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GENERIC DRUG NAME / COMPOUND NUMBER: Dimebon dihydrochloride / Latrepirdine dihydrochloride / PF-01913539

PROTOCOL NO.: B1451006

PROTOCOL TITLE: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled 26-Week Trial to Evaluate the Efficacy and Safety of Dimebon (PF-01913539) in Patients With Moderate-to-Severe Alzheimer's Disease

Study Centers: A total of 32 centers took part in this study and randomized subjects; 17 in the United States (US), 5 in Germany, 3 in Spain, 2 each in Canada, Poland, and Turkey, and 1 in Slovakia.

Study Initiation, Primary Completion, and Final Completion Dates:

Study Initiation Date: 25 September 2009
Primary Completion Date: 28 June 2010
Final Completion Date: 06 August 2010

The study was terminated prematurely.

Phase of Development: Phase 3

Study Objectives:

To assess the following primary and secondary objectives in subjects with moderate-to-severe Alzheimer's disease (AD) who were on a stable dose and regimen of memantine:

Primary Objectives: The co-primary objectives of this study were:

- To determine the effect of dimebon, as compared to placebo, on the primary measure of cognition, the Severe Impairment Battery (SIB) in subjects with moderate-to-severe AD; and

- To determine the effect of dimebon, as compared to placebo, on the primary measure of self-care and daily function, the Alzheimer's Disease Cooperative Study - Activities of Daily Living (severe) ($ADCS\text{-}ADL_{sev}$) scale in subjects with moderate-to-severe AD.

Secondary Objectives:

The key secondary objectives of this study were:

- To determine the effect of dimebon, as compared to placebo, on a measure of behavioral and psychiatric symptoms, the Neuropsychiatric Inventory (NPI) in subjects with moderate-to-severe AD;

- To determine the effect of dimebon, as compared to placebo, on a measure of AD-related psychosis, the sum of the delusions and hallucinations subdomain scores of the NPI in subjects with moderate-to-severe AD.

The additional secondary objectives of this study were:

- To determine the effect of dimebon, as compared to placebo, on a measure of global function, the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) in subjects with moderate-to-severe AD;

- To determine the effect of dimebon, as compared to placebo, on a secondary measure of cognition, the mini-mental state examination (MMSE), in subjects with moderate-to-severe AD;

- To evaluate the effect of dimebon and placebo on measures of resource utilization, the Resource Utilization in Dementia (RUD-Lite) and quality of life (EQ-5D) in subjects with moderate-to-severe AD;

- To explore the influence of subject covariates on dimebon pharmacokinetics (PK) and the relationship between dimebon exposure and efficacy and safety, in subjects with moderate-to-severe AD, using a population pharmacokinetic/pharmacodynamic (PK/PD) modeling approach;

- To determine the safety and tolerability of dimebon in subjects with moderate-to-severe AD.

METHODS

Study Design: This study was a Phase 3, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study of 6 months of dimebon treatment in subjects with moderate-to-severe AD who were on stable memantine treatment. The study evaluated 1 dose regimen of oral dimebon administered for 6 months (26 weeks) for the study's primary safety and efficacy analyses. Subjects were to be centrally randomized 1:1 into 2 groups (dimebon 20 mg 3 times a day [TID] and placebo). Subjects randomized to dimebon 20 mg TID received dimebon 10 mg TID for the first 7 days of therapy, before titration up to dimebon 20 mg TID for the remainder of the treatment period.

Prior to receiving their first dose of medication, subjects underwent efficacy and safety evaluations at Baseline (Visit 1). A telephone contact was made to the caregiver at the end of Week 1 to assess adverse events (AEs) and to reinforce instructions.

Subjects who completed the 26-week study were offered the opportunity to enroll into an open-label extension study (an open-label extension to the B1451006 protocol to evaluate the safety and efficacy of dimebon (latrepirdine, PF-01913539) in subjects with moderate-to-severe AD [NCT01066546]) until market availability in their respective countries. If subjects declined enrollment into the open-label extension study, they were to return to the clinic at Week 30, 4-weeks after cessation of study drug, for follow-up safety evaluations. The Schedule of Activities is presented in Table 1.

