A Placebo-controlled, Double-blind Trial of the Selective Aβ42-Lowering Agent, MPC-7869 (*R*-flurbiprofen) in Patients with Mild to Moderate Alzheimer's Disease

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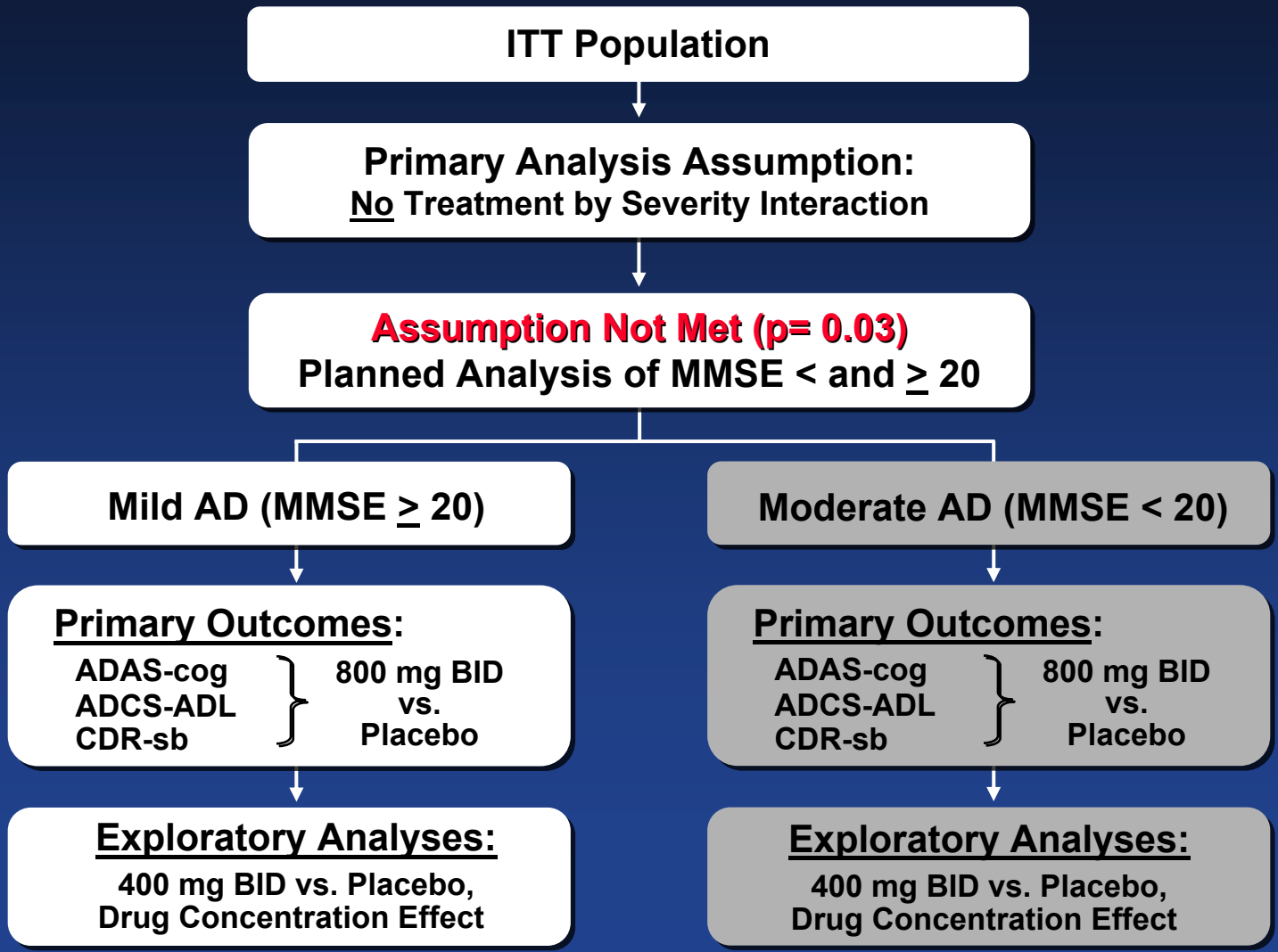
MPC-7869 Clinical Rationale

- 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 clinically safe doses

Phase 2 Study of MPC-7869 in Subjects with Mild to Moderate AD (MMSE 15-26)

- Multi-center, Randomized, Double-Blind, Placebo-Controlled
  - 31 sites in Canada and the United Kingdom
- 207 Subjects in 3 treatment groups (1:1:1)
  - 400 mg BID
  - 800 mg BID
  - Placebo BID
- 12 months treatment / stable ChEI allowed
- ADAS-cog; ADCS-ADL;CDR Sum of Boxes

