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 (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 PLUS: An Open-Label Extension of the CONNECTION Protocol (DIM14) Evaluating Oral Dimebon in Patients with Alzheimer's Disease

Protocol Number: DIM14EXT

Investigators: Multiple; same Investigators as the Phase 3 randomized, double-blind, placebo-controlled DIM14 Study.

Study Center(s): 63 (Thirty centers in the United States, 16 in the European Union, 10 in Chile, and 7 in Russia).

Publication (Reference): None

Phase of Development: Phase 3

Study Period (Years):

First Subject Enrolled: 01 DEC 2008

Last Subject Completed: 06 OCT 2010

Study Objectives:

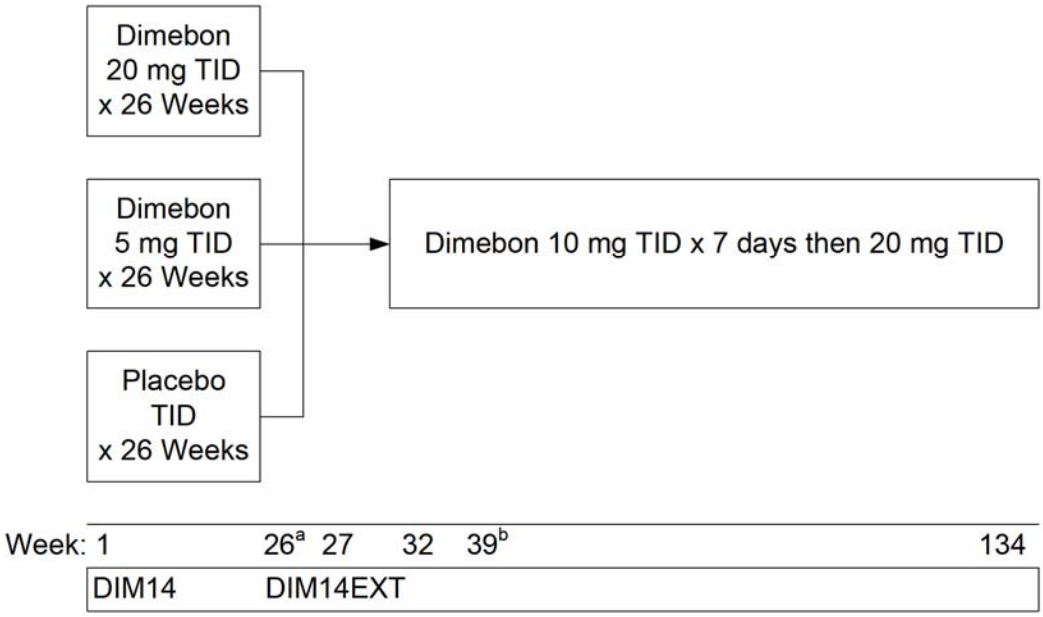
Primary Objective:

- To evaluate the long-term safety and tolerability of dimebon in Alzheimer's disease (AD) patients who had successfully completed 26 weeks of blinded treatment in the DIM14 (CONNECTION) Study.

Secondary Objectives:

- To characterize the effects of dimebon in the above patients over 12 months on:
  - Two measures of cognition, the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and the Mini-Mental State Examination (MMSE);
  - A global measure of function, the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus);
  - A measure of self-care and daily function, the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL);
  - A measure of behavior, the Neuropsychiatric Inventory (NPI);
- To characterize the impact of treatment with dimebon in the above patients over 12 months on a measure of health care utilization, the Resource Utilization in Dementia Lite © (RUD Lite).

Study Schematic:



[a] At Week 26, DIM14 patients were evaluated for DIM14EXT; each eligible patient for whom consent (and assent, if applicable) was obtained, began dimebon 10 mg TID initially and then 20 mg TID on DIM14EXT.
[b] And every 13 weeks thereafter for Follow-Up Visits.

Methods: This study, DIM14EXT (CONNECTION PLUS), was a Phase 3, open-label extension study to assess the safety, tolerability, and efficacy of dimebon in patients with AD who had successfully completed the 26-week Phase 3 randomized, double-blind, placebo-controlled study, DIM14.

