Efficacy and Safety of Tarenflurbil (Flurizan™), a Selective Aβ42-Lowering Agent, in Alzheimer's Disease: A Phase 2 Trial of up to 24 Months of Treatment

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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.

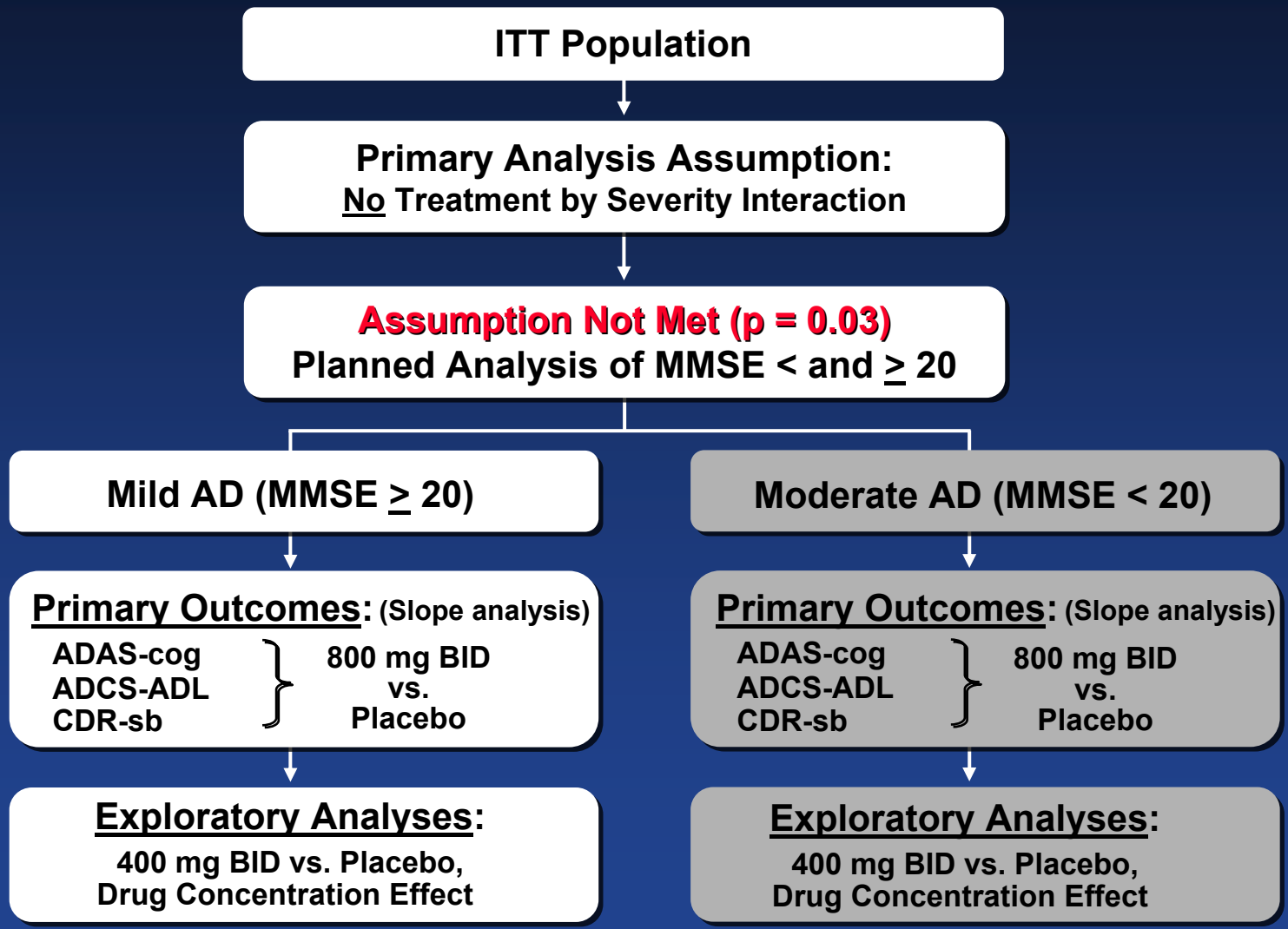
Tarenflurbil Clinical Rationale

- 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 Tarenflurbil 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-month 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

