Safety and Efficacy of Tarenflurbil in Subjects With Mild Alzheimer's Disease:

Results From an 18-month Multicenter Phase 3 Trial

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& the Tarenflurbil Phase 3 Study Group

Tarenflurbil Clinical Rationale

Tarenflurbil (Flurizan™, formerly R-flurbiprofen)

- 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]
- Phase 2 study provided evidence for dose-related effects on ADLs and global function in patients with mild AD[4]

[1]Eriksen et al. 2003 J Clin Invest 112:440, [2]Kukar et al. 2008 Nature 453:925,
[3]Kukar et al. 2007 BMC Neurosci 8:54, [4]Wilcock et al. 2008 Lancet Neurol 7(6):483

US Phase 3 Protocol Overview

- Mild Alzheimer's disease (MMSE 20-26)
- Stratified at randomization
  - Stable (≥6 months) cholinesterase inhibitor use/nonuse
  - Stable (≥3 months) memantine use/nonuse
- Two-arm study: 800 BID vs. placebo BID
- 18 months treatment, 30-day off-drug follow-up
- Efficacy endpoints (measured throughout)

Primary
- ADAS-cog and ADCS-ADL

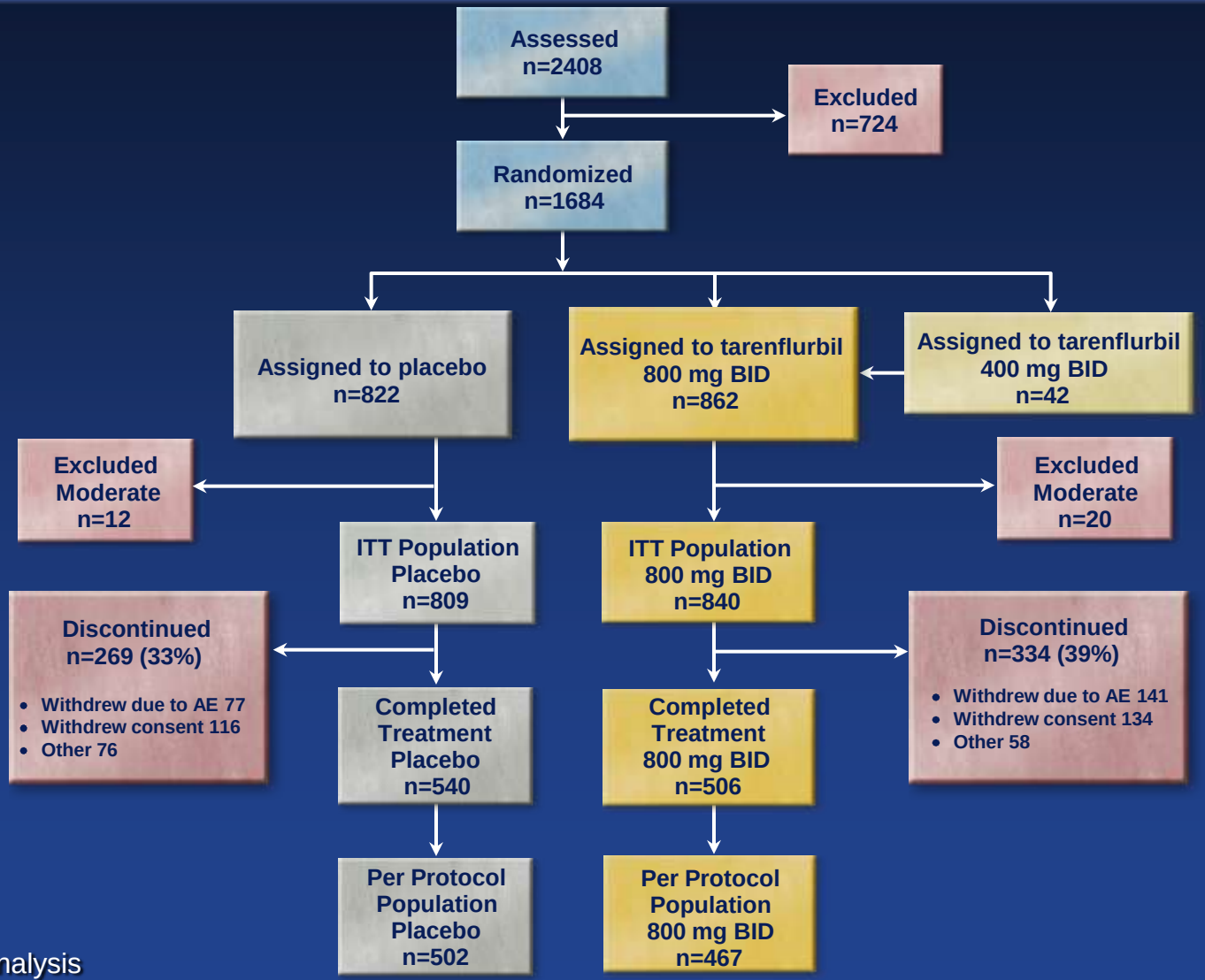
Key Secondary
- CDR Sum of Boxes (sb)

