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 (latrepirdine) (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: CONCERT: A Phase 3 Multicenter, Randomized, Placebo-Controlled, Double-Blind Twelve-Month Safety and Efficacy Study Evaluating Dimebon in Patients with Mild-to-Moderate Alzheimer's Disease on Donepezil

Protocol Number: DIM18

Investigators: United States, Australia, New Zealand, and Europe

Study Center(s): 118

Publication (Reference): *Bengt Winblad, L. Seely, B. Selby, A. Langenberg, D. Forer, and the International CONCERT Study Team.* The CONCERT Study: Results of a 12-month, placebo controlled, parallel group trial in patients with mild-to-moderate Alzheimer's disease in stable background therapy with donepezil. 12th International Stockholm/Springfield Symposium on Advances in Alzheimer Therapy, Stockholm, 09–12 MAY 2012.

Phase of Development: 3

Study Period (Years):

First Subject Enrolled: 31 MAR 2009

Last Subject Completed: 08 DEC 2011

Study Objectives

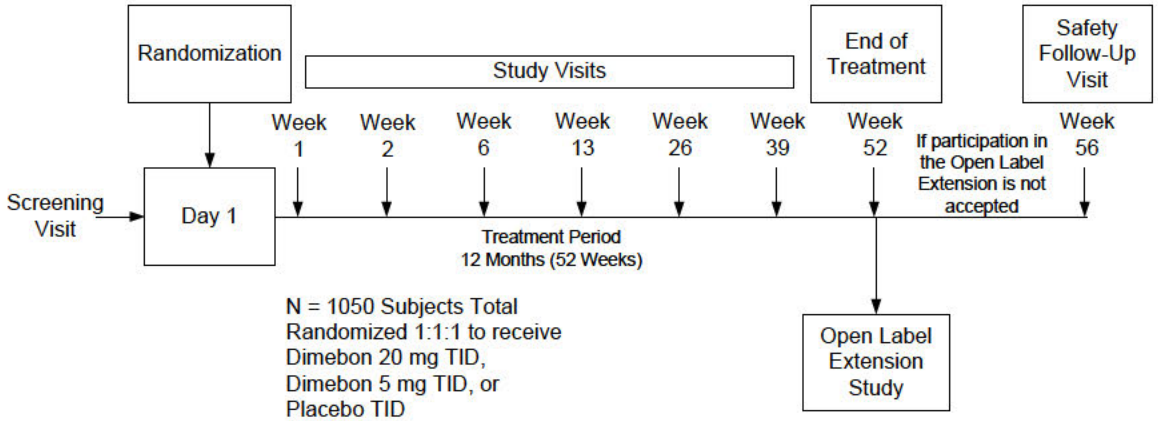
Co-Primary Objectives:

- To evaluate the efficacy of dimebon as compared to placebo on the primary measure of cognition and memory, the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog);
- To evaluate the efficacy 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).

Secondary Objectives:

- To evaluate the efficacy 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);
- To evaluate the efficacy of dimebon as compared to placebo on a measure of behavior, the Neuropsychiatric Inventory (NPI);
- To evaluate the pharmacoeconomic benefit of dimebon as compared with placebo using the Resource Utilization in Dementia Lite (RUD Lite©) instrument;
- To evaluate quality of life using the European Quality of Life 5-Domain Health Quality Assessment (EQ-5D) instrument;
- To evaluate the safety and tolerability of dimebon at 2 doses, 20 mg orally 3 times per day (TID) and 5 mg orally TID over 52 weeks;
- To obtain selected pharmacokinetic (PK) data for both the 5 mg TID and 20 mg TID doses of dimebon.

Study Schematic:



Methods:

This study was a multicenter Phase 3, randomized, double-blind, placebo-controlled safety and efficacy study of 12 months of dimebon (latrepirdine) treatment in patients with mild-to-moderate Alzheimer's disease (AD) who were stable on donepezil treatment. The study evaluated 2 doses of oral dimebon (20 mg TID and 5 mg TID) administered for 12 months (52 weeks) for the primary efficacy and safety analyses. Eligible patients had Screening Mini-Mental State Examination (MMSE) scores of 12 to 24 inclusive and were to be on treatment with donepezil at a stable dose of 10 mg daily for at least 4 months prior to Study Day 1. Patients were required to participate in the study with a caregiver who assisted the patient at least 5 days per week for at least 3 hours per day. Approximately 1,050 patients were to be centrally randomized 1:1:1 into 3 groups of 350 patients each (dimebon 20 mg TID, dimebon 5 mg TID, and placebo). Randomization was stratified by Screening MMSE (19 or less and greater than 19). Patients randomized to dimebon 20 mg TID received dimebon 10 mg TID for the first 7 days of study drug treatment, followed by an increase to dimebon 20 mg TID for the remainder of the treatment period.

Efficacy assessments including the ADAS-cog, ADCS-ADL, Clinician's Interview-Based Impression of Severity (CIBIS)/CIBIC-plus, NPI, and the MMSE were to be performed at the Baseline visit, and at the Week 13, 26, 39, and 52 Visits. The RUD Lite© and EQ-5D were to be performed at the Baseline visit and at the Week 26 and 52 Visits. An independent rater not involved in and blinded to other aspects of the trial was to administer the CIBIC-plus. The CIBIC-plus instrument in this trial was the ADCS – Clinician's Global Impression of Change (ADCS-CGIC). All other efficacy assessments were to be performed consistently by a second rater. Each rater was to continue to perform the same efficacy assessments for a specific patient throughout the study.

