ELND005 for Agitation and Aggression in Alzheimer's Disease (HARMONY-AD Study): *Phase 2/3 design and clinical outcomes*

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DISCLOSURES

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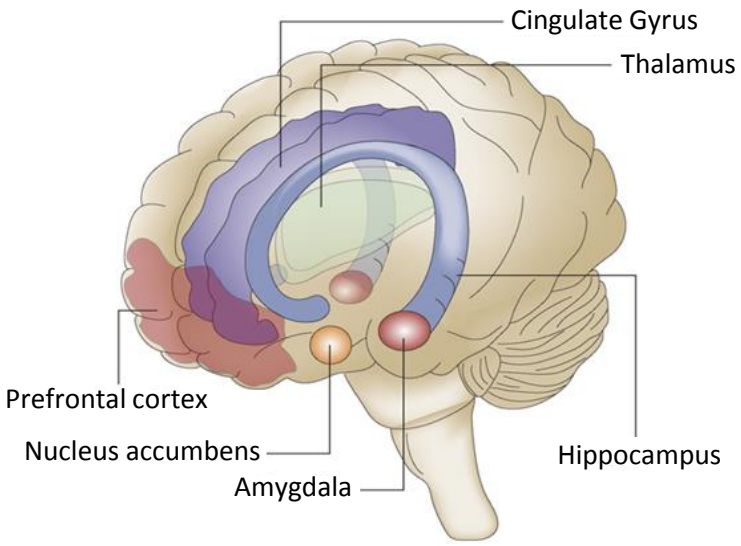
AGITATION/AGGRESSION IN ALZHEIMER'S DISEASE

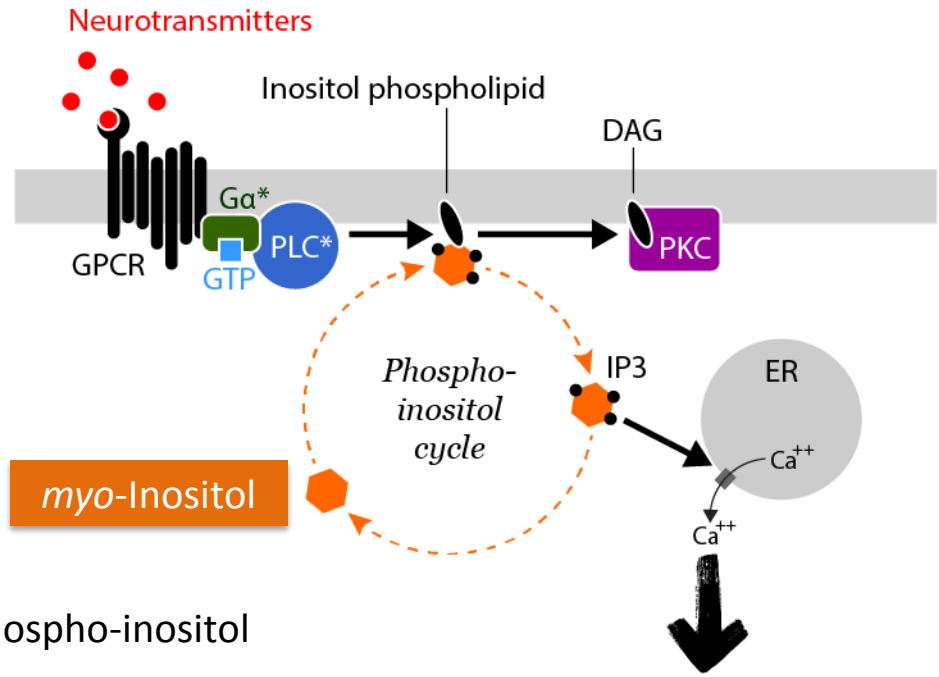
- 90% of AD patients develop neuropsychiatric symptoms (NPS) over the course of disease
- Up to 60% of AD patients develop agitation/aggression[1]

- Greater ADL impairment[2]
- Worse quality of life[3]
- Earlier institutionalization[4]
- Major source of caregiver burden[5]
- $10,000/year additional care costs[6]
- Shorter time to severe dementia[7]
- Accelerated mortality[7]

[1] Cummings J, Back C. (1998); [2] Lyketsos et al. (1997); [3] Gonzales-Salvador et al. (1999); [4] Steele et al. (1990); [5] Lyketsos et al. (1999); [6] Murman et al. (2002); [7] Peters et al. (2015)