Prospective Statistical Analysis Plan



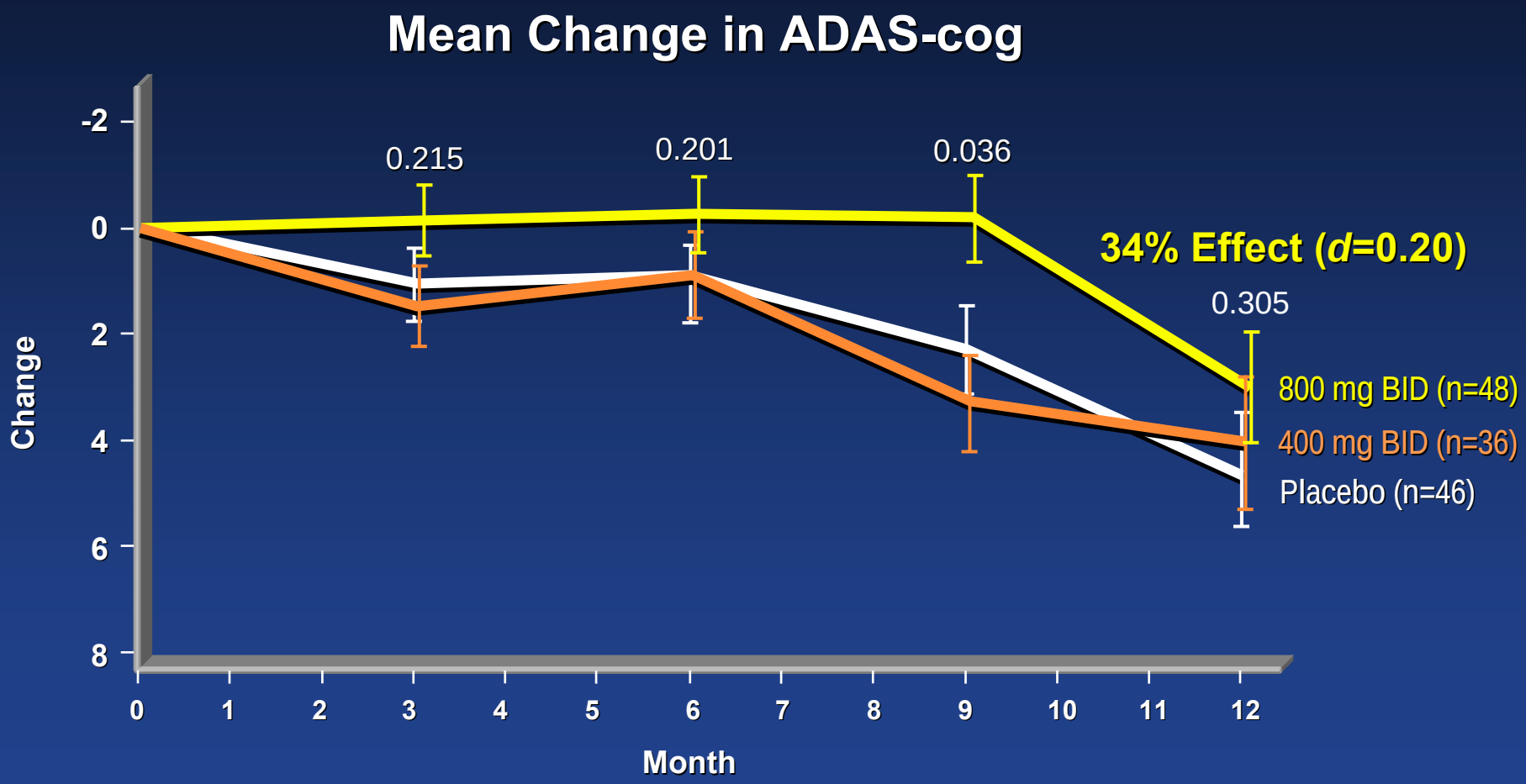
Demographics by Treatment Group

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
% 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

