ALZ-801, a Novel Prodrug of Tramiprosate Which Improves Cognition and Function in ApoE4-Positive Alzheimer's Disease Patients

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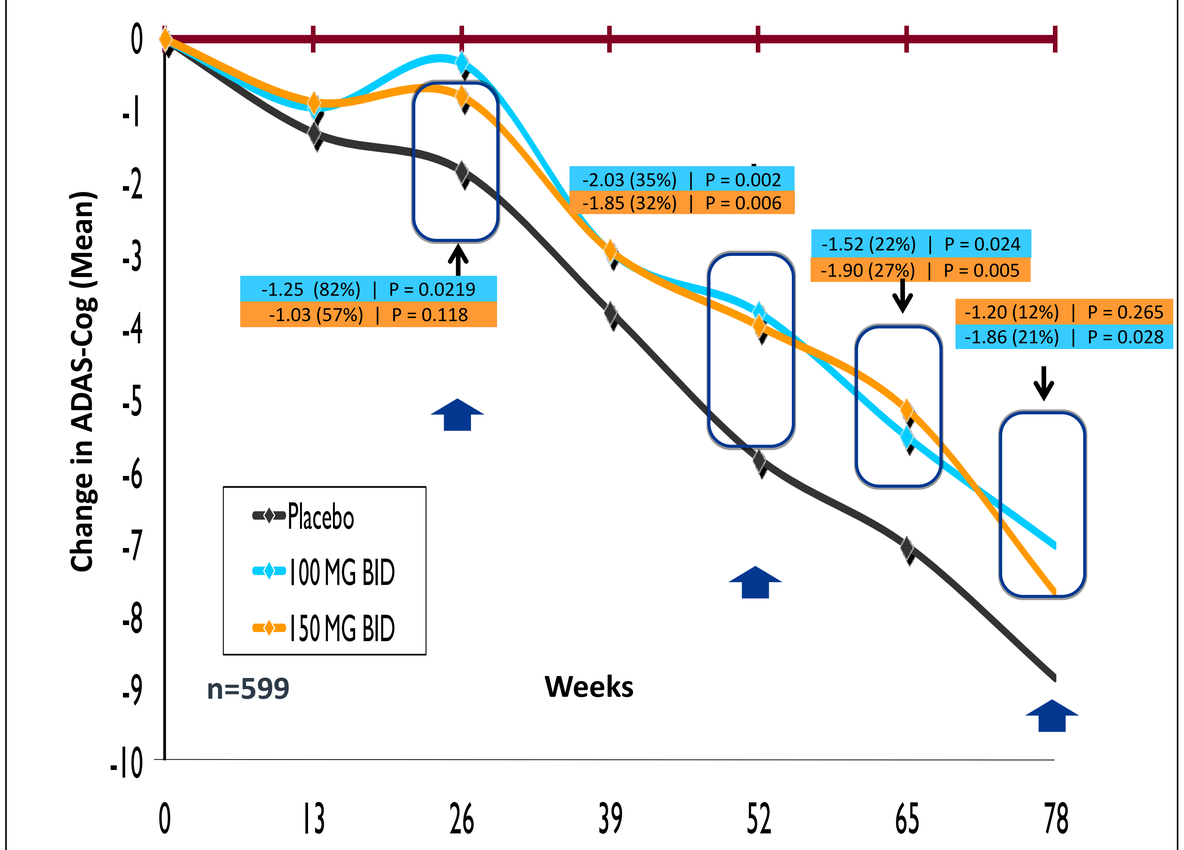
Introduction:

ALZ-801 is a novel, orally available small molecule prodrug of tramiprosate with improved pharmaceutical properties. Tramiprosate was advanced to a ~2,000 patient Phase 3 program which completed in 2007, and was deemed inconclusive by the FDA. Subsequent post-hoc analyses of ApoE4 positive patients (n=599) showed that tramiprosate produced a significant and clinically meaningful improvement in cognition and function at 6, 12 and 18 months on top of standard of care therapy. ALZ-801 has been optimized for improved absorption, improved GI tolerability and improved PK properties (i.e. longer t1/2 and decreased PK variability). Oral ALZ-801 increases the plasma and brain exposure of tramiprosate in animals 2-fold over tramiprosate administered at equimolar doses.

