Azeliragon (TTP488): From Futility to Fast Track

An examination of the risks of futility analysis and the precautions that should be taken when executing and interpreting these analyses

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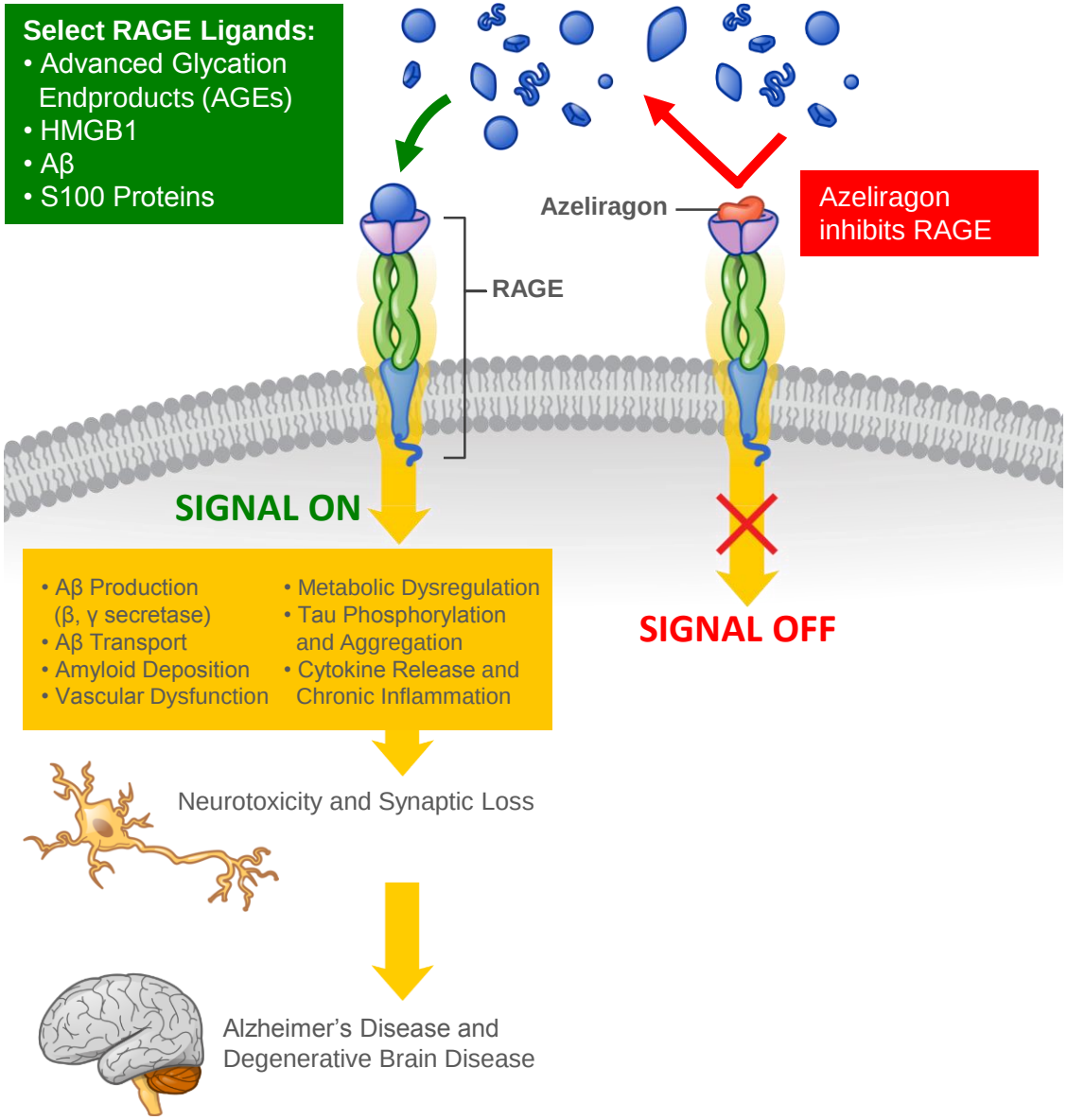
RAGE Inhibition:
A Novel Mechanism of Action for AD Treatment

AZELIRAGON INHIBITS THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (RAGE)

