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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*Disclosure: In the past year, SEB has been a consultant/CME speaker and/or received research support from Eisai, Janssen-Ortho, Lundbeck, Myriad Pharmaceuticals, Novartis, Pfizer, and Sanofi-Aventis.

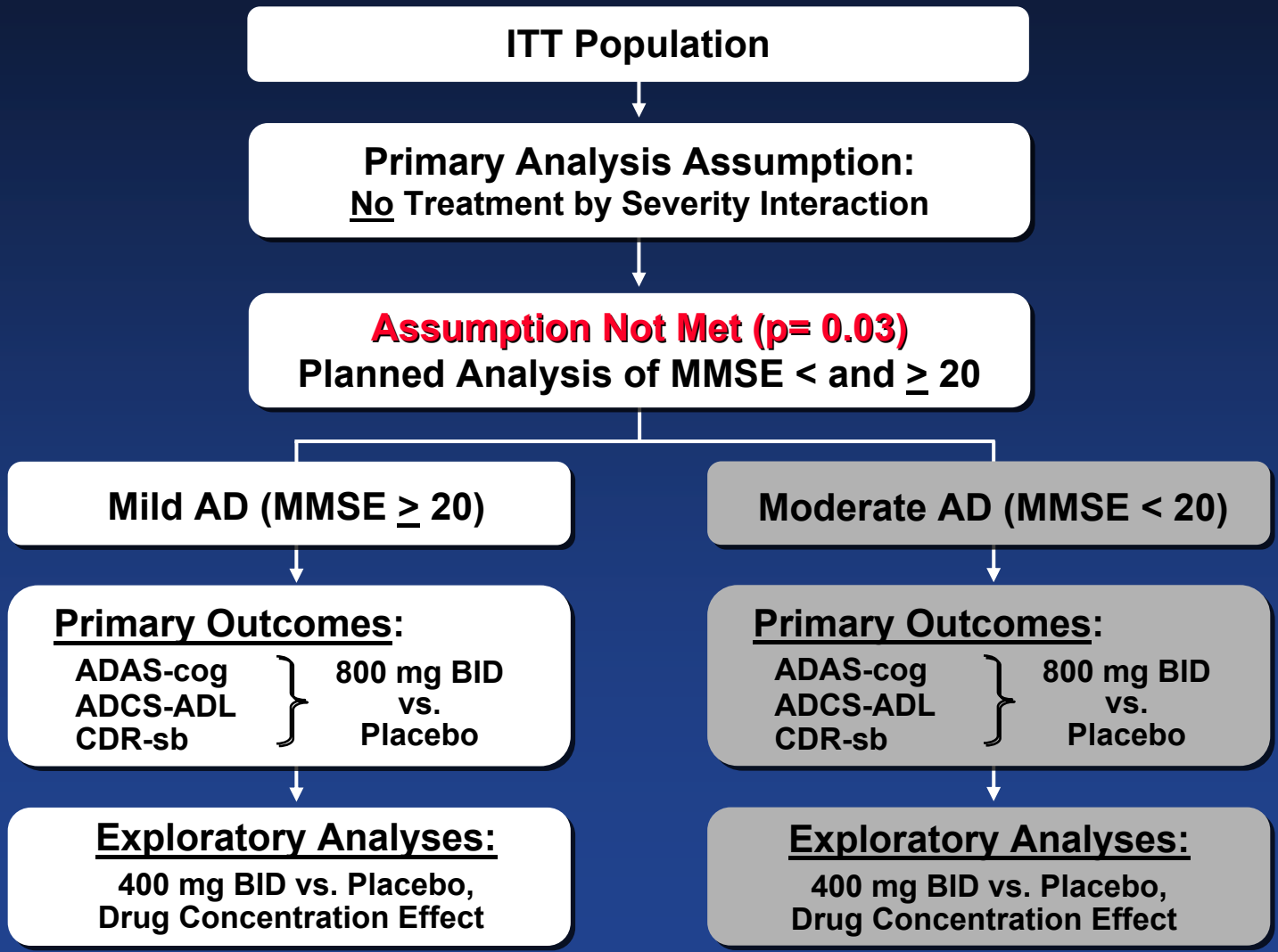
MPC-7869 Clinical Rationale

- 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-centre, 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