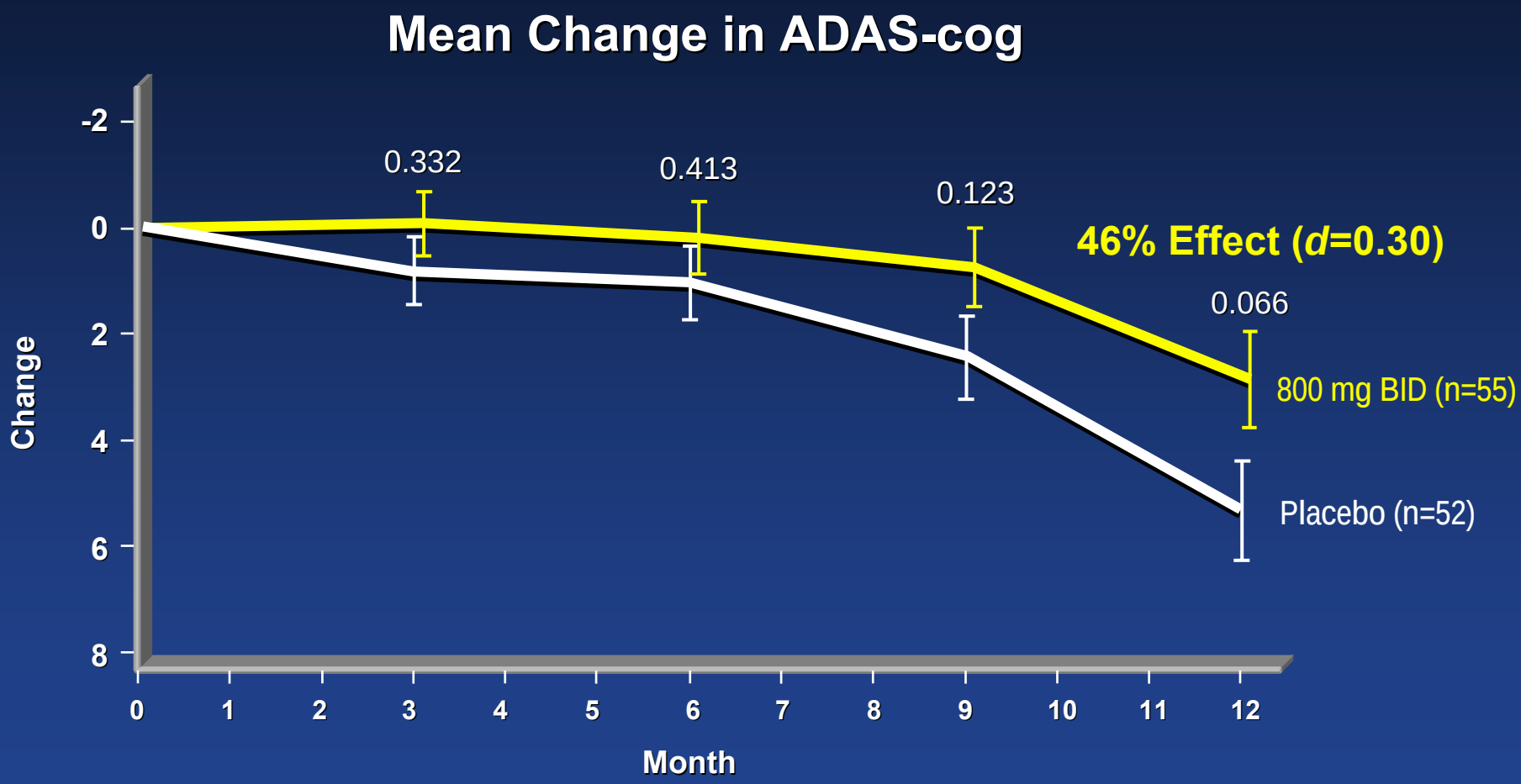
Cognition—Mild Subjects*

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



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

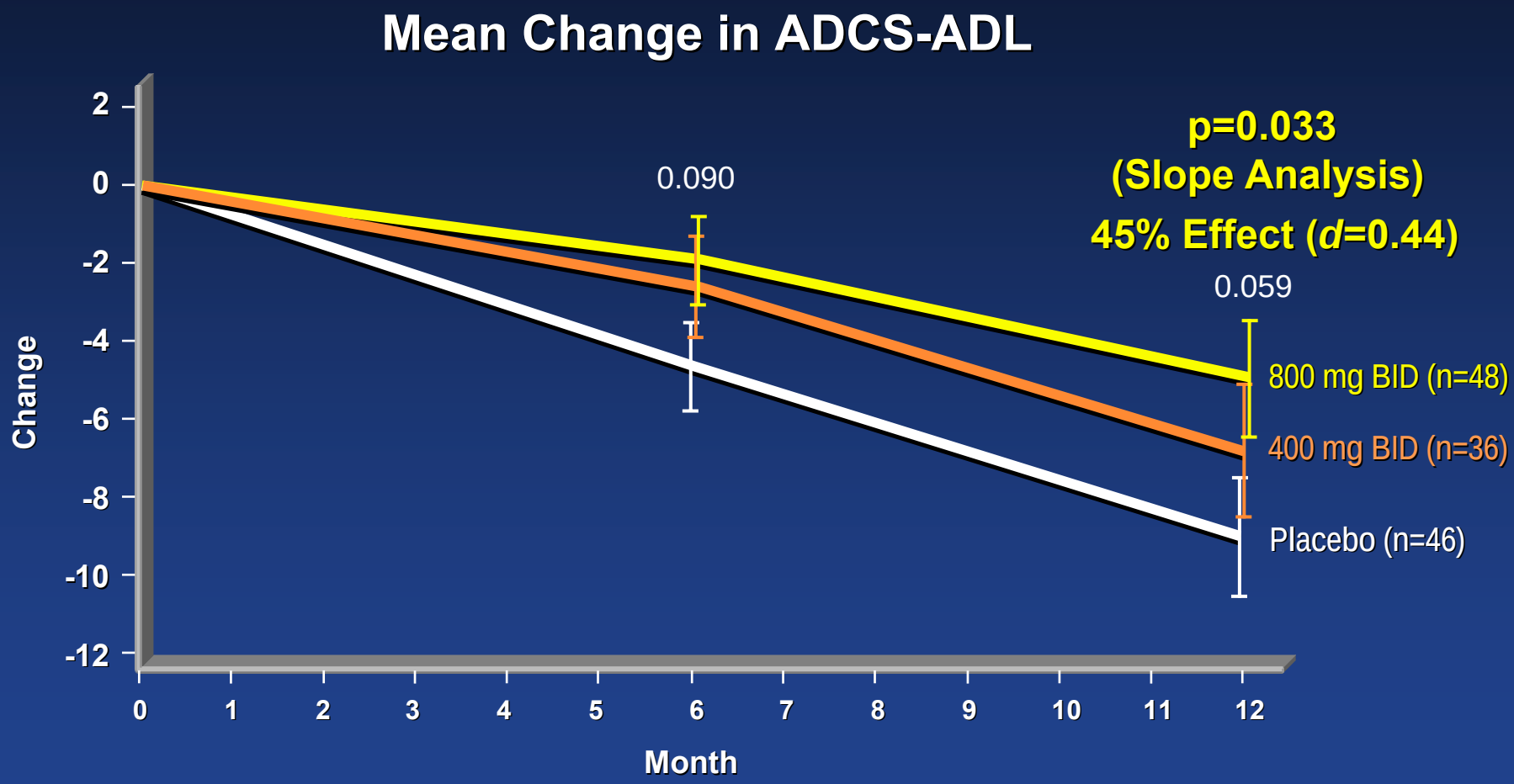
Cognition—Mild Subjects (ADAS-cog <40)
(800mg BID group, n=55, 83% of total)



