Tarenflurbil (MPC-7869, Flurizan), a Selective Aβ42-Lowering Agent, Delays Time to Clinically Significant Psychiatric Events in Alzheimer's Disease (AD): Analysis from a 12-Month Phase 2 Trial

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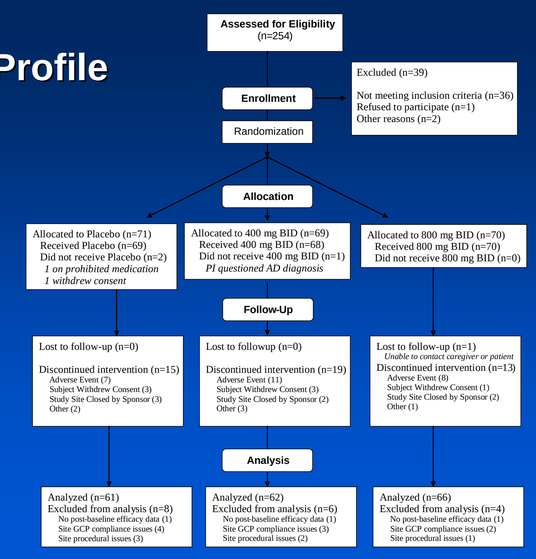
Tarenflurbil Clinical Rationale

- 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
- Hypothesis to be tested:
  - AD subjects receiving tarenflurbil will have a delay in the onset of psychiatric adverse events
  - Hypothesis is based on the potential disease-modifying effects of SALA agents

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). Therefore, they were analyzed separately ([1]Wilcock GK et al. 2006).
- 3 treatment groups (1:1:1), 400 mg BID, 800 mg BID and Placebo BID
- 12 months' treatment
  - Optional 1-year extension study available in Canada only
- Primary Efficacy: Cognition, Activities of Daily Living, Global Function
- Safety Endpoints
  - Incidence of adverse events
  - Changes in physical examinations
  - Clinical laboratory results
- A post hoc exploratory analysis was performed comparing the number of and time to adverse psychiatric events between treatment groups

Trial Profile



Baseline 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%
Mean Duration AChEI Use at Baseline (months)	16.0	19.7	16.9
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

Summary Results of Primary Outcomes ([1]Wilcock GK et al. 2006)

- Subjects with mild AD on 800 mg BID showed a reduced rate of decline (slope)

	At 12 months	At 24 months
Activities of Daily Living	d=44% (p=0.033)	d=67% (p=0.015)
Global Function	d=42% (p=0.042)	d=72% (p=0.0005)
Cognition (positive trend)	d=20% (p=0.327)	d=52% (p=0.109)

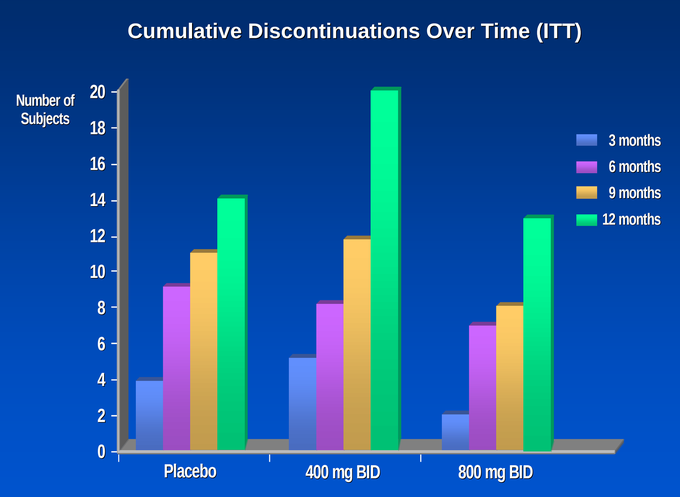
Safety: Adverse Events that Occurred in >5% of Patients or Demonstrated Statistical Significance (p<0.10)