Other Secondary
- MMSE
- NPI
- QOL-AD

133 Trial Sites* in the US

*Having enrolled ≥ 1 subject

Trial Profile



Preliminary analysis

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 $p \leq 0.05$
  2. ADAS-cog SA, $p \leq 0.05$
  3. ADCS-ADL SA, $p \leq 0.05$
  4. CDR-sb, CFB, $p \leq 0.05$
  5. CDR-sb SA

Imputation Method: Z-score LOCF

- a missing value at a given time point will be replaced with a value that is the same number of standard deviations from the treatment group mean at that time point as that subject's last observed value

z-score = (observed value – treatment group mean) / treatment group standard deviation

Baseline Characteristics (ITT)

	Placebo (n=809)	800 mg BID (n=840)
Age, yr mean (SD) range	74.7 (8.4) 53 – 100	74.6 (8.5) 53 – 100
% Female	52.5%	49.4%
Ethnicity (% white)	94.1%	94.9%
Weight, kg (mean BMI)	72.5 (26.3)	72.7 (26.1)
Time since diagnosis (months)	20.5	20.4
Education (% ≥ any college)	61.7%	63.0%
MMSE (SD)	23.3 (1.99)	23.3 (1.98)

Preliminary analysis

Mean Baseline Characteristics (ITT)

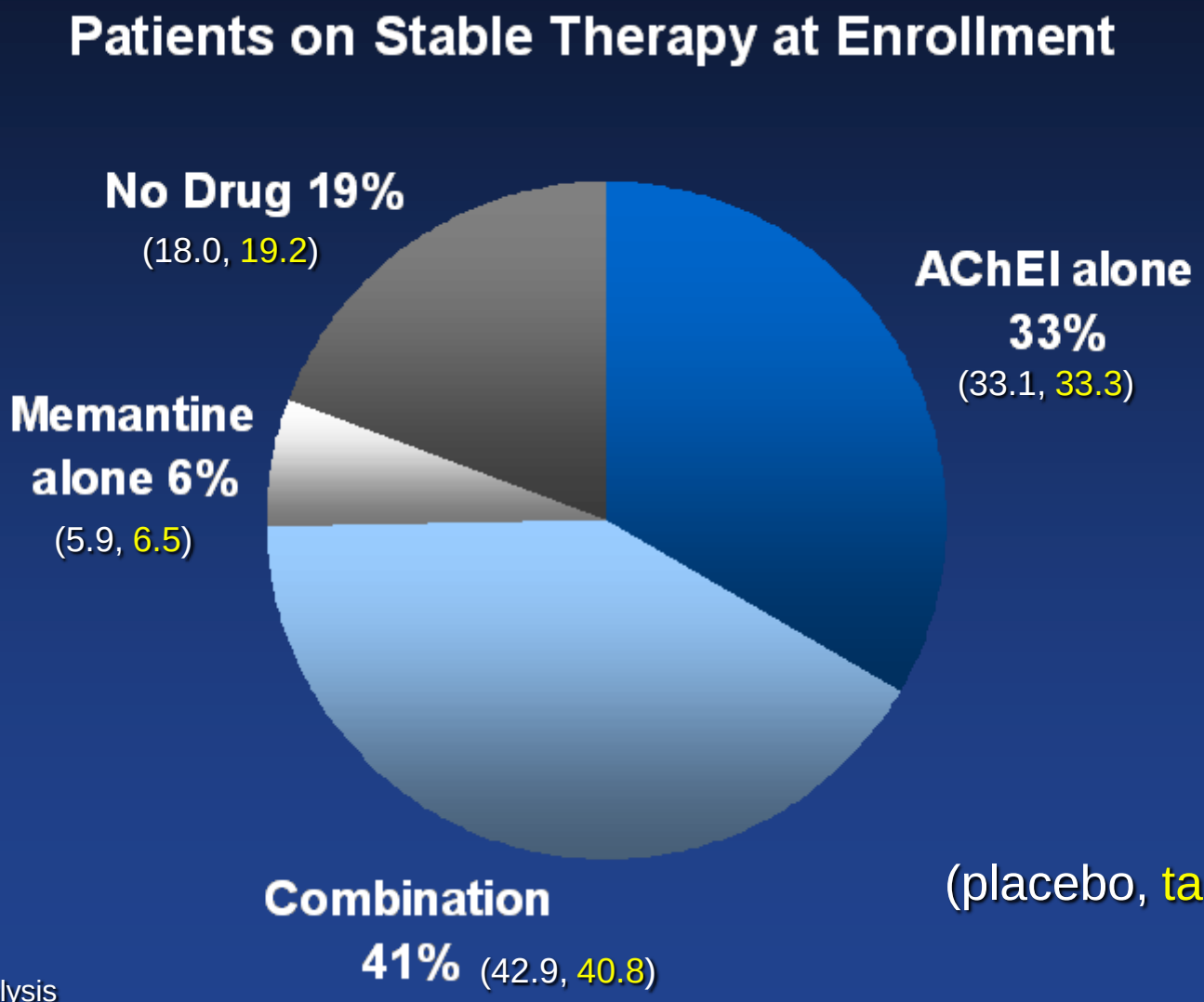
	Placebo (n=809)	800 mg BID (n=840)
ADAS-cog (*80 point)	25.7 (8.9)	26.1 (8.5)
ADAS-cog (70 point)	17.8 (7.7)	18.2 (7.4)
ADCS-ADL	63.6 (11.1)	63.6 (11.5)
CDR-sb	5.0 (2.4)	4.9 (2.3)