ELND005 FOR AGITATION/AGGRESSION: MECHANISM OF ACTION



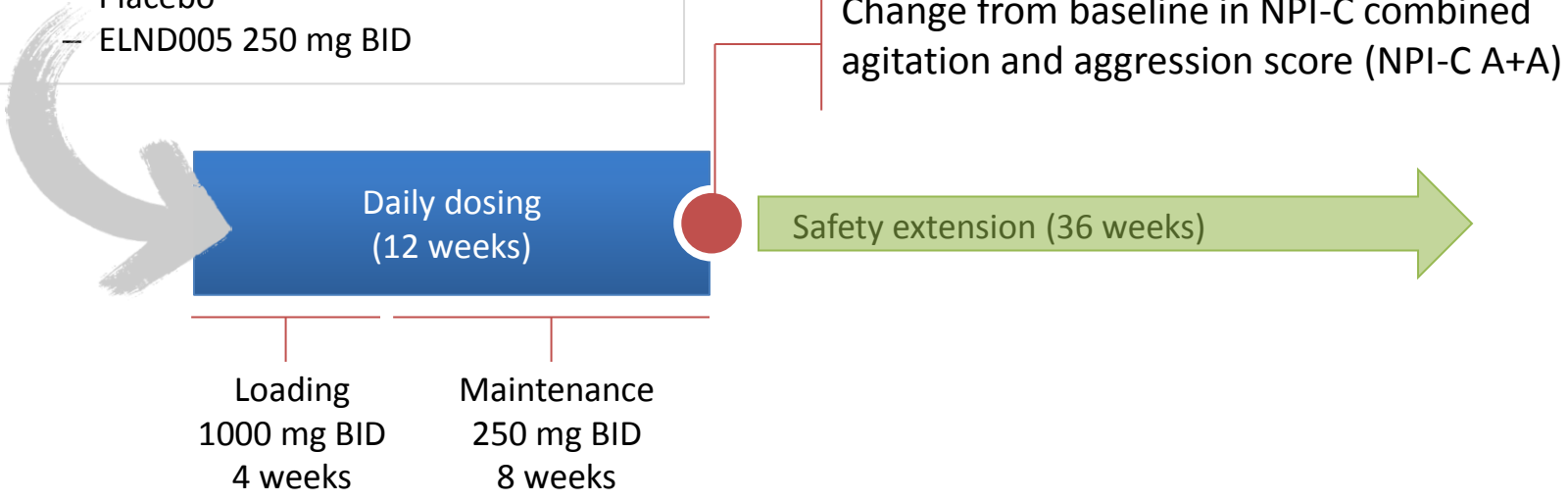


- *myo*-Inositol plays important role in the Phospho-inositol cycle and signaling of GPCR[1,2]
- *myo*-Inositol is found elevated in neuropsychiatric diseases including AD
- ELND005 (*scyllo*-Inositol) reduces brain *myo*-inositol levels by ~45%
- Regulation of myo-inositol may modulate neuronal signaling in response to neurotransmitters and growth factors