- Role of RAGE
  - Pre- and post-natal neuronal development
  - Low expression under normal conditions
- RAGE is a key upstream factor that we believe is responsible for progression of AD
  - Increased expression observed in autopsies of human AD brains
  - Higher levels of RAGE expression correlated with disease severity and progression
  - Affects neuronal, microglial and endothelial cells
- RAGE knockout mice resist Aβ plaque formation but otherwise normal



Azeliragon Phase 2b Study Design

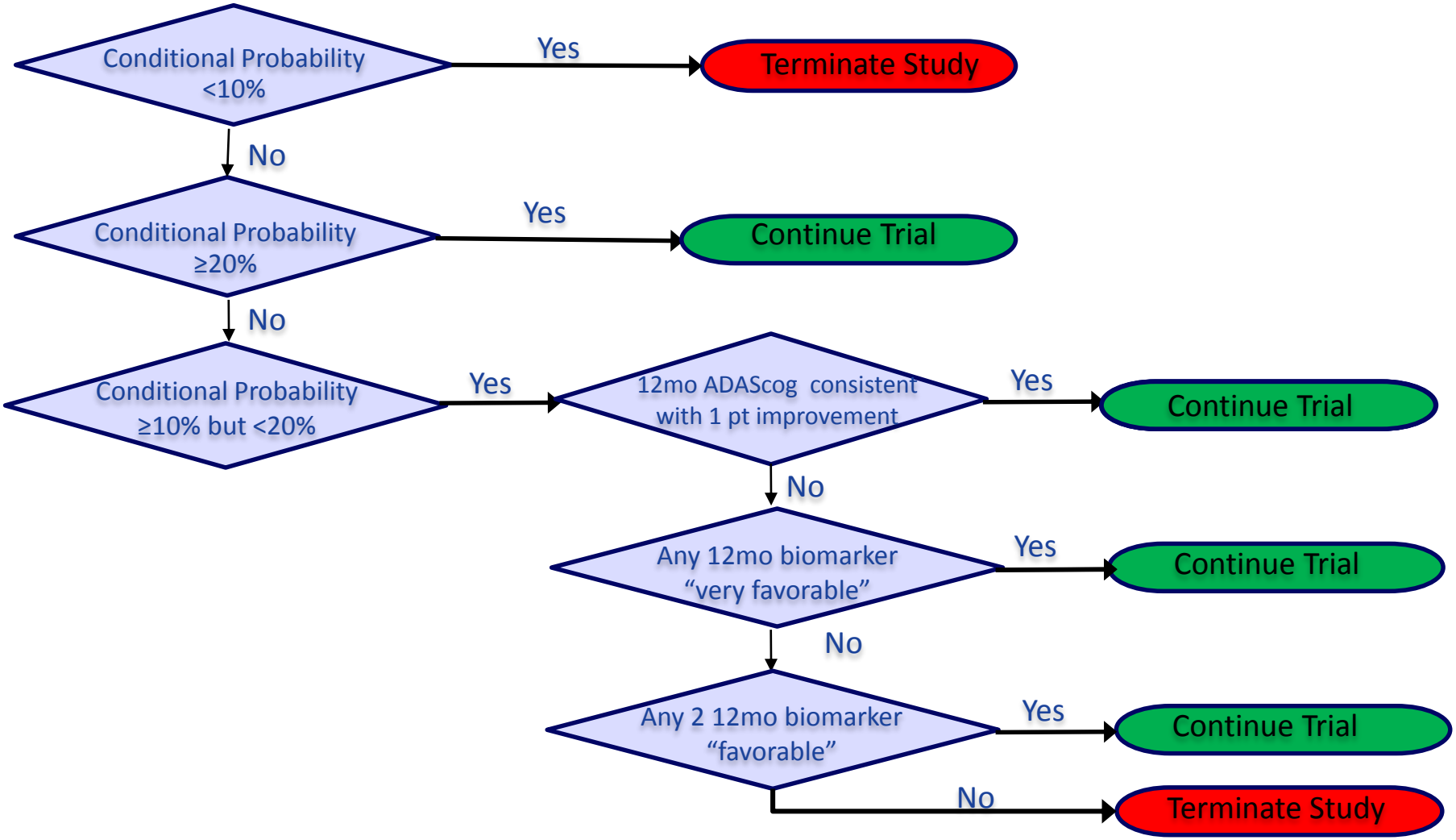
- Randomized, double-blind, placebo-controlled trial
- Mild to moderate AD (MMSE 14-26); N=399
  - Power of 80% to detect a treatment benefit of 3 points on the ADAS-COG_{11}
- Stable background therapy with cholinesterase inhibitors and/or memantine
- Three arms (1:1:1)
  - 60mg/d x 6 days, 20 mg/day x 18 months
    - Discontinued due to increase incidence of confusion, falls and greater ADAS-cog decline not seen with 5 mg/d or placebo
  - 15 mg/d x 6 days, 5 mg/day x 18 months
  - Placebo x 18 months
- Objectives:
  - ADAS-COG_{11} after 18 months of treatment with azeliragon vs placebo
  - Safety/tolerability of treatment with azeliragon vs placebo
- Otherwise known as TTP488, PF-04494700