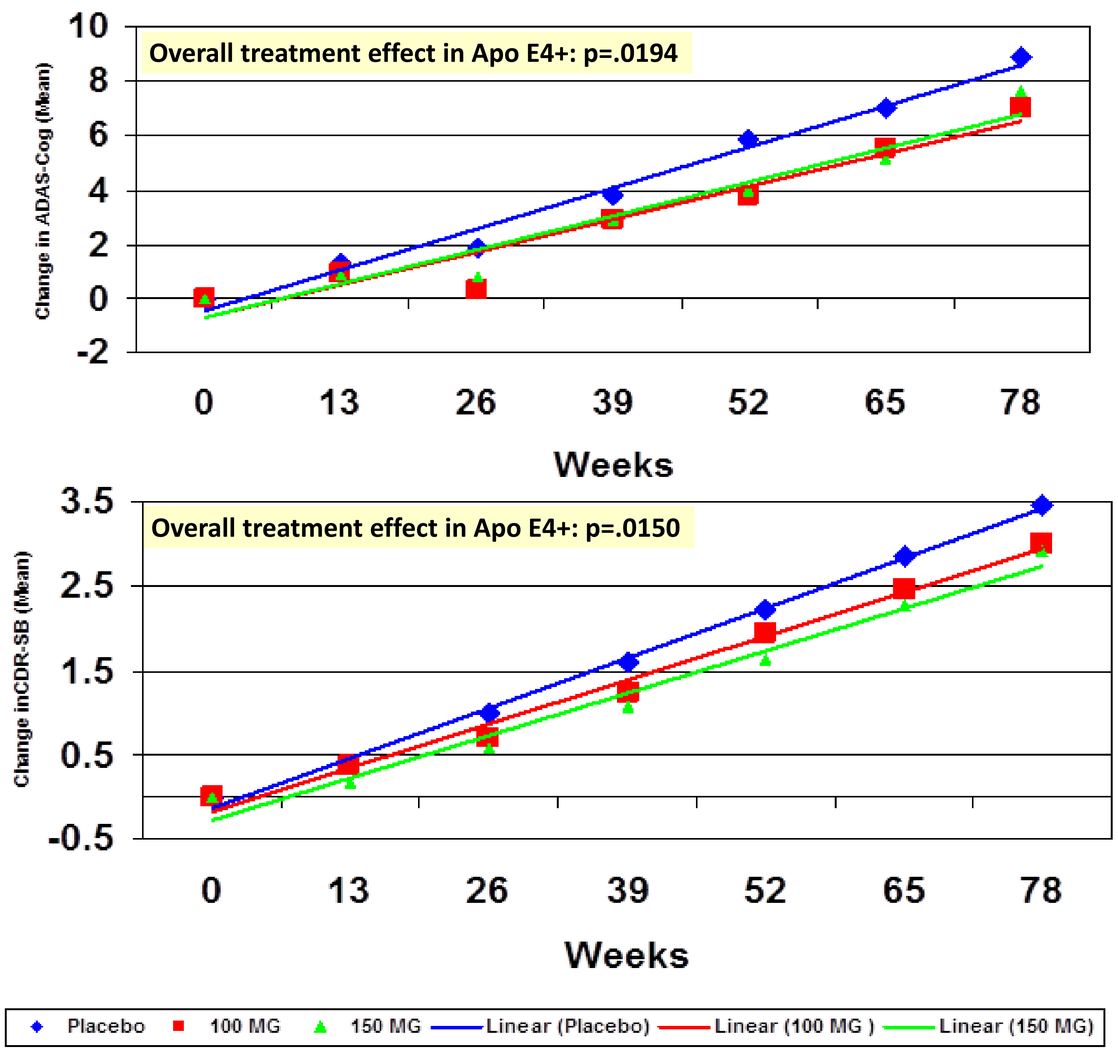
1 ALZ-801 Leverages Extensive Clinical Experience of Tramiprosate with 2,000 Subjects in Phase 2 and Phase 3 Studies