*Includes delayed recall subscale

Mean (SD)

Preliminary analysis

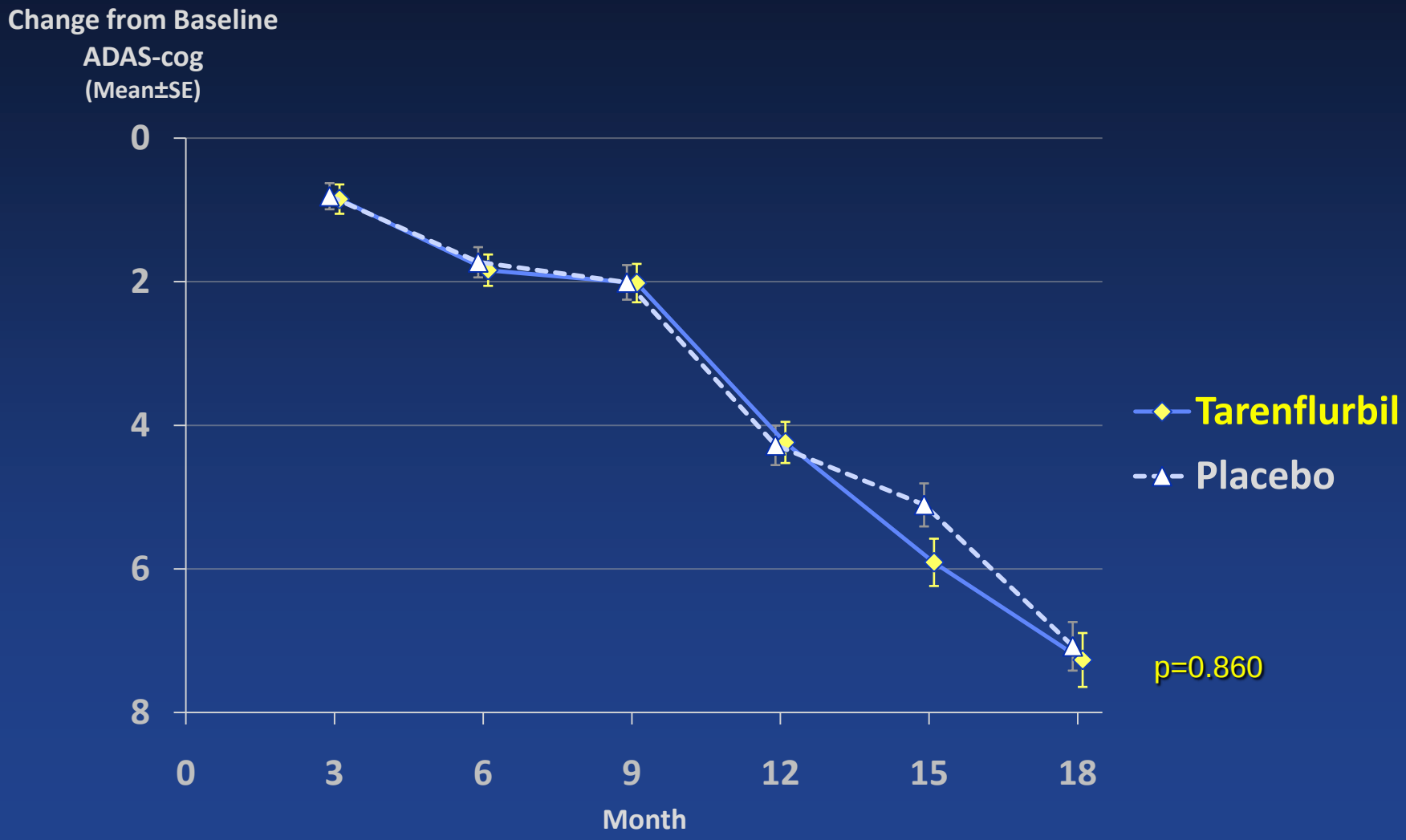
Concomitant AD Therapy



Preliminary analysis

Cognition — Change in ADAS-cog

