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

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*Disclosure: In the past 3 years, GKW has been a paid consultant for Eisai, Johnson & Johnson, Lundbeck, Marix Drug Development, Myriad Pharmaceuticals, Novartis, Pfizer, and Shire.

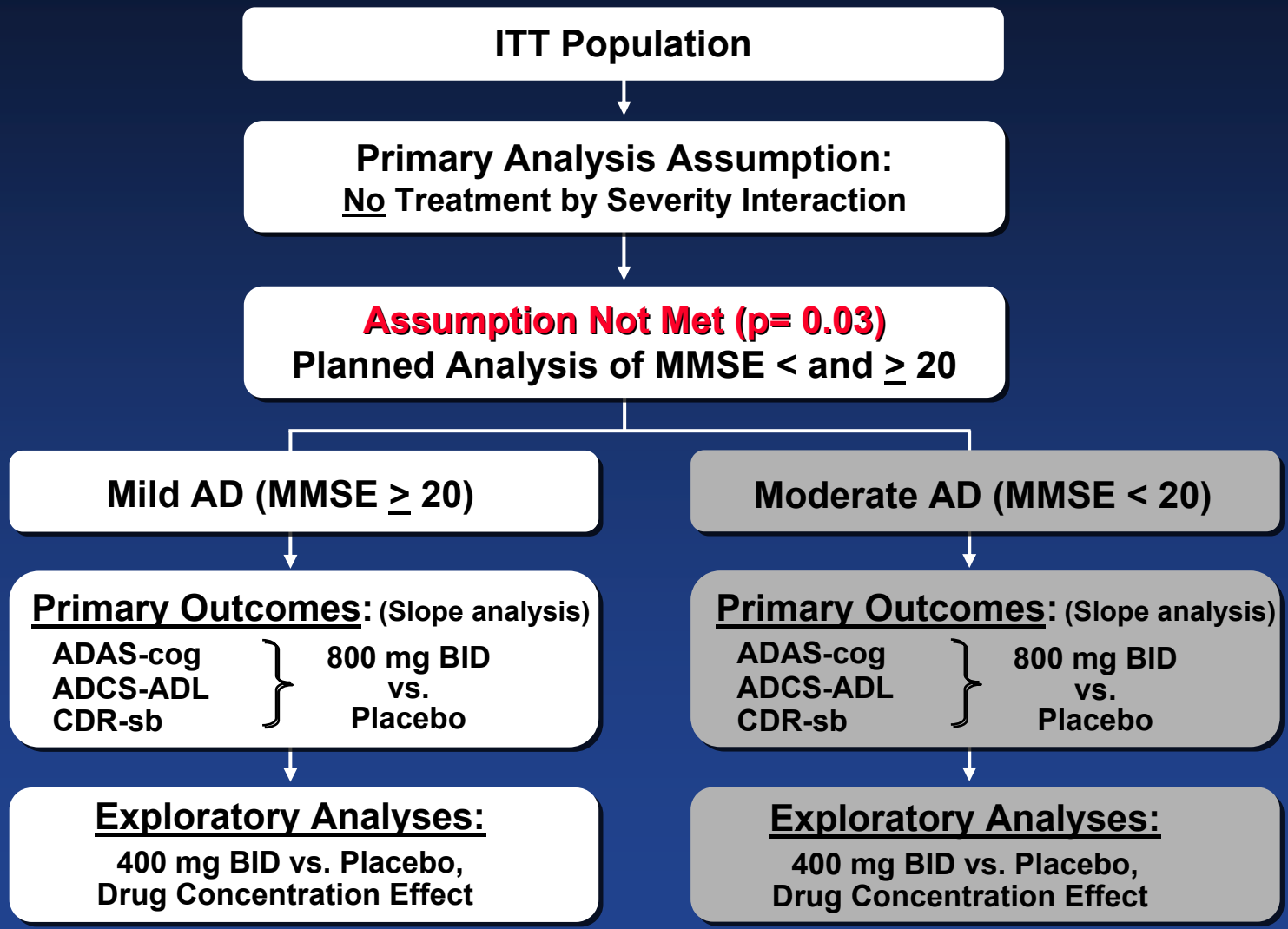
# MPC-7869 Clinical Rationale

- Selective Aβ42-Lowering Agent (SALA) *in vitro & in vivo*
  - Allosteric modulation of γ-secretase, not inhibition
- 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)