Safety and tolerability were assessed by recording of adverse events and by monitoring of vital signs, physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). Central laboratories were utilized for safety laboratory assessments and ECG assessments. An independent Data Monitoring Committee monitored safety data of the trial by blinded treatment group on an ongoing basis. The Data Monitoring Committee could request treatment group unblinding if safety concerns arose during the study.

Prior to dosing (Day 1), a whole blood sample was to be collected for cytochrome P450 (CYP) 2D6 and apolipoprotein E (ApoE) genotyping analyses.

Pharmacokinetic plasma samples to assess dimebon concentrations were to be collected on Day 1 and Week 13 at pre-specified times pre- and post-dose.

Patients who discontinued prior to completion of the Week 52 visit were to be evaluated as soon as possible and have Early Termination visit procedures completed. A Follow-up safety visit was to be scheduled four weeks after any Early Termination visit for a final Follow-up visit.

Patients who completed the 52-week study were offered the opportunity to enroll into an open-label extension study until commercial availability in their respective countries or until the study was stopped by the Sponsor. Patients who declined enrollment into the open-label extension study were to return to the clinic at Week 56, 4 weeks after cessation of study drug, for follow-up safety evaluations.

Number of Patients (Planned and Analyzed): Approximately 1,050 mild-to-moderate AD patients were planned. Actual enrollment was a total of 1003 patients; 321 patients randomized to dimebon 5 mg TID, 340 randomized to dimebon 20 mg TID, and 342 randomized to placebo TID. Two patients randomized to dimebon 20 mg and 1 patient randomized to placebo did not receive treatment with study drug; additionally, one patient (109-4357) randomized to placebo mistakenly received dimebon 5 mg and continued this treatment. Thus, among the 1000 patients who received at least 1 dose of study drug, 660 patients received dimebon (322 patients received 5mg dimebon and 338 patients received 20 mg dimebon) and 340 patients received placebo.

Table 2-1: Randomization and Study Drug Treatment Assignment

	Dimebon 5 mg TID	Dimebon 20 mg TID	Placebo TID	TOTAL
Randomized Patients	321	340	342	1003
Not Dosed with Study Drug	--	2	1	--
Received Incorrect Study Drug Assignment	--	--	1* (received dimebon 5 mg TID)	--
Patient Study Drug Treatment Received	322	338	340	1000

Diagnosis and Main Criteria for Inclusion: Inclusion: men or women ≥ 50 years of age; diagnosis of AD according to standard criteria; had been taking the cholinesterase inhibitor, donepezil, at a stable dose of 10 mg daily for at least 4 months* prior to Day 1; brain imaging within 12 months; women who were surgically sterile, postmenopausal, or willing to use a double-barrier method of birth control; men willing to use double-barrier birth control. 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 for at least 3 hours per day. Exclusion: major structural brain disease; major medical illness, physical disability, or unstable medical condition; clinically significant laboratory abnormalities; use of nondonepezil cholinesterase inhibitors within 4 months and/or memantine or other approved prescription therapy for AD within 90 days; participation in another dimebon trial; participation in investigational drug or device study within 30 days prior to study entry or 90 days prior to Day 1 if the investigational drug study involved therapy for AD.

*Modified in Protocol Amendment 2 (version 3.0) from the initial inclusion requirement for at least 6 months treatment with donepezil at a stable dose of 10 mg daily prior to Day 1, to 4 months.

Test Product, Dose, and Mode of Administration, Lot Number: 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, was indicated for TID oral administration in this protocol. There was to be a minimum of 4 hours between each dose. Study medication could be taken with or without food.

All patients were to receive 2 tablets of study drug TID during Week 1 and 1 tablet of study drug TID for the remaining 51 weeks.

Low-Dose Group: Dimebon, 5 mg (one 5 mg tablet plus one placebo tablet) orally TID × 1 week, then dimebon, 5 mg (one 5 mg tablet) orally TID × 51 weeks.

High-Dose Group: Dimebon, 10 mg (two 5 mg tablets) orally TID × 1 week, then dimebon 20 mg (one 20 mg tablet) orally TID × 51 weeks.

Tablets for both dosing groups were identical in appearance, taste, and odor.

Inactive components included: Lactose monohydrate, pregelatinized starch, talc, magnesium stearate, Opadry II™ film coating and sterile water.

Duration of Treatment: 52 weeks (12 months)

Reference Therapy, Dose, and Mode of Administration, Lot Number: Placebo tablets were identical in appearance, taste, and odor to the active dimebon tablets and included the following inactive components: lactose monohydrate, pregelatinized starch, talc, magnesium stearate, Opadry II film coating, and sterile water. There was to be a minimum of four hours between each dose. Study medication could be taken with or without food.

During the initial one-week titration period, patients randomized to placebo were to receive 2 tablets orally TID; thereafter, patients were to receive 1 tablet orally TID through Study Week 52.