Azeliragon Phase 2b Analysis

- Pre-specified interim analyses
  - Safety: 50% of subjects completed 6 months; 100% completed or withdrew prior to12 months
  - Futility: 12 months after all subjects randomized
- Primary analysis specified in protocol and SAP
  - Analysis of covariance (ANCOVA) with multiple imputation (MI)
- Supportive pre-planned analyses, using different methodologies to cope with missing data
  - Complete cases ANCOVA
  - Last observation carried forward (LOCF) ANCOVA
  - Generalized estimating equations (GEE)
  - Mixed model repeated measures (MMRM)

Azeliragon Phase 2b Futility Analysis Decision Rules

- 18 month data used to assess probability of rejecting null hypothesis at the end of trial
  - Single-criterion conditional power computed based on assumed continuation of observed trend



Azeliragon Phase 2b
12-Month Interim Analysis Results

- Conditional probability = 9.3%
  - Decision made to terminate study with subjects to discontinue dosing at next scheduled visit
  - While not a consideration in the futility decision algorithm, 5mg/day was associated with numerical favorable difference versus placebo based on median values

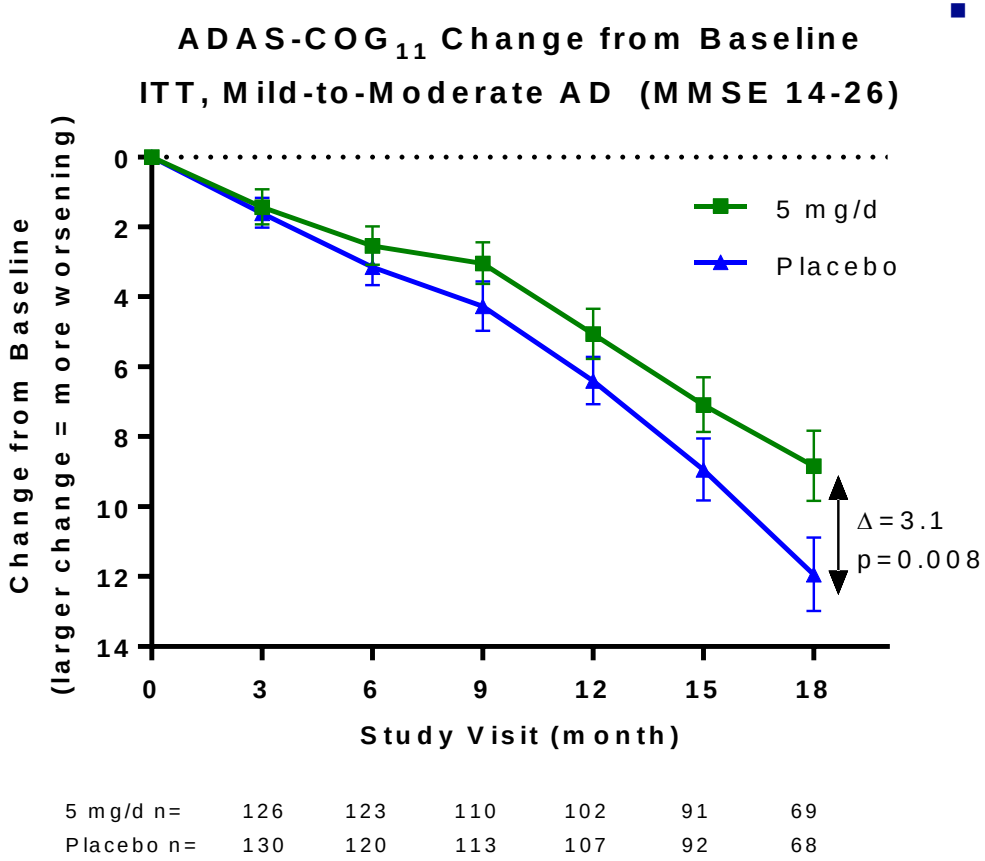
ADAS-COG$_{11}$ Change from Baseline at 18 months