Studies	N	Population	Duration	Endpoints
Phase 2	58	AD	3 months	Cognitive function Amyloid Aβ CSF level
Phase 2 Extension	42	AD	41 months	Open label, safety
Phase 2	24	Cerebral Amyloid Angiopathy	3 months	Neurological function Cognitive function
Phase 3 North America (NA)	1052	AD	18 months	Cognitive function Brain volume
Phase 3 NA Extension	738	AD	12 months	Open label, safety
Phase 3 Europe	975	AD	18 months	Cognitive function Brain volume

2 Phase 3: Tramiprosate Treatment of AD Patients Results in a Reduction in the ADAS-Cog Score



3 Phase 3: Tramiprosate Improves Cognition and Function in ApoE4+ Patients on Top of Standard of Care Treatment



Figures 2 and 3: Retrospective subgroup analysis in 599 ApoE4+ subjects using mixed effects repeated measures, covariate model (MERM) demonstrated a significant effect on both cognition and function utilizing ADAS-cog and CDR-SB.

4 ALZ-801 Produces Improved Brain Penetration of Tramiprosate in Mice

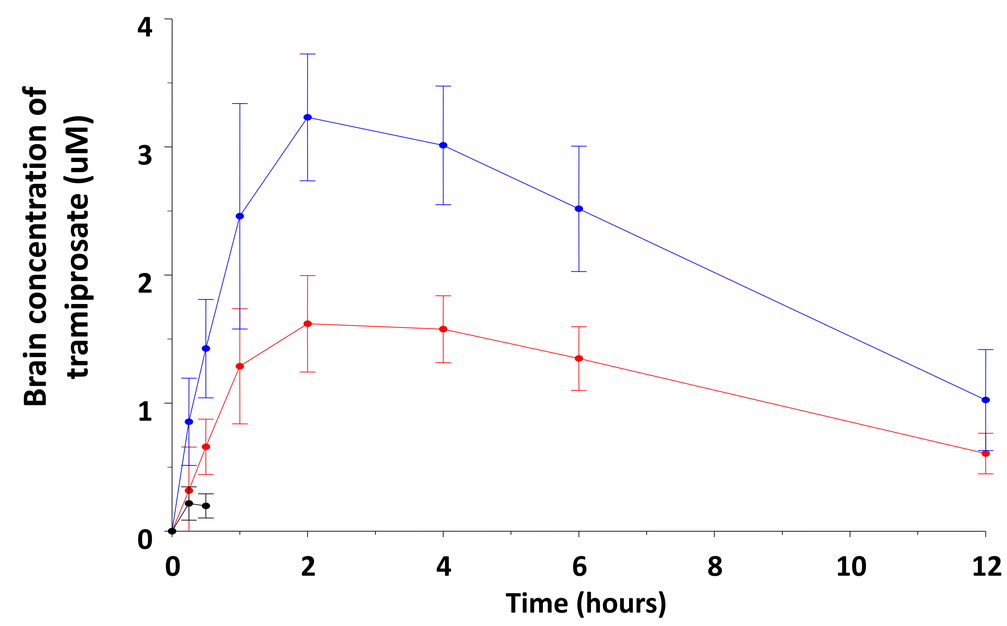


Figure 4: Brain exposure of tramiprosate after oral ALZ-801 or tramiprosate. The AUC ratio of brain tramiprosate exposure due to ALZ-801 compared to tramiprosate is ~2.1. Data shown are average mean ± SD from 3 experiments (n=18)

5 ALZ-801 Phase 1 SAD in Normal Healthy Elderly Subjects: PK PK Improvements over Tramiprosate

Extended t1/2 of Tramiprosate Following ALZ-801
Reduced Formation of Metabolite NRM5074 Following ALZ-801

