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

Jacobo Mintzer[1], Gordon Wilcock[2], Sandra Black[3], Kenton Zavitz[4], Mark Laughlin[4], Suzanne Hendrix[4]

[1]Department of Psychiatry, Medical University of South Carolina, USA; [2]Oxford University, UK; [3]Sunnybrook & Women's, University of Toronto, Canada; [4]Myriad Pharmaceuticals, Inc., Salt Lake City, UT, USA

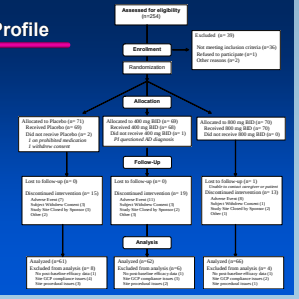
MPC-7869 Clinical Rationale

- 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:
  - Subjects receiving MPC-7869 will have a delay in the onset of psychiatric adverse events
  - Hypothesis is based on the potential disease modifying effects of SALA agents

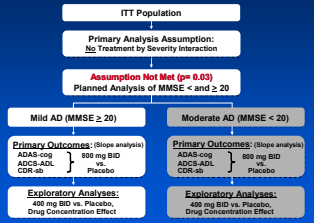
Methodology

- Randomized, Double-Blind, Placebo-Controlled Phase 2 Study
  - 31 sites in Canada and the United Kingdom
- Mild to moderate Alzheimer's (MMSE 15-26)
  - Stable cholinesterase inhibitor allowed
- 207 Subjects in 3 treatment groups (1:1:1)
  - 400 mg BID, 800 mg BID or Placebo BID
- 12 months treatment (optional 1 year follow-on study available in Canada)
- 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



Prospective Statistical Analysis Plan

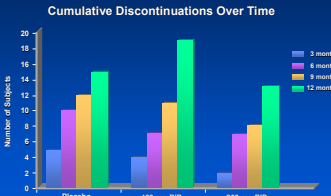


Demographics by Treatment Group

Mild patients (MMSE ≥20)

	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

Safety: Discontinuations Over Time



Overall discontinuations in 12 months – 20%

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

Preferred Term	Placebo (n=66)	400mg BID (n=71)	800mg BID (n=70)	Total (n=207)	Placebo vs 400mg BID	Placebo vs 800mg BID	400 vs 800mg BID
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	--	--
	Number of patients (%)				p value		

Safety: Patients with Adverse Events by Treatment Group

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

Safety Summary

- Overall, MPC-7869 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
- Adverse events (lower frequency than placebo)
  - psychiatric events (p=0.057, placebo vs. 800 mg BID)
  - urinary incontinence

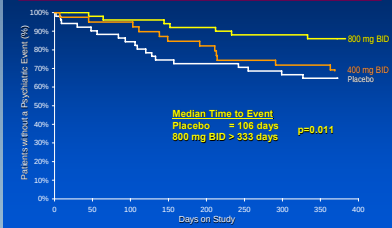
Psychiatric Disorder Adverse Events

Mild Patients (MMSE ≥ 20), Safety Population

Psychiatric Disorders (MedDRA)	Placebo (N=50)	400 mg BID (N=48)	800 mg BID (N=50)	Total (N=148)
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 (28.4%)
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 at Baseline

Conclusions

- MPC-7869 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 MPC-7869 may delay progression of AD
- Confirmatory Phase 3 Studies are ongoing

Reference:
[1]Black, SE et al. 2006. Neurology 66(5). Supplement 2, pA347

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