With z-score imputation

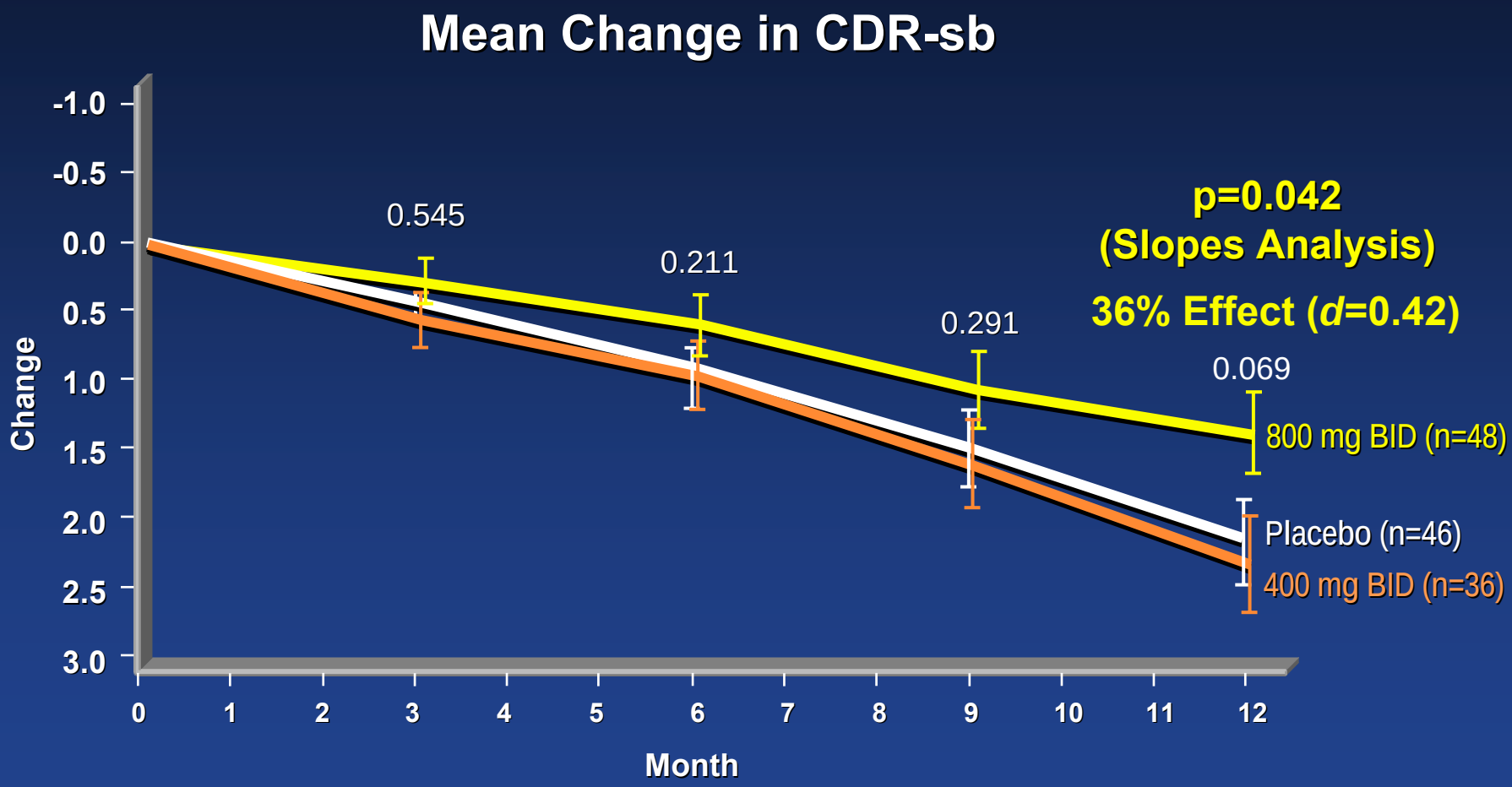
MPC-7869

Activities of Daily Living—Mild Subjects*



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

Global Function—Mild Subjects*

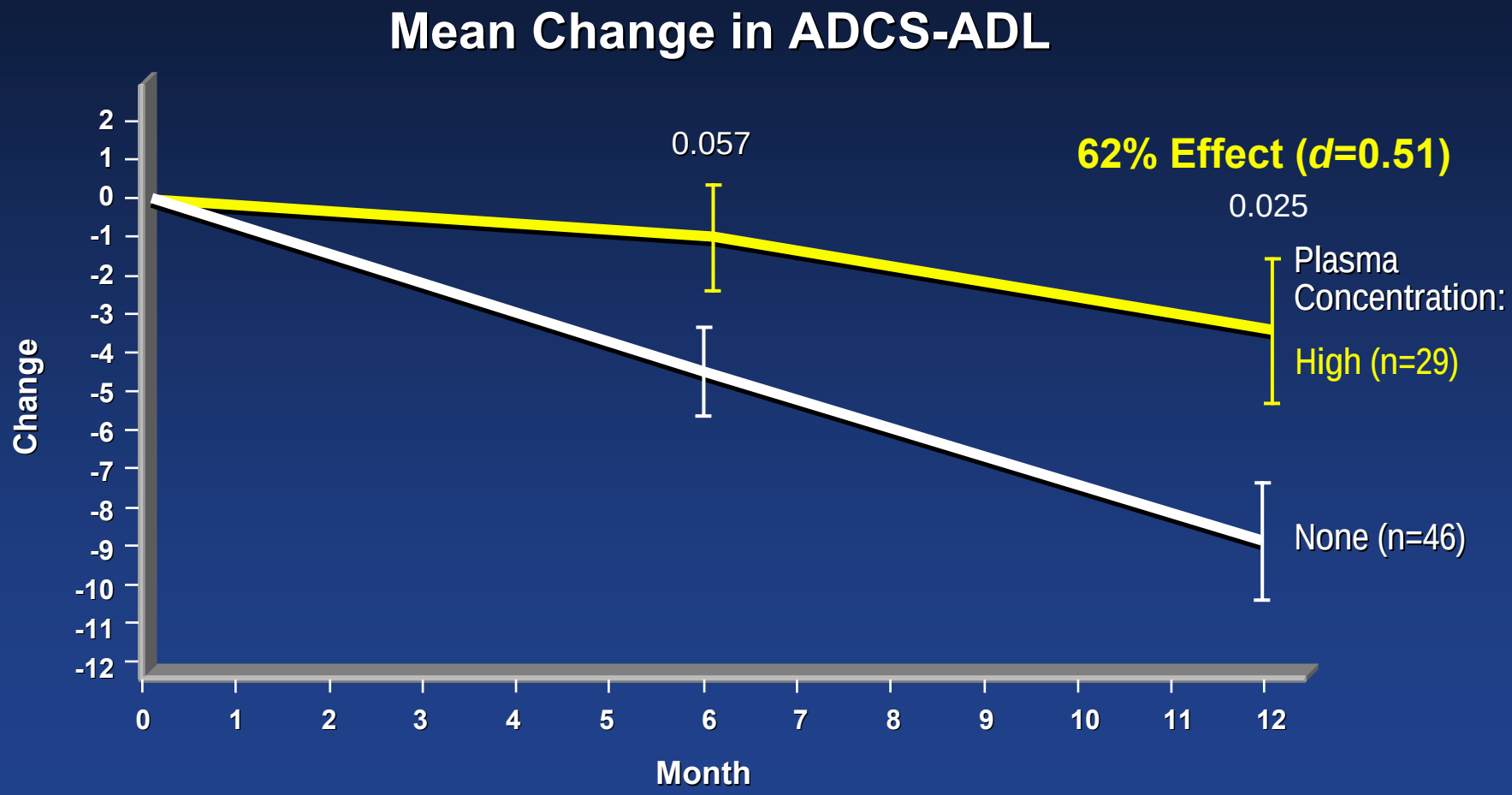


*MMSE ≥ 20 Score Patients Over Time, z-score imputation

Exploratory: Drug Concentration Effect

