SYNOPSIS

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

Name of Finished Product: Dimebon dihydrochloride (latrepirdine)

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

Study Number: DIM19

Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Six-Month, Safety and Efficacy Study of Dimebon in Patients with Moderate-to-Severe Alzheimer's Disease and Neuropsychiatric Symptoms

Investigators: South America and Europe

Study Centers: Approximately 70

Publication: None

Phase of Development: Phase 3

Study Period:

First Subject Enrolled: 29 OCT 2009
Last Subject Completed: 13 AUG 2010

Objectives:

Co-Primary Objectives:

- To evaluate the efficacy of dimebon (latrepirdine) as compared to placebo on a measure of behavior, the Neuropsychiatric Inventory (NPI);
- To evaluate the efficacy 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 (severe) (ADCS-ADL_{sev}).

Key Secondary Objectives:

- To evaluate the efficacy of dimebon as compared to placebo on the primary measure of cognition, the Severe Impairment Battery (SIB);
- To evaluate the efficacy of dimebon as compared to placebo on a measure of the psychosis of Alzheimer's Disease (AD) as measured by the delusions and hallucinations domains of the NPI;

Additional Secondary Objectives:

- To evaluate the efficacy of dimebon as compared to placebo on the secondary measure of cognition, the Mini-Mental State Examination (MMSE);
- To evaluate the efficacy 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);
- To evaluate the pharmacoeconomic impact of dimebon and placebo using the Resource Utilization in Dementia Lite (RUD Lite©) instrument;
- To evaluate quality of life using the EuroQoL 5 Domain Health Quality Assessment (EQ-5D) instrument;
- To evaluate the safety and tolerability of dimebon, 20 mg orally 3 times per day (TID), as compared to placebo;
- To obtain selected pharmacokinetics (PK) data for the 20 mg TID dosage regimen of dimebon.

Methods: This study was a multicenter, Phase 3, randomized, double-blind, placebo-controlled, safety and efficacy study of 6 months of dimebon treatment in patients with moderate-to-severe AD with behavioral and psychiatric symptoms. Patients with moderate-to-severe AD were defined as those with probable AD and a screening MMSE score of 5 to 14, inclusive. The study was terminated early by the sponsor after efficacy was not confirmed in a Phase 3 Alzheimer's disease study (DIM14) and the development of dimebon in moderate-to-severe AD patients was discontinued. This study was not terminated due to any safety issues.

All eligible patients must have been treated with donepezil at a stable dose (5 or 10 mg daily) for at least 4 months immediately prior to the Screening visit. To be considered at the Screening visit, patients must have had behavioral and psychiatric symptoms defined as (a) protocol-defined delusions and/or hallucinations (defined as an NPI score ≥ 6 on the domains of delusions and hallucinations, with delusions and/or visual or auditory hallucinations present at least intermittently for a minimum of 4 weeks), or (b) a minimum general level of neuropsychiatric symptomatology (defined as a total NPI score ≥ 15 but with an NPI score < 6 on the domains of delusions and hallucinations) and a score on the Cohen Mansfield Agitation Inventory (CMAI) of at least 15). To be considered still eligible at the Baseline visit, patients must again have met either criterion "a" or "b" prior to randomization. The study was designed to evaluate oral dimebon 20 mg TID administered for 6 months (26 weeks) for the primary efficacy and safety analyses. Patients were required to be living in the community or relatively independently in a nursing home or other institutional setting, to be ambulatory at least with assistance devices, and to have had a caregiver who assisted the patient at least 5 days per week for at least 3 hours per day.

Approximately 600 patients were to be centrally randomized 1:1 into 2 groups of approximately 300 patients each (dimebon 20 mg TID or placebo). Randomization was stratified by Screening MMSE (10 or less and greater than 10) and presence or absence of protocol-defined delusions and/or hallucinations as defined by criterion "a" above at the Baseline visit. Patients randomized to dimebon received dimebon 10 mg TID for the first 7 days of therapy, followed by titration up to dimebon 20 mg TID for the remainder of the treatment period.