Preferred Term	Placebo (n=66)	400 mg BID (n=71)	800 mg BID (n=70)	Total (n=207)	Placebo vs 400 mg BID	Placebo vs 800 mg BID	400 vs 800 mg BID
	Number of patients (%)				p value		
Diarrhea	5 (7.6)	8 (11.3)	7 (10.0)	20 (9.7)	0.565	0.765	1.000
Nausea	4 (6.1)	7 (9.9)	7 (10.0)	18 (8.7)	0.535	0.533	1.000
Dizziness	4 (6.1)	9 (12.7)	5 (7.1)	18 (8.7)	0.247	1.000	0.399
Urinary tract infection	5 (7.6)	7 (9.9)	5 (7.1)	17 (8.2)	0.766	1.000	0.764
Agitation	5 (7.6)	7 (9.9)	4 (5.7)	16 (7.7)	0.766	0.739	0.532
Confusional state	2 (3.0)	10 (14.1)	4 (5.7)	16 (7.7)	0.032	0.681	0.157
Upper respiratory tract infection	7 (10.6)	4 (5.6)	2 (2.9)	13 (6.3)	0.354	0.090	0.681
Vomiting	3 (4.5)	3 (4.2)	6 (8.6)	12 (5.8)	1.000	0.495	0.326
Headache	6 (9.1)	3 (4.2)	3 (4.3)	12 (5.8)	0.313	0.315	1.000
Constipation	3 (4.5)	4 (5.6)	4 (5.7)	11 (5.3)	1.000	1.000	1.000
Depression	4 (6.1)	1 (1.4)	6 (8.6)	11 (5.3)	0.196	0.746	0.063
Eosinophilia	0 (0)	3 (4.2)	6 (8.6)	9 (4.3)	–	0.028	
Nasopharyngitis	4 (6.1)	0 (0)	5 (7.1)	9 (4.3)	0.051	–	0.028
Pneumonia	0 (0)	3 (4.2)	5 (7.1)	8 (3.9)	–	0.058	–
Rash	0 (0)	5 (7.0)	3 (4.3)	8 (3.9)	0.059	–	–
Urinary incontinence*	6 (9.1)	0 (0)	1 (1.4)	7 (3.4)	0.011	0.057	–
Blood glucose increased	4 (6.1)	0 (0)	1 (1.4)	5 (2.4)	0.051	–	–

Safety: Patients with Adverse Events by Treatment Group

System Organ Class	Placebo n=66	400 mg n=71	800 mg n=70
Gastrointestinal	20	21	26
Infections/infestations	20	18	19
General disorders	10	16	15
Psychiatric disorders	23	26	14
Nervous system	12	21	14
Musculoskeletal	9	12	13
Blood/lymphatics (primarily eosinophilia)	1	5	11
Skin/subcutaneous tissue	8	12	11
Respiratory/thoracic	12	17	10
Renal/urinary disorders	8	4	8
Metabolism	4	7	7
Cardiac	1	6	5
Vascular disorders (primarily elevated bp)	1	8	6

Phase 2 Safety and Tolerability Summary



Overall discontinuations in 12 months ~ 20%

Safety

- Overall, tarenflurbil appeared very well tolerated
- Discontinuations due to AEs were comparable between 800 mg BID and placebo
- Adverse events (higher frequency than placebo)
  - Transient eosinophilia, mild anemia, bp elevation, lower respiratory infection, rash
- Fewer events than placebo
  - Urinary incontinence
  - Psychiatric events