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

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



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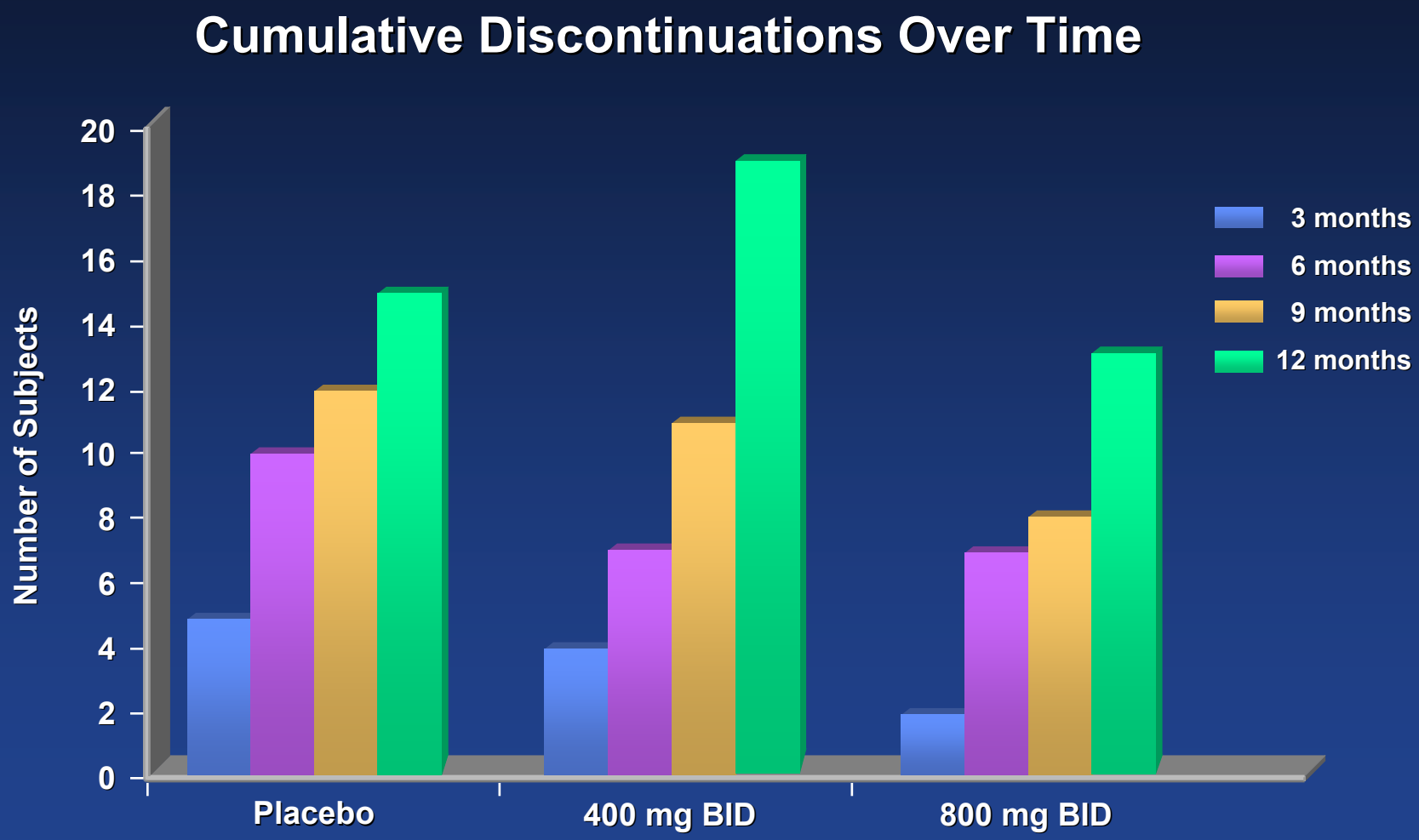
Discontinuations Over Time



Safety Summary

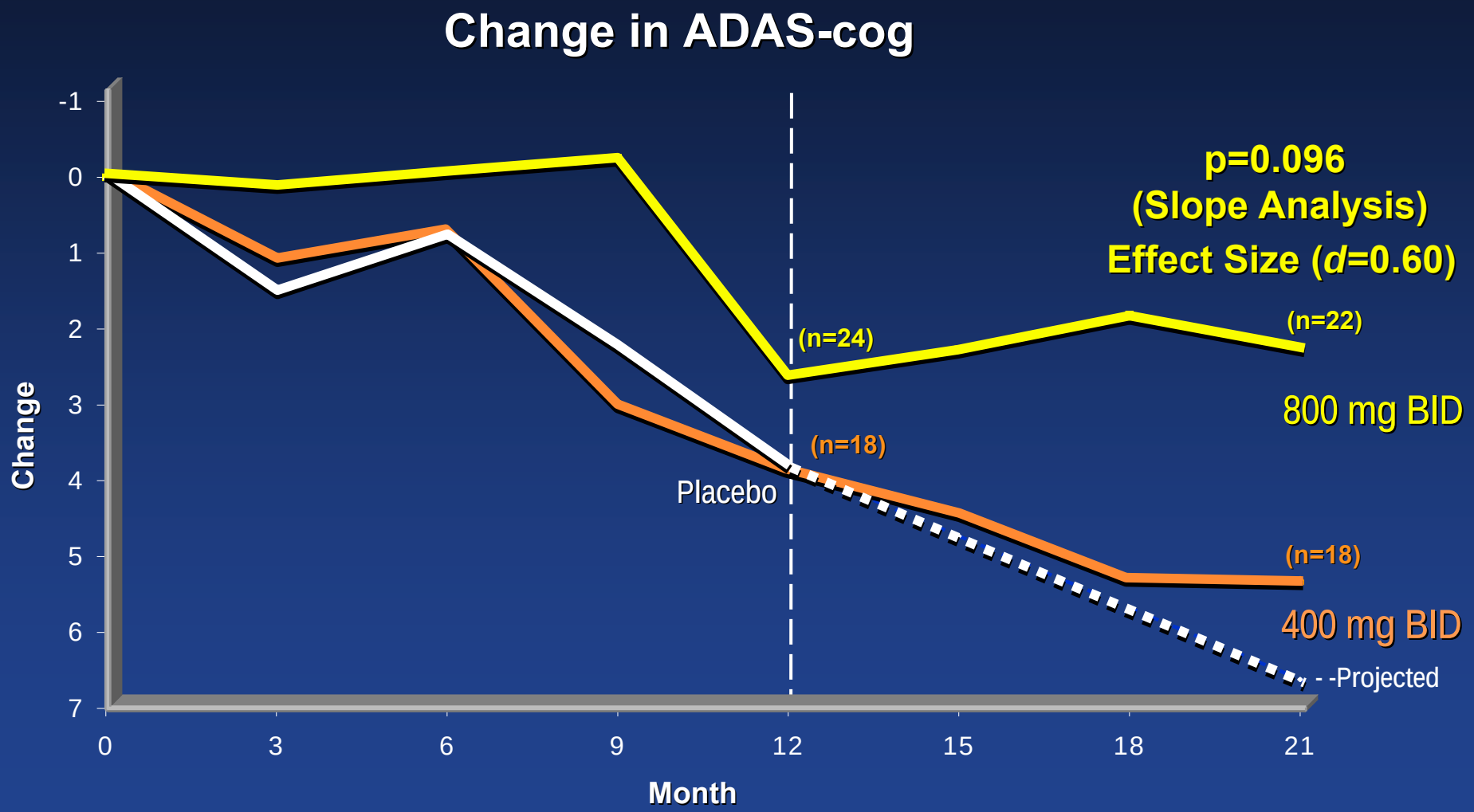
- Overall, MPC-7869 appeared very well tolerated
- Discontinuations due to AEs were comparable between 800 mg BID and placebo
- Adverse events (higher frequency than placebo)
  - transient eosinophilia, mild anemia, bp elevation, lower respiratory infection, rash
- Adverse events (lower frequency than placebo)
  - urinary incontinence, psychiatric events

