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: HORIZON-Plus: An Open-Label Extension of the HORIZON Protocol (DIM20) Evaluating the Safety of Dimebon (Latrepirdine) in Patients with Huntington Disease

Protocol Number: DIM20EXT

Investigators: Multiple; same as for the originating DIM20 study, the Phase 3 randomized, double-blind, placebo-controlled safety and efficacy study of patients with mild-to-moderate Huntington Disease (HD).

Study Centers: 64 sites; same as for the originating DIM20 study in North America, Europe, and Australia.

Publication (Reference): None

Phase of Development: Open-label extension of Phase 3

Study Period (Years):
First Patient Enrolled: 01 February 2010
Last Patient Completed: 17 June 2011

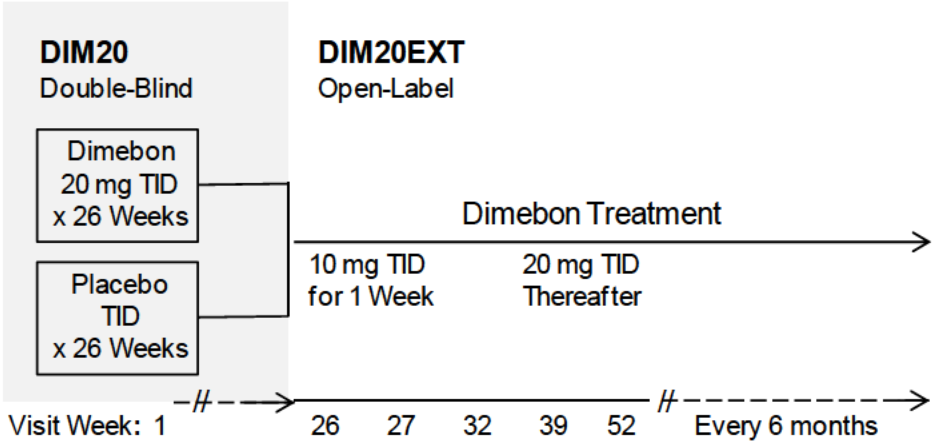
Study Objectives:
Primary Objective:

- To evaluate the long-term safety of dimebon (latrepirdine) in HD patients who successfully completed 26 weeks of blinded treatment in the HORIZON protocol (DIM20).

Secondary Objective:

- To observe the long-term functional and motor symptoms of HD during open-label treatment with dimebon, using the Unified Huntington Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) and Total Motor scores.

Study Schematic:



Methods: DIM20EXT was an open-label extension study of DIM20, an international Phase 3, randomized, double-blind, placebo-controlled safety and efficacy study of dimebon treatment in approximately 350 patients with mild-to-moderate HD. DIM20EXT was designed to evaluate the long-term safety of dimebon 20 mg 3 times per day (TID); to provide access to dimebon for DIM20 patients who successfully completed blinded treatment for 26 weeks; and to generate long-term data on the rate of functional and motor decline during treatment with dimebon. The sponsor terminated DIM20EXT on 11 April 2011 upon unblinding and analysis of the full dataset for DIM20, which revealed that the study did not meet its coprimary endpoints of the effect of dimebon compared with placebo on cognition and global function as measured by the Mini-Mental State Examination (MMSE) and Clinician Interview Based Impression of Change Plus Caregiver Input (CIBIC-Plus).

Eligible patients in DIM20 were offered the option to receive open-label dimebon in DIM20EXT upon successful completion of assessments at the week 26 visit in DIM20. Appropriate informed consent was obtained prior to study participation.

To enhance the tolerability of dimebon for patients receiving placebo in DIM20, all patients in DIM20EXT initiated treatment with dimebon 10 mg orally TID for 1 week. Thereafter, the dimebon dose was 20 mg TID. Dosing could be temporarily suspended due to an adverse event; if treatment was discontinued longer than 2 weeks, dosing resumed at 10 mg TID for 1 week followed by 20 mg TID thereafter. No permanent dose reduction was allowed.