[1]Wilcock et al. 2006

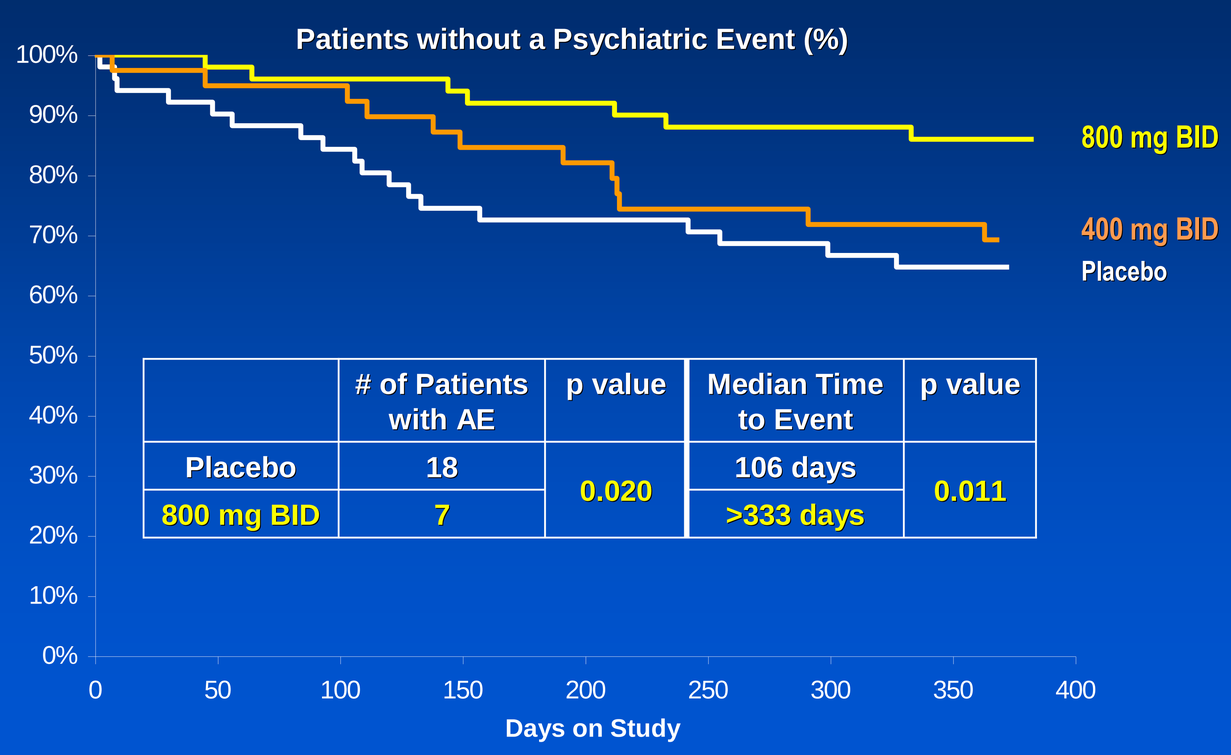
Psychiatric Disorder Adverse Events

Mild Patients (MMSE ≥ 20), Safety Population

Psychiatric Disorder (MedDRA)	Placebo (n=50)	400 mg BID (n=40)	800 mg BID (n=50)	Total (N=140)
Total Number of Adverse Events	21	17	10	48
Number of Patients With at Least One Adverse Event (Psychiatric Disorder)	18 (36%)	12 (30%)	7 (14%)	37 (26.4%)
Abnormal behaviour	1 (2%)	0	0	1 (0.7%)
Abnormal dreams	1 (2%)	0	0	1 (0.7%)
Aggression	2 (4%)	0	0	2 (1.4%)
Agitation	3 (6%)	2 (5%)	1 (2%)	6 (4.3%)
Anger	0	1 (2.5%)	0	1 (0.7%)
Anxiety	2 (4%)	2 (5%)	2 (4%)	6 (4.3%)
Apathy	1 (2%)	0	0	1 (0.7%)
Confusional state	2 (4%)	4 (10%)	0	6 (4.3%)
Delusion	0	1 (2.5%)	0	1 (0.7%)
Depression	2 (4%)	1 (2.5%)	4 (8%)	7 (5.0%)
Hallucination	1 (2%)	0	0	1 (0.7%)
Hallucination, visual	1 (2%)	1 (2.5%)	0	2 (1.4%)
Insomnia	1 (2%)	0	1 (2%)	2 (1.4%)
Libido increased	1 (2%)	1 (2.5%)	0	2 (1.4%)
Mood altered	0	0	1 (2%)	1 (0.7%)
Mood swings	0	1 (2.5%)	0	1 (0.7%)
Nightmare	1 (2%)	0	1 (2%)	2 (1.4%)
Paranoia	0	1 (2.5%)	0	1 (0.7%)
Psychotic disorder	0	1 (2.5%)	0	1 (0.7%)
Sleep disorder	1 (2%)	1 (2.5%)	0	2 (1.4%)

p = 0.020 (Placebo vs. 800 mg BID)

Time to Psychiatric Event by Treatment Group (Mild Patients, MMSE ≥ 20)



	# of Patients with AE	p value	Median Time to Event	p value
Placebo	18	0.020	106 days	0.011
800 mg BID	7		>333 days	

Conclusions

- Tarenflurbil has an attractive therapeutic and safety profile in patients with mild AD treated for 1 year, the vast majority of whom were already on standard-of-care therapy (acetylcholinesterase inhibitors)
- In addition to the reported[1] significant benefit observed in patients with mild AD in activities of daily living (p=0.033), global function (p=0.042) and a positive trend in cognition, this analysis revealed a significant reduction (p=0.020) in the number of and a delay in time to psychiatric events (p=0.011)
  - The most common psychiatric events reported in the placebo group were agitation, aggression, confusional state and depression
  - No significant effect was seen in the NPI (Neuropsychiatric Inventory) exploratory endpoint
- These results are consistent with the hypothesis that treatment with tarenflurbil may delay progression of AD
- Phase 3 studies of tarenflurbil (800 mg BID) in subjects with mild AD (MMSE 20-26) are ongoing

This study was funded by Myriad Pharmaceuticals, Inc.
PDF copies of this poster will be available at www.myriad.com

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