A Phase 3 Multicenter Trial of Tarenflurbil in Subjects with Mild Dementia of the Alzheimer's Type (Act-Earli-AD): Rationale and Methodology

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Tarenflurbil Clinical Rationale

- Selective Aβ42-lowering agent *in vitro* & *in vivo*[1,2]
  - γ-secretase modulator (GSM) via substrate targeting of APP, resulting in a less amyloidogenic Aβ profile
  - No effect on other substrates (eg, Notch)
- Improves spatial reference learning and memory performance in mice[3]
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  - Effective concentrations achievable in humans at doses that have been well tolerated
- Phase 2 study provided evidence for dose-related effects on ADLs and global function in patients with mild AD[4]

133 Trial Sites* in the US

*Having enrolled ≥ 1 subject

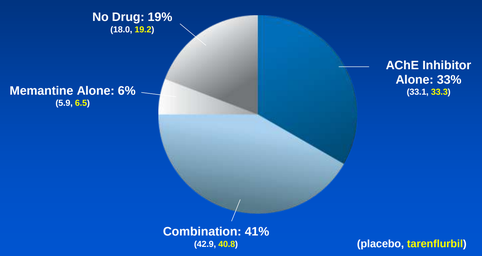
Pre-specified Analysis Plan

- Change from baseline (CFB) at 18 months
  - z-score, LOCF
- Slopes analysis (SA)
  - repeated measures linear mixed model
- 'Gatekeeper' approach to control for multiple comparisons

1. ADAS-cog and ADCS-ADL, CFB p ≤ 0.05
2. ADAS-cog SA, p ≤ 0.05
3. ADCS-ADL SA, p ≤ 0.05
4. CDR-sb, CFB, p ≤ 0.05
5. CDR-sb SA

Concomitant AD Therapy

Patients on Stable Therapy at Enrollment



(placebo, tarenflurbil)

Objectives/Outcomes

Primary

- Evaluate changes in cognition (Alzheimer's Disease Assessment Scale, cognitive subscale [ADAS-cog]) and activities of daily living (Alzheimer's Disease Cooperative Study, Activities of Daily Living [ADCS-ADL])

Key Secondary

- Assess changes in global function (Clinical Dementia Rating [CDR] Sum of Boxes)

Other Secondary

- Assess changes in cognitive function (Mini Mental State Examination [MMSE])
- Assess changes in behavior (Neuropsychiatric Inventory [NPI])
- Assess effect of treatment on quality of life of patients (Quality of Life – Alzheimer's Disease [QOL-AD]) and caregivers (Caregiver Burden Inventory [CBI])

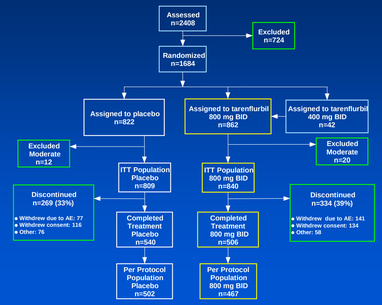
Inclusion Criteria

- Men and women ≥55 years of age, living in the community
- Diagnosis of dementia based on DSM-IV TR criteria and meet NINCDS-ADRDA criteria for probable AD
- Within the past 12 months (or at screening), have a CT or MRI scan demonstrating absence of clinically significant focal intracranial pathology
- Screening MMSE 20–26 (mild dementia), inclusive*
- Modified Hachinski Ischaemic score <4
- AChE inhibitors allowed if same medication taken for at least 6 months
- Memantine allowed if same medication taken for at least 3 months
- Subjects must have a reliable caregiver to participate in study visit assessments and verify daily compliance of study medication

DSM-IV TR = Diagnostic and Statistical Manual – Fourth Edition (text revision); NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

*Inclusion criteria originally included patients with moderate AD (MMSE 15–19).

Trial Profile (Subject Disposition)



Distribution by APOE Genotype

APOE Genotype	Controls*§ (n = 8,607)	AD Cases*§ (n = 5,930)	Tarenflurbil US Phase 3† (n = 1,315)
E2/E2	0.8	0.2	0.2
E2/E3	12.7	4.8	4.6
E3/E3	60.9	36.4	36.8
E2/E4	2.6	2.6	2.6
E3/E4	21.3	41.1	42.2
E4/E4	1.8	14.8	13.6
		58.5% E4 carriers	58.4% E4 carriers

- APOE genotype profile representative of typical AD population

*Caucasian population.
†Preliminary analysis.

Study Design

- Phase 3 multicenter, randomized, double-blind, placebo-controlled study
- Subjects randomized (1:1) to receive either tarenflurbil 800 mg* or placebo BID for 18 months
- At randomization, patients stratified according to:
  - Stable (≥6 months) use/nonuse of acetylcholinesterase (AChE) inhibitors
  - Stable (≥3 months) use/nonuse of memantine
- After screening, clinic visits occurred on day 1 and at months 1, 3, 6, 9, 12, 15, and 18
- Phone contact with caregiver occurred at week 2 and months 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, and 17
- 30-day off drug follow-up after treatment discontinuation

*Due to a protocol modification, a small group of patients (n=42) who were initially randomized to tarenflurbil 400 mg BID switched to 800 mg BID.

Exclusion Criteria

- History in past 2 years of epilepsy, focal brain lesion, or head injury
- Major psychiatric disorder, alcohol or substance abuse
- Hypersensitivity to flurbiprofen or NSAIDs, including COX-2 specific inhibitors
- Chronic use of NSAIDs LC
- History of GI bleeding (past 3 years) or ulcer (past 3 months)
- Renal, hepatic or metabolic disorders
- Use of investigational therapy (30 days prior to screening) or AD immunotherapy
- Uncontrolled cardiac conditions (NY Heart Assoc. Class 3 or 4)
- Anticoagulant therapy (eg, Warfarin) 12 weeks prior to Day 1
- Treatment with any CYP2C9 inhibitor or substrate (2 weeks prior to Day 1)

Demographics and Baseline Clinical Characteristics (ITT population)

	Placebo (n=809)	800 mg BID (n=840)
Mean (SD) age, yr	74.7 (8.4)	74.6 (8.5)
Female, %	52.5	49.4
Ethnicity, % White	94.1	94.9
Weight, kg (mean body mass index)	72.5 (26.3)	72.7 (26.1)
Time since diagnosis, mo	20.5	20.4
Education, % with any college	61.7	63.0
Mean (SD) MMSE	23.3 (1.99)	23.3 (1.98)
Mean (SD) ADAS-cog 13 (80-point)	25.7 (8.9)	26.1 (8.5)
Mean (SD) ADCS-ADL	63.6 (11.1)	63.6 (11.5)
Mean (SD) CDR-sb	5.0 (2.4)	4.9 (2.3)

Conclusions

- Act-Earli-AD was a well-powered, well-designed, and well-conducted trial in subjects with mild AD (MMSE 20-26)
  - 18 month study designed to assess potential effect of tarenflurbil on cognition, activities of daily living, and global function
  - Treatment groups were well matched at baseline
  - Stable concomitant AD therapy use provides opportunity to examine drug effect both as monotherapy and as add-on therapy with currently marketed AD medications
  - APOE genotype profile representative of typical AD population

References:

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2. Kukar et al. Nature 2008;453:925.
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