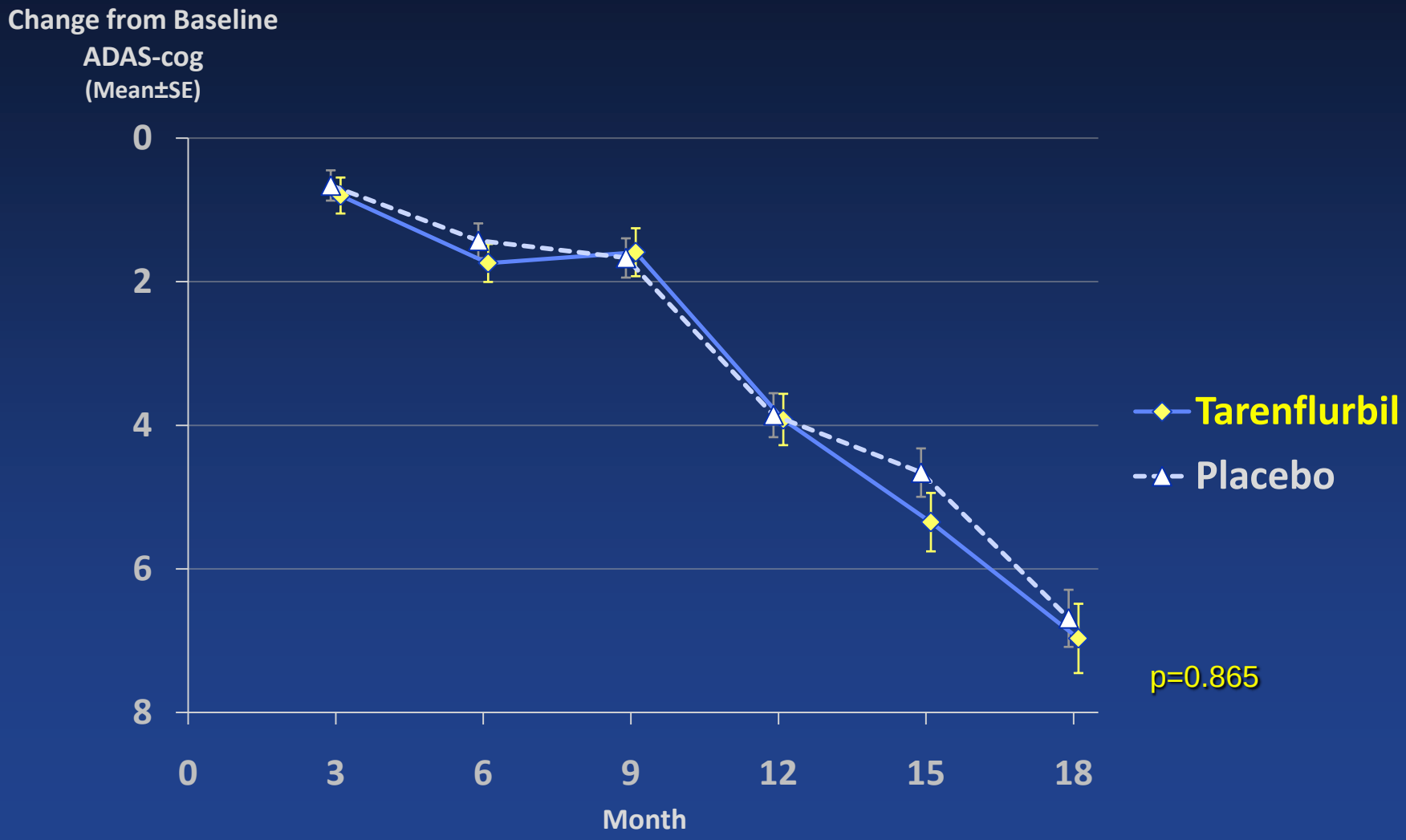
ITT Analysis



Preliminary analysis

Cognition — Change in ADAS-cog

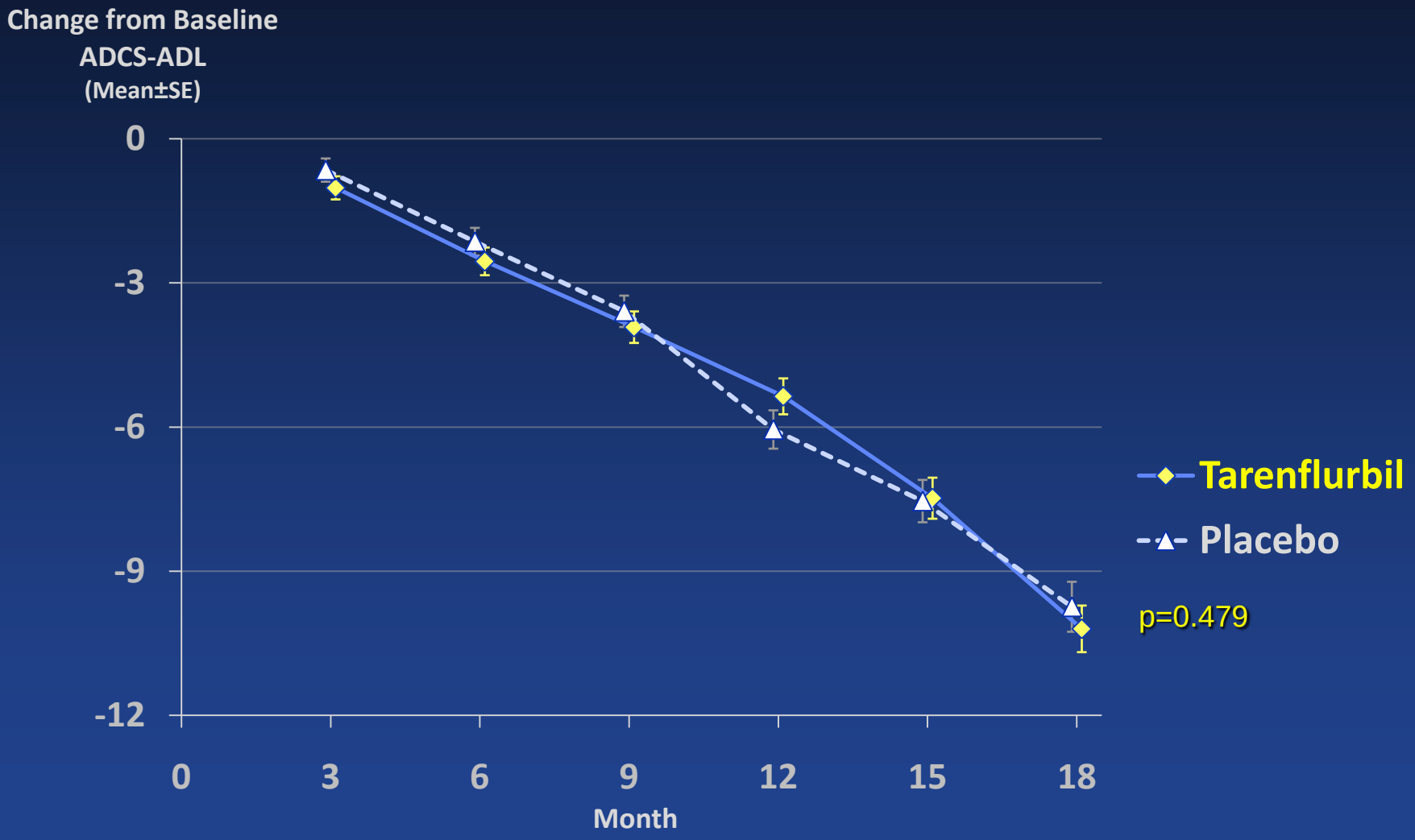
Per Protocol Analysis