- 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 study / stable AChEI allowed
- ADAS-cog; ADCS-ADL;CDR Sum of Boxes
- Optional 1 year follow-on study available in Canada

# Pre-specified Statistical Analysis Plan

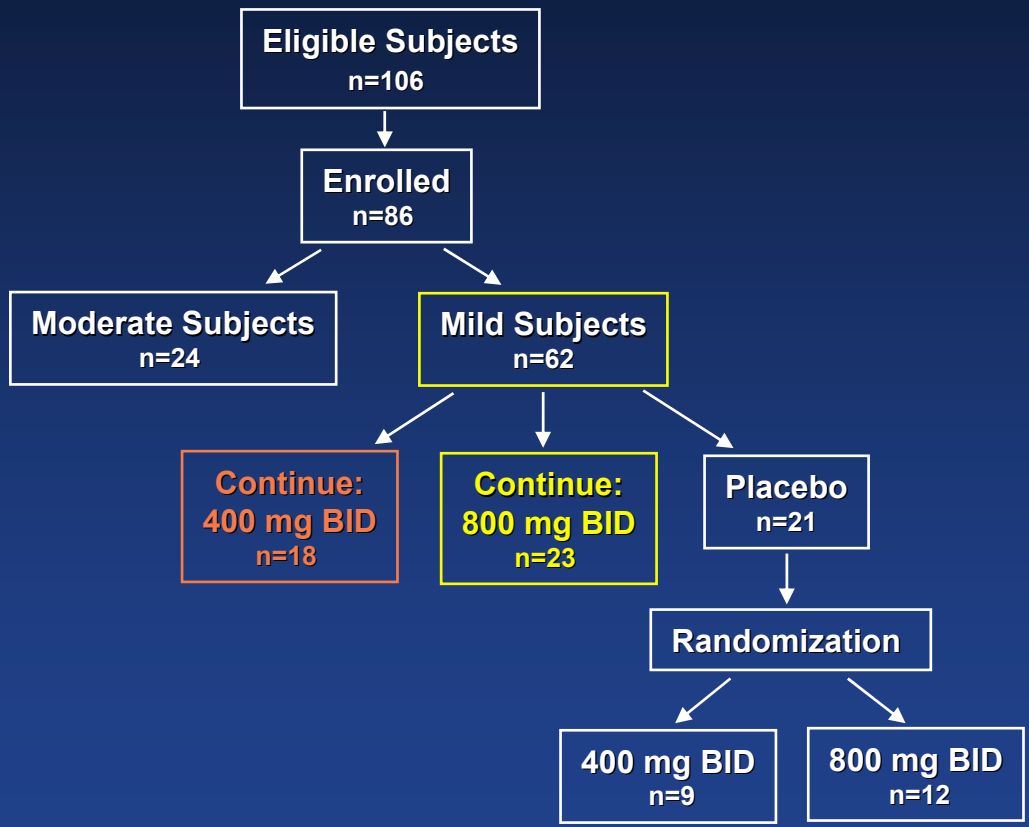


# Mean Baseline Characteristics in Mild AD (MMSE ≥20)

| | 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 | 58.9 | 61.4 | 59.8 |
| CDR-sb | 5.7 | 5.0 | 6.0 |