Criteria for Evaluation:
Efficacy:

Efficacy outcome measures in the study included the following:

1. Co-primary outcome measures in this study:
   a) A comparison between the mean change from Baseline to Week 52 in the dimebon 20 mg TID treatment group and the placebo group on the ADAS-cog;
   b) A comparison between the mean change from Baseline to Week 52 in the dimebon 20 mg TID treatment group and the placebo group on the ADCS-ADL;
2. Key secondary outcome measures in this study included:
   a) A comparison of rates of change in ADCS-ADL across time between the dimebon 20 mg TID treatment group and the placebo group;
   b) A comparison of rates of change over time (through Week 52) in change from baseline in the dimebon 20 mg TID treatment group and the placebo group on the ADAS-cog total score;
   c) A comparison between the mean change from Baseline to Week 52 in the dimebon 5 mg TID treatment group and the placebo group on the ADAS-cog;
   d) A comparison between the mean change from Baseline to Week 52 in the dimebon 5 mg TID treatment group and the placebo group on the ADCS-ADL;
3. Additional secondary endpoints for this study included:
   a) A comparison between the distributions of the dimebon 20 mg TID treatment group and the placebo group on the ADCS-CGIC at Week 52;
   b) A comparison between the mean change from Baseline to Week 52 of the dimebon 20 mg TID treatment group and the placebo group on the NPI;
   c) A comparison between the mean change from Baseline to Week 52 of the dimebon 20 mg TID treatment group and the placebo group on the MMSE;
   d) Comparisons of the dimebon 20 mg TID treatment group and the placebo group at Weeks 13, 26, and 39 for all outcomes except the RUD Lite© and EQ-5D;
   e) Comparisons of the dimebon 5 mg TID treatment group and the placebo group at Weeks 13, 26, and 39 for all outcomes and at Week 52 for outcomes other than the co-primary outcomes;
   f) An analysis of overall benefit (response) in individual patients at Week 52.
   g) RUD Lite© and EQ-5D data summarized descriptively by treatment group.

Safety:

The safety of dimebon 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, as well as the frequency of new laboratory and ECG abnormalities among the three treatment groups. Safety measures thus included adverse events, vital signs, physical examinations, ECGs, and clinical laboratory testing.

Pharmacokinetics:

Dimebon plasma concentrations were to be measured at Baseline and Week 13. The impact of covariates was to be evaluated in order to identify underlying factors responsible for the variability of PK parameters and to identify sub-populations.

Statistical Methods:

All efficacy analyses were conducted using the Intent-to-Treat (ITT) population defined as all randomized patients. Randomization was stratified by Screening MMSE (two strata: MMSE greater than 19 and MMSE less than or equal to 19) and all analyses incorporated the stratification. There were co-primary efficacy analyses, one based on the ADAS-cog and the other based on the ADCS-ADL. The ADAS-cog was generated from a total of 11 items and ranges from 0 to 70, with a higher score indicating greater cognitive impairment. The ADCS-ADL scale was from 0 to 78, with a higher score indicating greater function on activities of daily living. Both variables were analyzed using a mixed model repeated measures (MMRM) methodology. Treatment group, visit, treatment group by visit interaction, geographic region, and stratification factor

randomization MMSE category were included as fixed effects in the model and baseline value was included as a covariate. The co-primary analyses compared the mean changes from Baseline to Week 52 in the dimebon 20 mg TID and placebo groups using a 2-sided test at the 0.05 level of significance.

If and only if the co-primary endpoints were both significant at the 0.05 level, the testing of the key secondary endpoints were to be rank prioritized as listed above such that if statistical significance ($p < 0.05$) was not achieved for one of the endpoints, all key secondary endpoints of a lower rank would not be considered statistically significant for regulatory purposes.

In an assessment of maintenance of function, rates of change in ADCS-ADL and ADAS-cog scores across time were compared between the dimebon 20 mg TID and placebo groups. Initially, this comparison was made using an assumption of simple linearity. If the effect of treatment was not constant over time then the model was to be adjusted to account for curvature. For the CIBIC-plus ADCS-CGIC, the data were analyzed using MMRM methodology. The response variable was the equally-spaced scores for the categories of 1 = marked improvement, 2 = moderate improvement, 3 = minimal improvement, 4 = no change, 5 = minimal worsening, 6 = moderate worsening, 7 = marked worsening. Treatment group, visit, treatment group by visit interaction, geographic region, and stratification factor randomization MMSE category were included as fixed effects in the model and baseline CIBIS value was included as a covariate. The additional quantitative secondary outcome variables were analyzed using MMRM methodology similar to that described for the co-primary efficacy analyses. Comparisons between the mean change from Baseline to Week 52 in the dimebon 5 mg TID group and the placebo group were made for ADAS-cog and ADCS-ADL using the models for the primary analyses. These analyses were also to be carried out using a two-sided test at the 0.05 level of significance. No adjustments for multiple comparisons were made for testing of secondary outcomes. The secondary outcomes for the RUD Lite© and EQ-5D were summarized descriptively by treatment group.

Safety was assessed through summaries of adverse events, vital signs, physical examinations, ECGs and clinical laboratory test data (including change from Baseline). Safety analyses included all randomized subjects who receive any amount of study drug (safety population). All adverse events were coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events are presented by MedDRA system organ class and preferred term, relationship to study treatment, and severity. Descriptive statistics rather than inferential statistics were generally used. The PK data from this study were to be combined with PK data from other trials to build a population PK model.

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 of the baseline results to each of the subsequent visits were produced. In addition, mean changes from Baseline to each visit were computed. The percentage of patients in each treatment group with abnormal clinically-significant ECG findings was summarized by study visit.