Table 1. Schedule of Activities

End of Week	Screening Visit	Baseline Visit[a]	Blinded Treatment Phase (Dimebon 20 mg TID or Placebo): Weeks 1–26						Study Follow-Up[b]	Un-Scheduled Visit[c]
	Within 32 Days of Day 1	Day 1	1[d] (±2 Days)	2 (±2 Days)	6 (±5 Days)	12 (±5 Days)	18 (±5 Days	26/ET[*] (±5 Days)	30 (±7 Days)	Un-Scheduled Visit
Informed consent (subject and caregiver)	X									
Confirm diagnosis of AD: DSM-IV-TR, NINCDS-ADRDA	X									
Modified Hachinski Ischemic Score	X									
Inclusion/exclusion criteria	X	X								
Randomization and drug kit number (IVRS)		X				X				
Demographics	X									
Medical history, prior AD treatment	X	X								
Physical examination, including neurological examination	X	X						X	X	
Abbreviated physical examination				X	X	X	X			X
Height	X									
Weight	X	X				X		X		X
Vital Signs	X	X		X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X[e]			X	X	X	X	X[f]	X[f]
Laboratory safety assessments[g]	X	X			X	X	X	X	X[f]	X[f]
Urine drug screen	X									
Urine pregnancy test[h]	X	X						X		
Vitamin B_{12}, folate, TSH, free thyroxine, RPR (if positive confirm with FTA-ABS)	X									
Clinical lab serum sample for retention through end of study		X								
Blood Samples (APOE 4 and CYP2D6 genotyping)		X								
Pharmacokinetic samples (Three - Predose, 0.5 to 1.5, and 2.5 to 3.5 hours postdose)						X				X[i]
Dispense study drug (for TID dosing at home)		X				X				
SIB, ADCS-ADL_{sev}, NPI[j]		X			X	X	X	X		

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CIBIS/CIBIC-plus[j]		X				X		X		
MMSE[j]	X	X				X		X		
RUD-Lite[j]		X				X	X	X		
EQ-5D[j]		X				X		X		
Record and review adverse events		X	X	X	X	X	X	X	X	X
Study drug compliance and accountability				X	X	X	X	X		X
Subject and caregiver education (adverse event reporting, drug administration, visit schedule)	X	X	X	X	X	X	X	X		X

AD = Alzheimer's disease; ADCS-ADL$_{sev}$ = Alzheimer's Disease Cooperative Study - Activities of Daily Living (severe); APOE 4 = Apolipoprotein E 4; CIBIS/CIBIC-plus = Clinician's Interview-Based Impression of Severity/Clinician's Interview-Based Impression of Change plus caregiver input; CYP2D6 = Cytochrome P450 2D6; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision; ECG = electrocardiogram; EQ-5D = quality of life assessment developed by EuroQol group; FTA-ABS = fluorescent treponemal antibody - absorption; IVRS = interactive voice response system; MMSE = mini-mental state examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorder Association's Criteria; NPI = Neuropsychiatric Inventory; RPR = positive rapid plasma regain; TID = Three times a day; RUD-Lite = Resource Utilization in Dementia; SIB = Severe Impairment Battery; TSH = thyroid-stimulating hormone.