	N	Mean	SD	Median
Placebo	40	11.17	8.92	10.33
5 mg/d	44	10.18	9.81	8

  - Had conditional probability reached 10%, 12 month ADAS-COG$_{11}$ change from baseline difference between 5 mg/day and placebo = 1.34; study would have continued

	N	Mean	SD
Placebo	107	6.4	6.95
5 mg/d	102	5.06	7.24

Final Protocol Planned Analysis Demonstrates Azeliragon Met Pre-specified ADAS-COG$_{11}$ Primary Endpoint



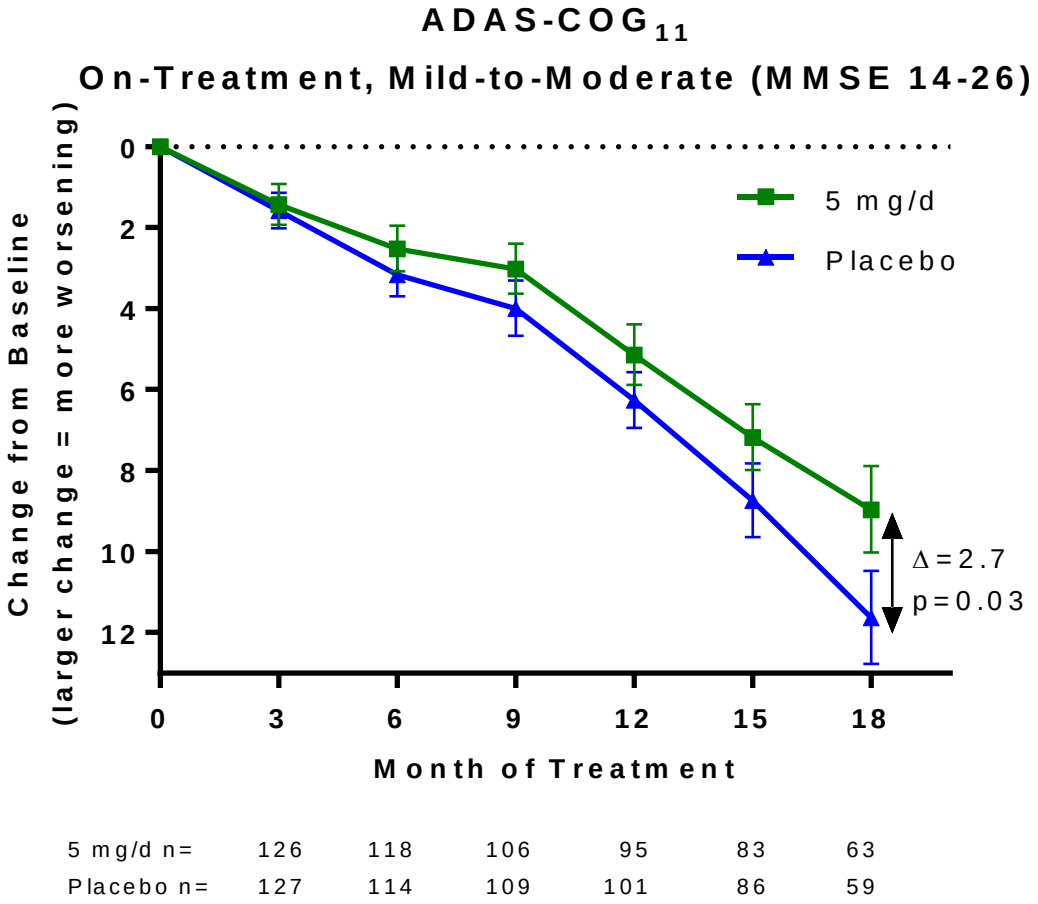
- Protocol-planned analyses, using different methodologies to cope with missing data, all show statistically significant differences in ADAS-COG$_{11}$ favoring 5 mg/d versus placebo