Summary and Conclusions:

Analysis Populations: The ITT Population included all 1003 enrolled patients. The Safety Population was defined as all patients who received any amount of study drug and included 1000 patients from the ITT Population. Two patients randomized to the dimebon 20 mg treatment group and one patient randomized to the placebo group did not receive treatment with study drug; additionally, 1 patient (109-4357) randomized to placebo mistakenly received initial study drug supply with blinded dimebon 5 mg, following which the patient continued to received blinded dimebon 5 mg study drug. This patient was analyzed for efficacy as placebo and analyzed for safety as dimebon 5 mg. 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 85.8% (861/1003) of the patients in the ITT Population.

Disposition and Baseline Characteristics: A total of 1003 patients were enrolled at 117 study centers in Western Europe (452/1003, 45.1%), the United States (427/1003, 42.6%), and Australia and New Zealand (124/1003, 12.4%). 119 centers received regulatory approval; however, patients were enrolled at 117 of these centers. The treatment groups were well-balanced across study regions. Of the 1003 patients, 340 were randomized to receive dimebon 20 mg TID, 321 were randomized to receive dimebon 5 mg TID, and 342 were randomized to receive placebo TID. Of the 1003 patients randomized, 792 (79.0%) completed the study per protocol. Seventy-one (20.9%) and 70 (21.8%) patients in the dimebon 20 mg and 5 mg treatment groups, respectively, discontinued the study early compared to 70 (20.5%) patients in the placebo treatment group. Reasons for early discontinuation from the study included: adverse event (85 patients; 32 dimebon 20 mg, 26 dimebon 5 mg, and 27 placebo patients), withdrawal of caregiver or patient consent (85 patients:

24 dimebon 20 mg, 33 dimebon 5 mg, and 28 placebo patients), protocol noncompliance (18 patients; 6 in each treatment group ; patient unable to continue (12 patients, 6 dimebon 20 mg, 1 dimebon 5 mg, and 5 placebo patients), lost to follow-up (4 patients, 1 dimebon 20 mg, 3 dimebon 5 mg, and none in the placebo treatment group), and "other" reasons (7 patients; 2 dimebon 20 mg, 1 dimebon 5 mg, and 4 placebo patients). No patients underwent early termination at the independent request of the Investigator.

The mean (± standard deviation [SD]) time in the study for all patients was 338.8 (±90.1) days for the dimebon 20 mg treatment group, 338.7 (±87.6) days for the dimebon 5 mg treatment group, and 338.6 (±89.8) days for the placebo treatment group. The mean time to study withdrawal for early termination was 208.0 days (±123.5) for the dimebon 20 mg treatment group, 213.4 (±112.2) for the dimebon 5 mg treatment group, and 202.3 (±118.7) for the placebo treatment group. The mean time to study withdrawal due to adverse events was 222.4 (±124.7) days for the dimebon 20 mg treatment group, 201.1 (±125.6) days for the dimebon 5 mg treatment group, and 199.0 (±137.2) days for the placebo treatment group.

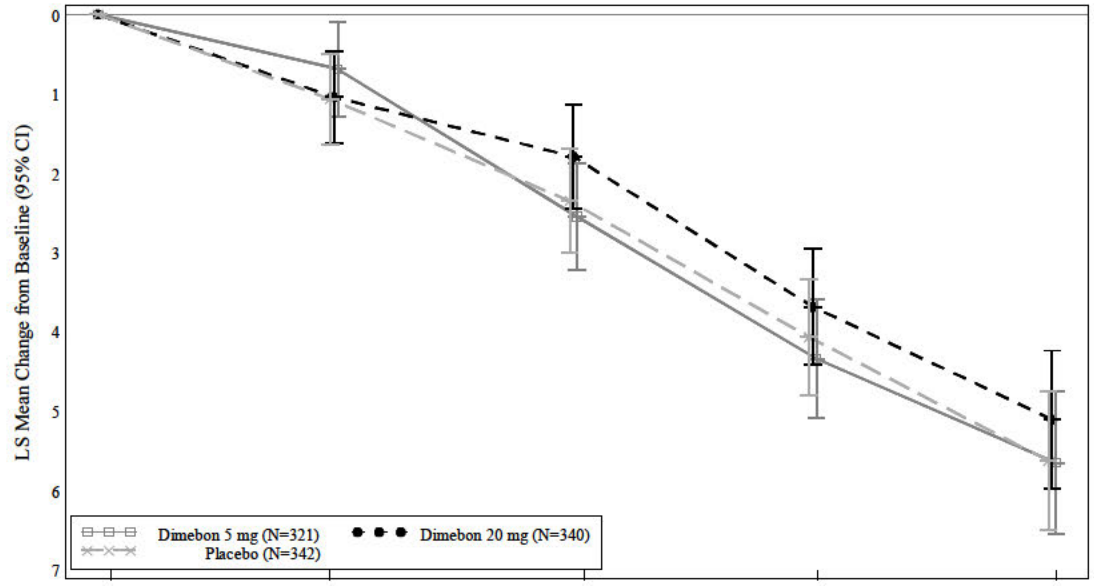
The treatment groups were also well-matched across groups for demographic characteristics and baseline efficacy assessments.