At the Screening visit, the MMSE and NPI were administered. If the NPI score for the domains of delusions plus hallucinations was less than 6 but the total score was at least 15, the CMAI was also performed. Efficacy assessments including the NPI and ADCS-ADL_{sev} were performed at the Baseline visit, and at the Weeks 6, 12, 18, and 26 visits. The Severe Impairment Battery (SIB) was performed at the Baseline visit and at Weeks 12, 18, and 26, while the MMSE was performed at the Screening and Baseline visits as well as at Weeks 12 and 26. The Clinician's Interview-Based Impression of Severity (CIBIS) was performed at the Baseline visit and the CIBIC-plus was performed at the Weeks 12 and 26 visits. The RUD Lite and EQ-5D were performed at the Baseline visit and at the Week 26 visit. An independent rater not involved in and blinded to other aspects of the trial administered the CIBIC-plus, which in this trial was the ADCS – Clinician's Global Impression of Change (ADCS-CGIC). All other efficacy assessments were to be performed by raters not necessarily blinded to other aspects of the trial. The same rater was to continue to perform the same efficacy assessments for a specific patient throughout the study for as long as possible.

Safety and tolerability were assessed by recording of adverse events (AEs) and serious AEs (SAEs) and by monitoring of vital signs, physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). Central laboratories were used for laboratory safety assessments and ECG assessments. An independent Data Monitoring Committee monitored safety data in the trial by blinded treatment group on an ongoing basis.

Prior to dosing (Day 1), a whole blood sample was collected for cytochrome P450 (CYP) 2D6 and apolipoprotein E (ApoE) genotyping analyses. PK plasma samples to assess dimebon plasma concentrations were collected on Day 1 and Week 12 at pre-specified times pre- and post-dose.

Patients who completed the 26-week study were to be offered the opportunity to enroll into an open-label extension study through marketing authorization in their respective countries. The extension study was not implemented due to the discontinuation of the double-blind study. Patients completing the study returned to the clinic at Week 30 for a safety follow-up visit. Those not completing the study returned to the clinic 4 weeks after an Early Termination visit triggered by cessation of study drug or early termination of the study by the sponsor for their safety follow-up evaluations.

Number of Patients (Planned and Analyzed): Approximately 600 moderate-to-severe AD patients with behavioral and psychiatric symptoms were planned. Actual enrollment was a total of 89 patients, with 41 having received dimebon and 48 placebo.

Diagnosis and Main Criteria for Inclusion:

1. Men and women ≥ 50 years of age with probable AD judged to be moderate-to-severe (based on a Screening MMSE of 5 to 14, inclusive) and who were diagnosed according to the following criteria:
   a. Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV-TR);
   b. National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorder Association's Criteria (NINCDS-ADRDA) for probable AD;
   c. MMSE score of 5 to 14, inclusive;
   d. Modified Hachinski Ischemic Score ≤ 4;
2. Met either criterion "a" or "b" (see below) at the Screening visit, and again either of these criteria at the Baseline visit:
   a. Protocol-defined delusions and/or hallucinations, defined as an NPI score ≥ 6 on the domains of delusions and/or hallucinations, with delusions and/or visual or auditory hallucinations present at least intermittently for a minimum of 4 weeks; or
   b. NPI total score ≥ 15 (without protocol-defined delusions and hallucinations) and a CMAI score ≥ 15;
3. Had symptoms of delusions and/or hallucinations, if present, that developed after the onset of dementia and that were judged by the investigator and caregiver to be severe enough to disrupt the patient's and/or other's functioning;
4. Willing and able to give informed consent. If, and only if, the patient was not competent, a mentally-competent legally-acceptable representative must have provided informed consent on his/her behalf, and the patient must have provided verbal assent, if appropriate per local ethics committee judgment and consistent with local laws;
5. Had brain imaging such as computed tomography (CT) and/or magnetic resonance imaging (MRI) within 12 months of enrollment, consistent with a diagnosis of probable AD without any other clinically significant comorbid pathologies found. If there had been a significant change in clinical status suggestive of stroke or other possible central nervous system disease as assessed by the investigator with onset between the time of the last CT or MRI and the Screening visit, the scan was to be repeated;
6. Had been taking the cholinesterase inhibitor, donepezil, with stable dosing at 5 or 10 mg/day for at least the last 4 months immediately prior to Screening (and with no intent to change for the duration of the study);
7. Ambulatory and permitted to use an assistance device (e.g., walker or cane);
8. Previously (in pre-AD condition) capable of reading, writing, and communicating effectively with others;
9. Had a caregiver who assisted (or directly supervised) the patient at least 5 days per week for at least 3 hours per day and had intimate knowledge of the patient's cognitive, functional, and emotional states, and of the patient's personal care. The caregiver must have been willing to accompany the patient to all study visits, supervise study drug administration, and (in addition to the patient) report AEs. The caregiver must have been willing and able to give informed consent, able to read and write, and capable of providing responses to the NPI, ADCS-ADL_{sev}, EQ-5D, CIBIC-plus, and RUD Lite assessment tools;
10. Living in the community or relatively independently in a nursing home or other institutional setting, with a caregiver as defined in Inclusion Criterion 9;
11. If female, were either (a) of childbearing potential and compliant in using adequate birth control 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 was in question, a follicle-stimulating hormone (FSH) level of > 40 milli international units per milliliter (mIU/mL) must have been documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must have been documented;
12. 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 have been documented. Adequate birth control for males was defined as a condom and spermicidal gel or foam, or abstinence throughout the duration of the study.

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) (latrepirdine), presented in a tablet formulation containing 20 mg or 5 mg active ingredient, was used for TID oral administration in this protocol.

All patients received 2 tablets of study drug TID during Week 1 and 1 tablet of study drug TID for the remaining 25 weeks. Dimebon-treated patients received 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.

Duration of Treatment: 26 weeks (6 months)

Reference Therapy, Dose and Mode of Administration, Lot Number: Placebo tablets were identical in appearance, taste, and odor to the active dimebon tablets and included the following inactive components: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and Opadry II™ film coating. A placebo matched the 5 mg active tablet (100 mg core) and a placebo matched the 20 mg active tablet (200 mg core). During the initial 1-week titration period, patients randomized to placebo received 2 tablets orally TID; thereafter, subjects received 1 tablet orally TID through the Week 26 visit.

Criteria for Evaluation:

Efficacy

1. Co-primary outcome measures:
   a. A comparison between the mean change from Baseline to Week 26 in the dimebon group and the placebo group on the NPI total score;
   b. A comparison between the mean change from Baseline to Week 26 in the dimebon group and the placebo group on the ADCS-ADL_{sev};
2. Key secondary outcome measures:
   a. A comparison between the mean change from Baseline to Week 26 of the dimebon group and the placebo group on the SIB;
   b. A comparison of the response rates based on the NPI domains of delusions and hallucinations at Week 26;
3. Additional secondary outcomes:
   a. A comparison between the mean change from Baseline to Week 26 of the dimebon group and the placebo group on the MMSE;
   b. A comparison between the distributions of the dimebon group and the placebo group on the CIBIC-plus (ADCS-CGIC) at Week 26;
   c. Comparisons of the dimebon group and the placebo group at Weeks 6, 12, and 18 for all outcomes, as applicable;
   d. RUD Lite and EQ-5D data summarized descriptively by treatment group.

Safety

The safety of dimebon was assessed by the frequency of SAEs, the frequency of discontinuation of study drug treatment due to AEs, the frequency and severity of AEs, and the frequency of new and clinically significant laboratory and ECG abnormalities.

