MPC-7869 (R-flurbiprofen), a Selective Aβ42-Lowering Agent, in Alzheimer's Disease: Results of a 12-Month Phase 2 Trial and 1-year Follow-on Study

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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 mice
- Effective concentrations achievable in humans at doses that have been well tolerated

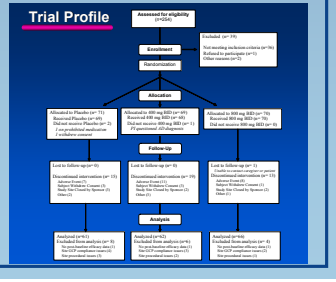
Methodology

- Multi-center, Randomized, Double-Blind, Placebo-Controlled Study
  - 31 sites in Canada and the United Kingdom
- Mild to moderate Alzheimer's (MMSE 15-26)
  - Stable cholinesterase inhibitor allowed
  - Men or women age ≥55 years living in the community
- 207 Subjects in 3 treatment groups (1:1:1)
  - 400 mg BID
  - 800 mg BID
  - Placebo BID
- 12 months treatment
  - optional follow-on study available in Canada

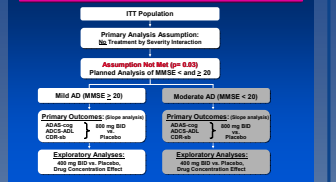
Outcome Measures

- Primary Efficacy (measured throughout)
  - Cognition
    - ADAS-cog
  - Activities of Daily Living
    - ADCS-ADL
  - Global Function
    - CDR Sum of Boxes
- Safety Endpoints
  - Incidence of adverse events
  - Changes in physical examinations
  - Clinical laboratory results
- Population Pharmacokinetics

Trial Profile



Prospective Statistical Analysis Plan



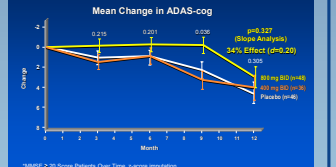
Demographics by Treatment Group

Mild patients (MMSE ≥20)

	Placebo (n=46)	400 mg BID (n=35)	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*

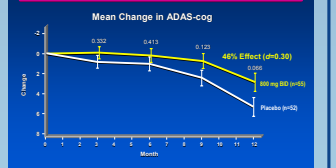
(800mg BID group, n=48, 73% of total)



*MMSE ≥ 20 Score Patients Over Time, z-score imputation

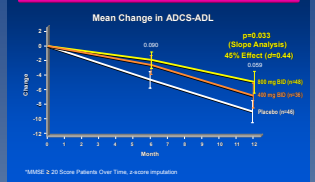
Cognition—Mild Subjects (ADAS-cog <40)

(800mg BID group, n=55, 83% of total)



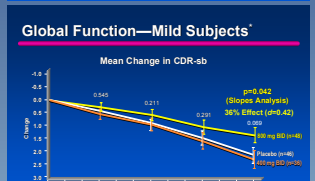
With z-score imputation

Activities of Daily Living—Mild Subjects*



*MMSE ≥ 20 Score Patients Over Time, z-score imputation

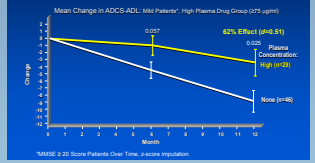
Global Function—Mild Subjects*



*MMSE ≥ 20 Score Patients Over Time, z-score imputation

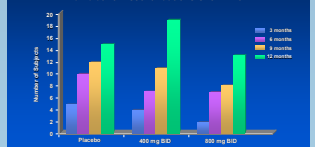
Exploratory: Drug Concentration Effect

- There was a significant plasma concentration response relationship
  - ADCS-ADL (p= 0.037), CDR-sb (p= 0.019)