Treatments: The mean number of days on treatment was comparable between treatment groups, including 323.5 (± 96.0), 322.9 (± 94.4), and 324.0 (± 95.1) for the dimebon 20 mg, dimebon 5 mg, and placebo treatment groups, respectively. The majority of patients had treatment for ≥ 52 weeks (57.7%, 62.1%, and 62.4%, for the dimebon 20 mg, dimebon 5 mg, and placebo treatment groups, respectively. An additional 26.6%, 20.2%, and 20.9%, respectively, completed 39 to 52 weeks treatment. Eighty percent to 100% compliance rate was achieved by 80.5%, 81.4%, and 82.1% in the dimebon 20 mg, dimebon 5 mg, and placebo treatment groups, respectively. One hundred percent of patients in all 3 treatment groups received at least 1 concomitant medication during the study. The most commonly used concomitant medications in the study population was donepezil, by protocol design (100%). The next most commonly used concomitant medications reported in ≥ 10% of the dimebon treatment groups included anilides (22.4%, 22.4%, and 20.5% in the dimebon 20 mg, dimebon 5 mg, and placebo treatment groups, respectively), acetylcholinesterase inhibitors (19.7%, 19.0%, and 24.3%, respectively), selective beta blocking agents (17.1%, 19.3%, and 18.7%, respectively), dihydropyridine derivatives (12.4%, 16.2%, and 12.9%, respectively), HMG CoA reductase agents (40.0%, 43.6%, and 38.6%, respectively), benzodiazepine derivatives (12.6%, 11.8%, and 9.4%, respectively), influenza vaccines (11.8%, 11.8%, and 14.6%, respectively), multivitamins (17.9%, 19.3%, and 18.7%, respectively), other lipid modifying agents (19.4%, 16.8%, and19.6%, respectively), platelet aggregation inhibitors excluding heparin (39.7%, 44.2%, and 38.6%, respectively), propionic acid derivatives (11.5%, 8.1%, and 9.6%, respectively), proton pump inhibitors (21.2%, 14.6%, and 16.7%, respectively), selective serotonin reuptake inhibitors (26.8%, 32.1%, and 27.5%, respectively), thiazides plan (5.6%, 10.0%, and 7.3%, respectively), thyroid hormones (14.1%, 14.6%, and 9.6%, respectively), unspecified herbal (10.0%, 10.9%, and 15.8%, respectively), and vitamin B_{12} (12.6%, 10.0%, and 11.1%, respectively).

Efficacy Results: There was no statistically significant benefit of dimebon over placebo for either of the co-primary endpoints or on any of the secondary endpoints. The results are shown in the figures below.

Analyses of subgroups (e.g., study site, age, sex, prior AD medicine use, prior donepezil use, geographic region, MMSE score at Screening, CYP2D6 metabolizer status, parameter subscale, category, or domain), 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.

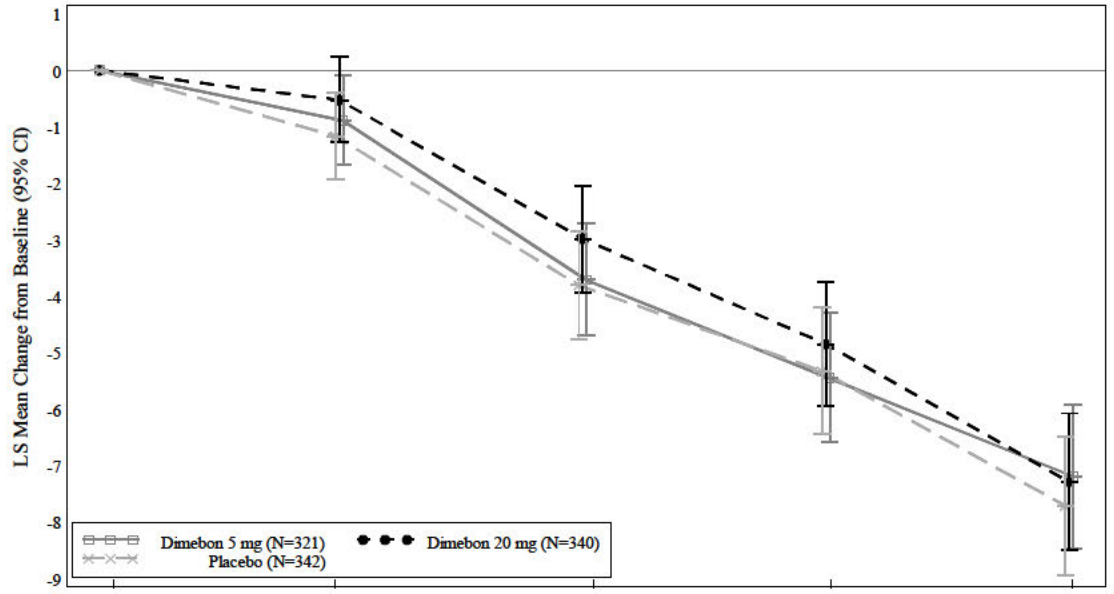
Figure 2-1: LS Mean (95% CI) Change from Baseline in ADAS-Cog at Weeks 13, 26, 39, 52
Intent-to-Treat Subjects – Observed Case