# Optional 12 Month Follow-on Study

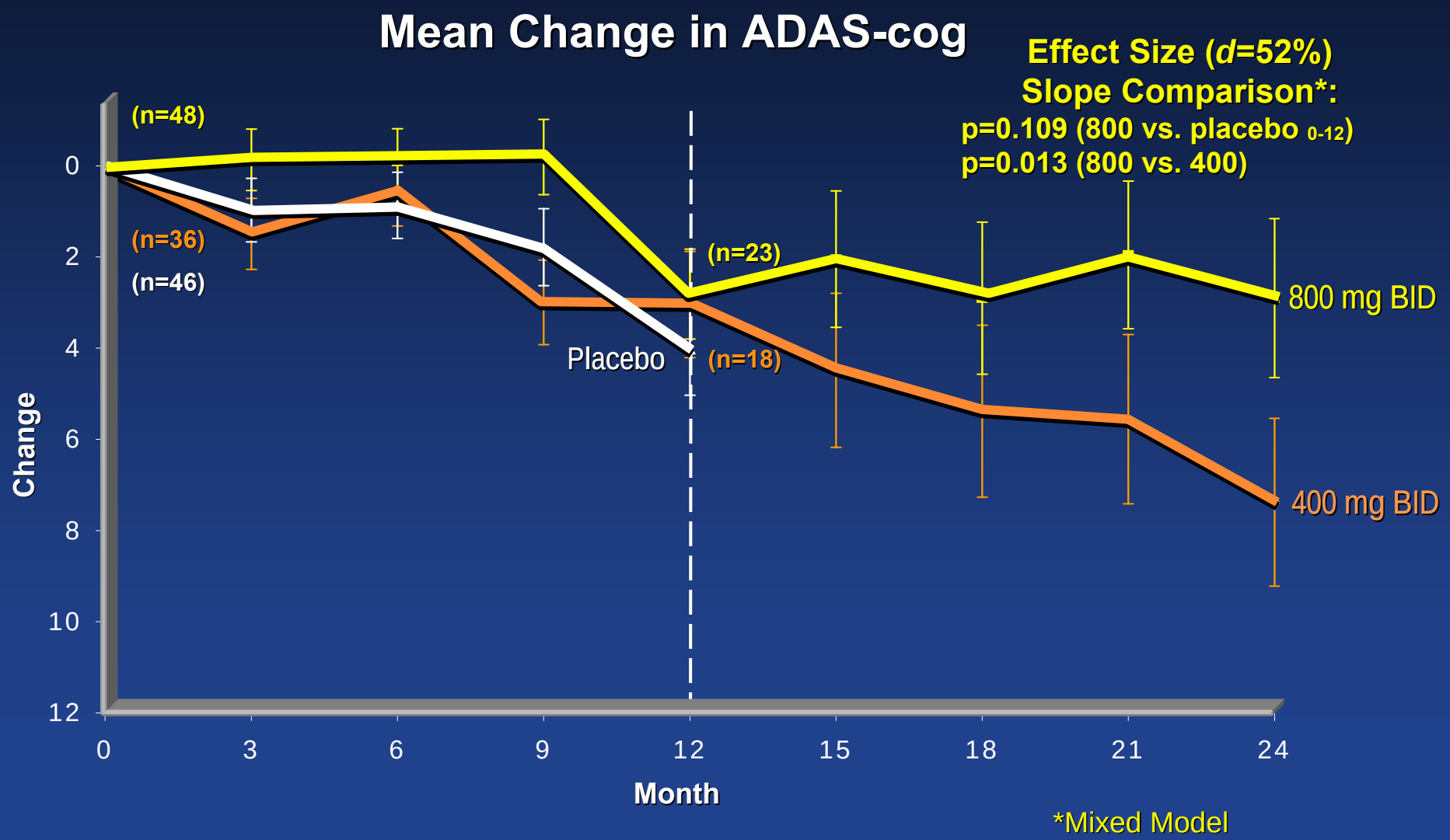
- Treatment groups remained blinded to subject/investigator




