A Placebo-controlled, Double-blind Trial of the Selective Aβ-42 Lowering Agent, MPC-7869 (*R*-flurbiprofen) in Patients with Mild to Moderate Alzheimer's Disease

Gordon Wilcock*, University of Bristol, UK

Sandra Black, Judy Haworth, Mark Laughlin, Suzanne Hendrix, Mary-Helen Binger, Kenton Zavitz, Edward Swabb, Adrian Hobden

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MPC-7869 Clinical Rationale

- Selective Aβ42-lowering agent *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 clinically safe doses

Effect of MPC-7869 in Subjects with Mild to Moderate AD

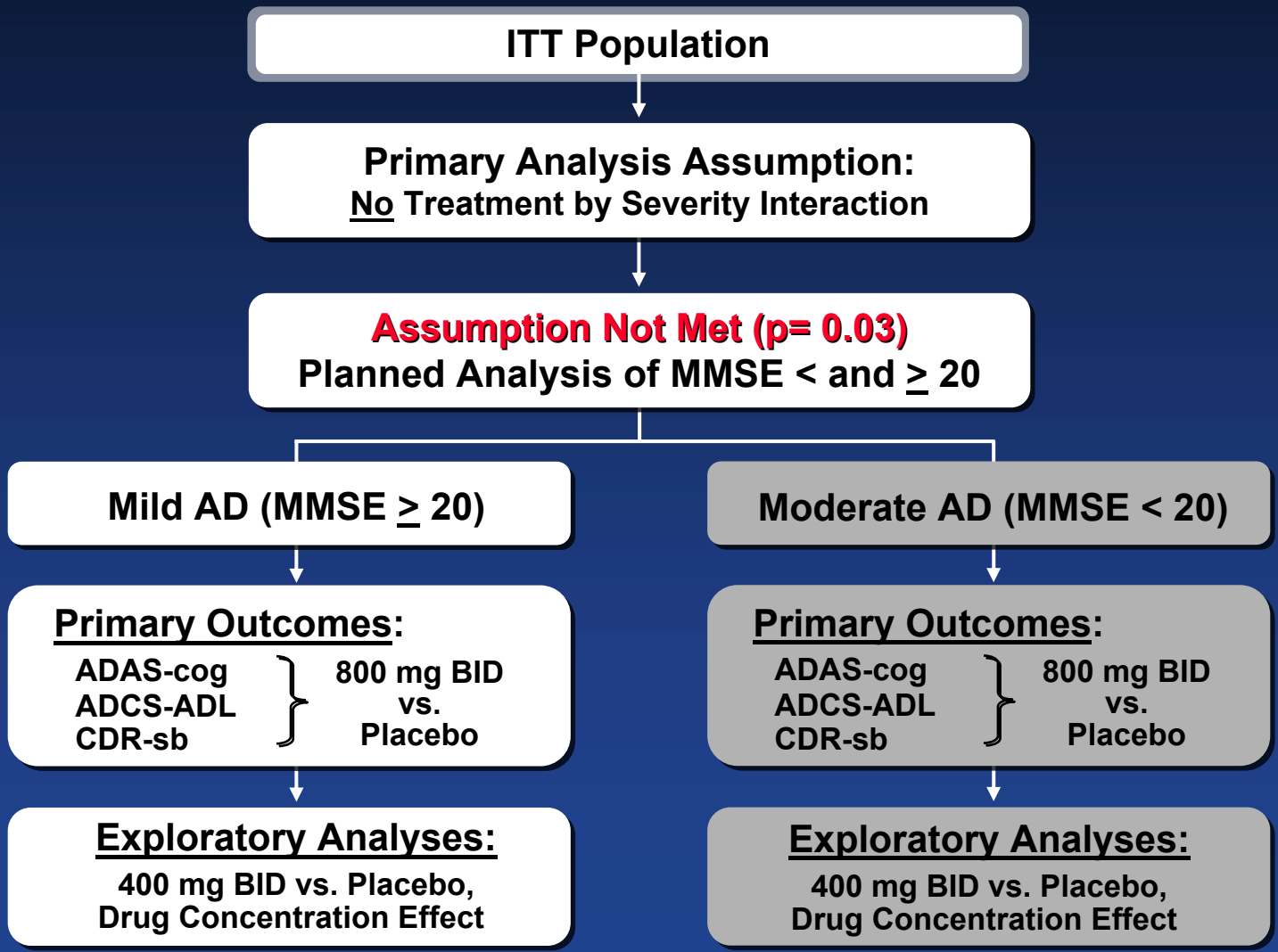
Phase 2 Study

- Multi-center, Randomized, Double-Blind, Placebo-Controlled
- 207 Subjects in 3 treatment groups (1:1:1)
  - 400 mg BID
  - 800 mg BID
  - Placebo BID
- 12 months treatment
- 31 sites in Canada and the United Kingdom

