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: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Dimebon in Patients with Mild-to-Moderate Huntington Disease

Investigators: Multicenter

Study Center(s): 64 sites in North America, Europe, and Australia

Publication (Reference): None

Phase of Development: 3

Study Period (Years):

First Patient Enrolled: 27 July 2009

Last Patient Completed: 09 February 2011

Objectives:

Co-Primary Objectives:

- To determine the effect of dimebon as compared to placebo on cognition as measured by the Mini-Mental State Examination (MMSE); and
- To determine the effect 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:

- To determine the effect of dimebon as compared to placebo on a measure of behavior, the Neuropsychiatric Inventory (NPI);
- To determine the effect 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 effect of dimebon as compared to placebo on a measure of motor impairment, the Unified Huntington Disease Rating Scale (UHDRS'99) Total Motor Score (TMS);
- To determine the safety of treatment with dimebon as compared to placebo; and
- To examine the relationship between dimebon plasma concentrations and efficacy and safety outcomes.

Methods: This study was a multicenter Phase 3, randomized, double-blind, placebo-controlled safety and efficacy study of dimebon treatment in patients with mild-to-moderate Huntington disease (HD). The study evaluated dimebon 20 mg three times daily (TID) administered orally for 6 months (26 weeks) compared with matching placebo TID for the primary safety and efficacy analyses. A total of 403 patients were centrally randomized 1:1 into the dimebon and placebo groups. Randomization was stratified by the use of concomitant tetrabenazine and study site. 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. Patients randomized to placebo received matching tablets without the active ingredient.

Efficacy assessments, including the MMSE, Clinician's Interview-Based Impression of Severity (CIBIS)/CIBIC-plus, NPI, ADCS-ADL, and the UHDRS'99 TMS, were performed at the Baseline/Day 1 visit and at the Week 13 and 26 visits. The MMSE was also performed at the Week 6 visit. An independent rater, not involved in and blinded to other aspects of the trial, administered the CIBIC-plus. The CIBIC-plus instrument in this trial was the 7-point Alzheimer's Disease Cooperative Study—Clinician's Global Impression of Change (ADCS-CGIC). All other efficacy assessments were performed consistently by a separate rater.

Safety and tolerability were assessed by the recording of adverse events and by the monitoring of vital signs,

physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). In addition, the Columbia Suicide Severity Rating Scale (CSSRS) was administered at each study visit to collect and record suicidal ideation and attempts in a standardized fashion. Central laboratories were utilized 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 throughout the study. Plasma samples to assess dimebon concentrations were collected at the Baseline/Day 1, Week 6, Week 13, and Week 26 visits at specified times pre-and post-dose.

Patients who completed the 26-week treatment course were offered the opportunity to enroll directly into an open-label extension study under a separate protocol (DIM20EXT). Patients who declined enrollment into the open-label extension study returned to the clinic 30 (± 7) days after cessation of study drug for a final safety follow-up visit.

Number of Patients (Planned and Analyzed): A sample size of 350 patients (175 per treatment group) was planned in order to provide approximately 99% power for this study to detect a 1.6 point difference between dimebon and placebo in MMSE scores and approximately 84% power to detect a 0.4 point difference in CIBIC-plus (ADCS-CGIC) scores at the two-sided 0.05 alpha level. The power calculations assumed a standard deviation of 3.2 for the MMSE, a standard deviation of 1.2 for the ADCS-CGIC, and a 10% dropout rate.

A total of 403 patients, 200 patients in the dimebon group and 203 patients in the placebo group, were enrolled and randomized in the study.

Diagnosis and Main Criteria for Inclusion:

Eligible patients were men and women aged 30 years or older with clinical features of HD and a cytosine adenine guanine (CAG) polyglutamate repeat expansion ≥ 36; a UHDRS'99 Total Functional Capacity (TFC) between 5 and 13, inclusive; a MMSE score between 10 and 26, inclusive; and subjective evidence of cognitive decline from pre-HD levels as assessed by the Investigator. Each patient was required to participate in the study with a caregiver who assisted and spent time with the patient for at least 5 days per week and for at least 3 hours per day. For patients taking tetrabenazine, doses must have been stable for at least 60 days prior to randomization. Doses of all other psychotropic medications or other medications to treat the symptoms of HD must have been stable for at least 30 days prior to randomization. Patients could not have evidence of unstable medical or psychiatric conditions, active suicidality, or a history of seizure disorder requiring ongoing medication.