- Study Complete, Database Lock June 27, 2006
- Preliminary 24 month analysis

# Cognition—Mild Subjects (MMSE ≥ 20 at Baseline)

## ITT analysis



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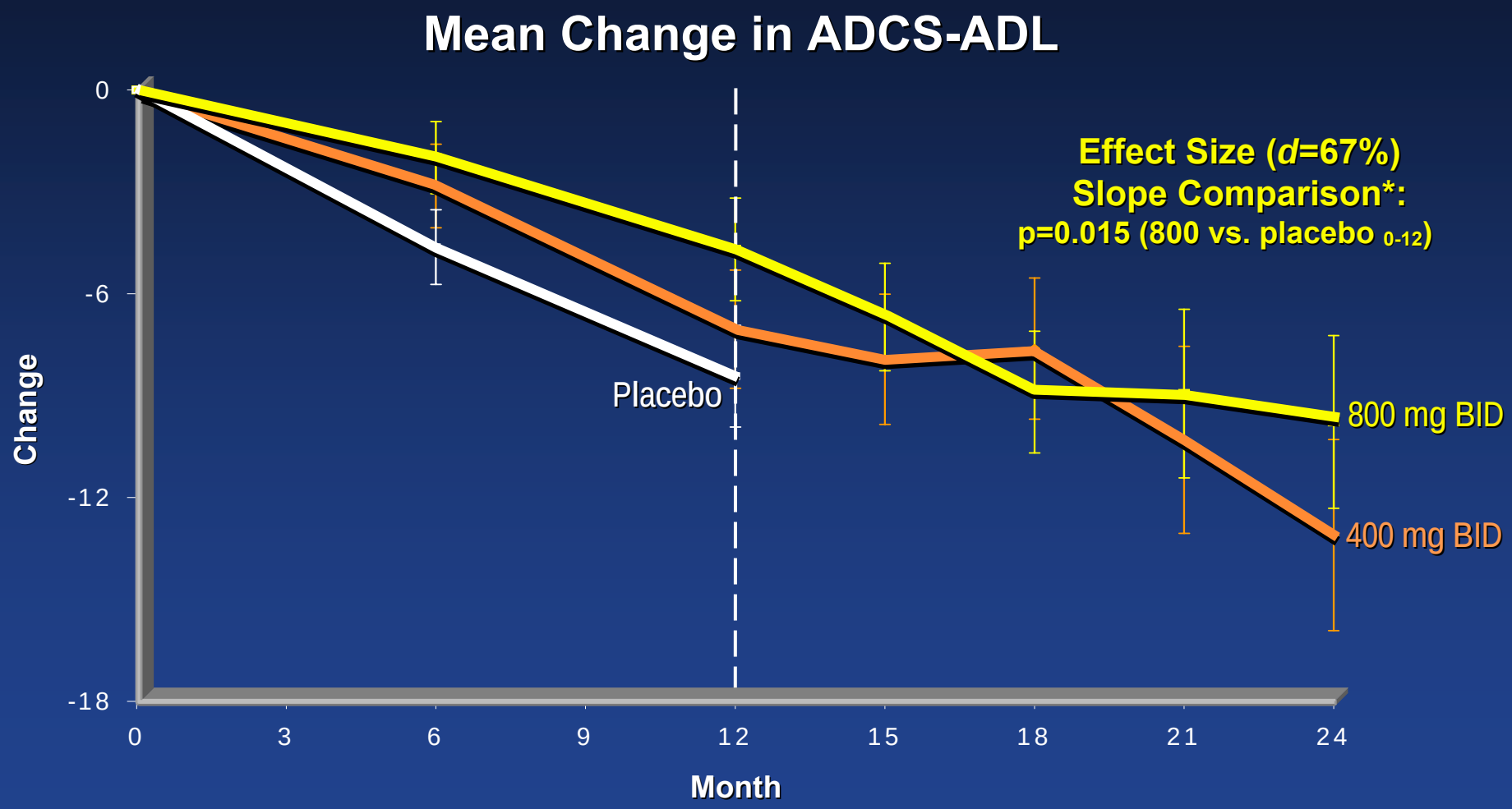
# Activities of Daily Living—Mild Subjects

