SYNOPSIS

Name of Sponsor: Medivation, Inc. (Medivation is now a wholly owned subsidiary of Pfizer Inc.)	***(For National Authority Use Only)***
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)	**Study Number:** DIM05
Title of Study: A Multi-Center, Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study of Dimebon in Subjects with Huntington's Disease	
Investigators: Multicenter, all sites were members of the Huntington Study Group (HSG)	
Study Centers: 17 active centers; of these, 16 centers enrolled patients (15 centers in the United States and 1 center in the United Kingdom).	
Publication (Reference): Kieburtz, K, McDermott MP, Voss TS, et al. A randomized, placebo-controlled trial of latrepirdine in Huntington disease. Arch Neurol 2010; 67(2):154-160.	
Study Period (Years): 18 July 2007 to 30 June 2008	**Phase of Development:** Phase 2

Objectives:

Primary Objective:

- To assess the safety and tolerability of dimebon (latrepirdine), 20 mg three times a day (TID), during 90 days of treatment in patients with Huntington disease (HD).

Secondary Objectives:

- To assess the impact of dimebon, 20 mg TID, during 90 days of treatment on cognitive, motor, and overall function in patients with HD; and
- To assess the pharmacokinetics (PK) of dimebon following multiple-dose administration.

Methods:

This was a Phase 2, randomized, double-blinded, placebo-controlled study of the safety and tolerability of dimebon 20 mg, administered orally TID for 90 days. Approximately 90 patients with mild-to-moderate HD and a Unified Huntington Disease Rating Scale (UHDRS) total functional capacity (TFC) $\geq$ 5 were planned for enrollment into the study. Patients were randomized to receive either dimebon 20 mg or matching placebo TID (1:1 ratio) for 90 days. Dosing was initiated with a single dose of dimebon 10 mg or matching placebo on Study Day 1 (within 21 days of the Screening visit). If this dose was well tolerated, patients received either dimebon 10 mg or matching placebo TID for the next six days. If the dose level of 10 mg TID was tolerated, the dose of study drug (dimebon or placebo) was increased to 20 mg TID on Study Day 8 and continued through Study Day 90. After completing the treatment with study drug, patients were followed for safety for an additional 14 days. Thus, the total duration of individual patient participation in the study was planned as 104 days.

Safety was assessed by recording adverse events (AEs), vital signs, physical examination findings, safety laboratory evaluations (blood chemistry, hematology, coagulation, and urinalysis), and electrocardiograms (ECGs) at each study visit. For women of child-bearing potential, urine pregnancy tests were collected at Screening and at the last Follow-up visit on Study Day 104. Tolerability was assessed as the ability to remain on the assigned dose of study drug at Study Day 90. Patients who were not able to complete the treatment

period were to continue in the study off study drug and to be followed for safety assessments and the UHDRS.

Exploratory efficacy assessments included the UHDRS performed at the Baseline/Day 1 visit and at the Study Day 30, 60, and 90 visits; and the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog; 14-item version), performed at the Baseline/Study Day 1 visit and at the Study Day 60 and Study Day 90 visits.

Pharmacokinetic sampling was planned for before and after the first dose of study drug at the Baseline/Study Day 1 visit and before and after a clinic-administered dose of study drug at the Study Day 8, 15, and 30 visits. In addition, PK samples were drawn at the time of collection of specimens for safety laboratory tests at the Days 60 and 90 visits and at Unscheduled visits, as appropriate. A blood sample for cytochrome P450 (CYP) 2D6 genotyping was to be collected at the Baseline/Study Day 1 visit to evaluate the effect of CYP2D6 metabolizer status on PK parameters.

Number of Patients (Planned and Analyzed):

Planned: Approximately 90 patients

Enrolled: 91 patients

Treated: 90 patients

Analyzed: 90 patients

Diagnosis and Main Criteria for Inclusion:

Patients were to be male or female, aged 29 years or older, with clinical features of HD (Stage I, II, or III and a TFC $\geq$ 5) and a confirmatory family history of HD or a cytosine adenine guanine (CAG) polyglutamate repeat expansion $\geq$ 36. Patients were to be ambulatory (not requiring skilled nursing care) and willing to abide by the instructions on seizure precautions. Patients who were taking psychotropic medications (including antidepressants and neuroleptics) or other non-excluded medications to treat the symptoms of HD (e.g., Coenzyme Q_{10} and minocycline) must have been on stable dosages for at least 30 days prior to the Baseline/Study Day 1 visit and were to maintain a constant treatment regimen throughout the study unless a modification was mandated by clinical considerations. Patients could not have evidence of unstable medical or psychiatric conditions or a history of seizures.