At the final DIM14 study visit (Week 26), upon completion of DIM14 procedures and assessments, patients were evaluated per the DIM14EXT Protocol for participation in this open-label extension study. Patient informed consent or assent, caregiver informed consent, and, if applicable, legally-acceptable representative informed consent for DIM14EXT were obtained for each patient who satisfied DIM14EXT inclusion and exclusion criteria. Treatment with open-label dimebon was initiated at 10 mg orally 3 times per day (TID) for 1 week for all eligible patients in order to maintain the blind for DIM14, which was ongoing during most of the time of conduct of DIM14EXT. Thereafter, all patients continued open-label study drug dosing with dimebon 20 mg TID.

Safety and tolerability were assessed throughout the study by monitoring adverse events, vital signs, physical examination findings, clinical laboratory measurements (hematology, chemistry, and urinalysis), and 12-lead electrocardiogram (ECG) recordings. Efficacy was assessed using the ADAS-cog, MMSE, CIBIC-plus, ADCS-ADL, NPI, and RUD Lite instruments.

DIM14EXT was discontinued by the Sponsor on 07 May 2010 because results from DIM14 did not show a significant dimebon treatment effect versus placebo on cognition, overall function, activities of daily living, or behavior.

Number of Patients (Planned and Analyzed): Enrollment of up to approximately 525 patients and analyses of all safety and efficacy data were planned; 514 patients were enrolled and safety data for these patients were analyzed. Because the study was discontinued by the Sponsor, efficacy data were not analyzed.

Diagnosis and Main Criteria for Inclusion: Eligible patients were those patients who had successfully completed 26 weeks of blinded treatment in DIM14 for whom Week 26 efficacy assessment (ADAS-cog, CIBIC-plus, MMSE, ADCS-ADL, NPI, and the RUD Lite [or at a minimum, Week 26 ADAS-cog]) data were available; women were surgically sterile, postmenopausal, or willing to use double-barrier methods of birth control; men were willing to use double-barrier birth control. Patients must not have had any major medical illnesses or unstable medical conditions that could have interfered with the ability to comply with study

procedures or abide by study restrictions or that could have interfered with safety information interpretation and must not have planned to use bupropion, clozapine, or nonselective antihistamines during participation in DIM14EXT.

Test product, Dose and Mode of Administration, Lot Number: The active pharmaceutical ingredient of dimebon is 2,3,4,5-tetrahydro-2,8-dimethyl-5-[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4,3-b]indole dihydrochloride. Immediate-release tablets are available in 5, 10, and 20 mg strengths based on the dihydrochloride salt. Dimebon is administered orally TID with a minimum of 4 hours between doses. Dimebon may be taken with or without food. All patients initially received dimebon 10 mg (administered as two 5 mg tablets) orally TID for 7 days, followed by the maintenance dose of 20 mg (administered as a single tablet) orally TID for the duration of study participation. The dimebon lot numbers are provided in Table 9.1-1.

Duration of Treatment: Dimebon dosing in DIM14EXT was initiated on 01 December 2008 and was anticipated to continue through marketing authorization of dimebon for the treatment of AD. The study was stopped by the Sponsor on 07 May 2010 in the context of the lack of dimebon efficacy in the Phase 3 DIM14 study. The actual duration of exposure to dimebon during DIM14EXT was variable, based on the timing of enrollment, but ranged from less than 1 week to 81 weeks, with a median of 38 weeks. Most patients discontinued study drug because of study closure.

Reference Therapy, Dose and Mode of Administration, Lot Number: This was an open-label study; there was no reference therapy.

Criteria for Evaluation:

Efficacy:

The secondary objectives of DIM14EXT were to characterize, as determined by the mean changes from the DIM14 baseline (by treatment group assigned in DIM14), through Week 78 the effects of dimebon on ADAS-cog, MMSE, CIBIC-plus, ADCS-ADL, NPI, and RUD-Lite scores.