(MMSE ≥ 20 at Baseline) **ITT analysis**




*Mixed Model



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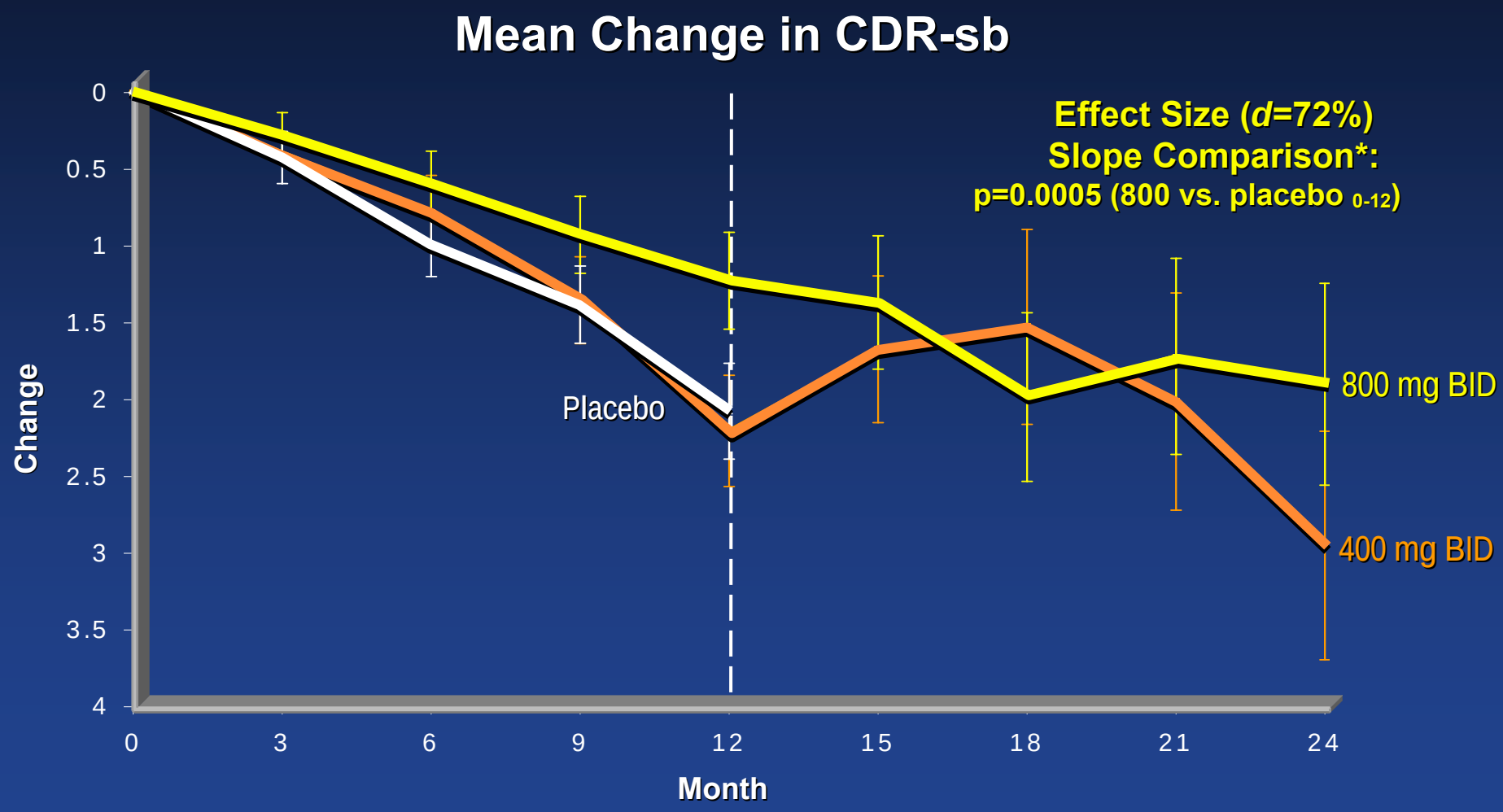
# Global Function—Mild Subjects

