

A Responder Analysis of Tarenflurbil (MPC-7869), a Selective Aβ42-Lowering Agent, in Mild Alzheimer's Disease (AD): Analysis from a Phase 2 Study of up to 24 months of Treatment

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Tarenflurbil Clinical Rationale

- Novel anti-amyloid treatment strategy for AD
- Selective Aβ42-Lowering Agent (SALA) *in vitro* & *in vivo*
 - Allosteric modulation of γ-secretase
- Reduces insoluble amyloid in mouse brain
- Improves spatial reference learning and memory performance in transgenic mice
- Effective concentrations in animal models achievable in humans at doses that have been well tolerated
- Phase 3 studies of tarenflurbil (800 mg BID) in subjects with mild AD (MMSE 20-26) are ongoing

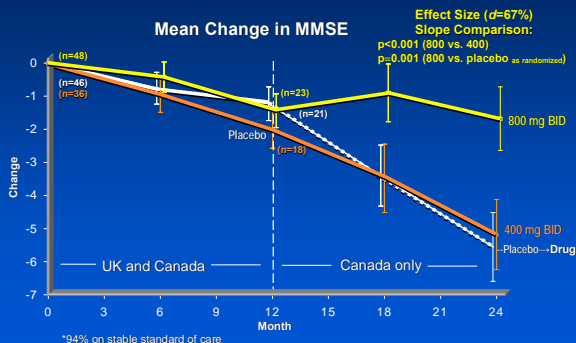
Methodology: Randomized, Double-Blind, Placebo-Controlled Phase 2 Study

- Subjects with mild to moderate AD (MMSE 15-26) at 31 sites in UK and Canada
 - A prespecified interaction analysis revealed that mild and moderate AD patients responded differently to tarenflurbil (p=0.03). They were, therefore, analyzed separately (Wilcock et al. 2006).
- 3 treatment groups (1:1:1), 400 mg BID, 800 mg BID or Placebo BID
 - Stable cholinesterase inhibitor allowed (94% of subjects on stable therapy)
- 12 months treatment (optional 1 year extension study available in Canada only)
 - Over 80% of the eligible patients elected to continue in this blinded study in which placebo patients were randomized into one of the two treatment groups and treated patients continued their previous dose. UK sites did not participate in months 12-24.
- Primary Efficacy: Cognition, Activities of Daily Living, Global Function
 - The MMSE was included as an exploratory measure of cognition.
- A post-hoc responder analysis was performed in subjects with mild AD (MMSE 20-26) in which a "responder" was conservatively defined as a subject who shows improvement or no decline (change of 0) compared to baseline over 24 months of treatment for a given outcome measure
 - Absolute Risk Reduction was defined as the difference between the observed event rates in two groups (placebo and 800 mg BID)

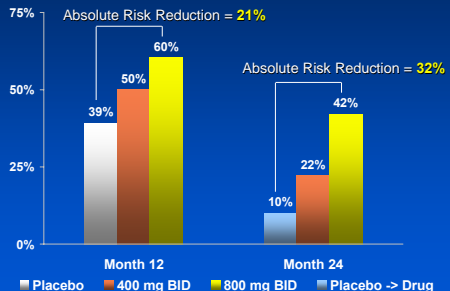
Demographics by Treatment Group

| Mild patients (MMSE 20 to 26) | Placebo (n=46) | 400 mg BID (n=36) | 800 mg BID (n=48) |
|-------------------------------|----------------|-------------------|-------------------|
| % of Total Patients | 75% | 58% | 73% |
| Age | 76 | 75 | 76 |
| % AChEI Use | 97% | 94% | 94% |
| MMSE | 22.9 | 23.1 | 22.8 |
| ADAS-cog (†80 point) | 27.5 | 28.6 | 28.3 |
| ADCS-ADL | 58.7 | 61.4 | 59.8 |
| CDR-sb | 5.7 | 5.0 | 6.0 |