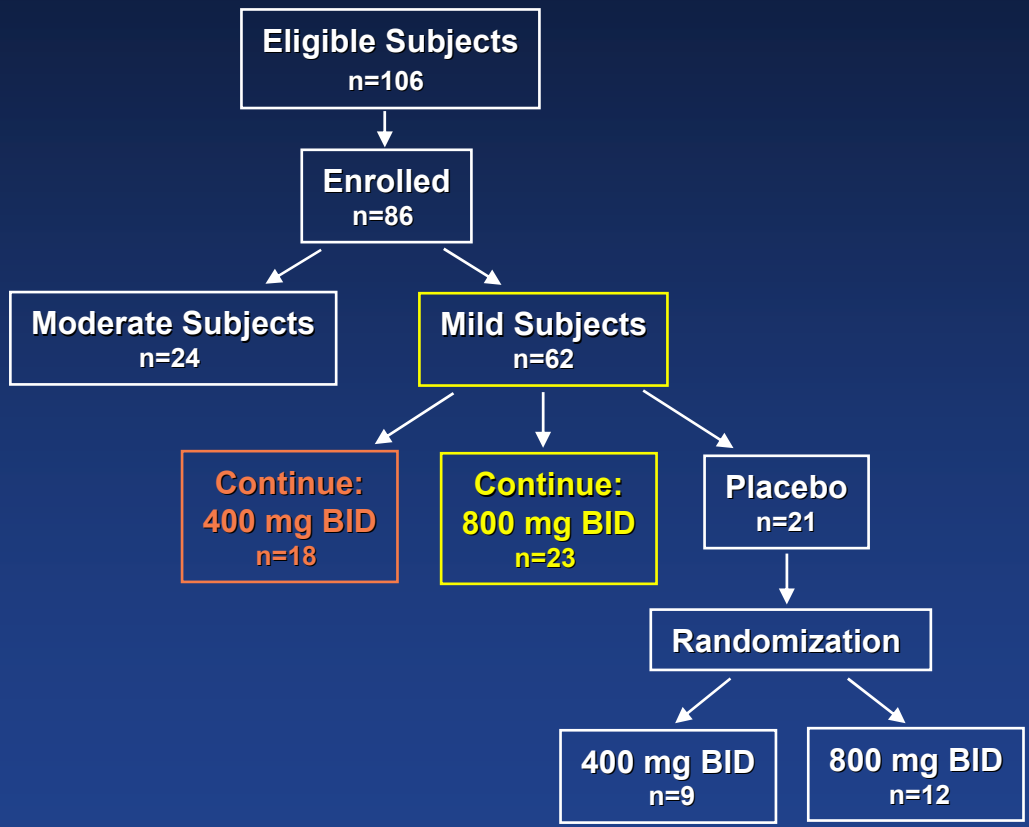


Mean Baseline Characteristics in Mild AD (MMSE ≥20)

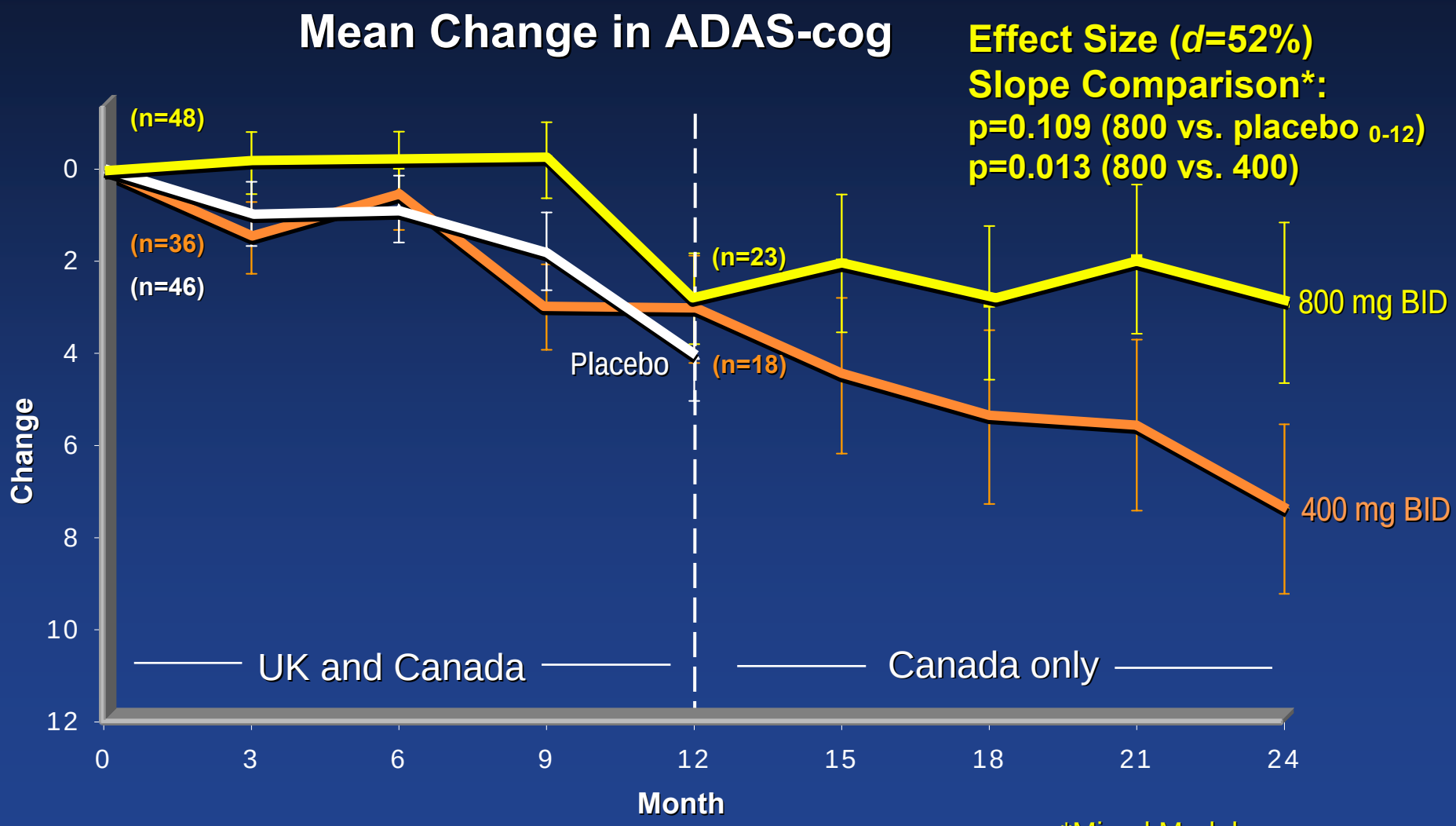
	Placebo (n=46)	400 mg BID (n=36)	800 mg BID (n=48)
% of Total Patients	75%	58%	73%
Age	76	75	76
% AChEI Use	97%	94%	94%
Mean Duration AChEI Use at baseline (months)	16.0	19.7	16.9
MMSE	22.9	23.1	22.8
ADAS-cog (*80 point)	27.5	28.6	28.3
ADCS-ADL	58.9	61.4	59.8
CDR-sb	5.7	5.0	6.0