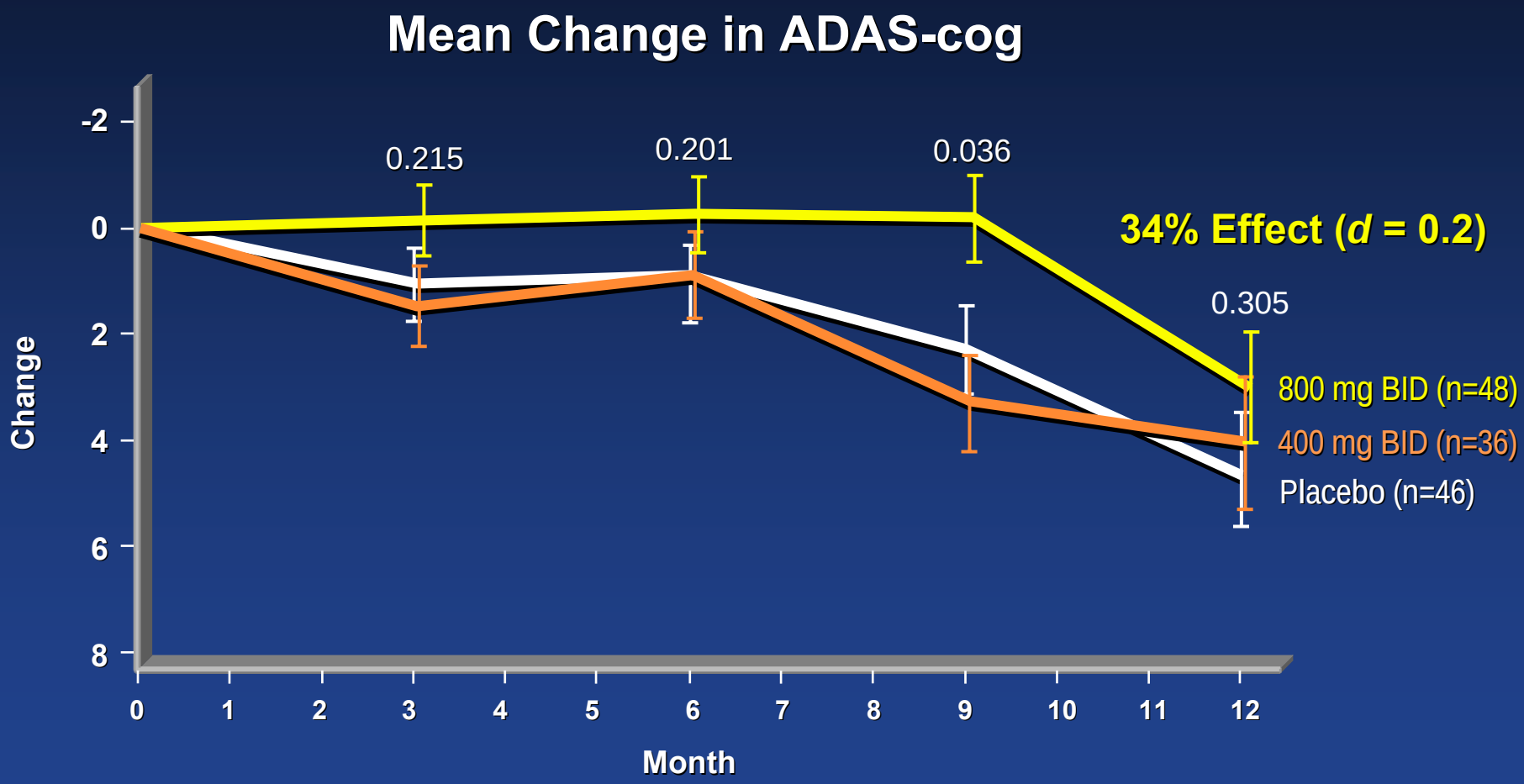


Baseline Characteristics in Mild AD(MMSE ≥20)