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.

Each patient in the dimebon group received two 5 mg tablets of dimebon orally TID during Week 1 and one 20 mg tablet of dimebon orally TID for the remaining 25 weeks.

Duration of Treatment: 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. There was a placebo to match the 5 mg active tablet (100 mg core) and a placebo to match the 20 mg active tablet (200 mg core). Each patient in the placebo group received two 5 mg tablets of placebo orally TID during Week 1 and one 20 mg tablet of placebo orally TID for the remaining 25 weeks.

Criteria for Evaluation:

Efficacy:

Co-Primary Efficacy Outcomes:

- A comparison between the mean changes from baseline in the dimebon 20 mg TID treatment group and the placebo group on the MMSE at Week 26;
- 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.

Secondary Efficacy Outcomes:

- 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;
- 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;
- 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 UHDRS'99 TMS.

Safety:

The safety of dimebon compared to placebo was 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, and the frequency of new laboratory and ECG abnormalities. In addition, the CSSRS was administered at each study visit to collect and record suicidal ideation and attempts in a standardized fashion.

Pharmacokinetic Outcomes:

There were no specific PK outcome measures for this study. Plasma samples for PK analysis were obtained from patients in the dimebon group and analyzed using a validated analytical method. Pharmacokinetic data from this study were planned to be used in conjunction with data from other studies to develop a population PK model that potentially linked dimebon exposure with efficacy and safety outcome measures.

Statistical Methods:

Primary efficacy analyses were conducted using the Intent-to-Treat (ITT) population. Eligible patients were centrally randomized and stratified by concomitant tetrabenazine use (yes/no) and study site. The co-primary efficacy analyses were the changes from baseline to the Week 26 visit in MMSE and the CIBIC-plus (ADCS-CGIC) scores at the Week 26 visit. The primary efficacy objective of the study was met if both co-primary analyses demonstrated superiority of dimebon over placebo at the two-sided 0.05 level.

The change in MMSE was analyzed using mixed model repeated measures (MMRM) methodology utilizing an unstructured covariance. Treatment group, visit, treatment group by visit interaction, and concomitant tetrabenazine use (yes/no) were included as fixed effects in the model and the baseline MMSE score was included as a covariate. The primary analysis compared the mean changes from Baseline to Week 26 in the dimebon 20 mg TID and placebo groups using a two-sided test at the 0.05 level of significance. Least squares means changes from baseline to Week 26 were compared to zero using a one sample t-test.

For the CIBIC-plus (ADCS-CGIC), the data from the placebo and the dimebon 20 mg TID group were compared using a stratified Cochran-Mantel-Haenszel mean score test using equally spaced scores for the categories of marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, and marked worsening with concomitant use of tetrabenazine, geographic region, and collapsed baseline CIBIS score as stratification factors. Due to sparseness of the data, geographic region was removed from the model. For this analysis, the last observation carried forward (LOCF) approach was used to impute missing data. Thus, a missing value at the time point of interest was replaced by the last available post-baseline non-missing value. The primary analyses compared the ADCS-CGIC at Week 26 between the dimebon 20 mg TID and placebo groups using a two-sided test at the 0.05 level of significance.

Analyses of the other secondary efficacy outcomes were performed using MMRM methodology, similar to that described for the MMSE analysis, and were carried out using a two-sided test at the 0.05 level of significance.

Safety was assessed through summaries of adverse events, vital signs, physical examinations, ECGs, and clinical laboratory test data (including change from baseline). In addition, the CSSRS was administered at each study visit and results were compared between treatment groups. Safety analyses included all randomized patients who received any amount of study drug (safety population). All adverse events were coded to Preferred Term, higher level term, and System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). The numbers and percentages of patients with adverse events were presented by MedDRA SOC and Preferred Term, relationship to study treatment, and severity. Descriptive statistics were generally used rather than inferential statistics.