Effect of MPC-7869 in Subjects with Mild to Moderate AD

- Mild to moderate Alzheimer's (MMSE 15-26)
- Stable cholinesterase inhibitor allowed
- Primary Efficacy outcomes (measured throughout)
  - Cognition
    - ADAS-cog
  - Activities of Daily Living
    - ADCS-ADL
  - Global Function
    - CDR Sum of Boxes

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
Gender (%M)	59%	58%	50%
% AChEI Use	100%	94%	94%
Education % College	43%	39%	29%

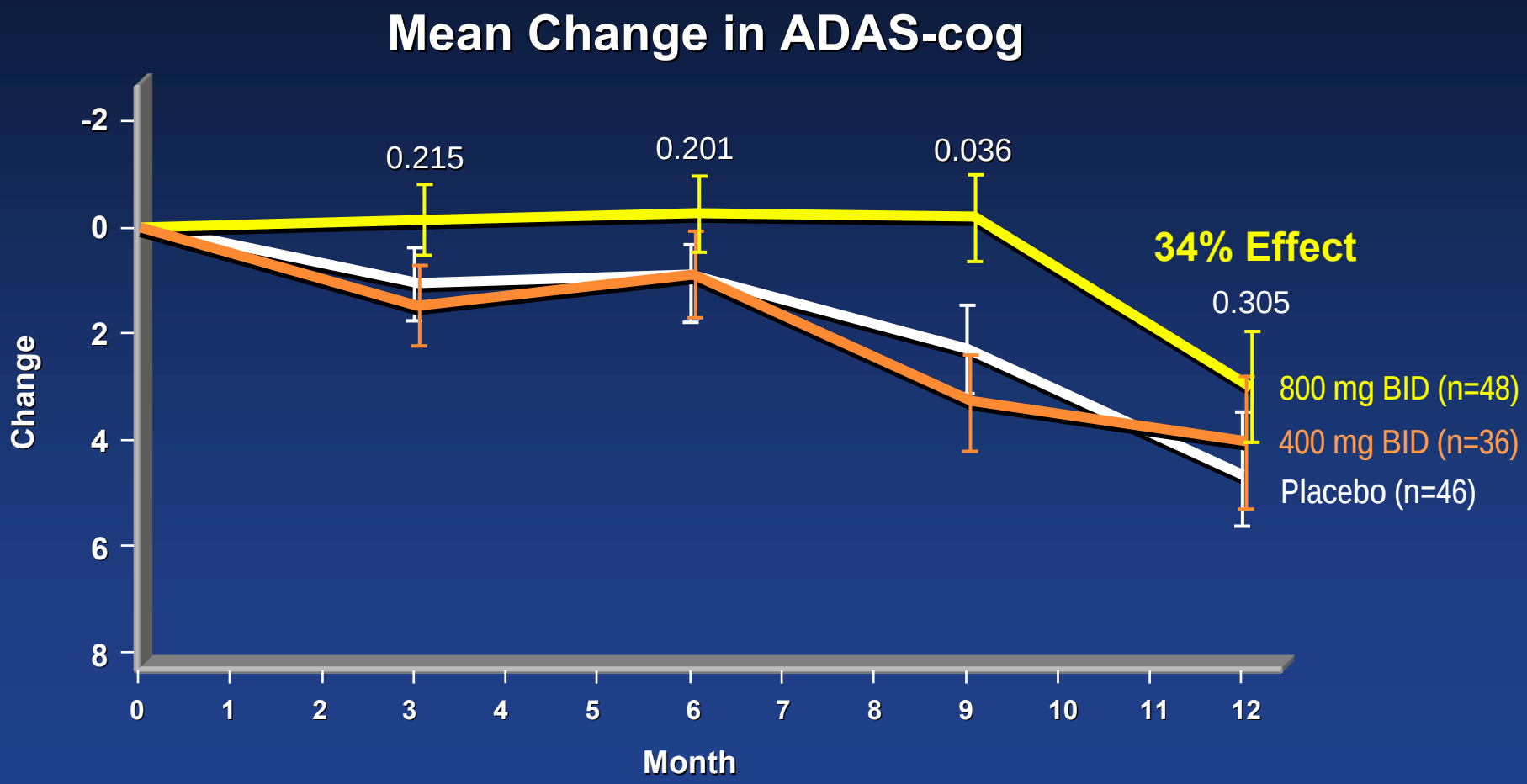
Baseline Scales

Mild patients (MMSE ≥20)