Safety:

The primary objective of DIM14EXT was to assess the safety and tolerability of dimebon through analyses of adverse events and results of clinical safety laboratory tests, vital sign assessments, physical examinations, and ECG recordings.

Statistical Methods: Safety analyses included all patients who received at least 1 dose of dimebon in DIM14EXT. Safety was analyzed through summaries of adverse events, the frequency of discontinuation of dimebon treatment due to adverse events, laboratory evaluations, and ECG recordings.

Analyses include all exposure to dimebon which may have started in either DIM14 or DIM14EXT, labeled in the in-text and after-text tables and in the listings as “DIM14 Extension or DIM14 Dimebon” or “DIM14EXT or DIM14 Dimebon,” and exposure to dimebon during DIM14EXT only, labeled as “DIM14 Extension,” “DIM14EXT,” or “DIM14EXT Only.” Patients who received placebo in DIM14 only contributed data to this report for the time they received dimebon in DIM14EXT and during any periods of relevant follow-up. Patients who received dimebon in DIM14 contributed data from both DIM14 and DIM14EXT to this report (for the purpose of providing safety information for cumulative exposure across both studies). Days on study were calculated using the first dose of dimebon in DIM14 or in DIM14EXT as Day 1, as appropriate. For safety analyses, baseline was defined as the last evaluation performed before the first dose of dimebon in either DIM14 or DIM14EXT. The exceptions were ECG parameters and adverse events. For ECGs, for each patient randomized to dimebon in DIM14, baseline is the mean of the 3 pretreatment values obtained before starting study drug in DIM14; for each patient randomized to placebo in DIM14, baseline is the last ECG recorded during DIM14 before enrollment in DIM14EXT. Adverse events which were ongoing at the time of enrollment in DIM14EXT, and which did not, by definition, limit participation to DIM14EXT, were captured as ongoing on the DIM14EXT adverse event case report form.

All adverse events were coded to preferred terms, higher level terms, and System Organ Classes (SOCs) using the Medical Dictionary for Regulatory Activities version 9.1. The numbers and percentages of patients with adverse events are presented by SOC and preferred term, relationship to study drug, and severity. Descriptive statistics were used.

Laboratory values were listed. Summary statistics (mean [standard deviation], median, minimum and maximum values) were provided for hematology and chemistry results and changes from baseline. Potentially

clinically significant hematology and chemistry values (changed 2 or more Common Toxicity Criteria for Adverse Events [version 4.0] grades from baseline) were provided. Shift tables of baseline results to each of the subsequent visits were produced for results of urine protein and blood. In-clinic and core laboratory ECG findings were listed by study visit.

Summary analyses did not include efficacy endpoints. Efficacy data are provided as listings only.

Summary and Overall Conclusions:

Efficacy Results:

Efficacy data were not analyzed in the context of the lack of dimebon efficacy in the preceding randomized, double-blind, placebo-controlled study, DIM14.

Safety Results:

Of the 514 patients who received dimebon across both the open-label DIM14EXT and the randomized, double-blind placebo-controlled DIM14 combined, or starting in DIM14EXT for those patients who received placebo during DIM14, 413/514 patients (80.4%) experienced a total of 2093 adverse events, 71 (13.8%) patients had serious adverse events, 62 (12.1%) patients had severe adverse events, and 39 (7.6%) patients discontinued study drug due to adverse events. Of the 2093 adverse events reported for dimebon-treated patients across both studies, 383 (18.3%) adverse events were considered by Investigators to be related to study drug.

In the open-label study, DIM14EXT only (with a median duration of dimebon exposure of 38 weeks [range < 1 week to 81 weeks]), 372/514 (72.4%) patients experienced 1272 adverse events; 61 (11.9%) patients had serious adverse events; 61 (11.9%) patients had severe adverse events, and 39 (7.6%) patients discontinued treatment due to adverse events. A total of 179 events (14.1%) reported for 106 patients (20.6%) were considered by Investigators to be related to study drug. Ten patients died during DIM14EXT. None of these deaths were considered by Investigators to be related to study drug.