Laboratory values were classified as less than the lower limit of normal, within normal limits, and above the upper limit of normal. Laboratory shift tables comparing baseline results to results at each of the subsequent scheduled visits, the lowest post-baseline results, and the highest post-baseline results by treatment group were presented separately for all hematology and chemistry parameters. Summary results of the central laboratory

ECG findings included the numbers and percentages of patients by treatment group with any new abnormality and with each distinct type of abnormality at any post-baseline assessment. In addition, the numbers and percentages of patients with a highest post-baseline QT Interval by the Fridericia Correction Formula (QTcF) category of ≤ 450 msec, > 450 and ≤ 480 msec, > 480 and ≤ 500 msec, and > 500 msec and the numbers and percentages of patients with a post-baseline change in QTcF of > 30 msec and > 60 msec were summarized. The percentages of patients in each treatment group with abnormal clinically-significant ECG findings, as assessed by the Investigator, were summarized by study visit.

Summary and Conclusions:

Analysis Populations

The ITT Population included all 403 enrolled patients. The Safety Population was defined as all patients who received any amount of study drug and included all 403 patients of the ITT Population. The Per-Protocol Population was defined as all patients who completed the study, were at least 80% compliant with study drug, and satisfied all eligibility criteria and included 88.6% (357/403) of the patients in the ITT Population.

Disposition and Baseline Characteristics:

A total of 403 patients were enrolled at 64 study centers in Western Europe (60.5%, 244/403), North America (35.7%, 144/403), and Australia (3.7%, 15/403). Of the 403 patients, 200 patients were randomized to receive dimebon and 203 patients were randomized to receive placebo.

A high percentage of patients (92.6%, 373/403) completed the study per protocol; 6.5% (13/200) in the dimebon group and 8.4% (17/203) in the placebo group discontinued the study early. Reasons for early discontinuation from the study included: adverse event (20 patients; 11 dimebon and 9 placebo patients), withdrawal of caregiver or patient consent (6 patients; 1 dimebon and 5 placebo patients), patient unable to continue (2 patients; 1 dimebon and 1 placebo patient), protocol noncompliance (1 placebo patient), and other (1 placebo patient). The mean (± SD) time in the study for all patients was 177.4 (± 30.5) days for the dimebon group and 177.6 (± 29.0) days for the placebo group. The mean time to study withdrawal for early terminations was 81.5 (± 62.7) days for the dimebon group and 102.7 (± 57.5) days for the placebo group. The mean time to study withdrawal due to adverse events was 83.3 (± 68.3) for the dimebon group and 104.8 (± 56.1) days for the placebo group.

Demographic characteristics and baseline efficacy assessments were well-balanced between treatment groups. The study population was predominantly white (95.3%, 384/403) and non-Hispanic (95.3%, 384/403) with a mean body mass index of 24.9 (± 4.7) kg/m^2, a mean age of 51.9 (± 10.0) years, a mean MMSE score of 22.3 (± 2.9), and a mean UHDRS TFC score of 7.5 (± 2.0). Approximately half (52.4%, 211/403) of the patients were female. All randomized patients had a documented clinical diagnosis of HD at Screening. The mean allele 1 CAG repeat length was 44.1 (± 3.2) and the mean allele 2 CAG repeat length was 18.4 (± 3.5).

The mean number of years since the onset of HD symptoms was 5.5 (± 3.6) years. Approximately 24.1% (97/403) of patients were currently seeing a mental health professional at baseline and these patients had done so for a mean of 4.9 (± 3.72) years. Approximately 13.9% (56/403) of patients had a history of suicidal ideation and 5.5% (22/403) had previously attempted suicide. A minority of patients (15.6%, 63/403) were receiving concomitant tetrabenazine at baseline.

All patients randomized to the dimebon group had cytochrome P450 (CYP) 2D6 genotyping data obtained and were classified as CYP2D6 ultra-rapid metabolizers (5.0%, 10/200), extensive metabolizers (77.5%, 155/200), intermediate metabolizers (8.0%, 16/200), or poor metabolizers (9.5%, 19/200). The most common CYP2D6 category in the placebo group was extensive metabolizer (82.8%, 168/203).