Scale	Placebo (n=46)	400 mg BID (n=36)	800 mg BID (n=48)
ADAS-cog (*80 point)	27.5	28.6	28.3
ADAS-cog (70 point)	19.1	19.9	19.4
ADCS-ADL	58.7	61.4	59.8
CDR-sb	5.7	5.0	6.0
MMSE	22.9	23.1	22.8

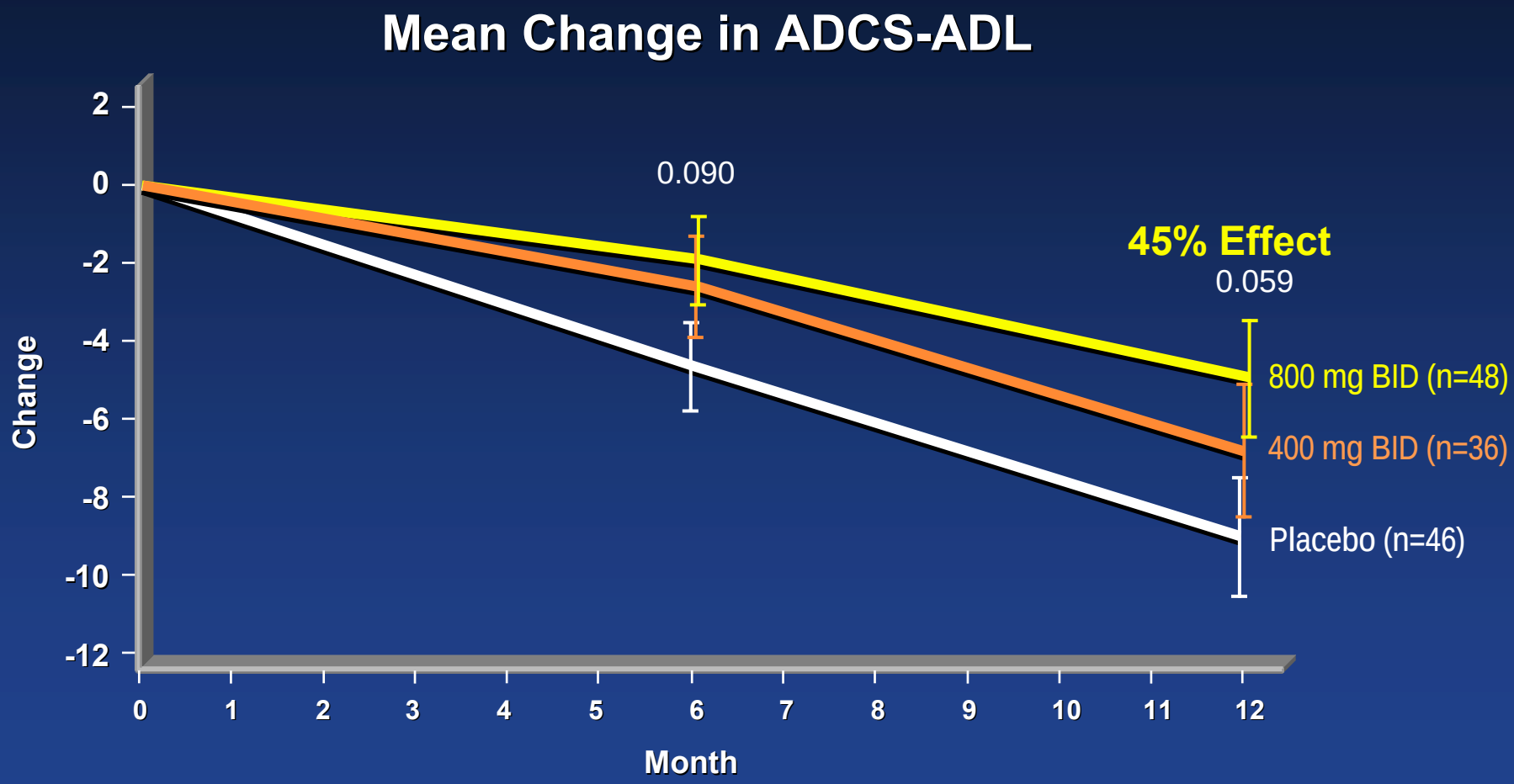
*Includes delayed recall subscale

Cognition—Mild Subjects*



*MMSE ≥ 20 Score Patients Over Time, LOCF

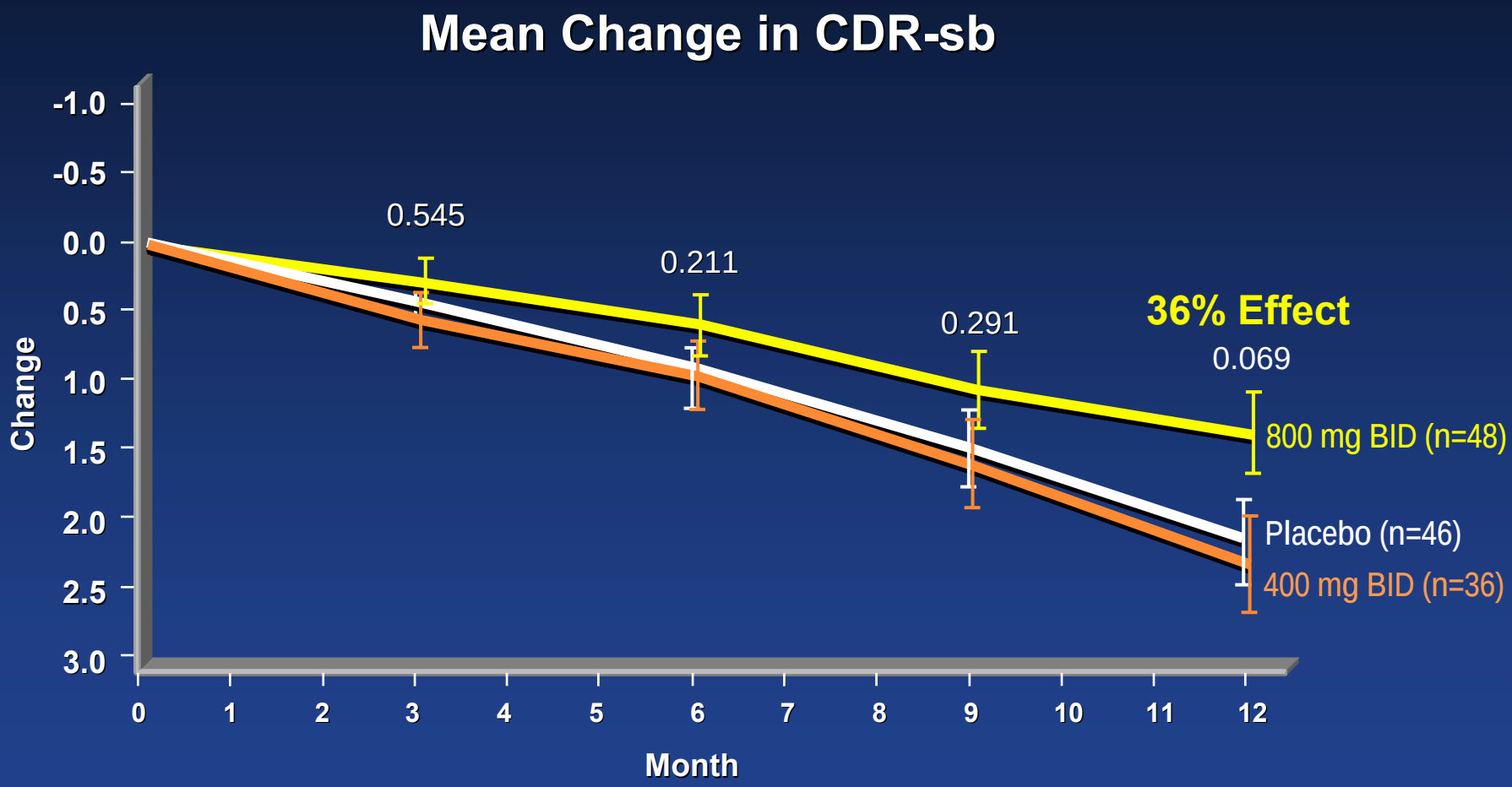
Activities of Daily Living—Mild Subjects*