Optional 12-Month Follow-on Study

- Treatment groups remained blinded to subject/investigator

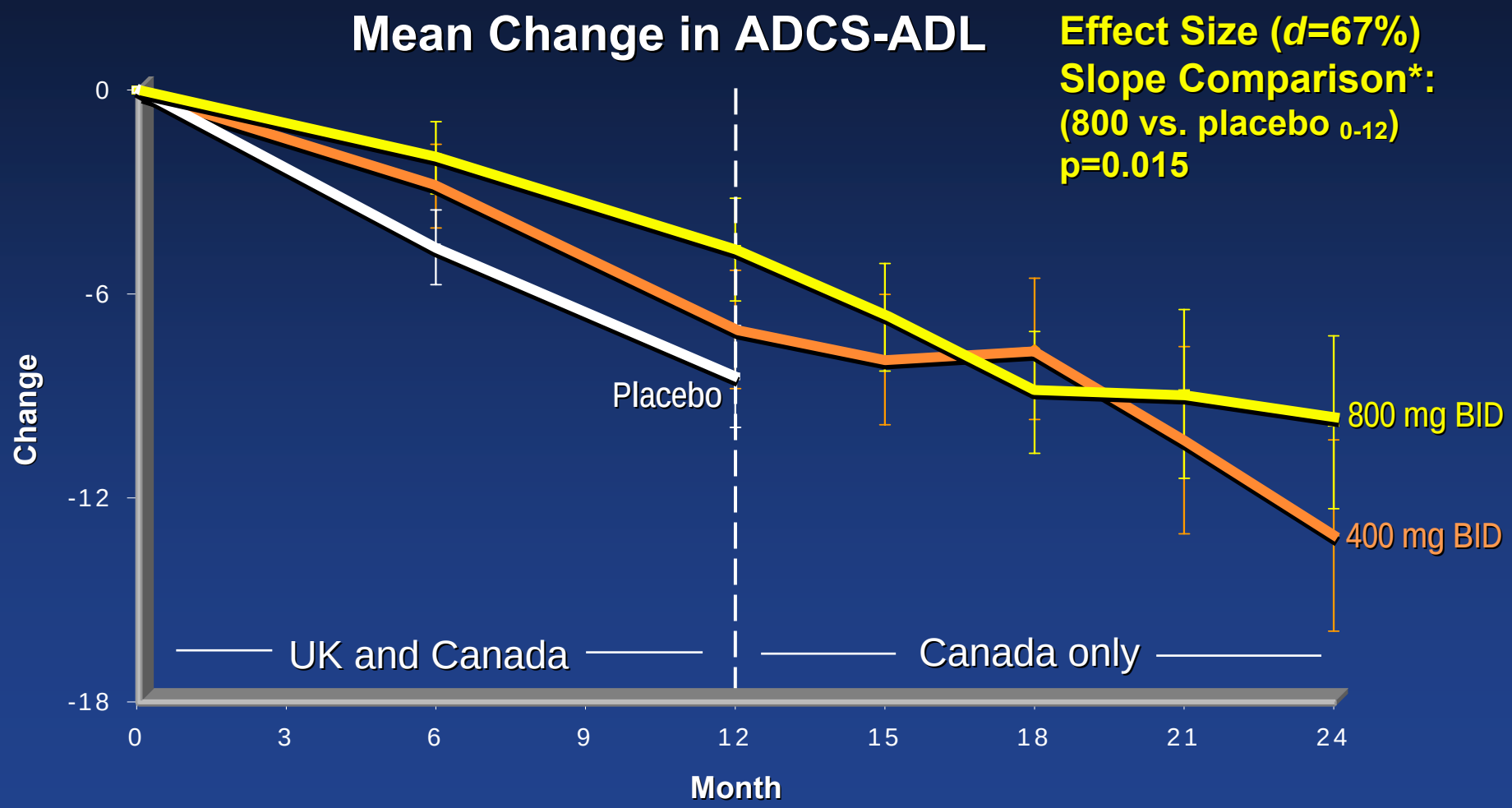


Cognition—Mild Subjects
(MMSE ≥ 20 at Baseline) ITT analysis



*Mixed Model

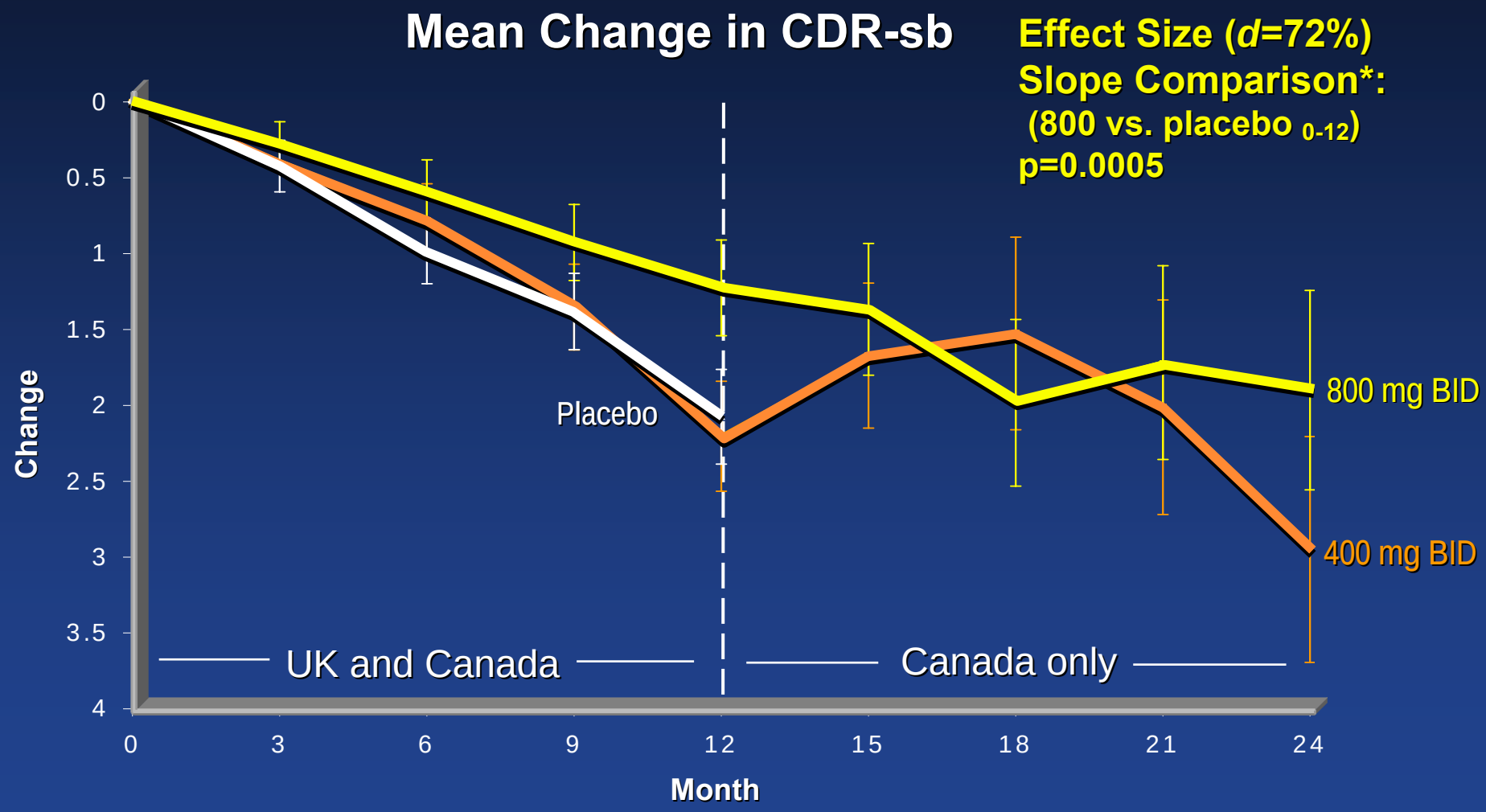
Activities of Daily Living—Mild Subjects
(MMSE ≥ 20 at Baseline) ITT analysis



*Mixed Model

Global Function—Mild Subjects

(MMSE ≥ 20 at Baseline) ITT analysis



*Mixed Model

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

- Patients treated for 24 months decline more slowly than those treated for only 12 months