a. Baseline Visit (Day 1) occurred within 32 days after the Screening Visit.
b. A Follow-up Visit occurred for subjects who discontinued study drug prior to the Week 26 Visit and for subjects who elected not to participate in open-label extension.
c. Unscheduled visits were performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the subject's request, or as deemed necessary by the Investigator.
d. Week 1 assessments were made via a telephone contact with the caregiver.
e. Three ECGs were taken over 15 minutes at the Baseline visit prior to study drug administration. Otherwise, only a single ECG was taken.
f. ECG and clinical laboratory tests as clinically indicated during Unscheduled and/or the Study Follow-Up Visits, as required for follow-up of any clinically significant ECG or clinical laboratory test data.
g. Laboratory safety assessments included serum chemistries, hematology, and urinalysis.
h. Urine pregnancy test was performed on women of child-bearing potential and was repeated as clinically indicated during the study, eg, to evaluate missed menses. Serum follicle-stimulating hormone level was measured, only at screening, to confirm female subject's postmenopausal status (only conducted if the subject had not had >1 year without menses and was not surgically sterile).
i. Pharmacokinetic samples were obtained on unscheduled visits prior to dosing and approximately 1 hour postdose if an unscheduled visit was conducted for medical work-up of an adverse event, if dosing occurred at that visit, or as a single random sample if no dosing occurred.
j. Every effort was made to perform the efficacy evaluations in the order specified with the EQ-5D first, SIB second, the ADCS-ADL$_{sev}$ third, NPI fourth, the CIBIS/CIBIC-plus fifth, MMSE sixth, and the RUD-Lite last.

Number of Subjects (Planned and Analyzed): A sample size of 576 subjects was targeted for randomization, with an allowance of up to 10% over-enrollment, for a maximum of 635 subjects. Based on the target of 576 subjects randomized, a sample size of 288 subjects per treatment group (dimebon or placebo) was planned. Due to early study termination by the Sponsor, 86 subjects (52 in the US, 10 in Germany, 9 each in Portugal and Spain, 3 in Turkey, 2 in Canada and 1 in Slovakia) were randomized and treated. All subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Men and women aged, ≥50 years with a diagnosis of probable AD, have had a MMSE score between 5 and 14 inclusive, who had been taking the medication memantine (ie, Namenda) for at least 6 months prior to this study, who had a caregiver who assisted the subject for at least 5 days per week for at least 3 hours per day, accompanied the subject to study visits, and who had an intimate knowledge of the subject's health states and personal care, were included in the study. Subjects who had taken medicines for AD other than memantine (eg, donepezil, rivastigmine, galantamine, tacrine) within 2 months prior to this study and who had dementia other than AD were excluded.

Study Treatment: The study drug, dimebon dihydrochloride, was supplied as 5- and 20-mg immediate-release film-coated tablets. During the initial 1-week titration period, subjects who were randomized to dimebon 20 mg TID received dimebon 10 mg TID (two 5 mg-tablets per dose) for the first 7 days. Thereafter, subjects received dimebon 20 mg TID (1 tablet per dose) through Week 26. During the initial 1-week titration period, subjects who were randomized to placebo received 2 placebo tablets orally TID. Thereafter, subjects received 1 tablet orally TID through Week 26. Memantine was available for oral administration as tablets containing 5 mg and 10 mg of memantine. Subjects were already taking memantine at randomization, and were to continue to receive the same formulation of memantine as was used at Baseline. Subjects and caregivers were instructed that the subject should take dimebon/placebo TID (in the morning, in the afternoon, and in the evening before going to sleep). Dimebon/placebo could be taken with or without food. If a dose of dimebon/placebo was missed by >4 hours, the subject was directed to skip that dose and take the next regularly scheduled dose. For ease of compliance, memantine was taken at the same time each day as prior to study participation. It was acceptable for subjects to take the twice daily doses of memantine concomitantly with any of the daily doses of blinded study medication (eg, with the morning and evening doses of dimebon/placebo).

Efficacy and Pharmacokinetic Endpoints:

Primary Endpoints:

There were two co-primary comparisons in this study:

- A comparison between the mean change from Baseline to Week 26 (last observation carried forward [LOCF]) in the dimebon treatment group and the placebo group on the SIB;

- A comparison between the mean change from Baseline to Week 26 (LOCF) in the dimebon treatment group and the placebo group on the ADCS-ADLsev.

Secondary Endpoints:

The key secondary comparisons for this study include:

- A comparison between the mean change from Baseline to Week 26 (LOCF) in the dimebon treatment group and the placebo group on the NPI total score;

- A comparison between the mean change from Baseline to Week 26 (LOCF) in the dimebon treatment group and the placebo group on the sum of the NPI delusions and hallucinations sub-domain scores.