The safety and tolerability of dimebon were assessed throughout the study by monitoring adverse events, vital signs, physical examinations, clinical laboratory evaluations, and 12-lead electrocardiograms (ECGs). The Columbia Suicide Severity Rating Scale was used to evaluate suicidal ideation and attempts. The long-term effectiveness of dimebon on clinical outcomes of disease progression was evaluated using serial functional (UHDRS TFC) and motor (UHDRS Total Motor) scores.

Patients could continue to receive dimebon until marketing authorization as long as they tolerated the treatment unless they withdrew informed consent or the investigator or sponsor withdrew treatment due to reasons specific to a subject. Also, the study could be terminated at the discretion of the sponsor or recommendation of the study Data Monitoring Committee (DMC).

Number of Patients (Planned and Analyzed):
Planned: The randomization cohort for DIM20 (planned 350 patients, actual 403 patients)
Analyzed: 362

Diagnosis and Main Criteria for Inclusion: Eligible patients diagnosed with HD must have successfully completed blinded treatment for 26 weeks and assessments at week 26 in DIM20: key efficacy assessments were the MMSE, CIBIC-Plus, Clinician Interview Based Impression of Severity (CIBIS), Neuropsychiatric Inventory (NPI), Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), and UHDRS'99 Total Motor score. Fertile males and females had to comply with specified measures to prevent pregnancy. Patients with major medical illnesses or unstable medical conditions with potential to interfere with study procedure compliance were excluded. Planned use of bupropion, clozapine, and nonselective antihistamines during the study was prohibited.

Test Product, Dose, Mode of Administration, Lot Number:
Test Product: 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 5 mg or 20 mg active ingredient.

Dose: Week 1: 2 tablets (5 mg each, total dose 10 mg) TID
After week 1: 1 tablet (20 mg) TID

Mode of Administration: Oral

Lot Numbers: [redacted] (20 mg), [redacted] (20 mg), [redacted] (5 mg), and [redacted] (20 mg)

Duration of Treatment: Planned until marketing authorization in each respective country, or until study termination at the discretion of the sponsor or recommendation by the DIM20 DMC.

Reference Therapy, Dose, and Mode of Administration, Lot Number: None

Criteria for Evaluation:

Efficacy: UHDRS TFC and UHDRS Total Motor score. Analysis population: Modified Intent-to-Treat (ITT) Population, defined as patients who had at least 1 scheduled DIM20 assessment after randomization for an HD progression outcome measure.

Safety: Adverse events, vital signs, Columbia Suicide Severity Rating Scale, brief physical examinations, clinical laboratory testing, and ECGs. Analysis population: Safety Population, defined as all patients who received at least 1 dose of dimebon.

Statistical Methods: The clinical database was locked 01 August 2011. Descriptive statistics were used to summarize all safety parameters for the safety population.

Adverse events were coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) version 11.0. The number and percentage of patients with adverse events are presented by MedDRA system organ class and preferred term.

The last assessment of safety data before initiation of dimebon served as the baseline reference for subsequent DIM20EXT assessments. Thus, the baseline reference was the week 26 visit for patients randomly assigned to placebo in DIM20, and the baseline reference was the initial visit in DIM20 for patients randomly assigned to dimebon.

Laboratory values were classified as less than the lower limit of reference range, within reference range limits, and above the upper limit of reference range. Laboratory shift tables display baseline results to each subsequent visit, and mean change from baseline to each visit was computed. The percentage of patients with clinically significant abnormal ECG findings was summarized by study visit.

Medications were coded using the World Health Organization Drug Dictionary version March 2007 with preferred name and therapeutic use. Each subject was counted once per class and once per preferred name within each medication summary.