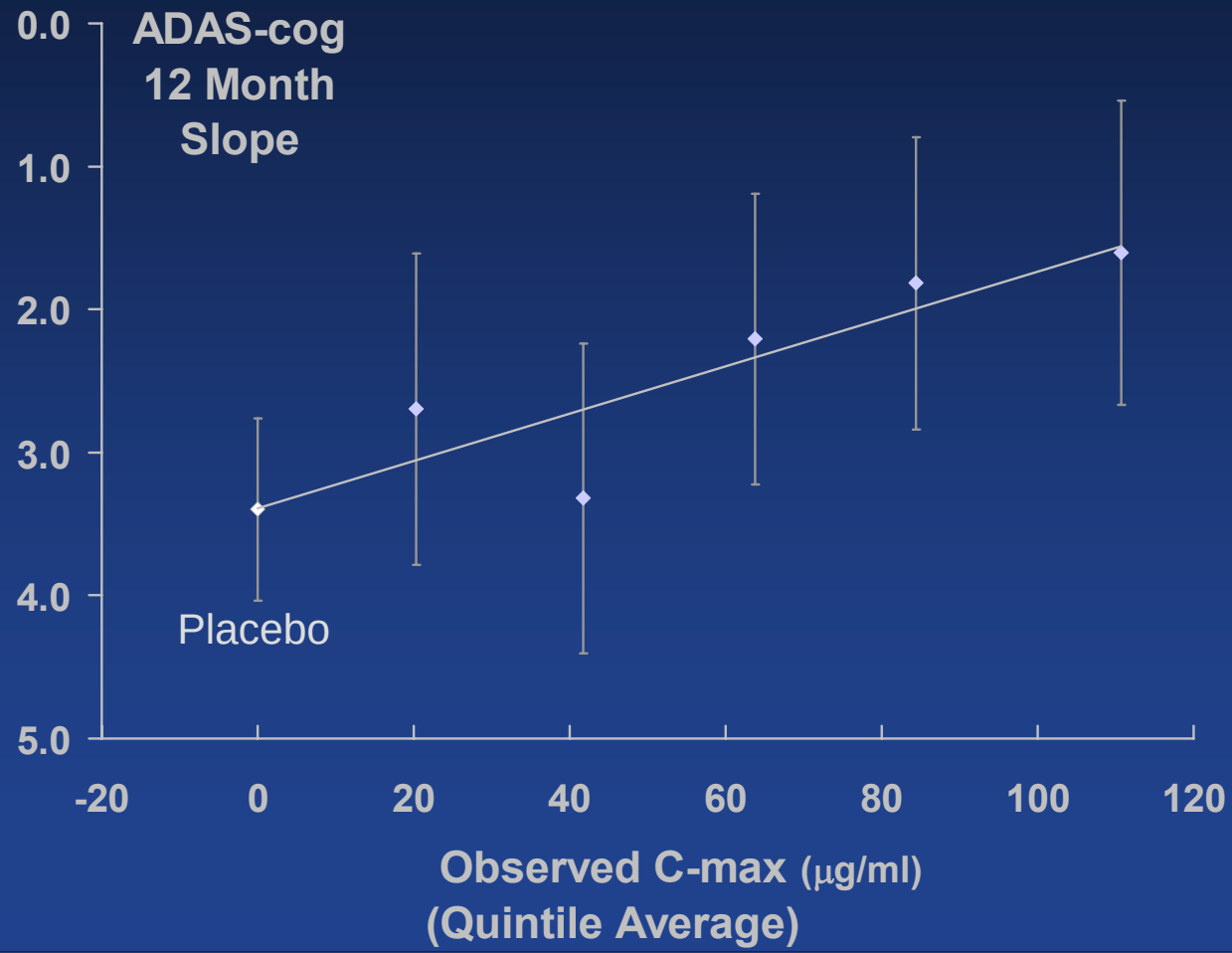
Annual Decline Rate Over 24 Months

	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

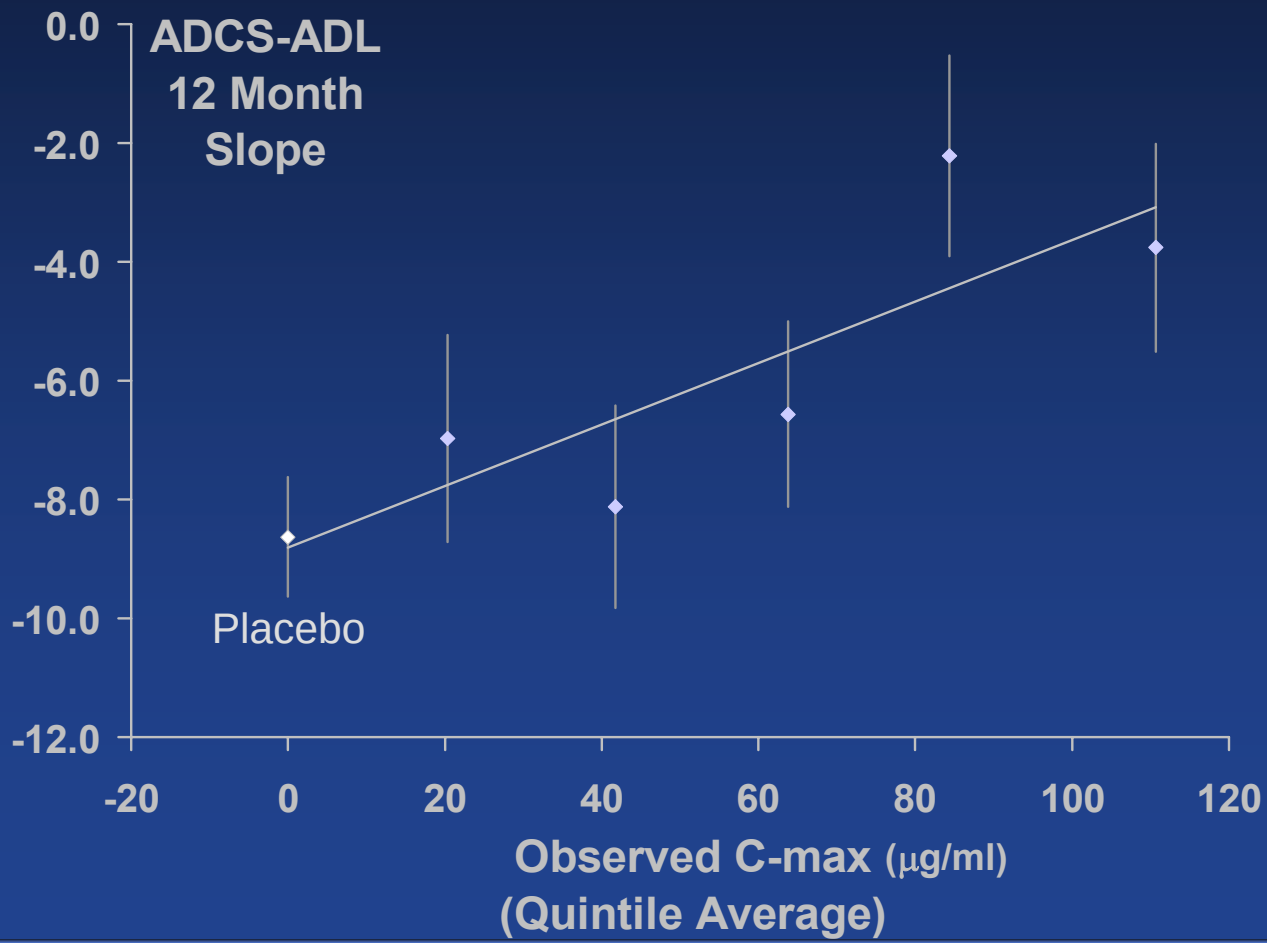
Exploratory Drug Concentration Response: Cognition