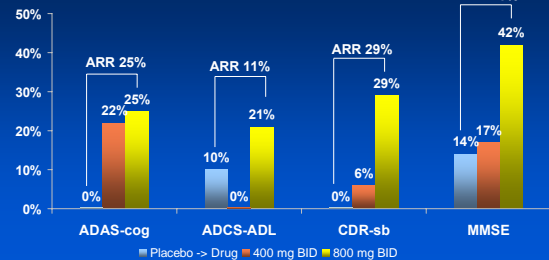
Cognition—Mild Subjects* (MMSE ≥ 20 at Baseline) ITT analysis



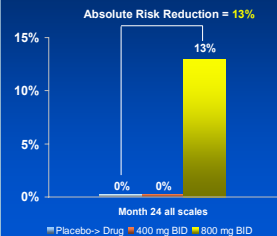
Percentage of Mild Patients Improved or with Zero Decline on At Least One Primary Outcome



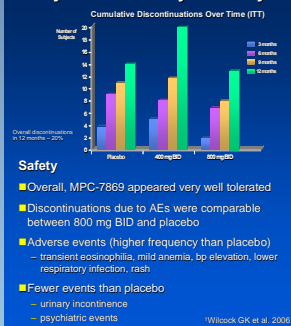
Percentage of Mild Patients Improved or with Zero Decline After 24 Months – Absolute Risk Reduction (ARR)



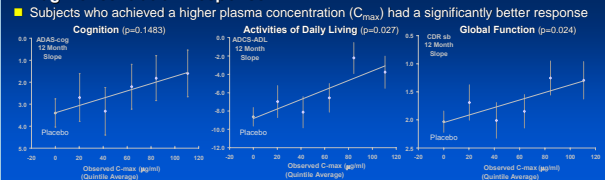
Percentage of Mild Patients Improved or with Zero Decline on All Three Primary Outcomes at Month 24



Safety and Tolerability Summary¹



Drug Concentration Response



Summary

■ Defining "responder" as "improvement or 0 decline from baseline over 12 or 24 months", subjects with mild AD treated with 800 mg BID tarenflurbil showed an increasing response rate over time (absolute risk reduction, Fisher's Exact p-value)

| | At 12 months | At 24 months |
|------------------------------|---------------|---------------|
| At least one Primary Outcome | 21% (p=0.063) | 32% (p=0.020) |
| Cognition (ADAS-cog) | 12% (p=0.273) | 25% (p=0.023) |
| Cognition (MMSE) | N.D. | 28% (p=0.055) |
| Act. Daily Living (ADCS-ADL) | 11% (p=0.240) | 11% (p=0.422) |
| Global Function (CDR-sb) | 18% (p=0.047) | 29% (p=0.010) |
| All 3 Primary Outcomes | 4% (p=0.678) | 13% (p=0.236) |

- Many patients treated with tarenflurbil improved or had no further decline
- ADLs are difficult to recover – improvement not common
- A plasma concentration response was observed with all three primary outcome measures

Conclusions

- Using a very conservative definition of "responder" (improvement or 0 decline from baseline), this analysis demonstrates an increasing response rate (absolute risk reduction) over time in subjects with mild AD treated with tarenflurbil
- These long-term and increasing response rates have not, to our knowledge, been observed previously in clinical studies of drugs in Alzheimer's disease
 - Results are consistent with the hypothesis that treatment with tarenflurbil may slow the underlying biological progression of AD
- Tarenflurbil has an attractive therapeutic and safety profile in patients with mild AD treated for 24 months, the vast majority of whom were already on stable standard of care therapy (acetylcholinesterase inhibitors)¹
- Confirmatory Phase 3 Studies are ongoing in subjects with mild AD (MMSE 20-26) treated for 18 months with 800 mg BID tarenflurbil vs. placebo (1:1)

This study was funded by Myriad Pharmaceuticals, Inc. All authors are employees of Myriad Pharmaceuticals, Inc.

PDF copies of this poster will be available at www.myriad.com

References:
¹Wilcock GK et al. 2006. *Alzheimer's and Dementia* 2(3), Supplement 1, pS81