Long-term progression of HD in DIM20EXT was to be compared between DIM20 dimebon and placebo treatment groups by evaluating change from screening value for UHDRS TFC or baseline value for UHDRS Total Motor score in DIM20 for each DIM20 or DIM20EXT assessment after baseline. Analysis of covariance (ANCOVA) was to include DIM20 treatment group, concomitant use of tetrabenazine (an antichorea therapy not prohibited in DIM20EXT, and a stratification factor at randomization in DIM20), and baseline value as effects in the model.

Summary and Overall Conclusions:

Efficacy Results:

Due to the early termination of the study, efficacy endpoints were not evaluated.

Safety Results:

The safety population included 362 patients who were enrolled in DIM20. No patient completed the extension study. The primary reason for early discontinuation was sponsor decision (study termination): 332 patients, 91.7%. Other reasons for early discontinuation were adverse event (20 patients, 5.5%), withdrawal of consent (9 patients, 2.5%), and lost to follow-up (1 patient, 0.3%).

Demographic analysis was not performed for the 362 patients in DIM20EXT. Demographic information for the 403 patients enrolled in DIM20 is as follows: The study population was predominantly White (95.3%) and non-Hispanic (95.3%) with a mean age of 51.9 (± 10.0) years, a mean body mass index of 24.9 (± 4.7) kg/m^2, a mean MMSE score of 22.3 (± 2.9), and a mean UHDRS TFC score of 7.5 (± 2.0). Approximately half of the patients in DIM20 were female (52.4%). All patients randomly assigned to treatment in DIM20 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.

The median duration of treatment in DIM20EXT was 19.0 weeks (range, 1.0-62.0 weeks). The mean (standard deviation [SD]) duration of treatment was 21.8 (10.96) weeks.

Overall, 210 of 362 patients (58.0%) experienced at least 1 adverse event during the extension study. Adverse events occurring in ≥ 2% of patients were fall (12.7%), chorea (3.6%), urinary tract infection (3.3%), depression, diarrhea, insomnia, and nasopharyngitis (each 3.0%), upper respiratory tract infection (2.8%), and irritability (2.5%). Sixteen patients (4.4%) experienced at least 1 serious adverse event. Two patients (0.6%)

experienced serious chorea. All other serious adverse events were unique including acute myocardial infarction, arthralgia, atrial fibrillation, benign breast neoplasm, lymph gland biopsy, infectious enteritis, fall, foot fracture, viral gastroenteritis, brain nuclear magnetic resonance imaging abnormal, aspiration pneumonia, post-procedural drainage, road traffic accident, suicidal ideation, syncope, thoracic vertebral fracture, uterine dilation and curettage, and wrist fracture. Three patients (0.8%) had adverse events leading to death: infectious enteritis, aspiration pneumonia, and road traffic accident (1 patient each). Eighteen patients (5.0%) experienced 1 or more adverse event leading to permanent discontinuation of study drug; dizziness, agitation, and fall were reported in 2 patients each. All other adverse events leading to discontinuation of study drug were unique. Relationship of adverse events to study drug and severity of adverse events were not summarized.

Five of 353 patients (1.38%) had a ≥ 2-grade shift from baseline in one or more hematology parameter: absolute lymphocytes (3 patients, 0.83%), absolute neutrophils (2 patients, 0.55%), and white blood cells (2 patients, 0.55%). Five of 353 patients (1.38%) had a ≥ 2-grade shift from baseline in one or more chemistry parameter: glucose (2 patients, 0.55%), potassium (2 patients, 0.55%), and creatinine (1 patient, 0.28%).

A total of 72 of 362 patients (19.9%) had an abnormal ECG result during the study. Data for vital signs, physical examination findings, and Columbia Suicide Severity Rating Scale results were not summarized.

Conclusions:

- Dimebon 20 mg TID was generally well tolerated in patients with mild-to-moderate HD.
- Due to the early termination of the study, efficacy endpoints were not evaluated.

Date of Report: 23 JUL 2012