

# Latrepirdine is Well-Tolerated in Patients With Alzheimer's Disease Receiving Memantine or Memantine Plus Donepezil

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## BACKGROUND

- Dimebon (latrepirdine) is an orally available, small synthetic molecule that is in Phase 3 clinical development as a potential treatment for Alzheimer's disease (AD) and Huntington disease (HD). Dimebon 20 mg 3 times daily (TID) is the dosing regimen used to date in published clinical trials for the treatment of patients with AD or HD.<sup>1,2</sup>
- The basis for the clinical effects of latrepirdine have not yet been fully elucidated but preclinical studies suggest the compound may enhance mitochondrial function in the setting of cellular stress, increase cell viability, and/or promote neurite outgrowth,<sup>3-6</sup> properties that might contribute to its mechanism of action. Recent studies suggest that latrepirdine is not a cholinesterase inhibitor or an NMDA-receptor antagonist at clinically relevant concentrations.<sup>7,8</sup> Latrepirdine is being evaluated in a large Phase 3 program, both as monotherapy and in combination with approved treatments for AD, including memantine and donepezil.
- Memantine, an NMDA-receptor antagonist, and 4 cholinesterase inhibitors, including donepezil, are currently approved for the symptomatic treatment of AD. Both memantine and donepezil produce modest improvements in cognition and other symptomatic characteristics of AD when used as monotherapy and as combination therapy.<sup>9-11</sup>
- Due to its mechanism of action being distinct from currently approved therapies, latrepirdine could potentially be used in combination with cholinesterase inhibitors or memantine to enhance treatment efficacy in AD. It is therefore important to assess whether latrepirdine can be safely co-administered with donepezil and memantine.
- In this study, we evaluated the safety, tolerability, and pharmacokinetics (PK) of latrepirdine in combination with memantine, with or without donepezil. Other studies have confirmed the safety and tolerability of latrepirdine combined with donepezil alone.<sup>12</sup>

## OBJECTIVE

- To assess the safety, tolerability, and steady-state PK of orally-administered latrepirdine in patients with AD on a stable dose and regimen of memantine or memantine with donepezil.

## METHODS

- This was a Phase 1, multicenter, randomized, double-blind, safety and tolerability study of latrepirdine in patients ≥50 years with AD (**Table 1**) and on a stable regimen of memantine 10 mg twice daily (BID) (**Cohort 1**); or memantine 10 mg BID plus donepezil 10 mg once daily (QD) (**Cohort 2**).

**TABLE 1** Key inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>Men and women aged ≥50 years old</li> <li>Probable AD by NINCDS-ADRDA criteria<sup>13</sup> or AD by DSM-IV-TR criteria<sup>14</sup></li> <li>Undergone brain imaging within 1 year of enrollment, consistent with probable AD without other clinically significant co-morbid pathologies</li> <li>Taking 10 mg memantine BID daily for at least 30 days prior to Study Day 1 and tolerating it well (<b>Cohort 1</b>) or taking memantine 10 mg BID plus 10 mg donepezil QD for at least 45 days prior to Study Day 1 and tolerating it well, including the absence of gastrointestinal side-effects (<b>Cohort 2</b>)</li> <li>Otherwise in good health and ambulatory</li> <li>Caregiver who is capable and willing to accompany the patient to all clinic visits and supervise study drug administration</li> </ul>	<ul style="list-style-type: none"> <li>Clinically significant condition or abnormality found at screening criteria</li> <li>History of seizure or head trauma</li> <li>Use of non-selective H<sub>1</sub> antihistamines within 15 days prior to study, or narcotic analgesics within 30 days prior to study</li> <li>For <b>Cohort 1</b>: taken cholinesterase inhibitors within 30 days prior to study. For <b>Cohort 2</b>: taken other cholinesterase inhibitors (non-donepezil) within 45 days prior to study</li> <li>Plans to change background anti-dementia therapy during 28-day dosing period</li> <li>Exposure to any investigational drug/device within 30 days of study, or 90 days if the study drug involved AD therapy</li> <li>Unstable psychiatric illness</li> </ul>

AD: Alzheimer's disease; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorder Association