[1] *Berridge et al. Cell. 1989;* [2] *Schloesser et al. Neuropsychopharm. 1989*

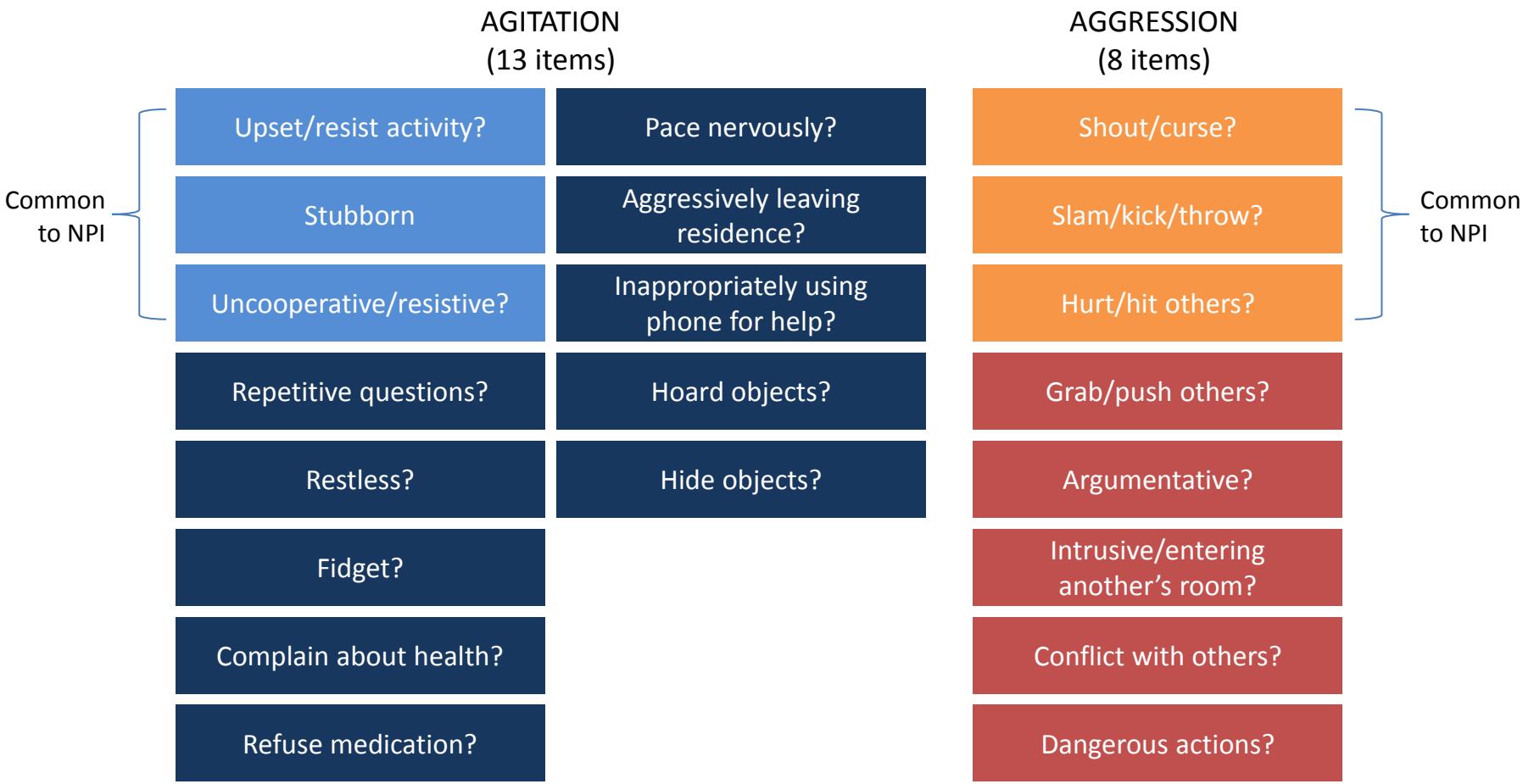
AG201: ELND005 PHASE 2 STUDY FOR THE TREATMENT OF AGITATION AND AGGRESSION IN AD

- N = 350
- Probable AD by NIA/AA criteria
- Stable AD drugs and psychotropics
- MMSE of 5 to 24 at screening
- NPI Agitation/Aggression ≥ 4
- Require pharmacological intervention
- Randomized to:
  - Placebo
  - ELND005 250 mg BID



NEUROPSYCHIATRIC INVENTORY – CLINICIAN RATING SCALE (NPI-C) AGITATION AND AGGRESSION DOMAINS (NPI-C A+A)

Max Score = 63 (addition of 21 item scores; severity 0 - 3)