*MMSE ≥ 20 Score Patients Over Time, LOCF

MPC-7869

Global Function—Mild Subjects*

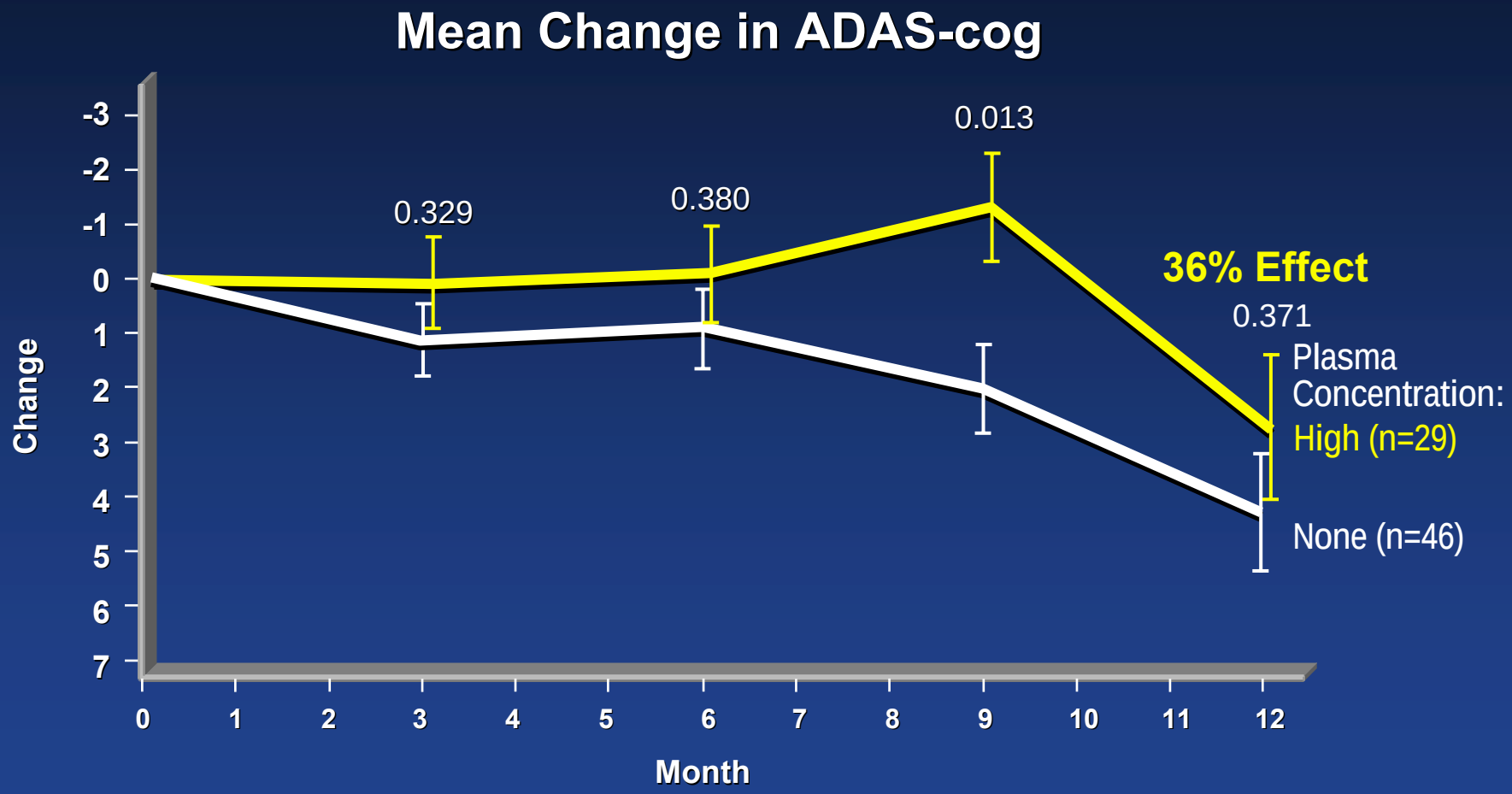


*MMSE ≥ 20 Score Patients Over Time, LOCF

Exploratory: Drug Concentration Effect

- There was a significant concentration response relationship (p= 0.038)
- High concentration was defined as plasma drug concentration above 75 µg/ml
- 29 mild patients had high drug concentrations (60% of 800 mg BID group)