	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

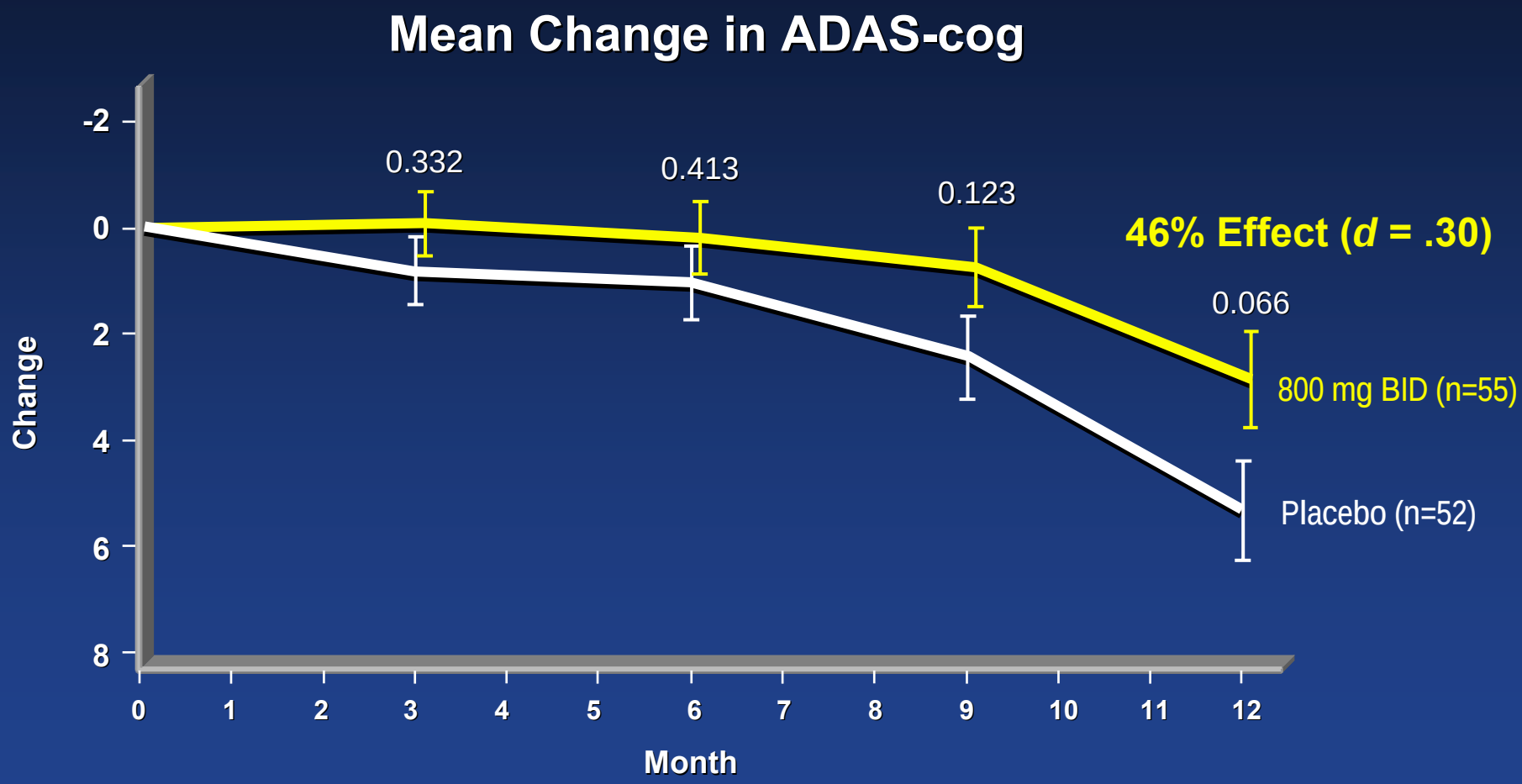
Cognition—Mild Subjects*

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



*MMSE ≥ 20 Score Patients Over Time, LOCF