## (MMSE ≥ 20 at Baseline) ITT analysis




*Mixed Model



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# Placebo Patients Re-randomized to Drug at 12 months ("Randomized Start")

- Patients treated for 24 months decline more slowly than those treated for only 12 months
  - Consistent with hypothesis for a disease modifying treatment

## Annual Decline Rate Over 24 Months

| | 24 months treatment at: | | 12 months placebo randomized to: | |
|---|---|---|---|---|
| | 400 mg BID (n=36) | 800 mg BID (n=48) | 400 mg BID (n=9) | 800 mg BID (n=12) |
| ADAS-cog | 3.72* | 2.20* | 6.30 | 5.67 |
| ADCS-ADL | -6.41 | -5.16* | -9.15 | -9.56 |
| CDR-sb | 1.45 | 1.12* | 1.93 | 1.44 |

*p<0.01, 24 vs. 12 months treatment

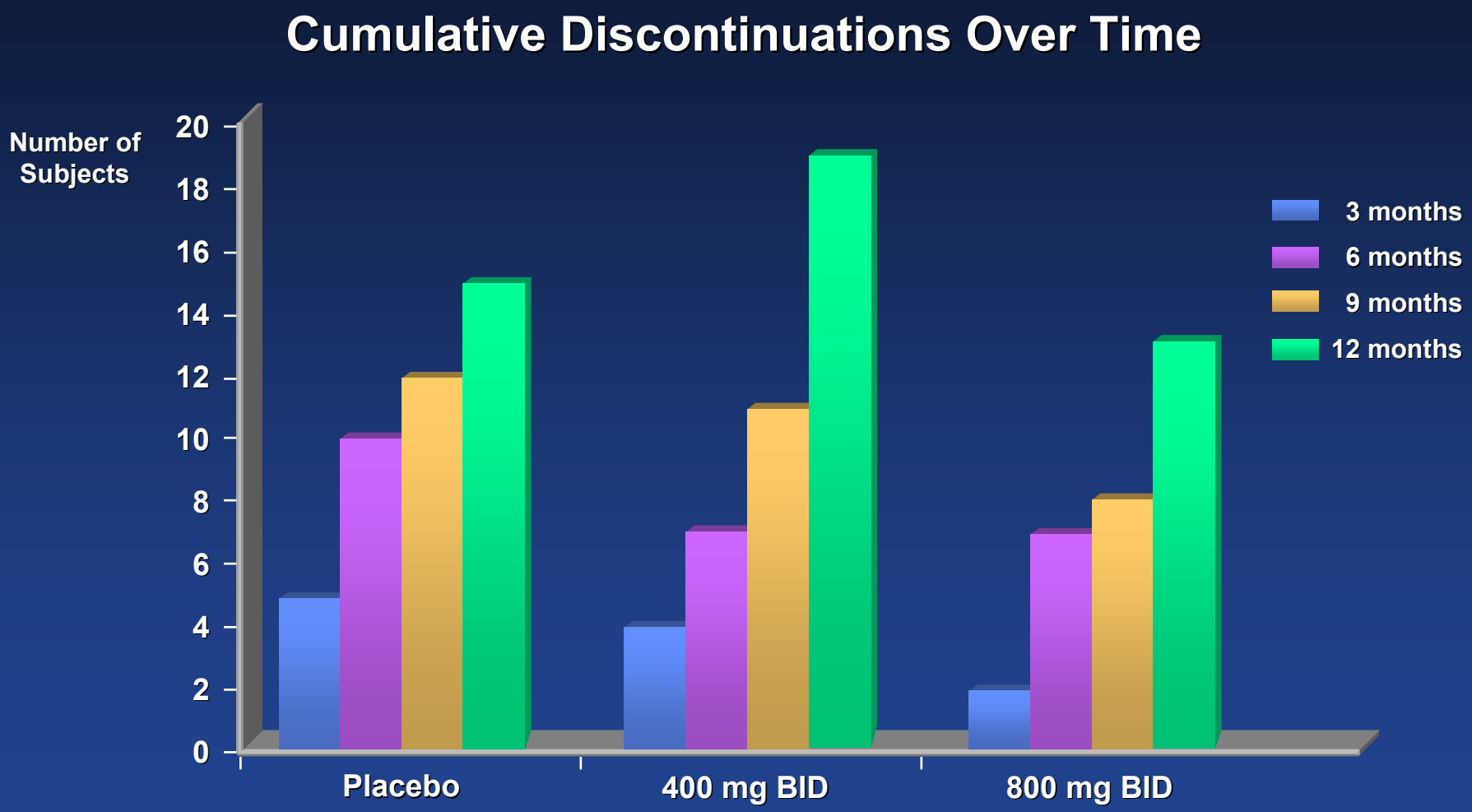
# Exploratory: Drug Concentration Effect