*MMSE ≥ 20 Score Patients Over Time, z-score imputation

Safety: Discontinuations Over Time



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

Preferred Term	Placebo (n=69)	400mg BID (n=68)	800mg BID (n=70)	Total (n=207)	Placebo vs 400mg BID	Placebo vs 800mg BID	400 vs 800mg BID
Diarrhea	6 (8.7)	7 (10.3)	7 (10.0)	20 (9.7)	0.779	1.000	1.000
Nausea	5 (7.2)	6 (8.8)	7 (10.0)	18 (8.7)	0.764	0.764	1.000
Dizziness	5 (7.2)	8 (11.8)	5 (7.1)	18 (8.7)	0.398	1.000	0.365
Urinary tract infection	5 (7.2)	7 (10.3)	5 (7.1)	17 (8.2)	0.562	1.000	0.559
Agitation	5 (7.2)	7 (10.3)	4 (5.7)	16 (7.7)	0.562	0.745	0.362
Confusional state	2 (2.9)	10 (14.7)	4 (5.7)	16 (7.7)	0.017	0.681	0.096
Upper respiratory tract infection	7 (10.1)	4 (5.9)	2 (2.9)	13 (6.3)	0.332	0.097	0.438
Vomiting	3 (4.3)	3 (4.4)	6 (8.6)	12 (5.8)	1.000	0.493	0.493
Headache	6 (8.7)	3 (4.4)	3 (4.3)	12 (5.8)	0.493	0.326	1.000
Constipation	3 (4.3)	4 (5.9)	4 (5.7)	11 (5.3)	0.718	1.000	1.000
Depression	4 (5.8)	1 (1.5)	6 (8.6)	11 (5.3)	0.366	0.745	0.116
Eosinophilia	0 (0)	3 (4.4)	6 (8.6)	9 (4.3)	--	0.028	--
Nasopharyngitis	4 (5.8)	0 (0)	5 (7.1)	9 (4.3)	--	--	0.058
Pneumonia	0 (0)	3 (4.4)	5 (7.1)	8 (3.9)	--	0.058	--
Rash	0 (0)	5 (7.4)	3 (4.3)	8 (3.9)	0.028	--	--
Urinary incontinence	6 (8.7)	0 (0)	1 (1.4)	7 (3.4)	0.028	0.063	--
Lower respiratory tract infection	0 (0)	4 (5.9)	1 (1.4)	5 (2.4)	0.058	--	--

Number of patients (%) — p value

Safety: Patients with Adverse Events by Treatment Group

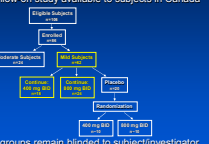
System Organ Class	Placebo	400 mg	800 mg
Blood/lymphatics (events reported)	1	5	11
Cardiac	2	5	5
Gastrointestinal	21	20	26
General disorders	10	16	15
Infections/infestations	20	18	19
Metabolism	5	6	7
Musculoskeletal	10	11	13
Nervous system	13	20	14
Psychiatric disorders	23	26	14
Renal/urinary disorders	8	4	8
Respiratory/thoracic	12	17	10
Skin/subcutaneous tissue	9	12	11
Vascular disorders (events reported)	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)
  - urinary incontinence, psychiatric events

Optional 12 Month Follow-on Study

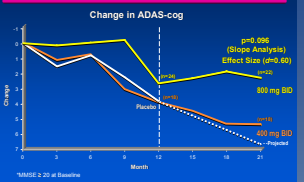
- Optional follow-on study available to subjects in Canada



- Treatment groups remain blinded to subject/investigator
- 21 month data available

Cognition—Mild Subjects*

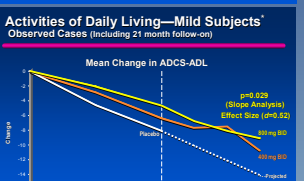
Observed Cases (Including 21 month follow-on)



*MMSE ≥ 20 at Baseline

Activities of Daily Living—Mild Subjects*

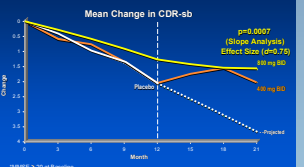
Observed Cases (Including 21 month follow-on)



*MMSE ≥ 20 at Baseline

Global Function—Mild Subjects*

Observed Cases (Including 21 month follow-on)



*MMSE ≥ 20 at Baseline

Conclusions

- Mild subjects showed benefit; moderate subjects did not
- Subjects with mild AD on 800 mg BID showed a reduced rate of decline (slope)

	At 12 months	At 21 months
Activities of Daily Living	d=44% (p=0.033)	d=52% (p=0.029)
Global Function	d=42% (p=0.042)	d=75% (p=0.0007)
Cognition (positive trend)	d=20% (p=0.327)	d=60% (p=0.096)

- Positive effects increasing over time on all scales
  - Proof of concept for a Selective Aβ42-Lowering (SALA) strategy in AD
- Confirmatory Phase 3 Study Ongoing in US
  - Mild AD, 1600 patients (1:1; 800 mg BID vs. placebo), 18 months