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



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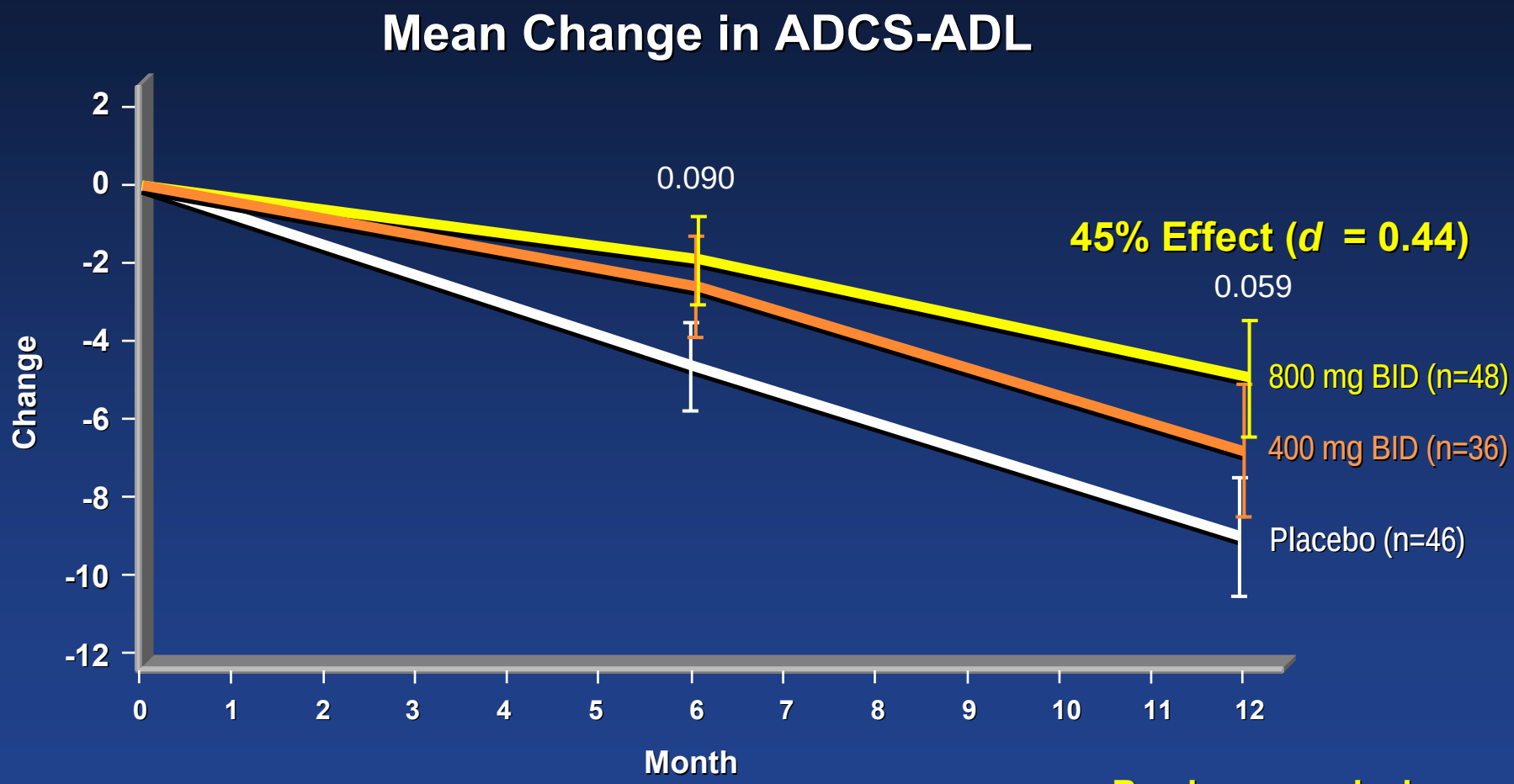
Activities of Daily Living—Mild Subjects*