Cognition—Mild Patients*, High Drug Group



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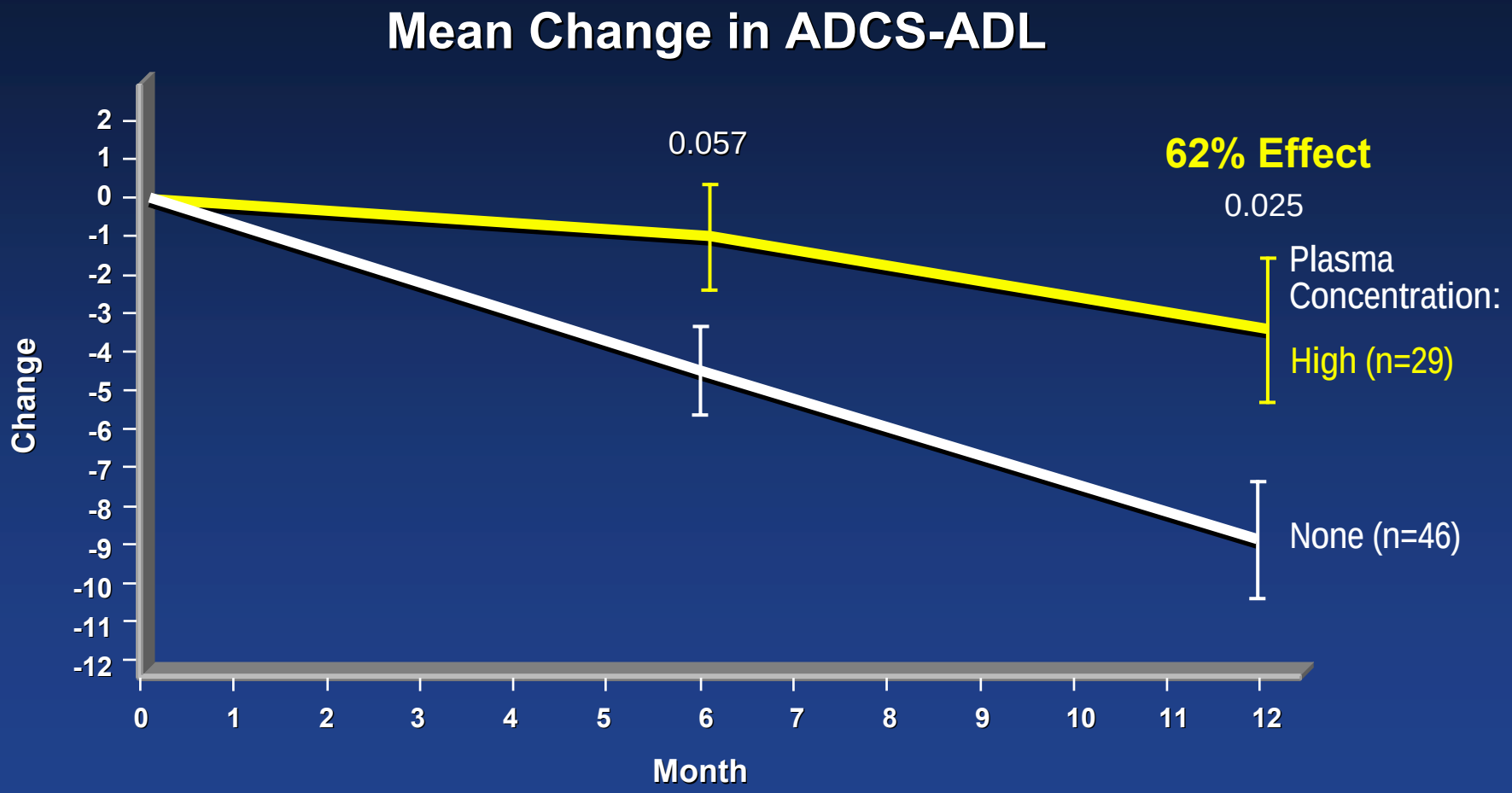
MPC-7869