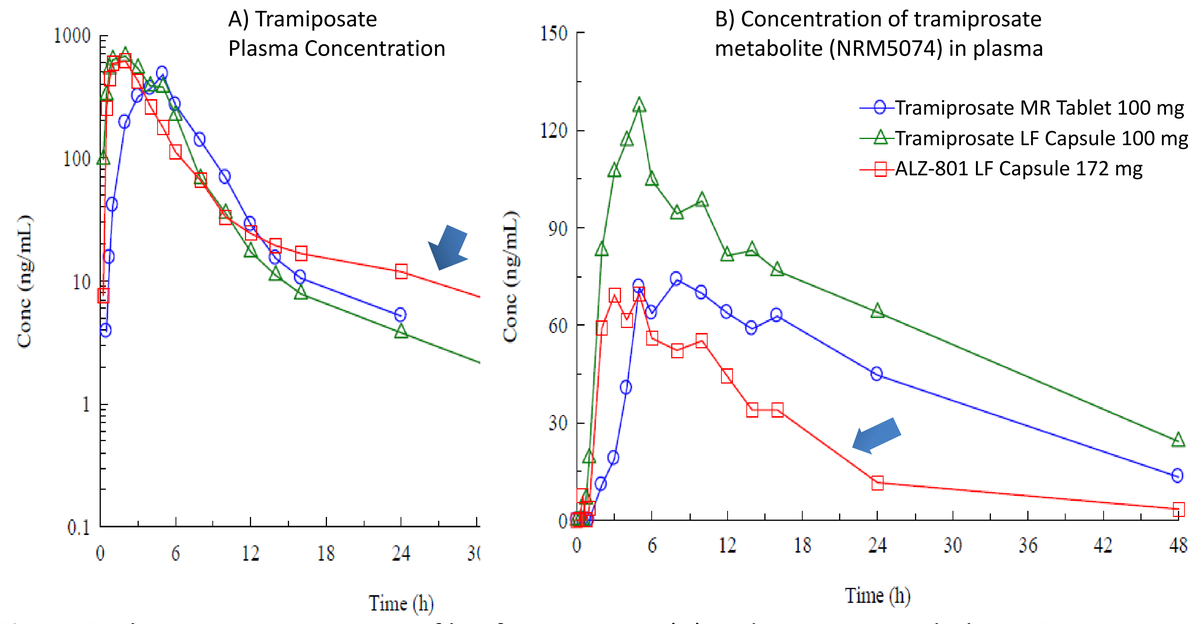


Figure 5: Plasma concentration profile of tramiposate (A) and primary metabolite NRM5074 (B) after a single oral dose ALZ-801 and tramiprosate (LF capsule and MR capsule) in healthy elderly subjects. Data shown are from 12 subjects per treatment . Dose of ALZ-801 (172 mg) is the molar equivalent of 100 mg of tramiprosate. Blue arrows highlight ALZ-801 PK curves.

6 Phase 1 SAD : ALZ-801 Displays Improved PK Properties Compared to Tramiprosate

Parameters	ALZ-801 LF Capsule (N=12)	Tramiprosate LF Capsule (N=12)	Tramiprosate MR Tablet (N=12)
Cmax (ng/ml)	**628 ± 100**	769 ± 228	506 ± 187
Tmax (h)	**2.0**	1.0	4.5
AUC_{0-t} (h x ng/mL)	**2,680 ± 448**	3,268 ± 1,128	2,355 ± 747
$T_{1/2}$ (h)	**14.9 ±3.9**	5.9 ± 5.2	4.9 ±2.6

Figure 6: SAD study in normal HV shows that orally administered ALZ-801 displays a reduction in PK variability superior to MR tablet or LF capsule tramiprosate. ALZ-801 loose filled capsule reduces PK variability by ~50% and, furthermore, the terminal t1/2 is extended to 14.9 hours, allowing once-daily dosing.

Conclusions:

- ALZ-801 demonstrates key advantages over tramiprosate:
  - Improved GI tolerability, (reduced nausea & vomiting)
  - Decreased inter-subject PK variability with ALZ-801
  - Extended t1/2 of 14.9 hours allows once-daily dosing
- Next study is Phase 1 MAD to confirm dose regimen for pivotal Phase 2/3
- Phase 2/3 study goals are to confirm efficacy on cognition, function, and disease modification in ApoE4+ AD patients