*MMSE ≥ 20 Score Patients Over Time, LOCF

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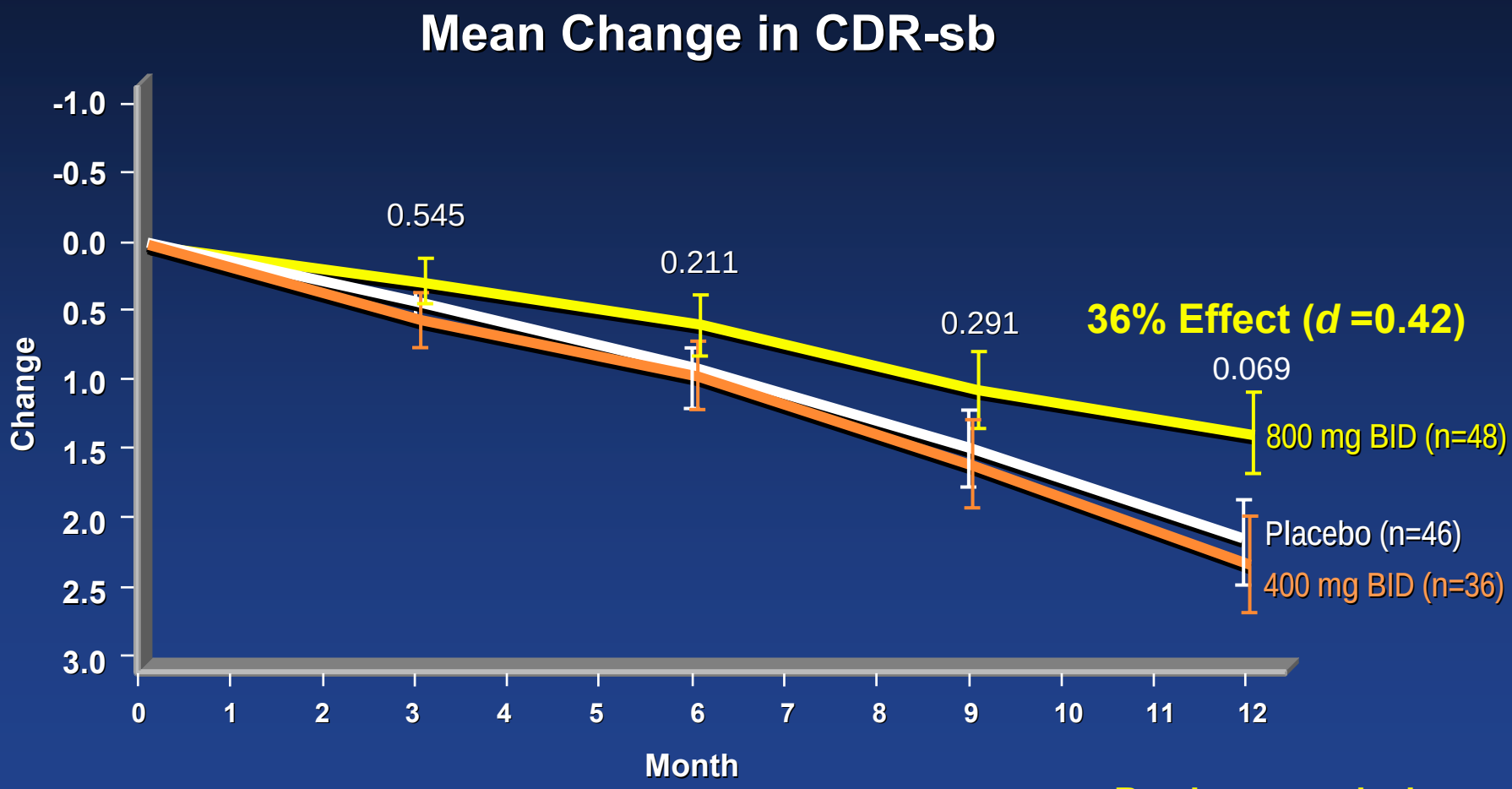
Global Function—Mild Subjects*