Activities of Daily Living— Mild Patients*, High Drug Group



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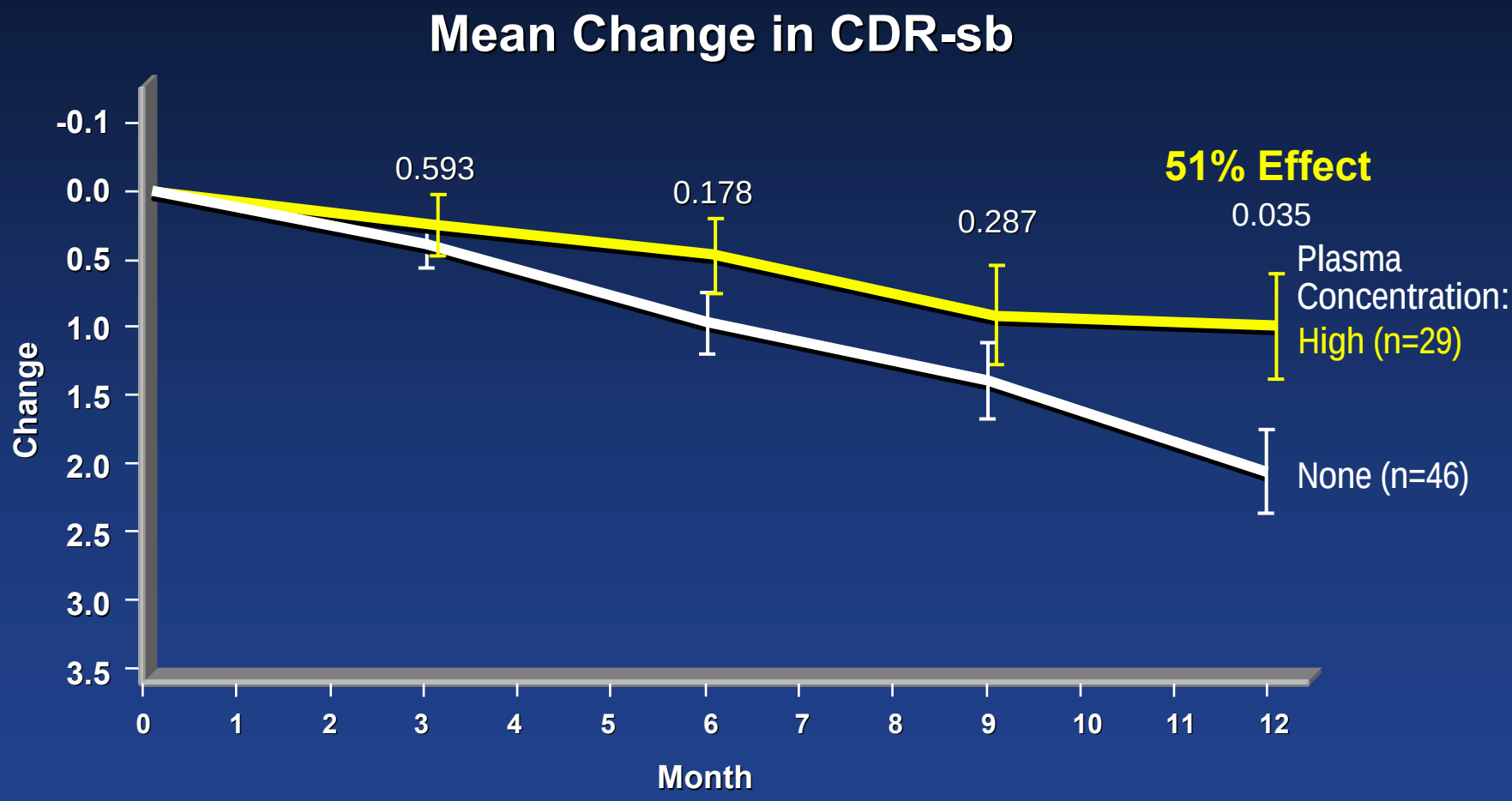
MPC-7869