- The 2 distinct cohorts were enrolled and randomized to receive latrepirdine or placebo (3:1 ratio). **Cohort 1** examined the safety, tolerability, and PK of latrepirdine and memantine. **Cohort 2** examined the safety, tolerability, and PK of latrepirdine, memantine, and donepezil. Enrollment in **Cohort 2** commenced when 8 patients from **Cohort 1** had completed 28 days with acceptable safety and tolerability.
- Latrepirdine administration for both cohorts was as follows:
  - Days 1–7**: latrepirdine 10 mg (or placebo) TID;
  - Days 8–28**: latrepirdine 20 mg (or placebo) TID.
- Latrepirdine was administered TID at approximately 8 am, 2 pm, and 8 pm; memantine was administered BID at approximately 8 am and 8 pm, and donepezil was administered QD at the same time as prior to study participation.
- Throughout the study, safety and tolerability were assessed by the monitoring of adverse events (AEs), physical examinations, vital signs, laboratory assessments, and 12-lead electrocardiographs.
- Multiple blood samples for latrepirdine PK analysis were collected on Day 14. Pre-dose (C<sub>trough</sub>) PK samples for latrepirdine and memantine (**Cohorts 1 and 2**) and steady-state (C<sub>ss</sub>) PK samples for donepezil (**Cohort 2**) were collected on Days 1, 7, 14, and 28.
- Following completion of double-blind treatment, all patients were offered open-label treatment with latrepirdine continuing until marketing authorization of the compound.

## RESULTS

### Patients

- In this study, 46 patients were randomized: 17 to **Cohort 1** (13 latrepirdine, 4 placebo) and 29 to **Cohort 2** (22 latrepirdine, 7 placebo) (**Table 2**). The overall mean age was 75.5 years, 37% were male, 98% were white. The mean duration since onset of AD symptoms was 6.2 years.

### Adverse Events and Safety

- Overall, 14/35 (40%) patients on latrepirdine and 4/11 (36%) on placebo reported ≥1 treatment-emergent adverse event (TEAE) (**Table 3**). The overall pattern of AEs for latrepirdine-treated patients was similar across **Cohorts 1 and 2**. The majority of AEs were mild in intensity. The most common AEs were fatigue, pyrexia, and urinary tract infection, each reported by 2/35 (6%) latrepirdine patients and 0/11 placebo patients. All other AEs were reported by single patients. Seven TEAEs in the latrepirdine group and 1 TEAE in the placebo group were deemed possibly or probably related to the study drug (**Table 4**). Two serious AEs (transient ischemic attack [TIA] and wandering) were reported in patients on latrepirdine (1 from each Cohort) – neither was considered related to study drug.
- No clinically significant laboratory abnormalities were noted.
- In **Cohorts 1 and 2**, 11/13 (85%) and 19/22 (86%) on latrepirdine completed 28-days' treatment; no discontinuations occurred in the placebo groups. Two (2) patients in **Cohort 1** (TIA and agitation) and 1 patient in **Cohort 2** (wandering) discontinued due to a TEAE; the other 2 discontinuations were due to withdrawal of consent.

### Pharmacokinetics

- After oral dosing at 20 mg TID in patients with AD, latrepirdine was absorbed rapidly, with a median time to maximum plasma concentrations (t<sub>max</sub>) of 2–3 hrs (data not shown).

**TABLE 2** Patient demographics

	Cohort 1			Cohort 2		
	Latrepirdine (n=13)	Placebo (n=4)	Total (n=17)	Latrepirdine (n=22)	Placebo (n=7)	Total (n=29)
Number male (%)	4 (30.8)	2 (50.0)	6 (35.3)	7 (31.8)	4 (57.1)	11 (37.9)
Mean age, years (SD)	79.8 (6.5)	72.3 (2.4)	78.1 (6.6)	73.1 (9.3)	77.0 (5.0)	74.0 (8.5)
Number white (%)	13 (100)	4 (100)	17 (100)	22 (100)	6 (85.7)	28 (96.6)
Mean duration since onset of AD symptoms, years (SD)	7.5 (3.5)	4.8 (1.7)	6.8 (3.3)	6.1 (2.8)	4.7 (1.7)	5.8 (2.6)