- Subjects who achieved a higher plasma concentration (C_{max}) had a better response (p=0.148)



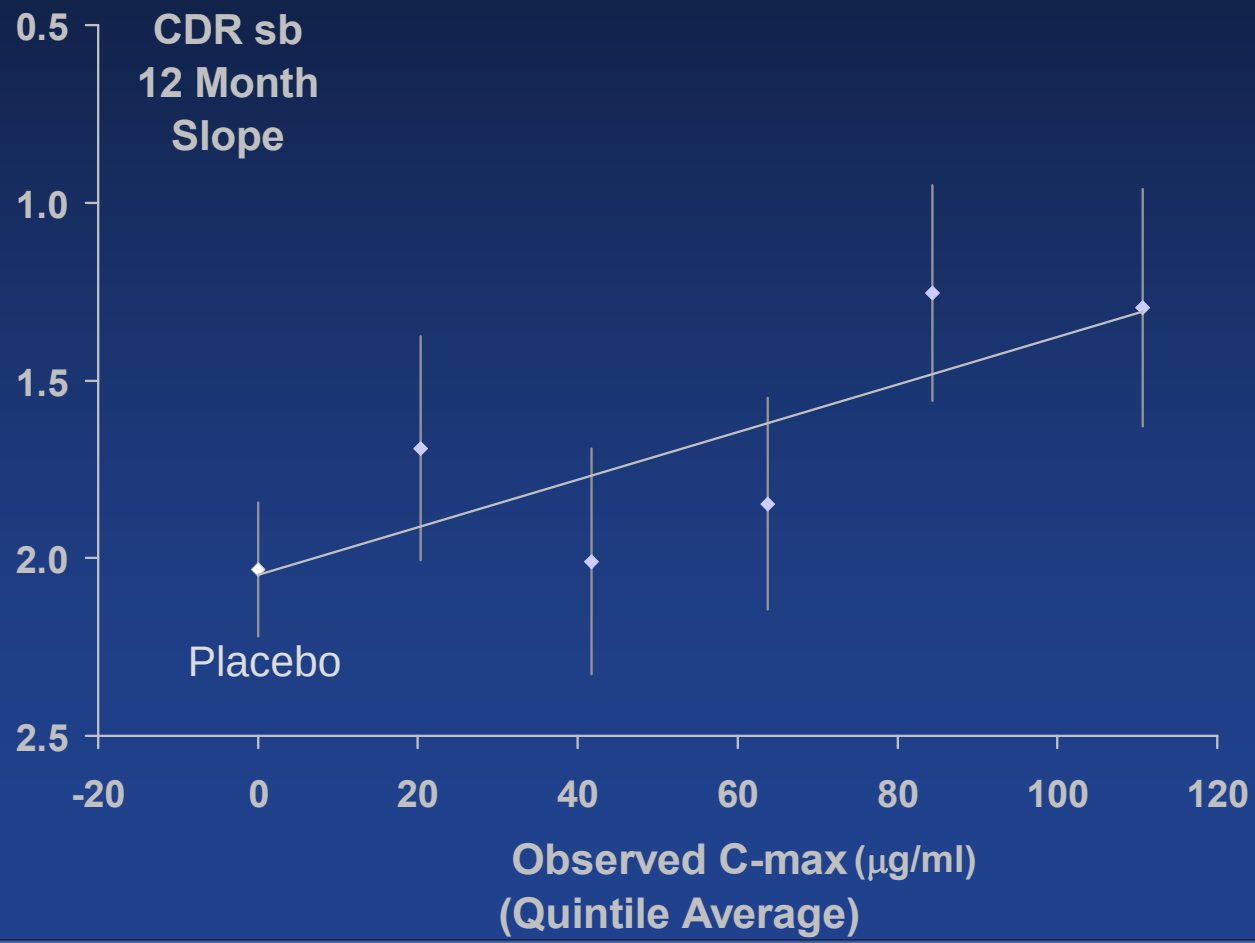
Exploratory Drug Concentration Response: Activities of Daily Living

- Subjects who achieved a higher plasma concentration (C_{max}) had a better response (p=0.027)



