post-dose).

Number of Patients: 525 patients planned; 598 patients randomized

Diagnosis and Main Criteria for Inclusion:

Inclusion: men or women ≥ 50 years of age; diagnosis of AD according to standard criteria; brain imaging within 3 months; women who were surgically sterile, postmenopausal, or willing to use a double-barrier method of birth control; men willing to use double-barrier birth control. Exclusion: major structural brain disease; major medical illness, physical disability, or unstable medical condition; clinically significant laboratory abnormalities; use of cholinesterase inhibitors or memantine within 90 days; participation in another dimebon trial; participation in investigational drug or device study within 30 days prior to study entry.

Test Product, Dose and Mode of Administration, Lot Number:

Dimebon dihydrochloride (2,3,4,5 tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4,3-b]indole dihydrochloride).

Low-dose group: dimebon, 5 mg (one 5 mg tablet plus one placebo tablet) orally TID for 1 week, then dimebon, 5 mg (one 5 mg tablet) orally TID for 25 weeks.

High-dose group: dimebon, 10 mg (two 5 mg tablets) orally TID for 1 week, then dimebon 20 mg (one 20 mg tablet) orally TID for 25 weeks.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Matching placebo: two placebo tablets orally TID for 1 week, then one placebo tablet orally TID for 25 weeks.

Criteria for Evaluation:

Efficacy Evaluations:

The study had co-primary outcome measures including: 1) a comparison between the mean changes from baseline in the dimebon 20 mg TID treatment group and the placebo group on the ADAS-cog total score at Week 26; and 2) a comparison of the distributions of the CIBIC-plus (ADCS-CGIC) at Week 26 in the dimebon 20 mg TID treatment group and the placebo group.

Key secondary outcome measures included: a comparison between the mean changes from baseline to Week 26 of the dimebon 20 mg TID treatment group and the placebo group on the ADCS-ADL total score; a comparison between the mean changes from baseline in the dimebon 5 mg TID treatment group and the placebo group on the ADAS-cog total score at Week 26; and a comparison of the distributions of the CIBIC-plus (ADCS-CGIC) at Week 26 in the dimebon 5 mg TID treatment group and the placebo group.

Other secondary outcome measures included: a comparison between the mean changes from baseline to Week 26 of the dimebon 20 mg TID treatment group and the placebo group on the NPI total score; a comparison between the mean changes from baseline to Week 26 of the dimebon 20 mg TID treatment group and the placebo group on the MMSE total score; and a comparison between the overall benefit (response) rates (defined as at least a 4-point improvement in the cognitive measure (ADAS-cog total score) and at least not worsening (maintenance/improvement) in the global and functional domains (CIBIC-plus and the ADCS-ADL total score at Week 26) of the dimebon 20 mg TID treatment group and the placebo group. Comparisons between the dimebon 5 mg TID group and the placebo group using the mean changes from baseline to Week 26 on ADCS-ADL total score, NPI total score, MMSE total score, and overall benefit response were also performed.

Safety Evaluations:

The safety of dimebon was assessed by the frequency and severity of AEs, the frequency of serious adverse events , the frequency of discontinuation of dimebon treatment due to an AE, vital signs, physical examinations, and the frequency of new laboratory and ECG abnormalities.

Pharmacokinetics Evaluations:

Dimebon plasma concentrations for all patients were tabulated by visit and reported by the elapsed time since the most recent dose.

Statistical Methods:

All efficacy analyses were conducted in an Intent-to-Treat (ITT) Population defined as all randomized patients who had a baseline outcome assessment and at least one scheduled post-baseline assessment.

Co-Primary Efficacy Endpoints:

There were two co-primary efficacy analyses, one based on the ADAS-cog total score and the other based on the CIBIC-plus (ADCS-CGIC). The co-primary analysis for the ADAS-cog total score compared the mean

changes from baseline in the dimebon 20 mg TID and placebo groups using a 2-sided test at the 0.05 level of significance. The co-primary analysis for the CIBIC-plus compared the distributions in the dimebon 20 mg TID and placebo groups, also using a 2-sided test at the 0.05 level of significance.