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

Dimebon 10 mg tablets were encapsulated in hard gelatin capsules and administered orally at an initial dose of dimebon 10 mg TID for one week, with escalation to dimebon 20 mg TID (2 × 10 mg capsules TID) through Study Day 90. Tablet Lot number: [redacted]; Capsule Lot numbers: [redacted], [redacted], [redacted], [redacted]

Duration of Treatment:

The maximum duration of the treatment phase was planned as 90 days (including both the Titration and Maintenance Phases of the study). The maximum time in the study was planned as 104 days.

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

Reference therapy was a matching placebo tablet encapsulated in a hard gelatin capsule, identical in appearance to the dimebon capsules, and administered orally TID. In order to match dimebon, one capsule was administered TID for one week followed by two capsules TID through the remainder of the dosing period. Tablet Lot number: [redacted]; Capsule Lot Numbers: [redacted], [redacted], [redacted], [redacted].

Criteria for Evaluation:

Safety Evaluations:

The primary safety outcome variable, tolerability, was defined as the ability of the patient to complete the 90-day dosing period on the assigned dosage of study drug (20 mg TID). The frequency and severity of AEs in the dimebon treatment group were compared with placebo. Other safety variables included vital signs, physical and neurological examination findings, safety laboratory evaluations, and ECGs. In addition, the UHDRS was included as a safety variable as well as an efficacy variable.

Exploratory Efficacy Evaluations:

Changes from the Baseline/Study Day 1 visit to the Study Day 90 visit were assessed for the following exploratory efficacy parameters: UHDRS scores for motor impairment (including chorea scores), cognitive impairment (Verbal Fluency Test, Symbol Digit Modalities Test, Stroop Interference Test), behavioral

symptoms, and Functional domains (Functional Assessment, Independence Score, TFC); MMSE scores; and ADAS-cog (14-item) scores.

Pharmacokinetic Evaluation:

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

Statistical Methods:

Sample Size:

The chosen sample size of approximately 90 patients provided 80% power to detect a 23%–25% difference in the tolerability rate between the treatment groups (e.g., 90% versus 67% or 85% versus 60%) using Fisher's exact test and a one-tailed 5% significance level. The sample size of 45 patients randomized to dimebon provided 93% probability that the lower limit of a 95% confidence interval for the true tolerability rate in this group was greater than 65%, given that the true tolerability rate was 85%. It also provided 84% probability that the lower limit of a 95% lower confidence interval for the true tolerability rate in this group was at least 75%, given that the true tolerability rate was 90%.

Analysis of the Primary Outcome Variable:

The primary outcome variable for this study (tolerability) was the ability of the patient to complete the 90-day treatment period on the assigned dose of study drug. A lower limit of 95% lower confidence interval for the proportion of patients able to tolerate the study drug was computed for each treatment group using the binomial distribution.[1] A comparison between the treatment groups regarding the proportions of patients able to tolerate the study drug was performed using a left-tailed Fisher's exact test. The Safety population was defined as all patients who were enrolled and received at least one dose of study drug and was used in all safety and tolerability analyses.

Analysis of Secondary Outcome Variables:

Individual AEs and abnormal laboratory test and ECG results were summarized overall and by treatment group. AEs were tabulated by treatment group, severity, and assessed relationship to study drug. For each AE, an upper limit of a 95% confidence interval (i.e., 97.5% upper confidence bound) for the proportion of patients experiencing the event was computed. Changes from Baseline to each visit in laboratory test results and vital signs were summarized overall and by treatment group (mean, standard deviation, median, quartiles, minimum, maximum).

For the analysis of exploratory efficacy assessments (UHDRS, MMSE, and ADAS-cog [14-item]), comparisons of mean change over time (Baseline/Study Day 1 to Study Day 90) between the treatment groups were performed using mixed-model repeated measures analysis of covariance (ANCOVA) models, with treatment group as the factor of interest and the baseline value of the outcome variable as a covariate. The model included terms for visit and the interaction between treatment group and visit. The 95% confidence intervals for the adjusted dimebon 20 mg TID – placebo differences in mean response (treatment effects) at Study Day 90 and other scheduled visits were determined. The UHDRS performed during the safety follow up at Study Day 104 was not included in the mixed model. The primary efficacy population was a modified-intent-to-treat (mITT) analysis that was defined as all enrolled patients with baseline and at least one post-baseline measurement for each assessment. Secondary efficacy populations included an Evaluable population defined as all patients in the mITT population who were exposed to study drug for at least 80% of the 90-day treatment period and who were on study drug at Study Day 90. Sensitivity analyses of the efficacy outcomes using a last observation carried forward (LOCF) method of imputation were also conducted on the mITT population.