Global Function—Mild Patients*, High Drug Group



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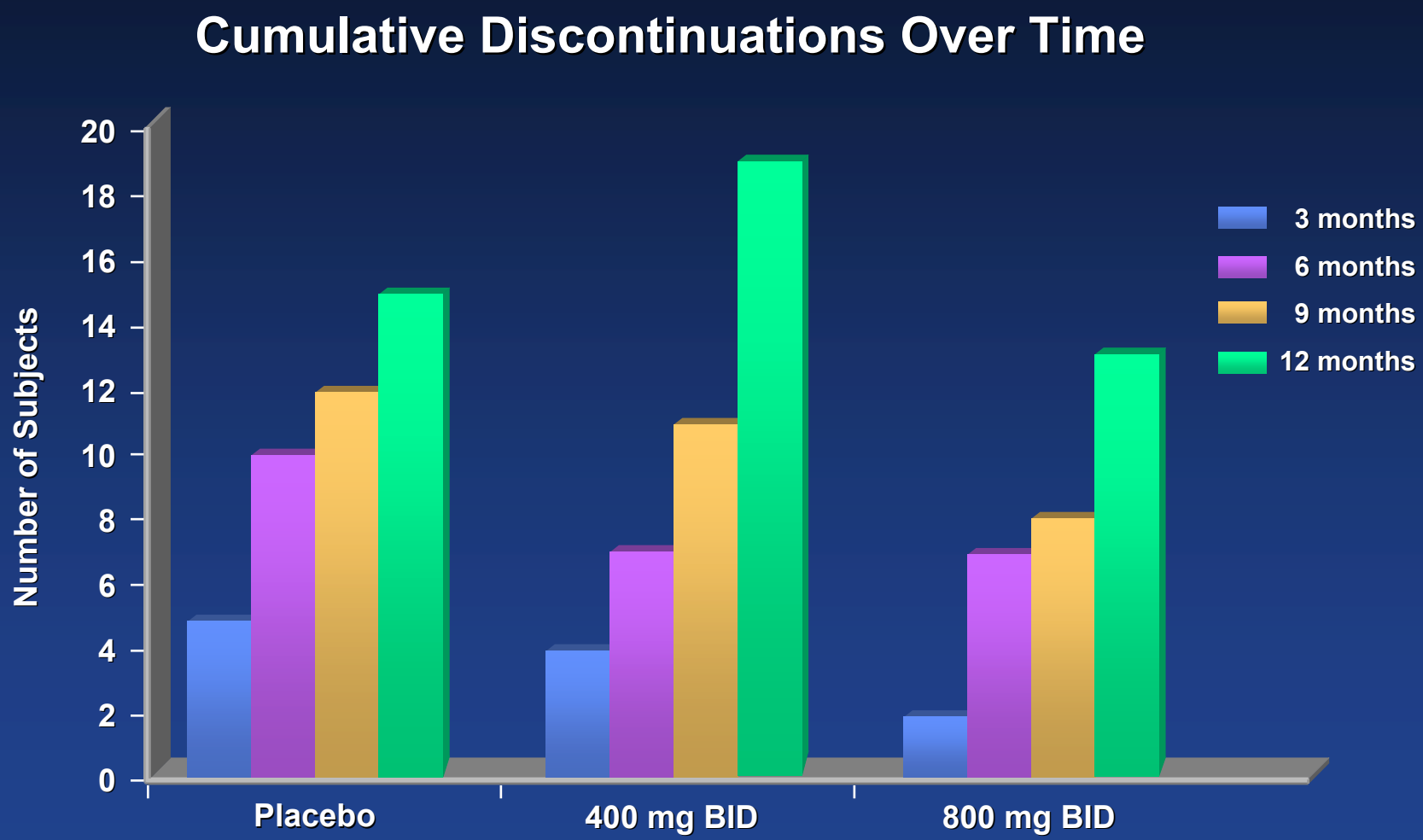
Discontinuations Over Time



Safety Summary

- Overall, MPC-7869 appeared very well tolerated
- Discontinuations over time were similar between treatment groups
- Observed transient dose-related eosinophilia
  - No apparent clinical significance
- No obvious safety differences between mild and moderate patients
- No obvious safety differences between 400 mg BID and 800 mg BID groups

Effect of MPC-7869 in Subjects with Mild to Moderate AD Over 12 Months

Phase 2 Summary:

- Mild and moderate AD subjects responded differently to treatment over 12 months
  - Mild subjects responded; moderate subjects did not
- Mild AD subjects on 800 mg twice daily showed positive trends in all 3 outcome measures
- Mild AD subjects with the highest blood levels of MPC-7869 showed statistically significant benefits in:
  - Activities of Daily Living
  - Global Function
  - and positive trends, (not statistically significant) in Cognition