	Baseline	Week 13	Week 26	Week 39	Week 52
5 mg	318	288	262	251	243
20 mg	333	300	284	273	260
Placebo	340	309	286	273	258

p = 0.3983

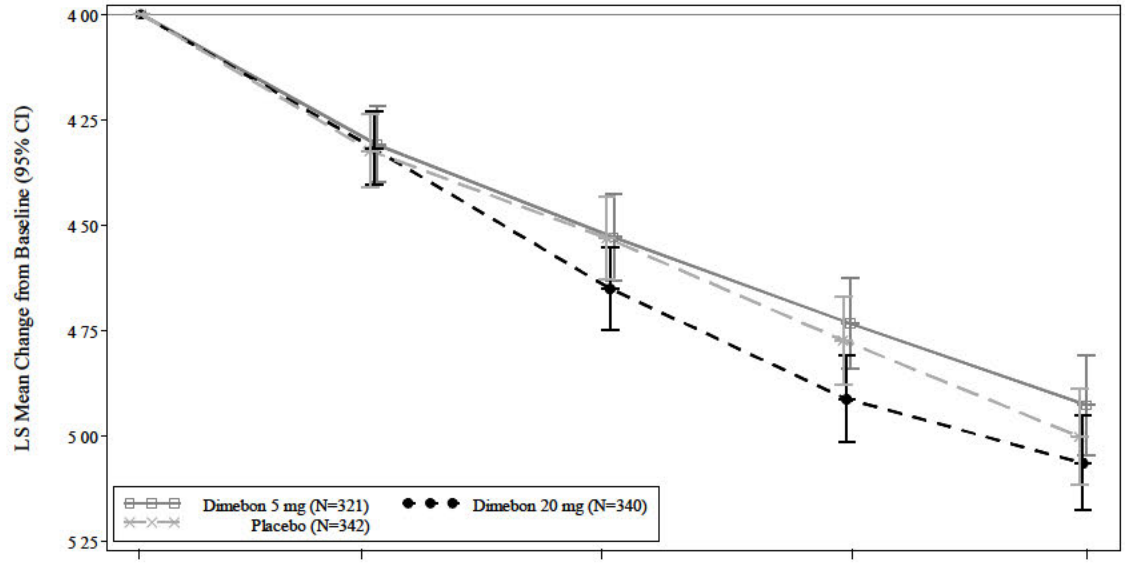
Figure 2-2: LS Mean (95% CI) Change from Baseline in ADCS-ADL at Weeks 13, 26, 39, 52
Intent-to-Treat Subjects – Observed Case



	Baseline	Week 13	Week 26	Week 39	Week 52
5 mg	314	282	259	251	241
20 mg	336	307	287	279	266
Placebo	334	302	285	270	264

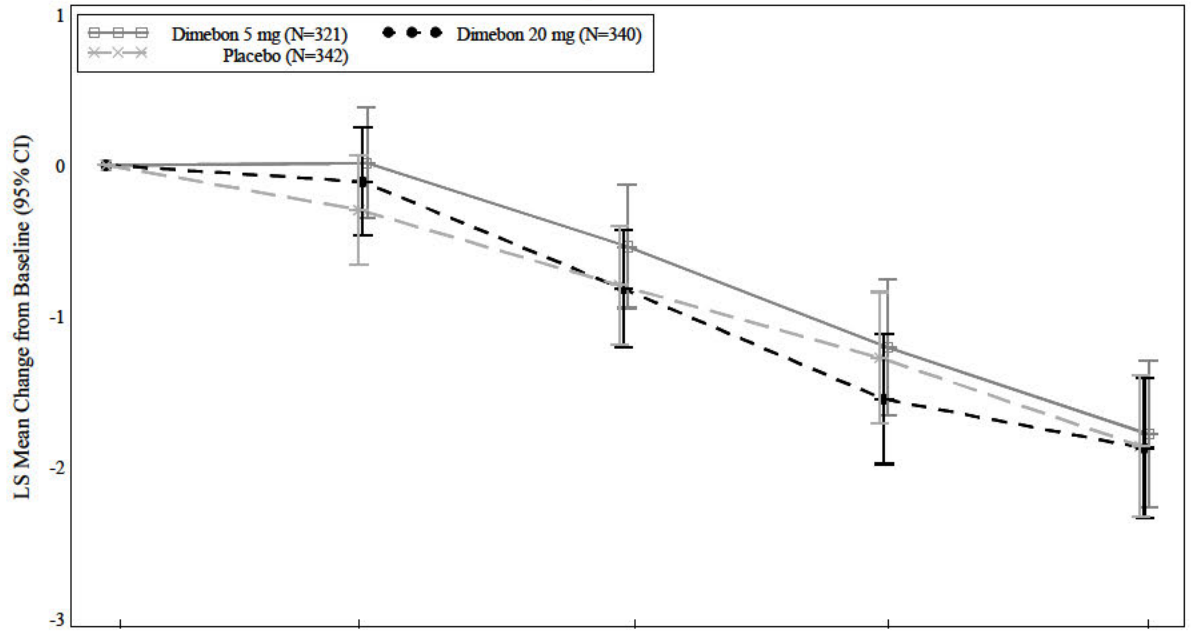
p = 0.6184

Figure 2-3: LS Mean (95% CI) Change from Baseline in CIBIC-plus at Weeks 13, 26, 39, 52
Intent-to-Treat Subjects – Observed Case