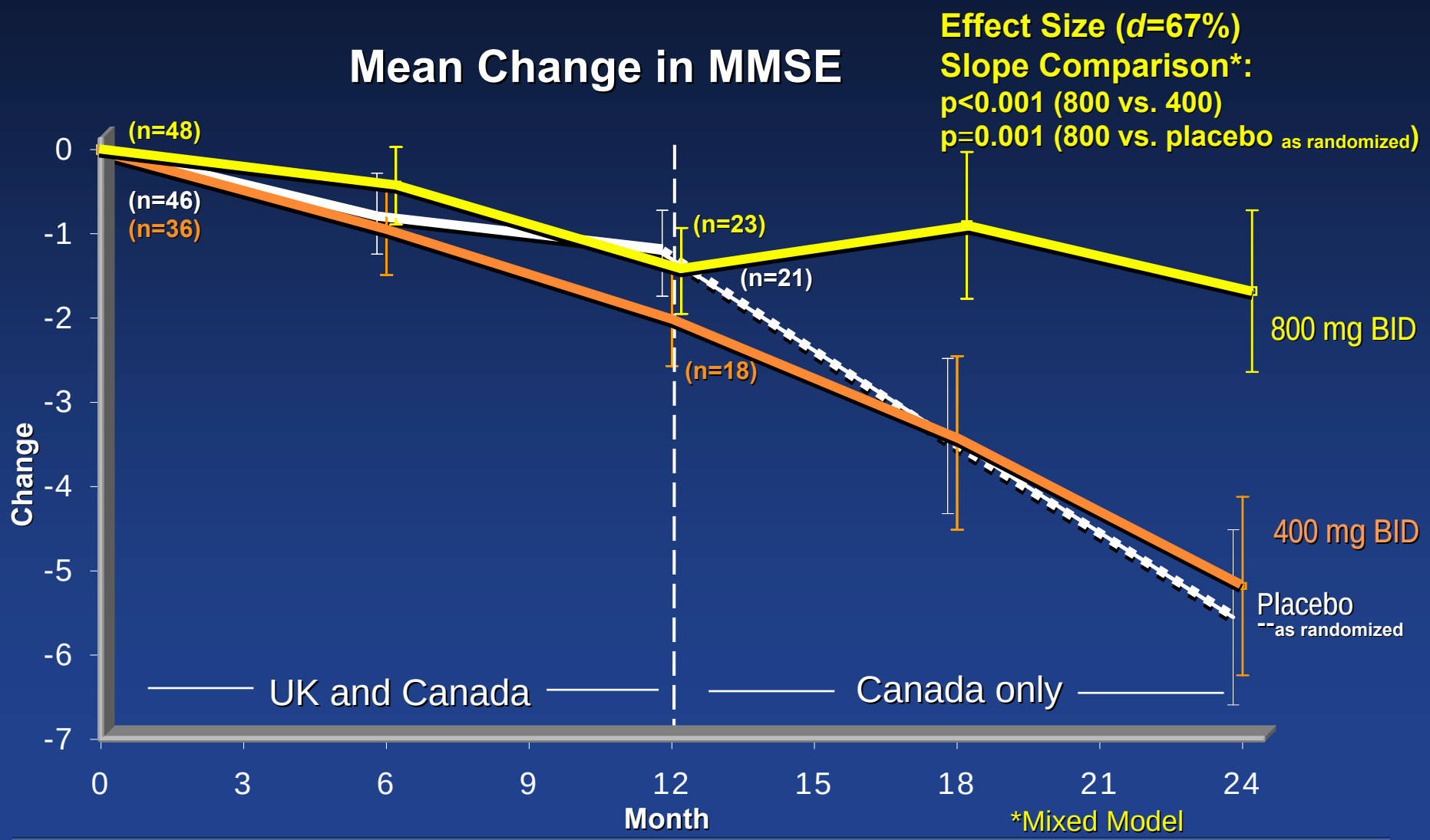
Exploratory Drug Concentration Response: Global Function

- Subjects who achieved a higher plasma concentration (C_{max}) had a better response (p=0.024)