- Patients who achieved a higher concentration* had a significantly better response

| | p-values | |
|---|---|---|
| | $C_{max}$ | AUC |
| ADCS-ADL | 0.034 | 0.037 |
| CDR-sb | 0.023 | 0.019 |
| ADAS-cog | 0.289 | 0.291 |

*Population Pharmacokinetic Analysis

# Discontinuations Over Time (ITT)




Overall discontinuations in 12 months ~ 20%

# Most Common AEs Leading to Discontinuation

| MedDRA Body System | Placebo (n=66) | 400 mg BID (n=71) | 800 mg BID (n=70) | Total (n=207) |
|---|---|---|---|---|
| Gastrointestinal | 3 (4.5%) | 2 (2.8%) | 2 (2.9%) | 7 (3.4%) |
| Metabolism and nutrition | 1 (1.5%) | 2 (2.8%) | 2 (2.9%) | 5 (2.4%) |
| Psychiatric | 3 (4.5%) | 0 | 2 (2.9%) | 5 (2.4%) |

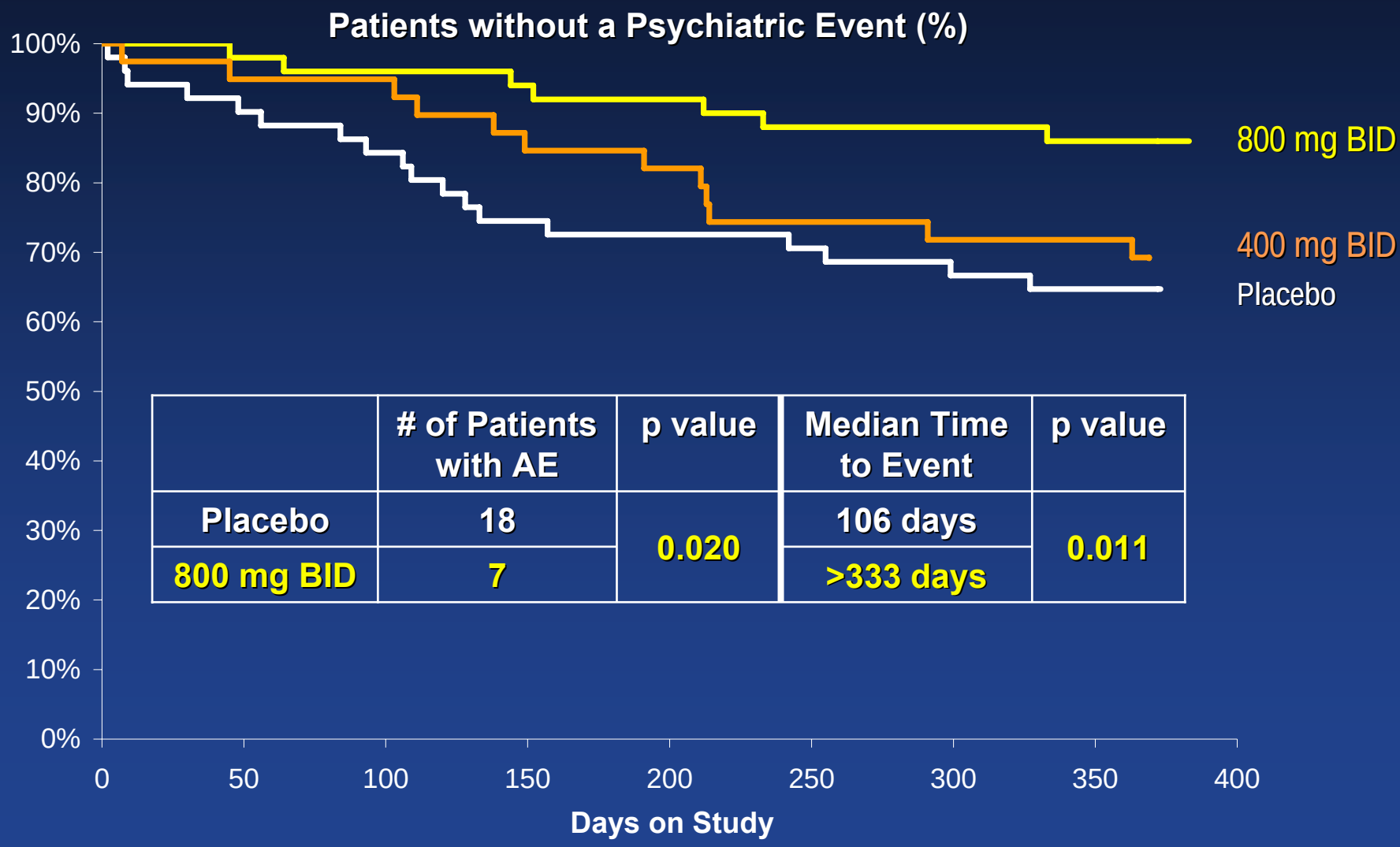
# Discontinuations Due to Disease Progression

| | Placebo | 400 mg BID | 800 mg BID |
|---|---|---|---|
| All patients | 6 (9.1%) | 2 (2.8%) | 1 (1.4%) |
| Mild patients | 4 (8.7%) | 1 (2.8%) | 0 |

# 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
- Fewer events than placebo
  - urinary incontinence
  - psychiatric events

# Time to Psychiatric Event by Treatment Group (Mild Patients, MMSE ≥ 20)




| | # of Patients with AE | p value | Median Time to Event | p value |
|---|---|---|---|---|
| Placebo | 18 | 0.020 | 106 days | 0.011 |
| 800 mg BID | 7 | | >333 days | |



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# Conclusions

- Subjects with mild AD on 800 mg BID showed a reduced rate of decline (slope)

| | At 12 months | At 24 months |
|---|---|---|
| Activities of Daily Living | d=44% (p=0.033) | d=67% (p=0.015) |
| Global Function | d=42% (p=0.042) | d=72% (p=0.0005) |
| Cognition (positive trend) | d=20% (p=0.327) | d=52% (p=0.109) |

- Positive effects increasing over time on all scales
  - Consistent with a Selective Aβ42-Lowering (SALA) strategy in AD
- Well tolerated up to 24 months

**Confirmatory Phase 3 Studies Ongoing in Mild Patients**