Optional Follow-on Study

- Optional follow-on study available to subjects in Canada
- 86 of 106 eligible subjects enrolled for additional 12 months treatment (Mild subjects, n = 62)
  - Placebo subjects (n=20) randomized to 400mg or 800mg BID
  - 400mg and 800mg BID subjects continue treatment
    - Mild subjects: 400mg (n=18), 800mg (n=24)
- Treatment groups remain blinded to subject/investigator
- 21 month data available

Cognition—Mild Subjects*

Observed Cases (Including 21 month follow-on)

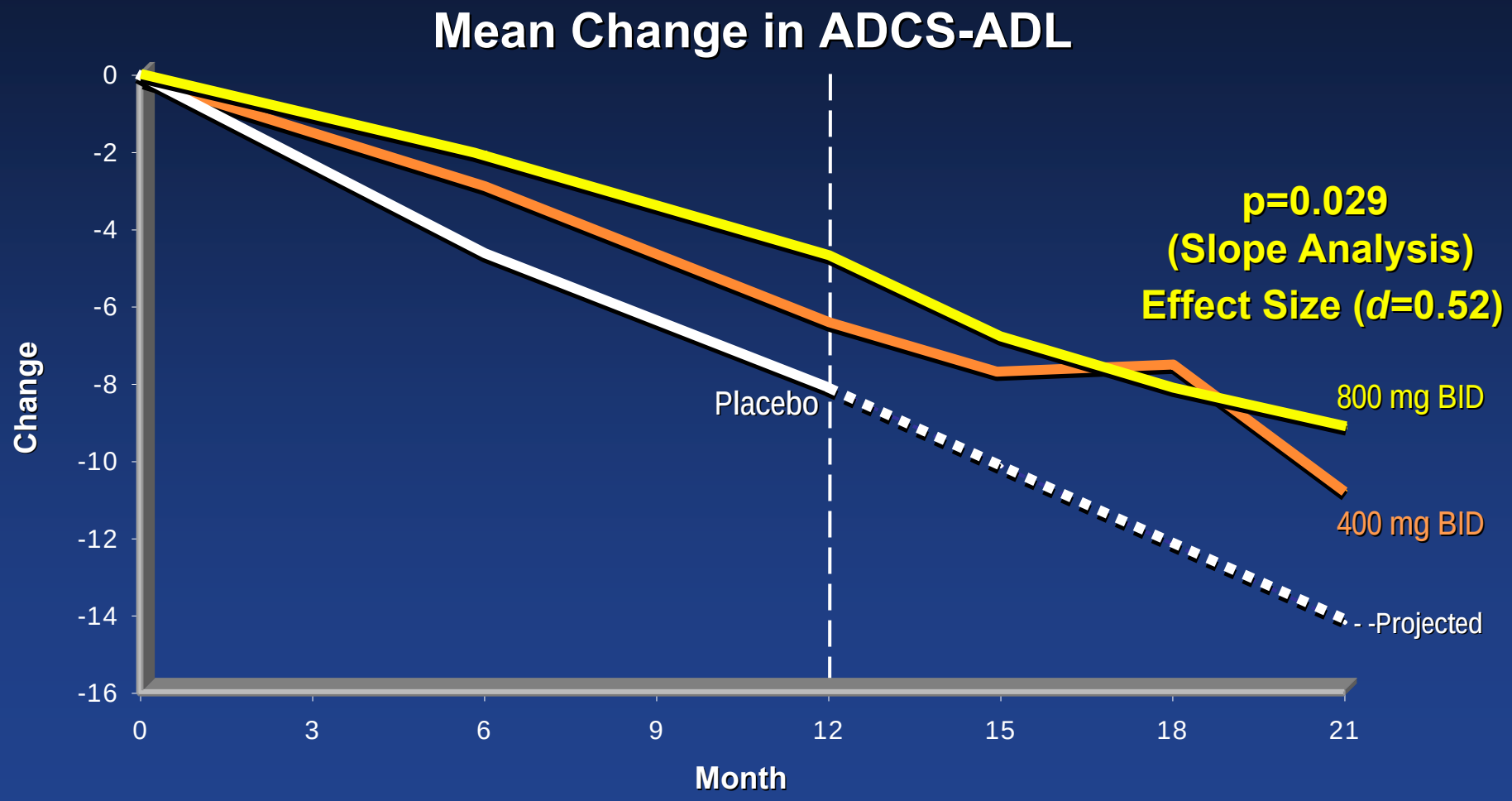


*MMSE ≥ 20 at Baseline

MPC-7869

Activities of Daily Living—Mild Subjects*

Observed Cases (Including 21 month follow-on)



*MMSE ≥ 20 at Baseline

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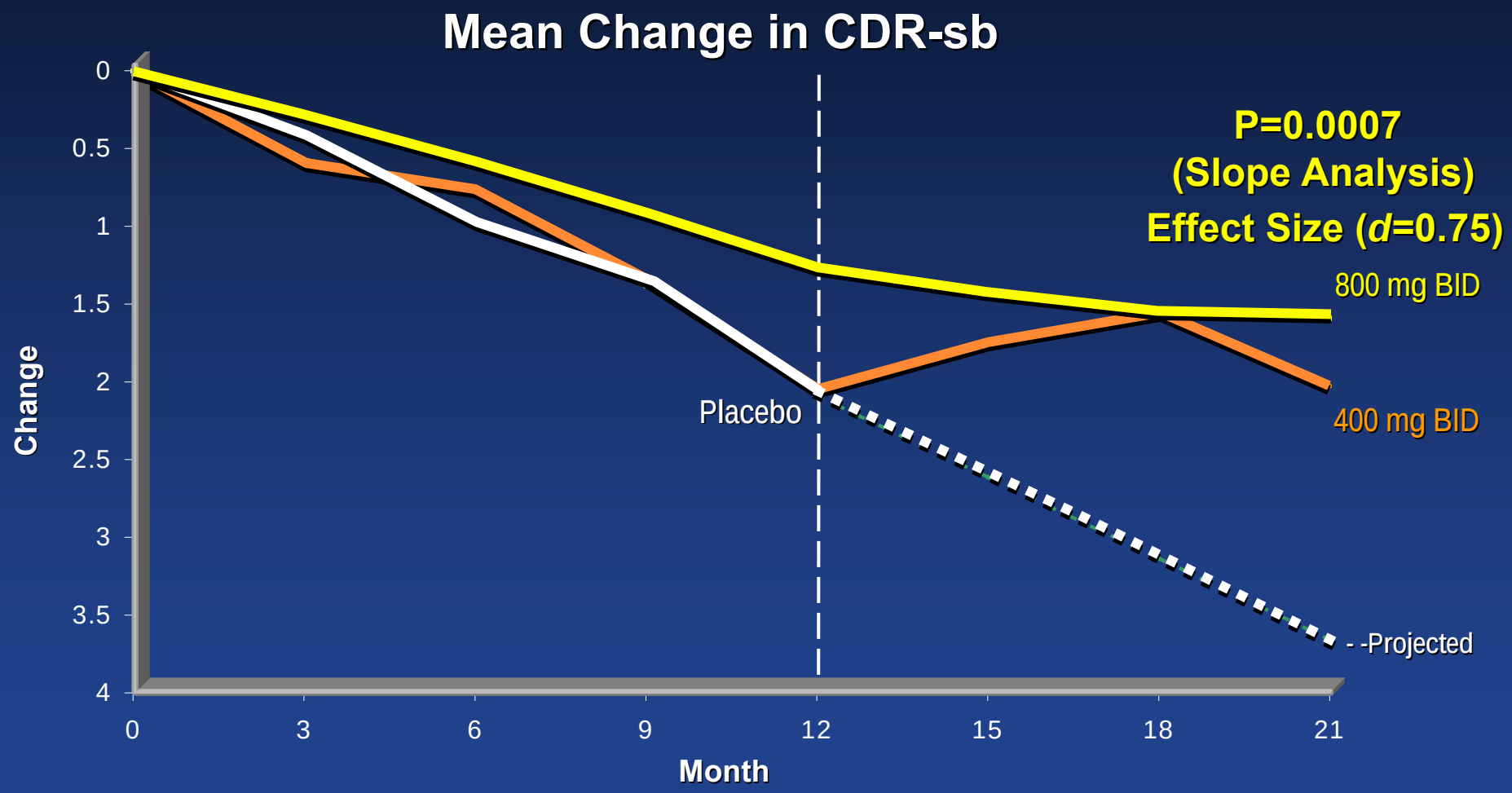
Global Function—Mild Subjects*

Observed Cases (Including 21 month follow-on)



*MMSE ≥ 20 at Baseline

MPC-7869

Conclusions: Phase 2 Study

- 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

Slides will be available at www.myriad.com