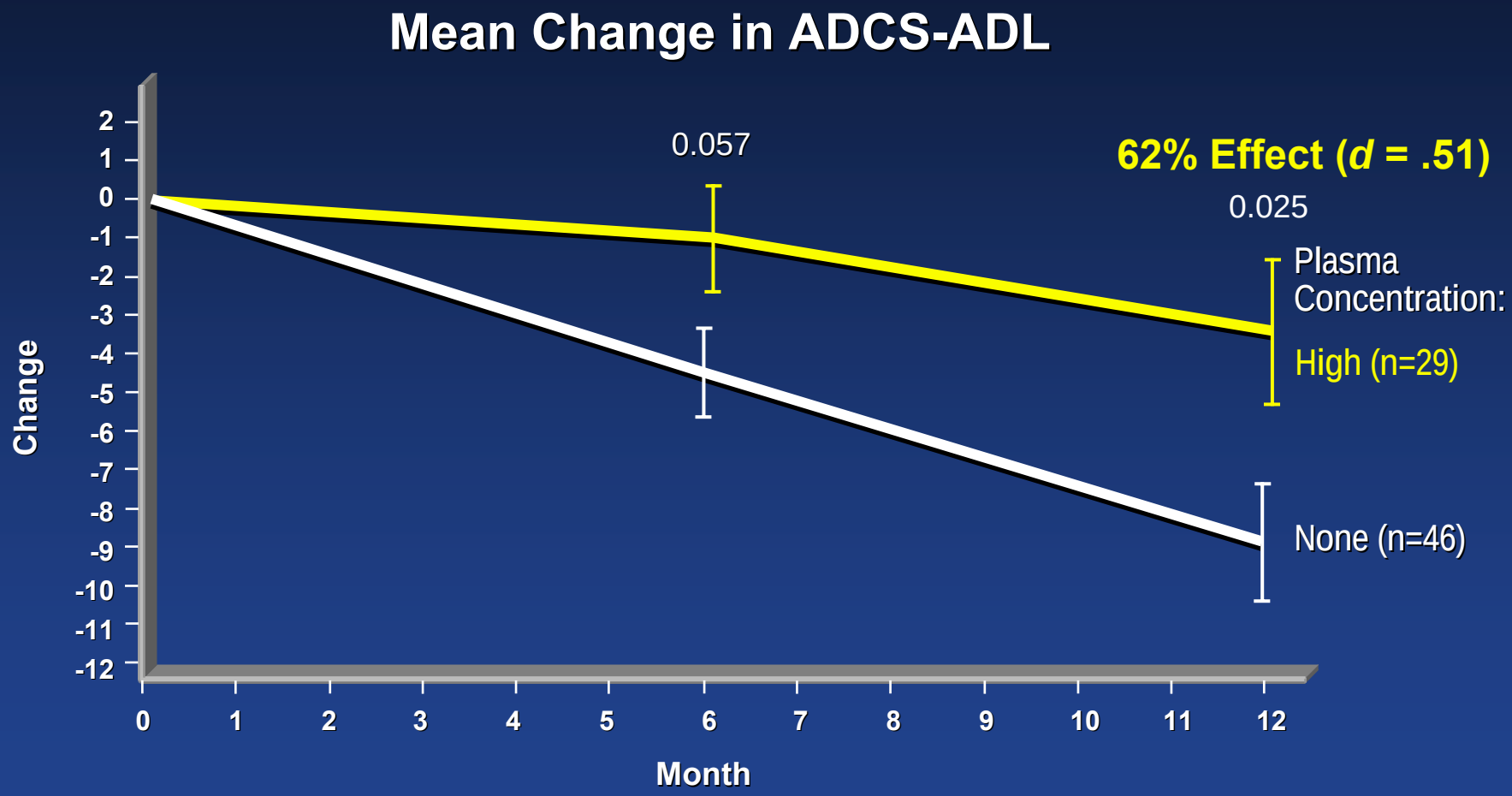
By slopes analysis: p=0.042

*MMSE ≥ 20 Score Patients Over Time, LOCF

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



*MMSE ≥ 20 Score Patients Over Time, LOCF