Pharmacokinetics

Dimebon plasma concentrations were measured at Baseline and Week 12.

Statistical Methods: No efficacy or PK analyses were conducted due to the early termination of the study by the sponsor for reasons unrelated to safety.

Safety Analyses

Safety was assessed through summaries of AEs, vital signs (including change from Baseline), physical examinations, ECGs, and clinical laboratory test data (including change from Baseline). Safety analyses included all randomized subjects who received at least 1 dose of study drug (safety population). All AEs were coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers and percentages of patients with AEs were presented by MedDRA system organ class and preferred term. Laboratory values and vital signs were summarized by potentially significant results. The percentages of patients in each treatment group with abnormal, clinically-significant ECG findings were summarized by study visit.

Results and Conclusions:

Safety Results

All 89 subjects enrolled (41 dimebon, 48 placebo) were included in the safety population (Table 14.1.1). Only three (7.3%) dimebon and two (4.2%) placebo patients completed the study as planned before the sponsor terminated the study and moderate-to-severe AD program. Overall, demographic and other baseline characteristics were well balanced between the 2 groups (Tables 14.1.3, 14.1.4, 14.1.5). The overall percentage of patients reporting at least one treatment-emergent AE was 65.9% in the dimebon group and 60.4% in the placebo group (Table 14.3.1.1). The most common AE by overall incidence was somnolence (15.7%), occurring in 10 patients (24.4%) with dimebon treatment and 4 patients (8.3%) with placebo treatment. The second most common was diarrhea (6.7%), occurring in 3 patients (7.3%) with dimebon treatment and 3 patients (6.3%) with placebo treatment; the third most common was agitation (5.6%) occurring in 0 patients with dimebon treatment and 5 patients (10.4%) with placebo treatment. Other events reported in at least 2 more dimebon patients compared to placebo patients were fall (4 [9.8%] dimebon, 0 placebo), aggression (2 [4.9%] dimebon, 0 placebo), constipation (2 [4.9%] dimebon, 0 placebo), diabetes mellitus (2 [4.9%] dimebon, 0 placebo), and syncope (2 [4.9%] dimebon, 0 placebo). Two patients, both in the dimebon group, had treatment-emergent AEs leading to discontinuation, one with syncope and another with aggression (Table 14.3.1.2). In the dimebon group, 3 patients (7.3%) had treatment-emergent SAEs, including loss of consciousness, syncope, and aggression; the only SAE in the placebo group (2.1%) was gastroenteritis (Table 14.3.2.1). No clinically important, treatment-related trends were seen in the analyses of potentially significant laboratory results (Tables 14.3.4.4 and 14.3.4.8); vital signs (Table 14.3.5.1.1); or ECGs (Tables 14.3.6.1). Overall, new ECG abnormalities were centrally reported in 16 (39%) of dimebon patients and 18 (37.5%) of placebo patients (Table 14.3.6.2). ECG abnormalities reported in at least 2 more dimebon patients compared to placebo patients were atrial premature complexes (4 [9.8%] dimebon, 2 [4.2%] placebo), intraventricular conduction defect (2 [4.9%] dimebon, 0 placebo), and ventricular premature complexes (3 [7.3%] dimebon, 0 placebo).

Conclusions

Dimebon was generally well tolerated in the patients with moderate-to-severe Alzheimer's disease with behavioral and psychiatric symptoms, who enrolled in this study, which was terminated early after efficacy was not confirmed in another Phase 3 Alzheimer's disease study (DIM14) and the development of dimebon in moderate-to-severe AD patients was discontinued. This study was not terminated due to any safety issues. As expected from previous experience, somnolence was the most common AE in the dimebon group and the AE that occurred at the highest rate compared to placebo. Other AEs and overall SAEs were reported with relatively low incidence, and no unexpected events or clinically important safety concerns were identified.

Date of Report: 13 SEP 2011