**TABLE 3** Subjects reporting at least one treatment-emergent adverse event

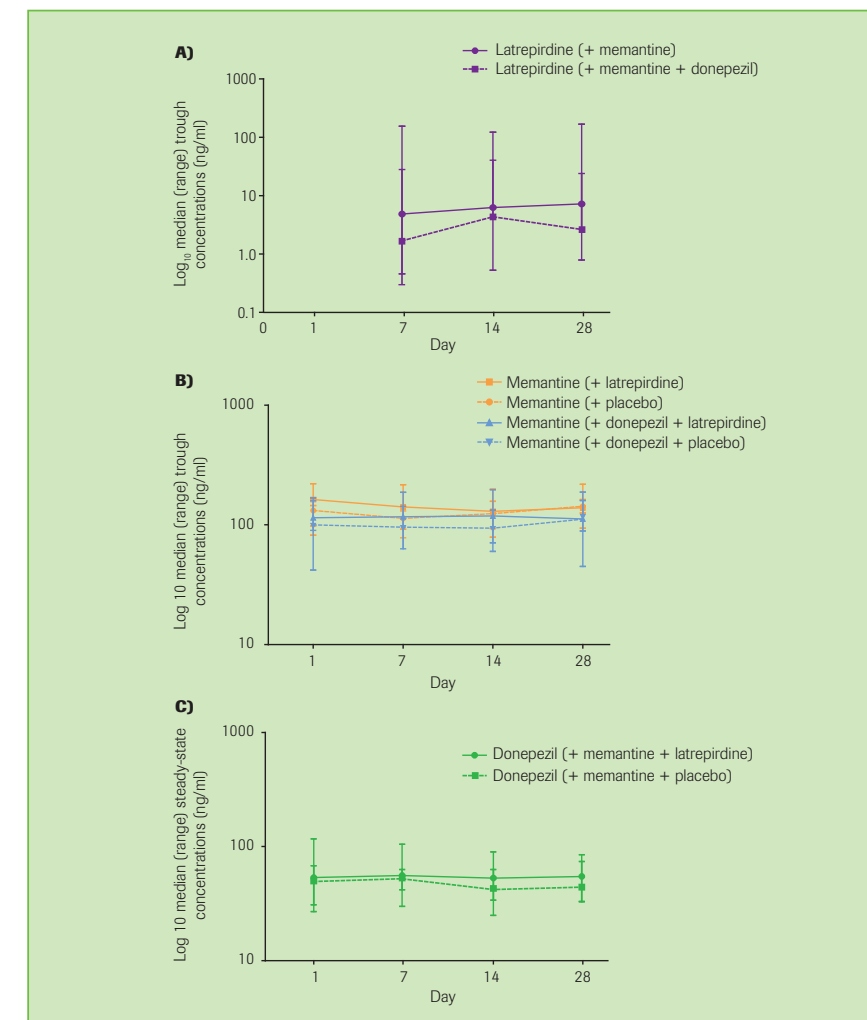
	Cohort 1		Cohort 2	
	Latrepirdine (n=13)	Placebo (n=4)	Latrepirdine (n=22)	Placebo (n=7)
Number of subjects reporting ≥1 adverse event (%)	5 (38.5)	2 (50.0)	9 (40.9)	2 (28.6)

**TABLE 4** Number of treatment-emergent adverse events considered possibly/probably related to study drug

Adverse Event (Preferred Term)	Latrepirdine Cohort 1 (n=13)	Latrepirdine Cohort 2 (n=22)	All Placebo (n=11)
Fatigue	0	2	0
Abnormal sensation in the eye	0	1	0
Diarrhea	0	0	1
Eructation	0	1	0
Sedation	1	0	0
Somnolence	0	1	0
Urinary tract infection	0	1	0

- Latrepirdine concentrations were similar over time comparing those on memantine with those on memantine plus donepezil background therapy (**Figure 1A**) and fell well within the concentration ranges observed with latrepirdine monotherapy in previous studies (data not shown), suggesting latrepirdine is not affected by co-administration of memantine or memantine plus donepezil.
- The steady-state C<sub>trough</sub> for memantine (**Cohorts 1 and 2**) and C<sub>ss</sub> for donepezil (**Cohort 2**) – collected before and during latrepirdine or matching placebo administration – suggest that the PK properties of memantine and donepezil are not affected by latrepirdine (**Figure 1B and C**).

**FIGURE 1** Median (range) pre-dose trough concentrations (C<sub>trough</sub>) for (A) latrepirdine and (B) memantine (**Cohorts 1 and 2**) and (C) steady-state concentrations (C<sub>ss</sub>) for donepezil (**Cohort 2**)



## CONCLUSIONS

- Consistent with the tolerability profile of latrepirdine as monotherapy for AD, the addition of latrepirdine to background treatment of memantine – either as monotherapy or in combination with donepezil – was well-tolerated in this study.
- No changes in the PK of latrepirdine, memantine, or donepezil were observed when latrepirdine treatment was added to existing, stable therapy with memantine or memantine plus donepezil.

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**ACKNOWLEDGMENTS** This study was sponsored by Medivation, Inc., and Pfizer Inc. Medivation Inc., and Pfizer Inc are developing dimebon (latrepirdine) as a potential treatment for AD and HD. Editorial support for the production of this poster was provided by Tina Morley of UBC Scientific Solutions, and funded by Medivation Inc., and Pfizer Inc.

**AUTHOR DISCLOSURES** Dr. Porsteinsson has received research support from Medivation, Inc., and Pfizer Inc and consulting fees from Medivation, Inc. Dr. Selby and Dr. Wang are employees of Medivation, Inc. Dr. Tariot has received research support and consulting fees from Medivation, Inc. and Pfizer Inc.