Additional secondary efficacy endpoints for this study included:

- A comparison at Week 26 (LOCF) of the dimebon treatment group and the placebo group on the CIBIC-plus;

- A comparison between the mean change from Baseline to Week 26 (LOCF) of the dimebon treatment group and the placebo group on the MMSE;

- Comparisons of the dimebon treatment group and the placebo group at Weeks 6, 12, and 18 (LOCF) for all outcomes, as applicable;

- RUD-Lite and EQ-5D data to be summarized descriptively by treatment group.

Pharmacokinetics:

- The PK secondary endpoints were PK parameters derived from the population PK model, as appropriate to the data.

Safety Evaluations: Safety and tolerability were assessed at protocol-specified times by recording of AEs and by monitoring of vital signs, physical examinations, safety laboratory evaluations, and 12-lead ECGs. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product were reported. AEs of loss of consciousness or unobserved fall where loss of consciousness could not be ruled out were considered to be important medical events and were reported within 24 hours of becoming aware of the event. If the event met serious adverse event (SAE) reporting criteria, the event was also reported as an SAE. For SAEs, the reporting period to Sponsor or its designated representative began from the time that the subject provided informed consent, through and including 28 calendar days after the last administration of the investigational product. Any SAE occurring any time after the reporting period was promptly reported if a causal relationship to investigational product was suspected. AEs (serious and non-serious) were recorded on the case report form from the time the subject had taken at least 1 dose of study treatment through the subject's last visit. An independent Data Monitoring Committee monitored safety data in the study by blinded treatment group on an ongoing basis.

Statistical Methods:

Safety Analysis Set: Safety analyses included all randomized subjects who received at least 1 dose of study drug, including partial doses.

Safety data was presented in descriptive tables. The incidence and severity of AEs was displayed by treatment group, overall, and by causality. All AE tables were displayed overall as well as by AD stratum, psychotropic therapy status, Cytochrome P450 2D6 (CYP2D6) metabolizer status, and subject's use of concomitant medications that were known to be CYP2D6 inhibitors. Safety data was assessed through summaries of AEs, the frequency of discontinuation of dimebon treatment due to AEs, laboratory evaluations (including change from Baseline), ECGs, vital signs (including change from Baseline), and listings of physical examination data. All AEs were coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (version 13.0).

Efficacy analyses were planned in the Statistical Analysis Plan (SAP) but were not performed due to early termination of the study. The efficacy results for each subject were listed.

PK analyses were planned in the SAP, but no PK samples were analyzed and PK/PD analyses were not performed due to early termination of the study.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. Of the 145 subjects screened for this study, 86 subjects were randomized and treated: 44 in the dimebon group and 42 in the placebo group. All subjects were analyzed for AEs. Most subjects discontinued the study early due to study termination by the Sponsor: 34/44 (77.3%) dimebon subjects and 35/42 (83.3%) placebo subjects.

Table 2. Subject Disposition

Number (%) of Subjects	Dimebon	Placebo
Screened: 145		
Assigned to study treatment	44	42
Treated	44 (100)	42 (100)
Completed	3 (6.8)	2 (4.8)
Discontinued	41 (93.2)	40 (95.2)
Subject died	0	1 (2.4)
Related to study drug	1 (2.3)	1 (2.4)
Adverse event	1 (2.3)	1 (2.4)
Not related to study drug	40 (90.9)	38 (90.5)
Lost to follow-up	1 (2.3)	0
Other	1 (2.3)	0
Protocol violation	1 (2.3)	0
Study terminated by sponsor	34 (77.3)	35 (83.3)
Subject no longer willing to participate in study	3 (6.8)	3 (7.1)
Analyzed for safety		
Adverse events	44 (100)	42 (100)
Laboratory	42 (95.5)	42 (100)

Demography: Demographic characteristics including years since AD diagnosis for all subjects are summarized by treatment in Table 3. Dimebon and placebo treatment groups were similar in demographic and baseline characteristics.