Preliminary analysis

Activities of Daily Living — ADCS-ADL

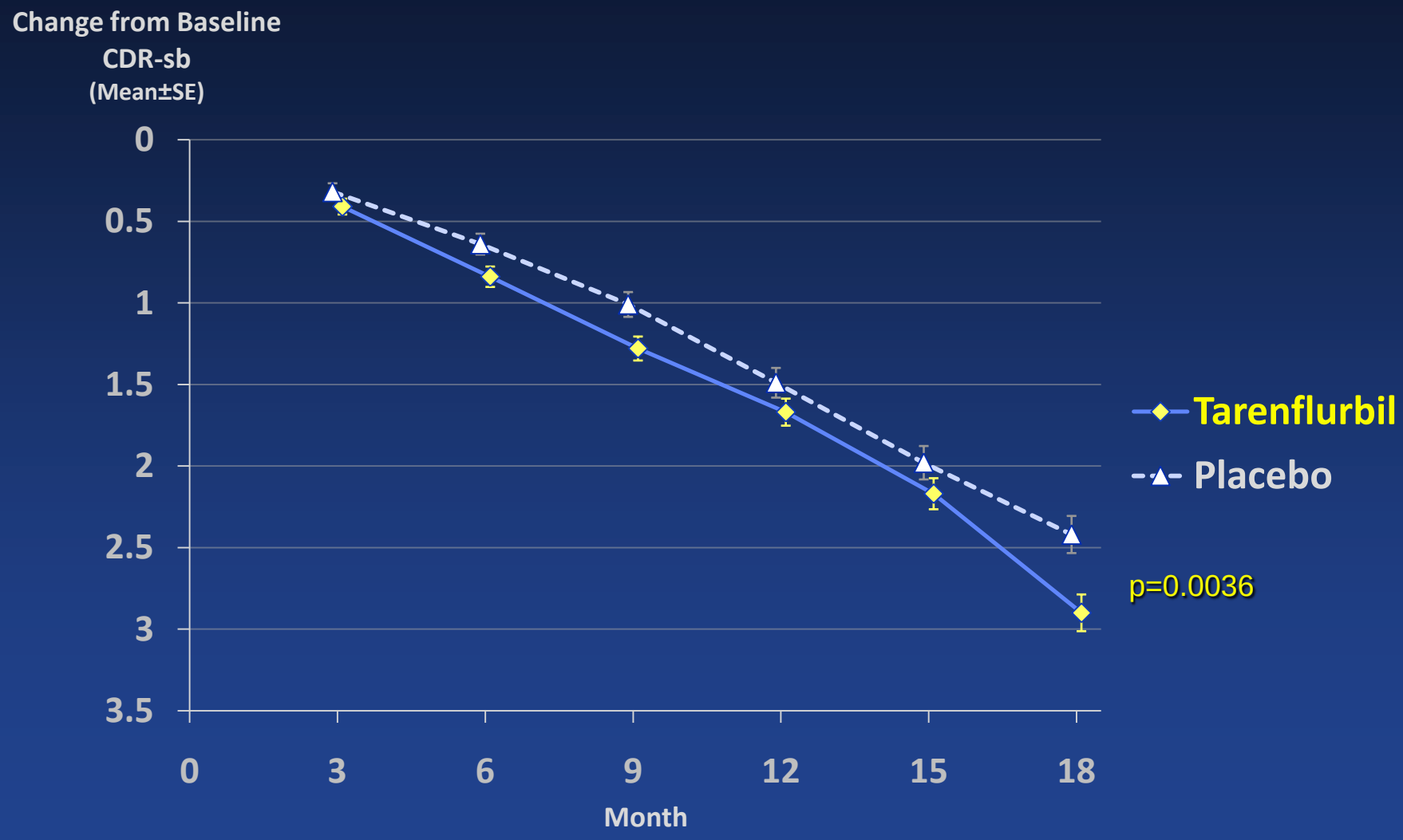
ITT Analysis



Preliminary analysis

Global Function — CDR-sb

ITT Analysis