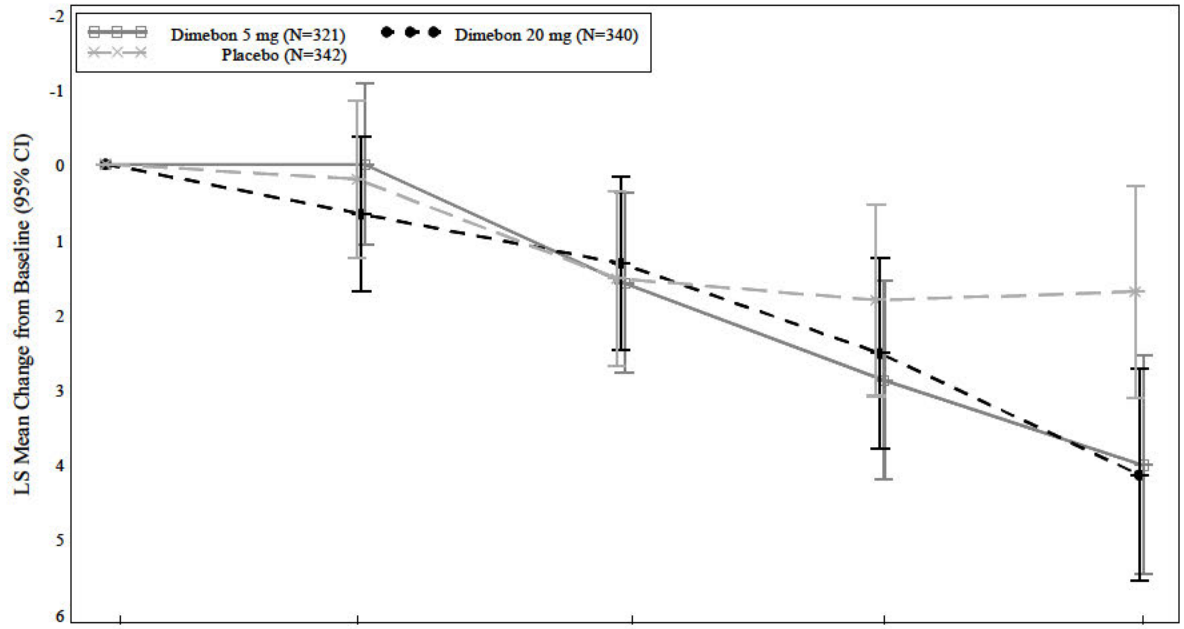
	Baseline	Week 13	Week 26	Week 39	Week 52
5 mg	321	292	268	254	244
20 mg	338	310	283	274	267
Placebo	340	310	290	275	267

Figure 2-4: LS Mean (95% CI) Change from Baseline in MMSE at Weeks 13, 26, 39, 52
Intent-to-Treat Subjects – Observed Case



	Baseline	Week 13	Week 26	Week 39	Week 52
5 mg	321	293	266	257	244
20 mg	338	308	291	280	268
Placebo	341	313	289	277	267

Figure 2-5: LS Mean (95% CI) Change from Baseline in NPI at Weeks 13, 26, 39, 52
Intent-to-Treat Subjects – Observed Case



	Baseline	Week 13	Week 26	Week 39	Week 52
5 mg	320	289	266	257	246
20 mg	337	309	288	279	267
Placebo	338	307	289	277	268

Safety Results: Dimebon was generally well tolerated and the adverse event profile observed in this study was consistent with the adverse event profile described in the dimebon Investigator's Brochure version 7.0, dated 17 JUN 2011. Overall adverse event rates, serious adverse event rates, and deaths were similar across the 3 treatment groups as shown below and were consistent with other studies in AD populations. Twenty-one percent of patient discontinued early from the study, with < 10% of patients with early discontinuation from this 52-week study due to an adverse event and <10% of patients withdrawing consent (as also detailed above).

Approximately 83% of patients reported at least 1 treatment-emergent adverse event in the dimebon 20 mg (280/338, 82.8%), dimebon 5 mg TID (266/322, 82.6%) and placebo TID (279/340, 82.1%) groups. There were no clinically relevant differences in the frequency of treatment-emergent adverse events by system organ class. The most common (≥ 5% of patients in any treatment group) treatment-emergent adverse events by Preferred Term in the dimebon 20 mg TID, dimebon 5 mg TID and placebo TID groups, in descending overall order for the dimebon 20 mg TID group were fall (13.9%, 15.5%, and 17.1%, respectively), urinary tract infection (13.9%, 12.7%, and 12.1%), headache (9.2%, 6.5% and 4.4%, respectively), cough (7.7%, 4.7%, and 7.4%, respectively), somnolence (7.7%, 6.5%, and 6.2%, respectively), diarrhea (7.4%, 8.1% and 10.9%, respectively), dizziness (7.1%, 3.4%, and 3.8%, respectively), dry mouth (5.3%, 2.5%, and 3.8%, respectively), insomnia (5.3%, 2.5%, and 4.1%, respectively), asthenia (5.0%, 5.3%, and 4.1%, respectively), agitation (4.7%, 6.2%, and 6.5%, respectively), depression (4.7%, 7.1%, and 3.2%, respectively), arthralgia (4.4%, 3.4%, and 5.3%, respectively), depressed mood (3.0%, 4.3%, and 5.9%, respectively), rash (2.7%, 5.6%, and 2.4%, respectively), and contusion (1.5%, 5.3%, and 3.5%, respectively). Treatment-emergent adverse events reported in at least 5% of patients in the dimebon 20 mg TID group and with a numerically higher frequency than patients in the placebo treatment group were urinary tract infection, headache, cough, somnolence, dizziness, dry mouth, insomnia, and asthenia.