Table 3. Demographic Characteristics

Number (%) of Subjects	Dimebon	Placebo
Number of subjects	44	42
Sex		
Male	17 (38.6)	12 (28.6)
Female	27 (61.4)	30 (71.4)
Age (years)		
50-59	2 (4.5)	1 (2.4)
60-69	9 (20.5)	8 (19.0)
70-79	20 (45.5)	16 (38.1)
80-85	10 (22.7)	9 (21.4)
>85	3 (6.8)	8 (19.0)
Mean (SD)	74.3 (8.0)	76.5 (8.8)
Range	54-93	55-93
Race		
White	43 (97.7)	41 (97.6)
Black	1 (2.3)	0
Other	0	1 (2.4)
Weight (kg)		
Mean (SD)	71.0 (15.0)	68.9 (10.6)
Range	37.5-107.5	47.0-93.4
Body mass index (kg/m²)[a]		
Mean (SD)	26.8 (4.2)	26.9 (4.1)
Range	18.4-35.7	19.6-39.2
Height (cm)		
Mean (SD)	162.4 (11.6)	160.3 (9.3)
Range	138.0-188.0	135.0-183.0
Years since AD diagnosis[b]		
Mean	4.3	4.1
Range	1.1-13.0	0.5-12.2

AD = Alzheimer's disease; SD = standard deviation.
a. Body mass index was calculated as weight/(height*0.01)^2.
b. Duration (years) from first diagnosis of AD to Day 1 of study.

Efficacy and Pharmacokinetic Results:

Efficacy analyses were not performed due to early termination of the study.

No PK samples were analyzed and PK/PD analyses were not performed due to early termination of the study.

Safety Results:

Treatment-emergent non-serious AEs (all causalities) are presented in Table 4.

Table 4. Treatment-Emergent Non-Serious Adverse Events (All Causalities) (Frequency Rate ≥5%)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	Dimebon	Placebo
Evaluable for adverse events	44	42
With adverse events	10 (22.7)	8 (19.0)
Gastrointestinal disorders	1 (2.3)	3 (7.1)
Nausea	1 (2.3)	3 (7.1)
General disorders and administration site conditions	1 (2.3)	3 (7.1)
Oedema peripheral	1 (2.3)	3 (7.1)
Infections and infestations	5 (11.4)	2 (4.8)
Urinary tract infection	5 (11.4)	2 (4.8)
Psychiatric disorders	5 (11.4)	2 (4.8)
Agitation	5 (11.4)	2 (4.8)

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Medical Dictionary for Regulatory Activities (version 13.0) coding dictionary applied.

Treatment-emergent AEs (treatment-related) are presented in Table 5.

Table 5. Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and Preferred Term	Dimebon N	Placebo N
Evaluable for adverse events	44	42
Gastrointestinal disorders	1	3
Diarrhoea	0	1
Eructation	1	0
Faecal incontinence	1	0
Nausea	0	2
General disorders and administration site conditions	1	2
Fatigue	1	1
Gait disturbance	1	0
Oedema peripheral	0	1
Investigations	1	1
Blood pressure systolic	1	0
Electrocardiogram T wave amplitude decreased	0	1
Nervous system disorders	3	2
Dizziness	1	0
Headache	1	1
Hypersomnia	1	0
Somnolence	0	1

Adverse events and serious adverse events are not separated out.
N = number of subject.
Subjects are only counted once per treatment for each row.
Medical Dictionary for Regulatory Activities (version 13.0) coding dictionary applied.

Treatment-emergent SAEs (All causalities) are presented in Table 6.