Preliminary analysis

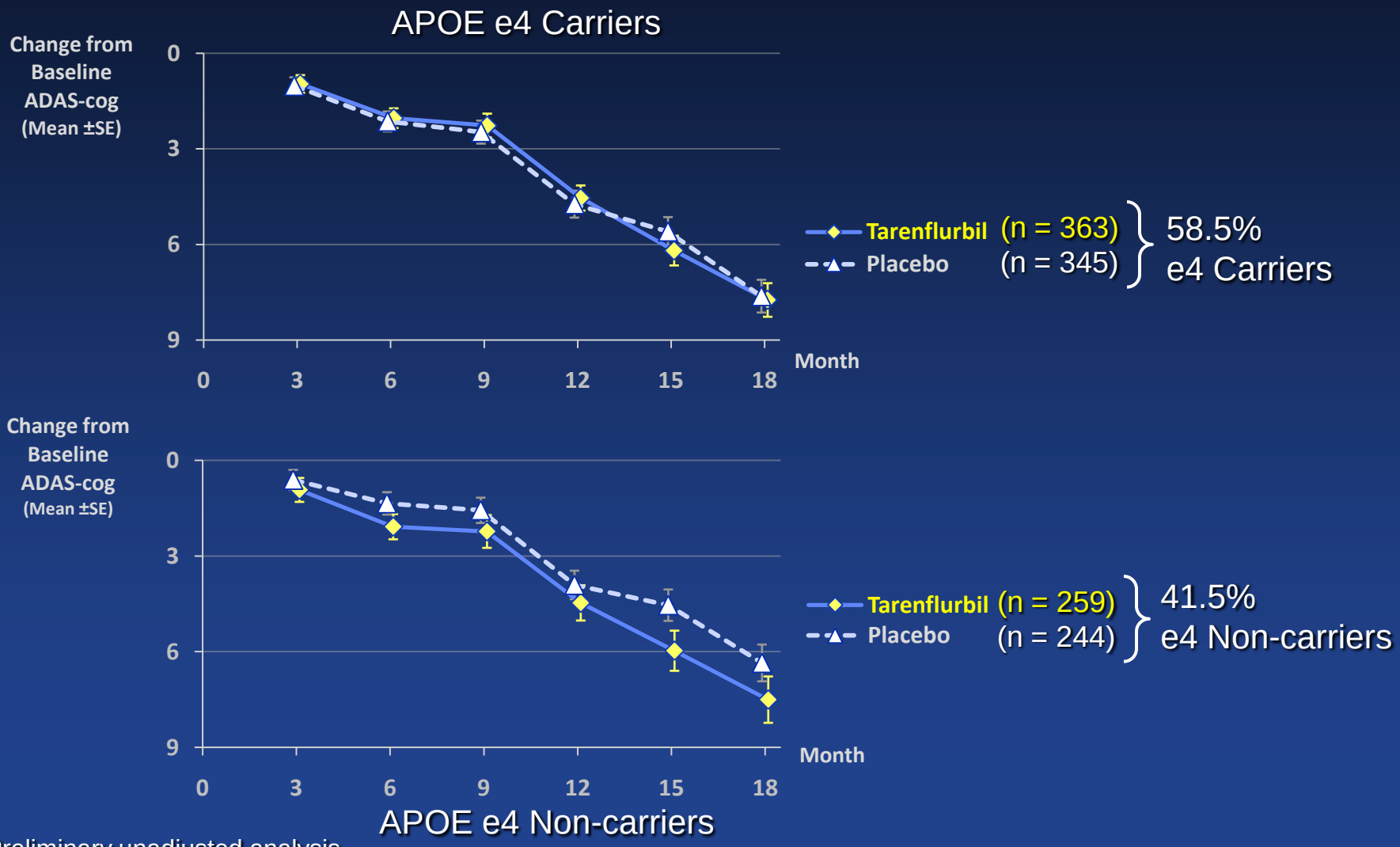
Additional Analyses

- Pre-specified in SAP
  - Baseline scale severity
  - Baseline MMSE
  - ‘Improver’ analysis
  - ‘Progresser’ analysis
  - Concomitant AD med use
  - PK (full analysis pending)
- Post-hoc
  - Gender
  - BMI
  - CYP2C9 genotype (full analysis pending)
  - APOE genotype