Statistical Methodology	p-value
Primary analysis specified in protocol and SAP • ANCOVA with MI imputation	0.008
Supportive Analyses	
• Complete Cases ANCOVA	0.02
• LOCF ANCOVA	0.03
• GEE	0.03
• MMRM (random effects)	0.04

Galasko et al. Neurology 2014;82:1536-1542

Azeliragon Phase 2b On-Treatment Analysis

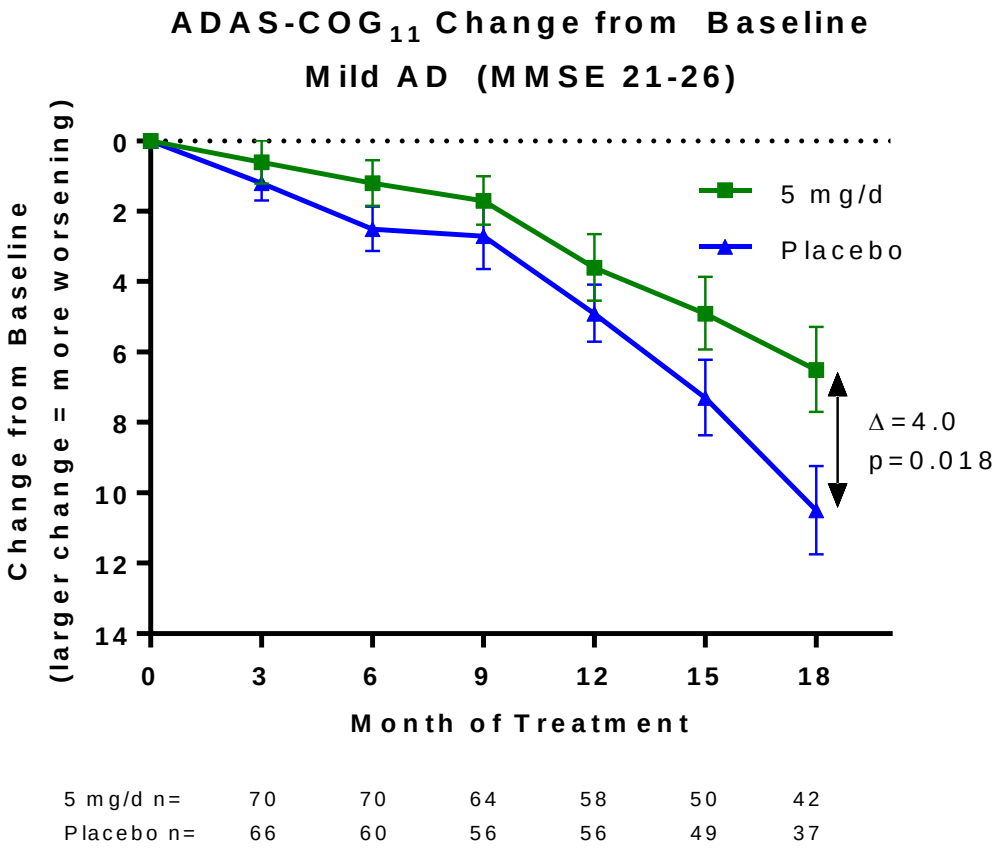
- On-treatment analysis included all available on-treatment data where "on-treatment" defined as date of last dose plus 45 days (taking into account half-life of ~18 days)
  - Note: the 6 subjects receiving 5 mg/d excluded from this analysis had measureable azeliragon concentrations at 18 months, supporting use of the ITT analysis as on-treatment
- Significant 2.7 point difference from placebo at 18 months