Infections and Infestations was the System Organ Class with the highest incidence of all-causality adverse events, which occurred in 33.1% of dimebon-treated patients across both DIM14EXT and DIM14 combined and in 24.7% of dimebon-treated patients in DIM14EXT only.

All-causality adverse events that occurred in 5% or more of dimebon-treated patients across both DIM14EXT and DIM14 combined included urinary tract infection (13.2%) and fall (10.1%). The other adverse events that occurred in 5% of more of patients in the dimebon group across both DIM14EXT and DIM14 combined were, in order of frequency, headache, somnolence, diarrhea, depression, insomnia, agitation, irritability, dizziness, dry mouth, constipation, and hypertension. All-causality adverse events that occurred in 5% or more dimebon-treated patients in DIM14EXT only were urinary tract infection (9.7%) and fall (6.6%). No other adverse events occurred in 5% or more of patients in DIM14EXT only.

Convulsion or grand mal convulsion was reported in 3 patients (0.6%) during DIM14EXT. For 2 of the patients, the events were witnessed and tonic-clonic activity was observed, and, for 1 patient, the event was a possible seizure with focal tremor associated with a diagnosis of hypertensive encephalopathy. For 2 patients, the events led to study drug discontinuation, and for 1 patient (Patient 50343-2038), repeated tonic-clonic seizures (4 adverse events) were reported after the fact, and, following their discovery, the patient was lost to follow-up, but the patient had continued study drug for several months without apparent aggravation of the seizure disorder. This patient had been randomized to receive dimebon 5 mg TID during the prior DIM14 Study.

Most adverse events in dimebon-treated patients that occurred across both DIM14 and DIM14EXT combined and in DIM14EXT only were considered to be mild or moderate by an Investigator. Across DIM14 and DIM14EXT combined, 12 (2.3%) dimebon-treated patients had fifteen 24-hour notification events. During DIM14EXT, 8 (1.6%) patients had eight 24-hour notification adverse events. Adverse events reported as 24-hour notifications in DIM14EXT were fall (4 patients) and loss of consciousness, syncope, and presyncope (each 1 patient).

Haematuria, reported in 2.3% patients receiving dimebon in both DIM14 and DIM14EXT and in 1.6% patients in DIM14EXT only, was the laboratory abnormality most commonly reported as an adverse event. No adverse events of haematuria were considered by Investigators as possibly, probably, or definitely related to study drug. These laboratory findings were generally without clinical sequelae and without findings of red blood cells in the urine microscopic analyses. The Dimebon Investigator's Brochure summarizes recent investigations of the

observation of a high rate of urine hemoglobin positivity on dipstick testing in several dimebon program studies, including DIM14, that revealed that the M7 metabolite of dimebon, which is the most common metabolite and excreted in the urine, cross-reacts with the pseudoperoxidase assay used in the urine dipstick test, resulting in a false positive finding. Adverse events based on abnormal clinical laboratory tests considered related to study drug occurred in no more than 1.0% of patients receiving dimebon in both DIM14 and DIM14 combined or in DIM14 only. Most abnormal laboratory value adverse events were considered unrelated to study drug.

No clinically significant changes in vital sign variables based on mean changes during the study were observed in DIM14EXT. Mean systolic blood pressure values were lower than mean baseline values at every study visit, and mean diastolic blood pressure values were lower than mean baseline values at all except 2 study visits; there was not, however, a consistent trend toward decreasing blood pressure over the course of the study. The abnormalities observed in laboratory assessment, vital sign, ECG, and physical/neurological examination data did not raise any concerns of clinically significant signals related to dimebon treatment.

Conclusions:

Dimebon was generally well tolerated in open-label DIM14EXT for up to 81 weeks by patients with Alzheimer's disease who had previously completed 26 weeks of blinded treatment in DIM14.

Efficacy data from the ADAS-cog, MMSE, CIBIC-plus, ADCS-ADL, NPI and RUD-Lite instruments were not analyzed in the context of the lack of dimebon efficacy being demonstrated in DIM14, following which this study was terminated for nonsafety reasons.

Date of Report: 18 JUL 2012