Analysis of Pharmacokinetic Data:

Variability in the dosing intervals and collection times created a PK data set that was not amenable to standard statistical analyses and was insufficient for a standard PK analysis. The PK data from this study will be combined with data from future trials to build a population PK model for HD patients, using appropriate statistical methods.

Summary and Conclusions:

Disposition and Baseline Characteristics:

Ninety-one patients were enrolled in the study and were randomized into two treatment groups (1:1 ratio; 46 dimebon; 45 placebo). Eighty-two of 91 patients (90.1%) completed the study, while 9 patients (9.9%) (4 dimebon; 5 placebo) discontinued the study early. Reasons for early discontinuation from the study included: AEs (4 patients; 2 dimebon, 2 placebo), withdrawal of patient consent (4 patients; 2 dimebon, 2 placebo), and Sponsor's decision as a result of a protocol violation (1 placebo patient prior to first dose of study drug). The study population was predominantly white (89.0%) with a mean age of 52.7 years and a mean TFC of 8.1. Eighty-nine of 91 randomized patients (97.8%) had a documented clinical diagnosis of HD at Screening; the remaining two patients (placebo treatment group) met the HD inclusion criteria, but refused to have the clinical diagnosis of HD included in their records, for confidentiality reasons. The mean number of years since the onset of HD symptoms was 4.1 years. Demographic characteristics were well balanced across treatment groups, with the exception of a decreased proportion of female patients in the dimebon treatment group compared to the placebo treatment group. The two treatment groups were also similar with respect to baseline efficacy assessments.

Forty-two of the 46 patients randomized to the dimebon treatment group had CYP2D6 genotyping data: 29 patients were classified as CYP2D6 extensive metabolizers (EM), three patients as CYP2D6 ultra-rapid metabolizers (UM), six patients as CYP2D6 intermediate metabolizers (IM), and three patients as CYP2D6 poor metabolizers (PM). One dimebon-treated patient was classified as "EM or UM," because the patient had a duplication of the CYP2D6 gene, and it could not be determined which allele was duplicated.

Ninety of the 91 randomized patients (98.9%) received at least one dose of study drug and thus were included in the Safety population for the primary safety and tolerability analyses. One patient (placebo treatment group) was enrolled but was discontinued from the study prior to the first dose of study drug as a result of a protocol violation and was not included in subsequent analyses.

Tolerability Results:

Seventy-six of the 90 patients in the Safety population (84.4%) completed the 90-day dosing period on the assigned dose of study drug (40 of 46 patients randomized to dimebon [87%; lower limit of the 95% confidence interval of 74%]; 36 of 44 patients randomized to placebo [81.8%; lower limit of the 95% lower confidence interval of 67%]). There was no statistically significant difference between the two treatment groups in the percentage of patients completing 90 days of dosing ($p = 0.832$).

Safety Results:

Sixty-seven of 90 patients (74.4%) in the Safety population experienced one or more AEs during the study. The incidence of AEs in the dimebon treatment group (32 of 46 patients [69.6%]) was similar to the placebo treatment group (35 of 44 patients [79.5%]). There were no differences between the two treatment groups in the overall incidence of AEs or the frequency of AEs (by organ class or preferred term) during the 90-day treatment period. The only AEs reported in at least 5% of patients in the dimebon treatment group and with a numerically higher frequency than patients in the placebo treatment group were headache (13.0% dimebon treatment group vs. 6.8% placebo treatment group) and somnolence (6.5% vs. 2.3%). The incidence of treatment-related AEs (assessed as possibly, probably, or definitely related to study drug by the Site Investigator) was comparable in the dimebon treatment group and the placebo treatment group (45.7% and 54.5%, respectively). The most frequently reported treatment-related AEs in the dimebon treatment group included headache (4 of 46 patients [8.7%]), somnolence (3 patients [6.5%]), and dizziness (3 patients [6.5%]). The most frequently reported treatment-related AEs in the placebo treatment group included nausea (5 of 44 patients [11.4%]), irritability (3 patients [6.8%]), and headache (3 patients [6.8%]).