Preliminary analysis

APOE4 Carriers vs Non-carriers

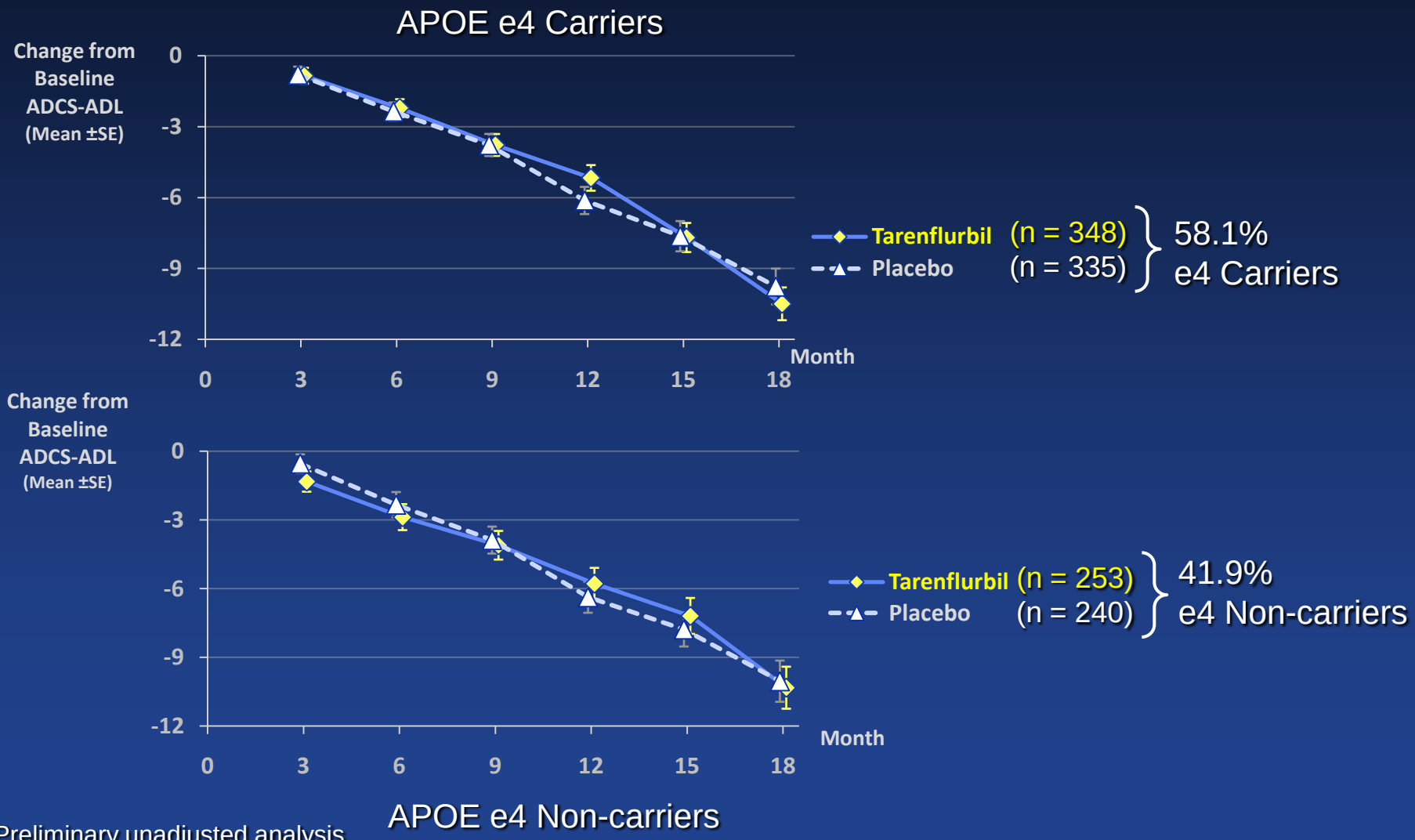
ADAS-cog ITT Analysis



Preliminary unadjusted analysis

APOE4 Carriers vs Non-carriers

ADCS-ADL ITT Analysis



Preliminary unadjusted analysis

Overall Adverse Events (0-18 months)

	Placebo (n=821)		800 mg BID (n=860)	
Subjects w/ AE	85.7%	704	88.5%	761
Discontinued for AE	11.6%	95	18.4%	158
Subjects w/ SAE	19.9%	163	22.7%	195
Deaths	2.2%	18	2.8%	24

Preliminary analysis

Key Safety Findings

- AEs in general reflect the expected symptom profile of a population with Alzheimer's disease
  - In most, AEs were well balanced between tarenflurbil and placebo
- However, there were a few signals for increased AEs:

Adverse Event	Placebo (n=821)	800 mg BID (n=860)
Anemia	4.5%	9.7%
Infection (pneumonia, H. zoster, sepsis)	2.9%	6.9%
Gastrointestinal Ulcer	0.4%	1.7%

  - We have yet to examine correlations between AEs, concomitant medication use and/or pre-existing conditions

Preliminary analysis

Conclusions

- Well-powered, well-designed, and well-conducted trial in mild AD (MMSE 20-26)
  - Treatment groups were well matched at baseline
  - Placebo decline rates were as expected for 18 months
    - ADAS-cog 7.1 points (SD 9.2)
    - ADCS-ADL 9.8 points (SD 14.0)
    - CDR-sb 2.5 points (SD 3.1)
- No difference in outcomes for the efficacy parameters
  - Subgroup and sensitivity analyses consistent with primary analysis
- Tarenflurbil was generally well tolerated
  - Slightly higher incidence of anemia, infections and GI ulcers vs placebo

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