At Screening, suicidal behavior and/or ideation using the CSSRS was reported in approximately 20% of patients in the dimebon (19.5%, 39/199) and placebo (21.7%, 44/203) groups and self-injurious behavior with no suicide attempt was reported in one patient (0.5%) in the dimebon group and three patients (1.5%) in the placebo group.

Treatments

The median number of days on treatment was 183 in both treatment groups and ranged from 5.0 to 211.0 days in all subjects. Most patients (92.3%, 372/403) had treatment for ≥ 24 weeks. The mean overall compliance rate was approximately 95.8% (SD ± 8.39) in the dimebon group and 97.4% (SD ± 8.64) in the placebo group.

Approximately 96% of patients in the dimebon (96.5%, 193/200) and placebo (96.1%, 195/203) groups received at least 1 concomitant medication during the study. The most commonly used concomitant medications in the dimebon group were selective serotonin reuptake inhibitors (46.0%, 92/200); benzodiazepine derivatives (24.5%, 49/200); and diazepines, oxazepines, and thiazepines (21.5%, 43/200). The most commonly used concomitant medications in the placebo group were selective serotonin reuptake inhibitors (42.9%, 87/203); benzodiazepine derivatives (20.7%, 42/203); and diazepines, oxazepines, and thiazepines (19.7%, 40/203).

Efficacy Results:

The efficacy of dimebon in the treatment of HD was not demonstrated in this study. Co-primary endpoints were change in MMSE and CIBIC-plus scores at Week 26 for patients in the dimebon group compared to patients in the placebo group. The mean MMSE scores at Week 26 were significantly increased (i.e., improved) from mean baseline scores for patients who received dimebon ($p < 0.0001$) or placebo ($p < 0.0001$). However, the co-primary endpoint of MMSE at Week 26 did not demonstrate a statistically significant improvement for patients in the dimebon group compared to patients in the placebo group ($p = 0.3866$). The mean CBIC-plus scores at Week 26 were not significantly changed from mean baseline scores for patients who received dimebon ($p = 0.4873$) or placebo ($p = 0.6955$) and the co-primary endpoint of CIBIC-plus at Week 26 did not demonstrate a statistically significant improvement for patients in the dimebon group compared to patients in the placebo group ($p = 0.7938$).

Statistically significant improvements were also not observed in the secondary endpoints of ADCS-ADL score, NPI score, or UHDRS'99 TMS for patients in the dimebon group compared to patients in the placebo group. The mean ADCS-ADL scores were significantly decreased (i.e., worsened) from mean baseline scores for patients who received dimebon at Week 26 ($p = 0.0128$), but not significantly changed for patients who received placebo at Week 26 ($p = 0.2420$). However, the difference between the dimebon and placebo groups in ADCS-ADL were not statistically significant at Week 26 ($p = 0.2806$). The mean NPI scores were significantly decreased (i.e., improved) from mean baseline scores for patients who received dimebon ($p = 0.0084$) or placebo ($p = 0.0036$) at Week 26, but the difference between the dimebon and placebo groups in NPI scores were not statistically significant at Week 26 ($p = 0.8151$). The mean UHDRS TMS was significantly increased (i.e., worsened) from mean baseline scores for patients who received dimebon ($p = 0.0149$) or placebo ($p = 0.0461$) at Week 26, but the difference between the dimebon and placebo groups in UHDRS TMS was not statistically significant at Week 26 ($p = 0.7161$).

Analyses of subgroups (e.g., study site, MMSE score at Screening, CYP2D6 metabolizer status, parameter subscale, category, or domain, age, sex, tetrabenazine use, geographic region), sensitivity analyses (e.g., ANCOVA, LOCF, MMRM), and other patient populations (i.e., Per-Protocol Population) did not demonstrate a statistically significant benefit of dimebon compared to placebo.

Safety Results:

Safety data were collected for up to 30 weeks. Safety results were similar between the dimebon and placebo treatment groups.