The majority of patients who experienced AEs had AEs that were assessed as mild in intensity (highest reported level of intensity during the study). Patients experiencing mild AEs occurred with a similar incidence within the two treatment groups (37.0% dimebon patients, 36.4% placebo patients, respectively). Severe AEs occurred in four patients randomized to dimebon and three patients randomized to placebo (8.7% and 6.8% of each total treatment group, respectively). Of the four patients in the dimebon treatment group who experienced severe AEs during the study, three patients experienced severe AEs that were considered by the Site Investigator to be treatment-related. The severe AEs experienced by the three patients randomized to placebo were considered not treatment-related. There were no deaths reported in this study.

Three patients (one randomized to dimebon [2.2%], and two randomized to placebo [4.5%]) experienced a total of four serious adverse events (SAEs) during the study. Of these, one dimebon-treated patient experienced an SAE of [redacted] (assessed as possibly related to study drug) and discontinued study drug due to the SAE, yet completed the study off of study drug; one placebo-treated patient permanently withdrew from the study after experiencing an SAE of [redacted] (assessed as unlikely related to study drug); the other placebo-treated patient had discontinued study drug due to several non-serious AEs but remained in the study off of study drug and then while off of study drug permanently discontinued the study as a result of two SAEs ([redacted]; both assessed as unrelated to study drug). Eleven patients (five randomized to dimebon [10.9%] and six randomized to placebo [13.6%]) permanently discontinued study drug due to AEs. Of these, four patients (two dimebon-treated and two placebo-treated) discontinued the study with AE reported as the primary reason for study withdrawal.

There were no clinically meaningful differences in the incidence of abnormalities between treatment groups for any clinical laboratory parameter or vital sign. There were no notable differences in findings arising from physical and neurological examinations in either treatment group. There were no ECG abnormalities in the dimebon treatment group that were assessed as clinically significant. In contrast, three patients in the placebo treatment group had ECG findings that were assessed as clinically significant.

Exploratory Efficacy Results:

There were no statistically significant differences between the two treatment groups in the cognitive, motor, or functional domains of the UHDRS. There was a pattern of numerical improvement at each post-baseline visit with dimebon (compared with placebo) in UHDRS behavioral scores; however, the magnitude of the treatment effect was small (2.0 point treatment difference) and did not reach statistical significance at Study Day 90 ($p = 0.27$).

A statistically significant improvement in cognition was observed in dimebon-treated patients (compared with placebo) at three months (Study Day 90), as measured by the MMSE (1-point treatment difference; $p = 0.03$). The treatment difference was driven primarily by improvement in the dimebon treatment group compared with stable performance in the placebo group. In a post-hoc subgroup analysis that evaluated patients with greater cognitive impairment at Baseline (MMSE score < 27), there was a greater point differential between dimebon-treated patients as compared with placebo-treated patients (1.6-point treatment difference; $p = 0.008$);

There were no statistically significant differences between the two treatment groups in the ADAS-cog (14-item) scores.

The UHDRS, MMSE, and ADAS-cog (14-item) results obtained for the primary mITT population were similar to those obtained for the Evaluable population and mITT population using a LOCF sensitivity analysis.

Pharmacokinetic Results:

Dimebon plasma concentrations exhibited a high degree of inter-patient variability, consistent with observations in studies in HD patients, Alzheimer's disease (AD) patients, and healthy volunteers.

Overall Conclusions:

- Dimebon 20 mg TID administered for 90 days to patients with HD was generally safe and well tolerated, with tolerability defined by the ability to remain on the assigned dose of study drug at Study Day 90;
- There were no statistically significant differences between treatment groups in the cognitive, motor, or functional domains of the UHDRS or the ADAS-cog (14-item). Cognitive benefit was suggested by statistically significant improvement on the MMSE in the dimebon treatment group compared to the placebo treatment group; this treatment difference increased in a subset of patients with greater baseline cognitive impairment on this assessment;
- The suggestion of cognitive benefit as measured by the MMSE in the exploratory efficacy analyses in this study along with the findings of a well-tolerated treatment regimen support the further development of dimebon for the indication of improved cognition in patients with HD.

Date of Report: 16 FEB 2010