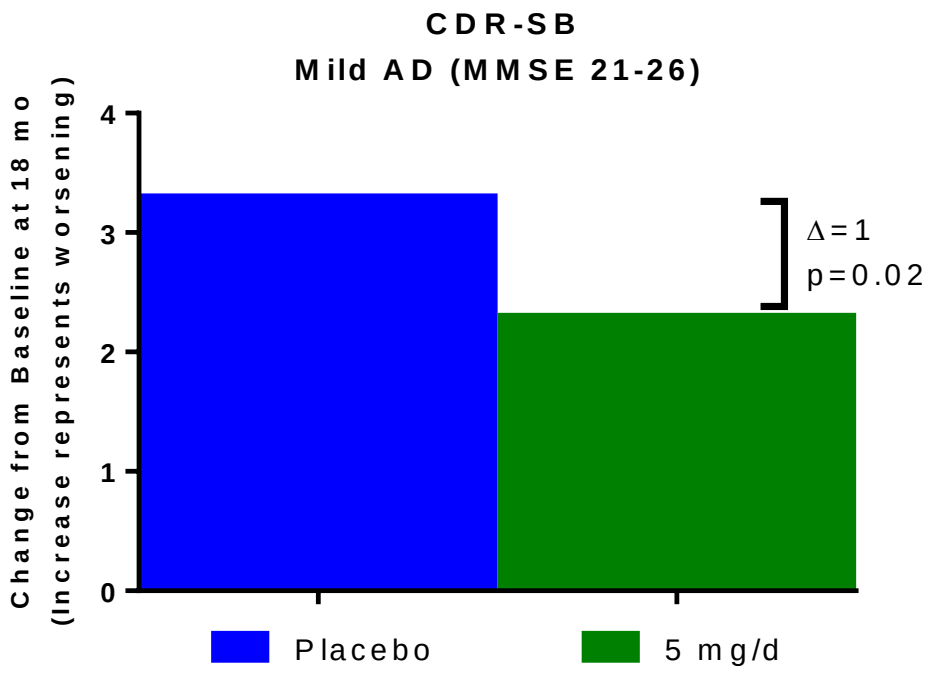


Burstein et al. BMC Neurology 2014

Azeliragon Phase 2b Mild (MMSE 21-26) Sub-group

- Evaluation shows more pronounced efficacy in mild AD patients, including statistically significant improvement in both ADAS-COG$_{11}$ and CDR-SB





Futility Analysis

- The discordance between the positive results of the final analysis and the prediction from the futility analysis is most likely resolved understanding the specific attributes of the futility analysis
- Data were used only from patients who had completed 18 months of treatment at the time of the analysis
  - On only ~1/3 of patients with data available (40 in 5 mg/day, 44 in placebo)
- This analysis was based on a single snapshot, a single variable, and a single statistical model different than protocol planned final analysis
  - Futility analyses, if performed, should consider including several variables or dimensions to protect against premature termination.
  - Statistical model used for the futility analysis was different from the statistical model used for the protocol planned final analysis
- Conducted on preliminary dynamic ADAS-COG$_{11}$ data
  - Post hoc attempts to replicate futility analysis based on snapshot of final database conclude study should have continued (i.e. >20% conditional probability)

STEADFAST Study: Phase 3 Clinical Trial Under SPA

- Randomized, double-blind, parallel group, 18-month trial in 800 patients with mild AD (MMSE 21-26)
  - Enrollment commenced in April 2015
- Two independently powered sub-studies (sub-study A and sub-study B) under a single protocol:
  - Each study (n=400) will have 2 arms: 5 mg/day of azeliragon and placebo
  - All patients will remain on standard of care: AChEI ± memantine
- Co-Primary Endpoints: ADAS-COG_{11} and CDR-SB
- Secondary Endpoints:
  - Imaging: MRI volumetric measures, FDG-PET
  - ADCS-ADL, NPI, MMSE, COWAT, CFT, RUD, DEMQOL
  - Biomarkers: Plasma Aβ

alzheimer's STEADFAST STUDY

Conclusions

- Futility analyses in AD trials may be misleading and argue for conducting the full analysis plan even when futility criteria are met
- The results of the ITT analysis, the four sensitivity analyses, the on-treatment analysis and the mild sub-group analysis justify further investigation of low dose azeliragon in Phase 3
- Phase 3 STEADFAST Study initiated in April 2015 under an FDA-agreed SPA

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www.steadfastalzheimers.com
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