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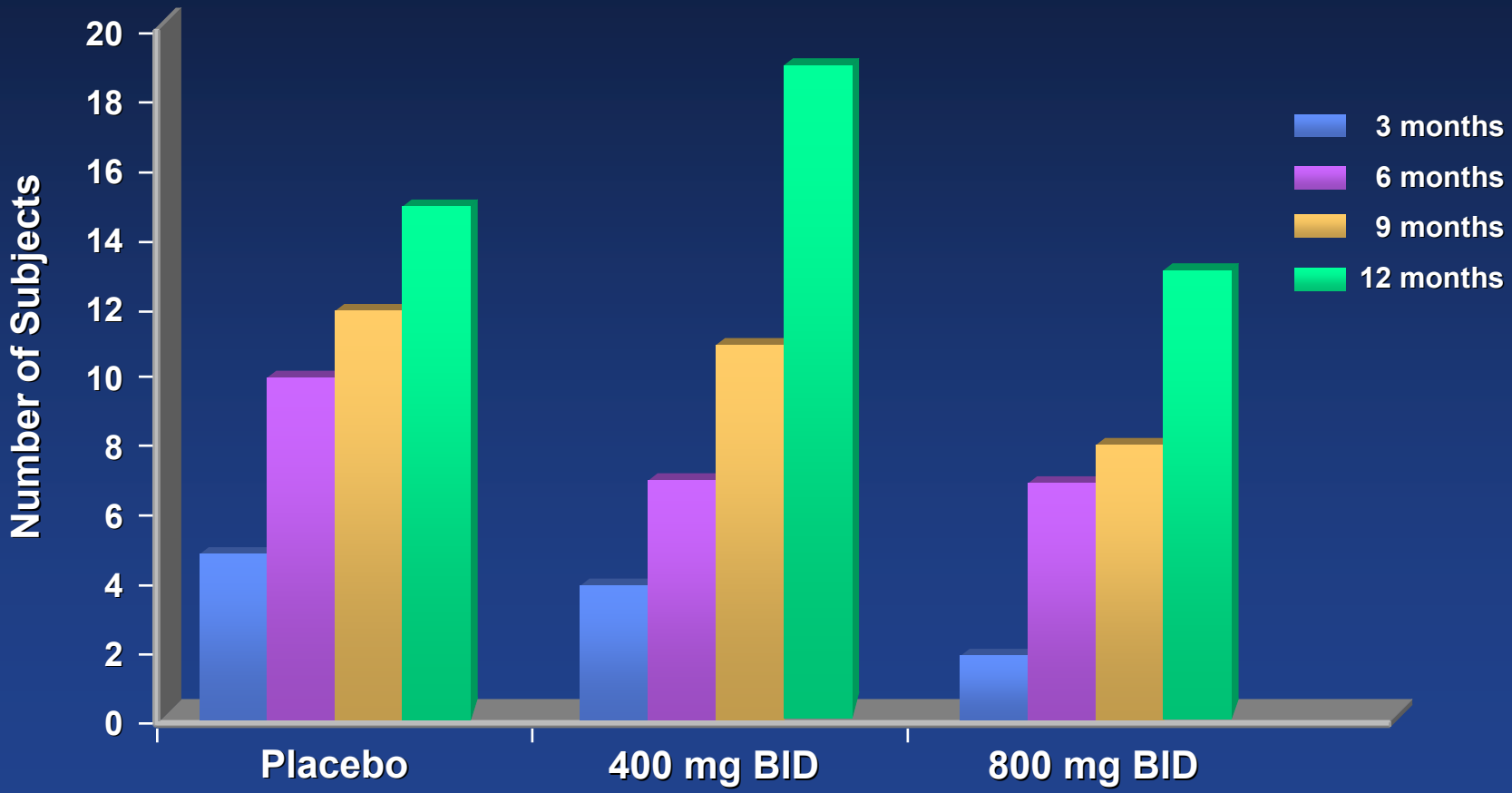
Safety Summary

- 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, mild rash
- Adverse events (lower frequency than placebo)
  - urinary incontinence, psychiatric events