Table 6. Treatment-Emergent Serious Adverse Events (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and Preferred Term	Dimebon	Placebo
Evaluable for adverse events	44	42
With adverse events	4 (9.1)	3 (7.1)
Blood and lymphatic system disorders	1 (2.3)	0
Anaemia	1 (2.3)	0
Cardiac disorders	0	1 (2.4)
Cardiomyopathy	0	1 (2.4)
Infections and infestations	1 (2.3)	1 (2.4)
Pneumonia	1 (2.3)	0
Urinary tract infection	0	1 (2.4)
Musculoskeletal and connective tissue disorders	1 (2.3)	0
Osteoarthritis	1 (2.3)	0
Nervous system disorders	0	1 (2.4)
Encephalopathy	0	1 (2.4)
Vascular disorders	1 (2.3)	0
Poor peripheral circulation	1 (2.3)	0

Subjects are only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
Medical Dictionary for Regulatory Activities (version 13.0) coding dictionary applied.

None of SAEs experienced by subjects were considered related to study treatment.

Death: One subject in placebo group experienced an SAE of cardiomyopathy and died on Day 121. The SAE was considered by the Investigator to be severe in severity and not related to study treatment.

Discontinuations: Subjects who permanently discontinued treatment and the study due to AEs are presented in Table 7. Two subjects, both in the severe AD stratum, were permanently discontinued from treatment and the study due to non-serious treatment-related AEs: 1 dimebon subject with hypersomnia and 1 placebo subject with nausea. Both of these AEs were reported as resolved.

Table 7. Permanent Discontinuations Due to Adverse Events

Serial Number	Sex/Age[a] (years)	AE Start Day[b]	AE Preferred Term[c]	Severity	Causality	SAE[d]
Dimebon						
1	F/70	5	Hypersomnia	Mild	Study drug	No
Placebo						
2	F/67	10	Nausea	Moderate	Study drug	No

This table includes subjects who discontinued treatment and the study due to AEs.
AE = adverse event; F = female; SAE = serious adverse event.
a. Age at Screening.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Medical Dictionary for Regulatory Activities version 13.0 coding applied.
d. SAE according to Investigator's assessment.

Four subjects had their dose of study drug temporarily discontinued or reduced due to AEs: 3 subjects in the dimebon group and 1 subject in the placebo group.

Of the subjects evaluable for laboratory abnormalities, 29/42 (69.2%) dimebon-treated subjects and 25/42 (59.5%) placebo-treated subjects had laboratory test abnormalities that met the predefined criteria for potential clinical concern (without regard to baseline abnormality).

In general, the incidence of laboratory test abnormalities was comparable between the dimebon and placebo groups (except as noted below), and no laboratory abnormalities were considered to be clinically significant. A review of the urine dipstick results suggested a treatment-related increase in the frequency of positive tests for urine blood/hemoglobin in the dimebon group (17/41 [41.5%] subjects) relative to the placebo group (3/40 [7.5%] subjects). A review of the urine microscopic analysis results for those subjects who had microscopic examinations performed did not reveal any notable differences in the number of subjects with elevated urine red blood cell counts between dimebon (4/29 [13.8%] subjects) and placebo (2/27 [7.4%] subjects) treatment groups.

The number of subjects with vital signs (blood pressure and heart rate) and ECG results that met the predefined criteria for potential clinical concern was similar between the dimebon and placebo treatment groups, and no vital signs or ECG abnormalities were considered to be clinically significant.

CONCLUSIONS:

- Primary and secondary efficacy and PK/PD objectives were not assessed as this study was terminated early by the Sponsor for reasons unrelated to safety.

- In this study, dimebon treatment at a dose of 20 mg TID for up to 26 weeks was well tolerated in subjects with moderate-to-severe AD who were on stable memantine treatment.

- There were no clinically-concerning safety or tolerability signals observed in any of the subject subgroups assessed, including the covariates of AD stratum, psychotropic therapy use, CYP2D6 inhibitor use, and CYP2D6 metabolizer status. Subjects who were receiving background psychotropic therapy had a higher observed incidence of AEs than those subjects not receiving psychotropic medications. However, due to the small sample sizes in the various subgroups, no definitive conclusions could be drawn from this study regarding the impact of these covariates on dimebon safety and tolerability.