The percent of patients with at least one related treatment-emergent adverse events (assessed as possibly, probably, or definitely related to study drug by the Principal Investigator) was comparable between the dimebon 20 mg TID, dimebon 5 mg TID, and placebo TID treatment groups (33.7%, 30.8%, and 30.0%, respectively). Adverse events reported in association with either dimebon 20 mg TID or dimebon 5 mg TID at a rate of ≥ 2% include diarrhea, dry mouth, asthenia, headache, somnolence, nausea, dizziness and insomnia.

Most 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 20 mg TID, dimebon 5 mg TID, and placebo TID groups assessed as mild (20.1%, 17.7%, and 20.3%, respectively), moderate (11.5%, 12.1%, and 9.1%, respectively), or severe (2.1%, 0.9%, 0.6%, respectively), were generally comparable.

Seventy (20.7%) in the dimebon 20 mg TID group, 50 (15.5%) in the dimebon 5 mg TID group, and 52 (15.3%) in the placebo TID group reported at least one serious adverse event during the study. Numerically more patients in the dimebon 20 mg TID group reported an adverse event in the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC (dimebon 20 mg TID (22/338, 6.5%); dimebon 5 mg TID (17/322, 5.3%); placebo TID (16/340, 4.7%). Examination of the individual events which occurred in the dimebon 20 mg TID group at greater frequency than the placebo group include: B-cell lymphoma (n = 1), colon cancer stage III (n = 1), hemangioma (n = 1), lung neoplasm (n = 2 dimebon 20 mg vs n = 1 placebo), malignant melanoma stage 1 (n = 1), ovarian cancer (n = 1), pancreatic cancer (n = 2), pleural mesothelioma (n = 1), prostate cancer (n = 3 dimebon 20 mg vs n=1 placebo)), squamous cell carcinoma of the skin (n = 4 in dimebon 20 mg vs. n=1 placebo), T-cell lymphoma (n = 1), and transitional cell carcinoma (n = 1). Review of the events in the dimebon 5 mg TID group (bladder papilloma, bladder transitional cell carcinoma stage 1, Bowen's disease, bronchial carcinoma, malignant melanoma stage II, meningioma, non-small cell lung cancer, rectal cancer, seborrhoeic keratosis (all events with n = 1), and squamous cell carcnimona of the skin (n = 4) did not further distinguish a clinical pattern. These events are known to occur in this elderly population. No safety signal was detected.

In the dimebon 20 mg TID and 5 mg TID treatment groups, 10 patients (3.0%) and 6 patients (1.9%), respectively, experienced a serious treatment-emergent adverse event considered at least possibly related to study drug, versus 2 (0.6%) of patients in the placebo TID treatment group. The related serious adverse events in the dimebon 20 mg TID group, reported for one patient unless otherwise specified, included syncope (n = 3 patients), partial seizures, facial bones fracture , dizziness, cerebral haemorrhage, agitation, abnormal behavior, and inguinal hernia. The events in the dimebon 5 mg TID group included grand mal convulsion (n = 2), syncope, sick sinus syndrome with sinus arrest and syncope (3 events, n = 1 patient), aggression and

dizziness (2 events, 1 patient), and thrombocytopenia. The events in the placebo TID group included aggression and agitation (2 events, 1 patient) and hemorrhagic stroke. Six patients reported a seizure, including 2 (0.6%) in the dimebon 20 mg TID group, 1 (0.3%) in the dimebon 5 mg TID group, and 3 (0.9%) in the placebo TID group.

Deaths were reported for 8 (2.4%) patients in the dimebon 20mg TID treatment group, 3 (0.9%) patients in the dimebon 5 mg TID treatment group and 6 (1.8%) patients in the placebo TID treatment group. No clinically relevant difference between the dimebon groups and placebo was noted. The larger number of deaths in the dimebon 20 mg TID treatment group is consistent with the numeric increase in the diagnoses in the Neoplasms system organ class (Preferred Term for events resulting in death includes endstage dementia, intracerebral hemorrhage, ovarian cancer, T-cell lymphoma, pneumonia, pancreatic carcinoma and metastatic pancreatic carcinoma, pleural mesothelioma).

There were no clinically meaningful differences in the incidence of abnormalities between treatment groups for any clinical laboratory parameter. ECG monitoring did not identify a safety signal. There were no notable differences between treatment groups in findings of physical examinations or neurological examinations.

Pharmacokinetic Results:

Pharmacokinetic samples collected at baseline and Week 13 were not analyzed, given the overall lack of demonstrated efficacy in this study.

Conclusions:

Conclusions:

In this multinational study, conducted in patients with mild-to-moderate AD receiving stable background therapy with donepezil, dimebon was well tolerated but failed to demonstrate a benefit over placebo on any of the cognitive, functional, or behavioral clinical endpoints.

- There was no statistically significant benefit of dimebon over placebo for either of the co-primary endpoints or on any of the secondary endpoints. The rate of placebo decline in the CONCERT Study was within the range of expectations for the study population.
- Treatment with dimebon 20 mg TID for 52 weeks was generally well-tolerated in this population of patients with mild-to-moderate AD on stable background therapy with donepezil.

Report Date: 23 July 2012