Cumulative Discontinuations Over Time

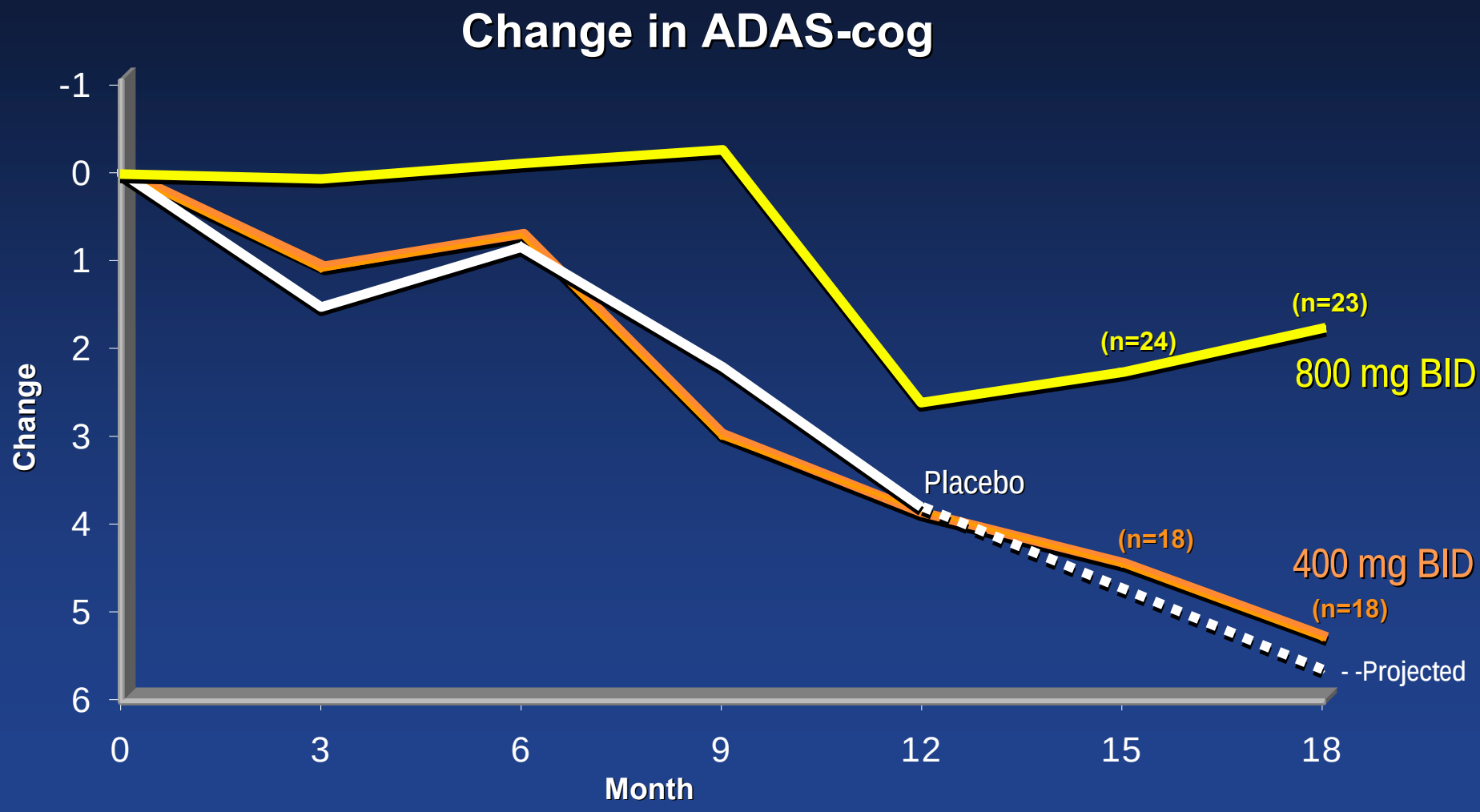


Optional Follow-on Study

- Optional follow-on study available to subjects in Canada
- 86 of 106 eligible subjects enrolled for additional 12 months treatment
  - Placebo subjects randomized to 400mg or 800mg BID
  - 400mg and 800mg BID subjects continue treatment
- Treatment groups remain blinded to subject/investigator
- 18 month ADAS-cog data available

Cognition—Mild Subjects*

Observed Cases (Including 18 month follow-on)



*MMSE ≥ 20 at Baseline

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Conclusions

Phase 2 Summary:

- Mild subjects benefited; moderate subjects did not
- At 12 months, mild AD subjects on 800 mg BID showed
  - statistically significant benefits in Activities of Daily Living and Global Function (slope analysis)
  - Positive trends in Cognition
- Good tolerability, no significant safety concerns

Follow-on study (blinded to dose) at 18 months

- 800 mg BID continues to show benefit