Approximately 68% of patients had at least one treatment-emergent adverse event in the dimebon (68.5%, 137/200) and placebo (68.0%, 138/203) groups. There were no clinically relevant differences between the dimebon and placebo groups in the overall incidence of treatment-emergent adverse events or the frequency of treatment-emergent adverse events by SOC. The most common ($\geq$ 5% of patients in either treatment group) treatment-emergent adverse events by Preferred Term in the dimebon and placebo groups, in descending overall order, were fall (15.0% vs. 15.8%, respectively), chorea (8.0% vs. 3.9%, respectively), somnolence (5.5% vs. 6.9%, respectively), headache (5.5% vs. 3.5%, respectively), and fatigue (5.0% vs. 0%, respectively). Treatment-emergent adverse events reported in at least 5% of patients in the dimebon group and with a numerically higher frequency than patients in the placebo treatment group were chorea, headache, and fatigue.

The incidence of related treatment-emergent adverse events (assessed as possibly, probably, or definitely related to study drug by the study site Investigator) was comparable in the dimebon (28.0%, 56/200) and placebo (31.0%, 63/203) groups. The most common (occurring in > 2% of patients in either treatment group) related treatment-emergent adverse events by Preferred Term in the dimebon and placebo groups were dry mouth (4.5% vs. 1.0%, respectively), somnolence (4.0% vs. 5.4%, respectively), fatigue (4.0% vs. 0%, respectively), chorea (3.5% vs. 1.5%, respectively), fall (3.0% vs. 3.9%, respectively), headache (3.0% vs. 2.5%, respectively), and diarrhoea (1.5% vs. 3.0% , respectively). The majority of patients who experienced

treatment-emergent adverse events had adverse events that were assessed as at worst mild or moderate in intensity. The incidences of treatment-emergent adverse events in the dimebon and placebo groups assessed as mild (39.5%, 79/200 vs. 35.5%, 72/203, respectively), moderate (25.5%, 51/200 vs. 27.1%, 55/203, respectively), or severe (3.5%, 7/200 vs. 5.4%, 11/203, respectively) were comparable.

The incidence of serious treatment-emergent adverse events was similar between treatment groups. Ten serious adverse events were reported in 9 patients (4.5%) in the dimebon group and 15 serious adverse events were reported in 12 patients (5.9%) in the placebo group. In the dimebon group, no serious adverse event by Preferred Term was reported in more than one patient. In the dimebon group, two serious adverse events (gait disturbance and anxiety) in two patients were considered possibly related to study drug. In the placebo group, three serious adverse events (rib fracture, intentional self-injury, and convulsion) in three patients were considered possibly related to study drug. No patients in the dimebon group experienced adverse events of convulsion. One death occurred during the study in the dimebon group. The cause of death was respiratory arrest secondary to a serious adverse event [redacted] that was assessed by the Investigator as unrelated to study drug.

Approximately 5% of patients discontinued the study with the primary reason for early termination of adverse event in the dimebon (5.5%, 11/200) and placebo (4.4%, 9/203) groups. There was no single adverse event leading to early termination reported by more than one dimebon or placebo patient.

There were no clinically meaningful differences in the incidence of abnormalities between treatment groups for any clinical laboratory parameter. No patient had ECG findings that were abnormal, changed from baseline, and considered clinically significant. There were no notable differences between treatment groups in findings of physical examinations or neurological examinations.

Suicidal behavior and/or ideation were measured with the CSSRS up to Week 30. There were no suicide behaviors reported after Baseline in the dimebon group and one suicide attempt [redacted] in the placebo group. Suicide ideation was lower in the dimebon group than in the placebo group at Baseline ([redacted]), Week 2 ([redacted]), Week 6 ([redacted]), and Weeks 13 and 18 ([redacted]).

Conclusions:

- Treatment with dimebon 20 mg TID for 26 weeks did not improve measures of cognition or overall function compared to placebo.
- Treatment with dimebon 20 mg TID for 26 weeks was generally well-tolerated in this population of mild-to-moderate HD patients.

Date of Report: 23 JUL 2012