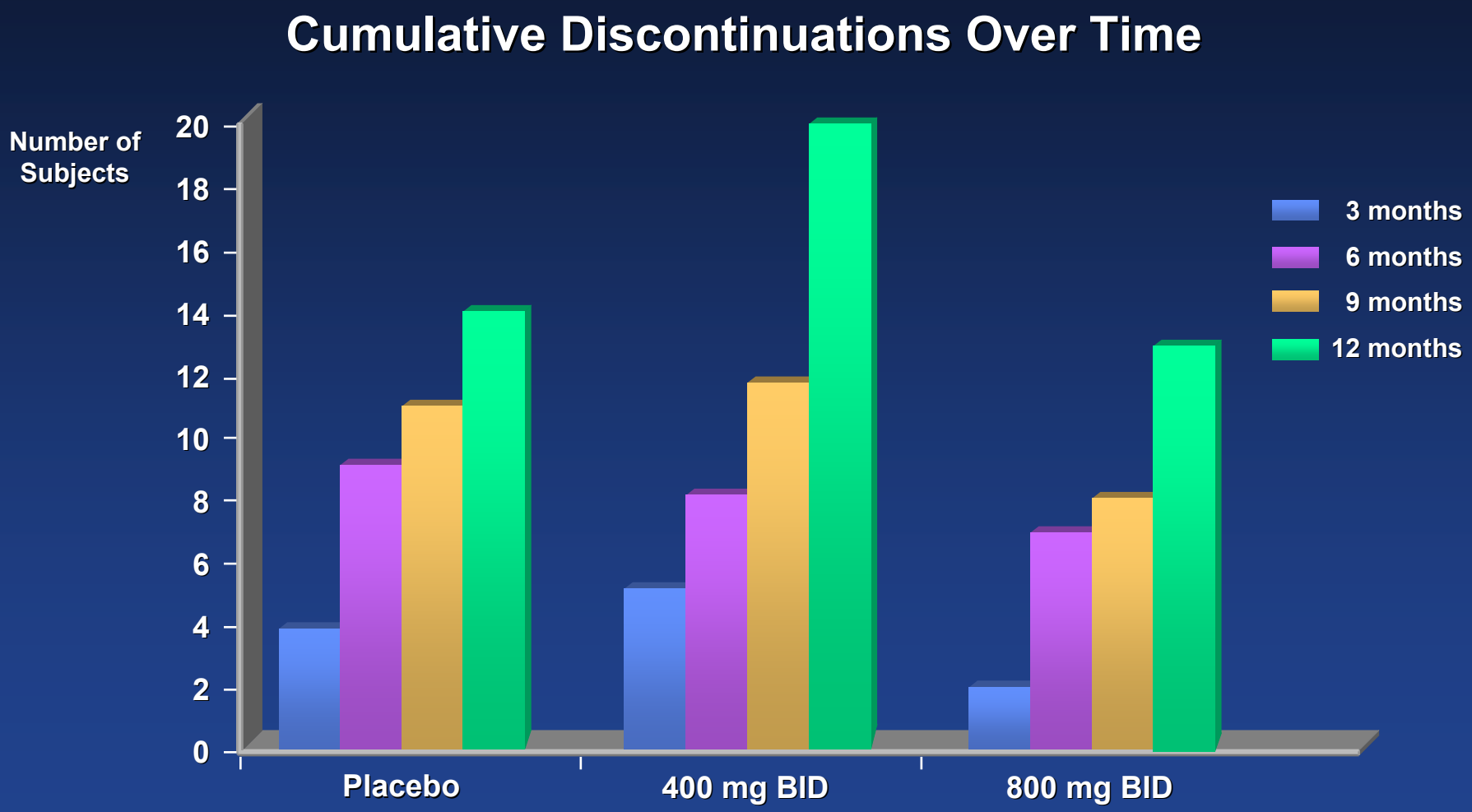


Exploratory Cognition—Mild Subjects

(MMSE ≥ 20 at Baseline) ITT analysis



Discontinuations Over Time (ITT)



Overall discontinuations in 12 months ~ 20%

AD2: Most Common AEs Leading to Discontinuation (0-12 months)

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%)

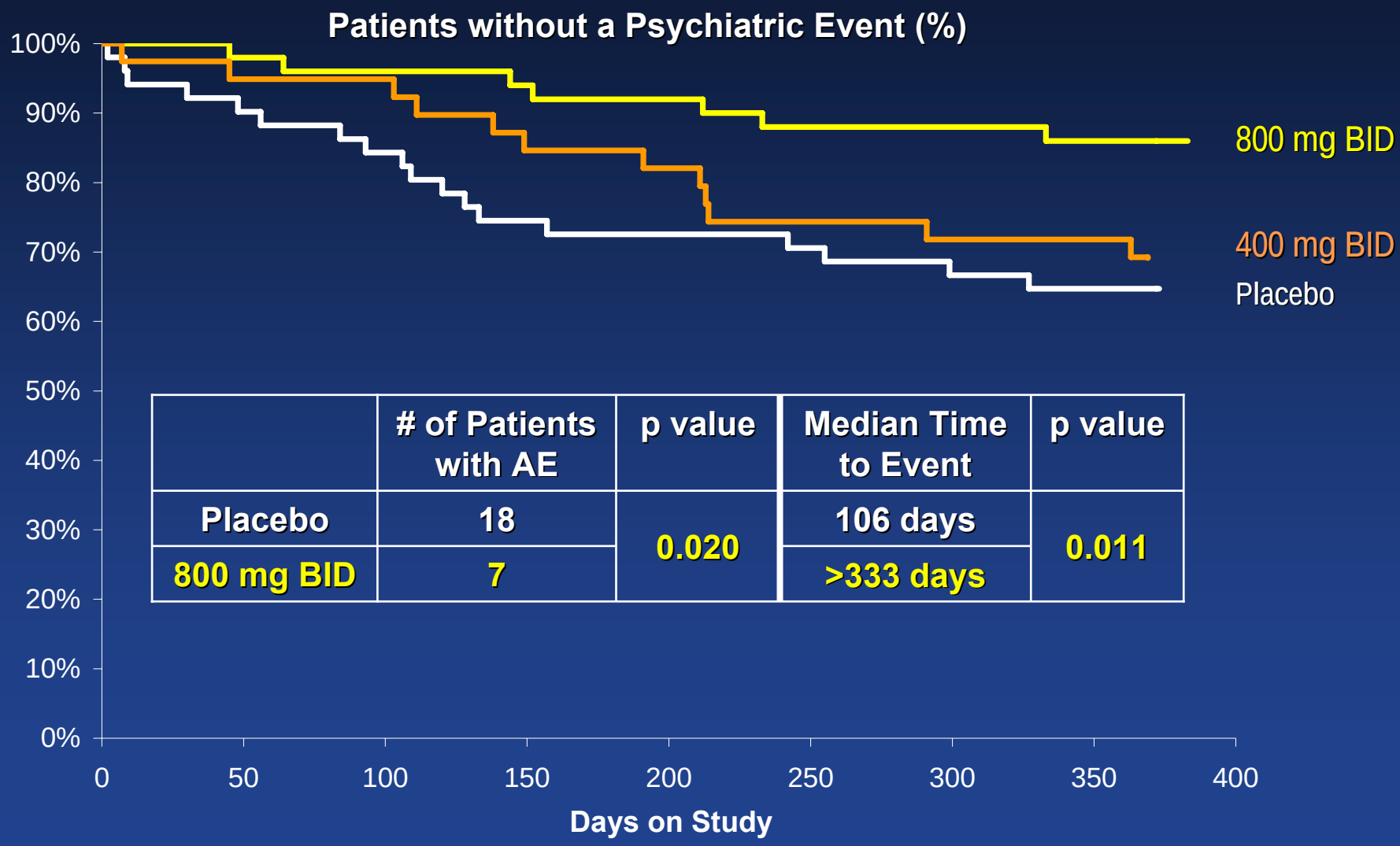
Discontinuations Due to Disease Progression (0-12 months)

	Placebo (n=66)	400 mg BID (n=71)	800 mg BID (n=70)
All patients	6 (9.1%)	2 (2.8%)	1 (1.4%)
Mild patients	4 (8.7%)	1 (2.8%)	0

AD2: Safety Summary

- Flurizan was 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

Posthoc: 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	

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 predicted effects of a disease modifying agent
- Well tolerated up to 24 months

Confirmatory Phase 3 Studies ongoing in Mild Patients