Secondary Efficacy Endpoints:

- Key secondary efficacy endpoint: Mean change on the ADCS-ADL total score from Baseline to Week 26 comparing dimebon 20 mg TID to placebo;
- Key secondary efficacy endpoint: Mean change on the ADAS-cog total score from Baseline to Week 26 comparing dimebon 5 mg TID to placebo;
- Key secondary efficacy endpoint: Distributions of CIBIC-plus score at Week 26 comparing dimebon 5 mg TID to placebo;
- Mean change on the NPI score from Baseline to Week 26 comparing dimebon 20 mg TID to placebo;
- Mean change on the MMSE score from Baseline to Week 26 comparing dimebon 20 mg TID to placebo;
- Overall benefit (response) rates at Week 26 comparing dimebon 20 mg TID to placebo;
- Mean change on the ADCS-ADL total score from Baseline to Week 26 comparing dimebon 5 mg TID to placebo;
- Mean change on the NPI score from Baseline to Week 26 comparing dimebon 5 mg TID to placebo;
- Mean change on the MMSE score from Baseline to Week 26 comparing dimebon 5 mg TID to placebo;
- Overall benefit (response) rates at Week 26 comparing dimebon 5 mg TID to placebo;
- The Type 1 error rate was preserved for the key secondary endpoints by fixed sequence testing.

Pharmacokinetic Analyses:

Descriptive statistics were used to summarize the dimebon plasma concentrations by dose group for each collection timepoint at Baseline and at Weeks 1, 2, 6, 12, 18, and 26.

Safety Analyses:

Safety was assessed through summaries of AEs, laboratory evaluations, ECGs, vital signs, and physical examinations.

Summary and Conclusions:

Disposition and Baseline Characteristics:

A total of 598 patients were enrolled, 200 in each of the dimebon groups and 198 in the placebo group. Overall, patient disposition was similar between the dimebon and placebo groups. Approximately 90% of patients completed the study. AEs were the reason for withdrawal in less than 5% of patients across all treatment groups.

The treatment groups were well matched with regard to demographics and other baseline characteristics and to baseline efficacy measurements. The majority of the patients were enrolled in the US and Chile.

Efficacy Results:

No statistically significant improvements for either the 20 mg or the 5 mg group relative to placebo were achieved on the co-primary or secondary endpoints at weeks 12 or 26.

Pharmacokinetics Results:

Based on mean and median concentration values, an approximate 4-fold increase in dimebon concentrations was seen between the 5 and 20 mg doses, demonstrating that dimebon exposures increased proportionally with dose.

Safety Results:

Safety results showed that the drug was generally safe and well tolerated. AEs were approximately equally distributed between the dimebon 20 mg and placebo groups, with slightly fewer in the 5 mg group. The numbers of patients with SAEs were similar among the three groups. A total of 144 patients (72.0%) with at least one AE were reported in the dimebon 20 mg group and 147 (74.2%) in the placebo group, while there were 123 (61.5%) in the 5 mg group. While urinary tract infection, somnolence, and fall were the most common events reported overall in 9.7%, 8.5% and 8.2% of the total number of patients, respectively, those events reported at ≥5% frequency and more commonly than placebo were somnolence (11.0% and 4.5% in the dimebon 20 mg TID and dimebon 5 mg TID groups, respectively, vs. 10.1% in the placebo TID group), headache (9.5% and 5.5%, vs. 5.6%), dry mouth (8.5% and 5.5% vs. 6.6%), dizziness (7.5% and 3.5% vs. 5.1%), depression (6.0% and 3.5% vs. 3.5%), constipation (5.5% and 5.5% vs. 3.5%),), and fatigue (2.5% and 5.5% vs. 4.0%respectively.

No clinically important trends were observed in laboratory test results, ECGs, vital signs, or physical examinations.

Conclusions:

The efficacy of dimebon in the treatment of patients with mild-to-moderate AD was not demonstrated by the results of this trial. Dimebon was safe and well tolerated in this study of patients with mild-to-moderate AD.

Date of Report: 19 JUL 2012