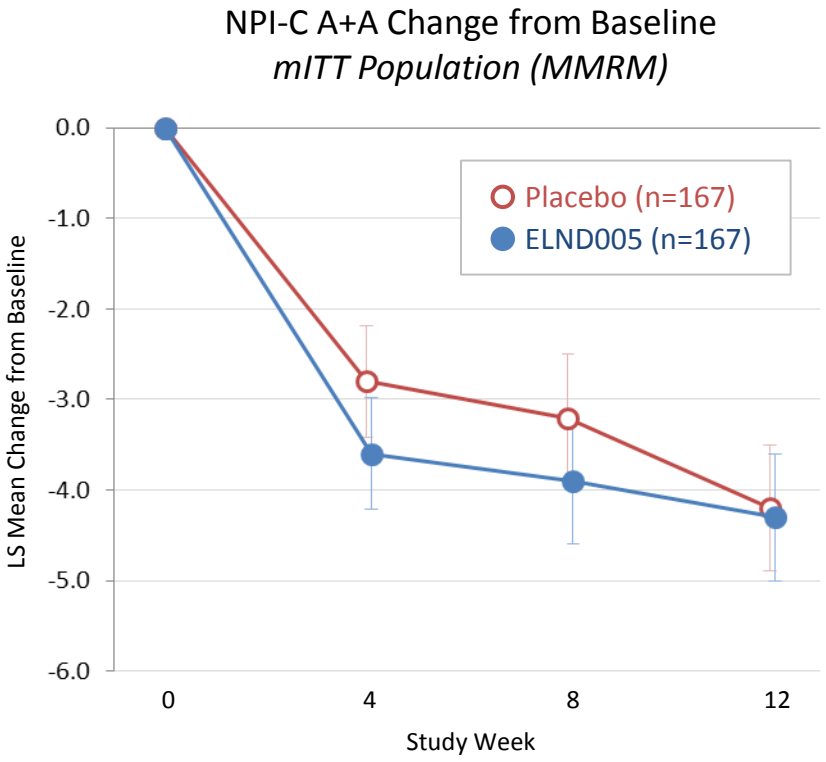


De Medeiros et al. 2010

AG201 STUDY POPULATION SUMMARY

	PLACEBO	*ELND005*
Randomized (Safety population)	175	175
mITT population	167	167
Completed	157	157
Discontinued	18	18
Adverse events	*7*	*8*
Withdrawal by subjects	*9*	*7*
Other	*2*	*3*
BASELINE CHARACTERISTICS (mITT POPULATION)		
Gender (M/F, %)	43% / 57%	45% / 55%
Race (% Caucasian)	86%	88%
Age (Mean ± SD)	75.9	76.2
Region – North America	91%	91%
Mild/moderate AD (MMSE ≥ 16)	49%	45%
Psychotropic medication use	55%	55%
Anti-depressants / Anti-psychotics	*47% / 20%*	*47% /20%*
Apo E4 positive	56%	57%
Baseline MMSE (mean ± SD)	15.0 (5.9)	14.2 (5.7)
NPI-C A+A (mean ± SD) (max score 63)	19.1 (10.9)	18.3 (9.8)
NPI agitation/aggression (mean ± SD) (max score 12)	7.2 (2.4)	7.3 (2.6)
Total NPI (mean ± SD) (max score 144)	47.8 (26.6)	46.6 (24.4)

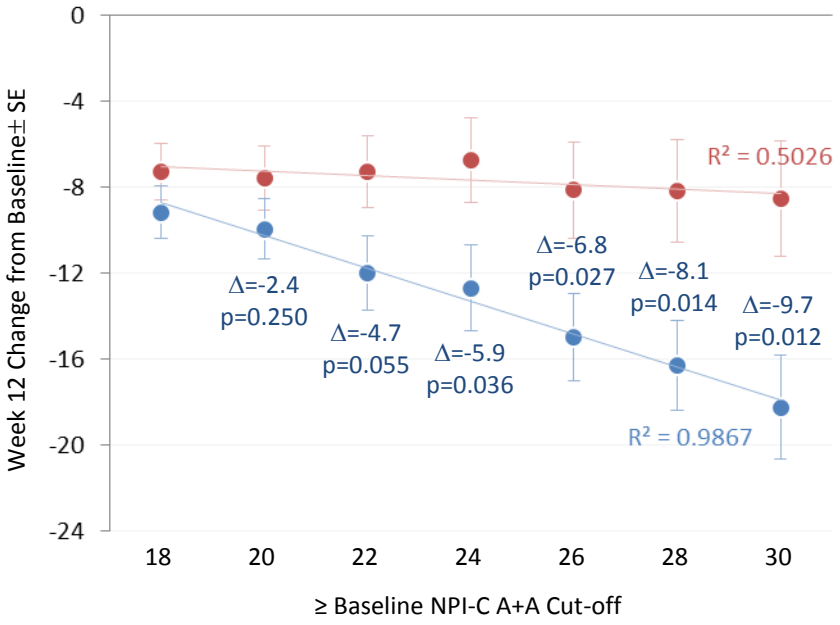
PRIMARY OUTCOME: NPI-C AGITATION + AGGRESSION



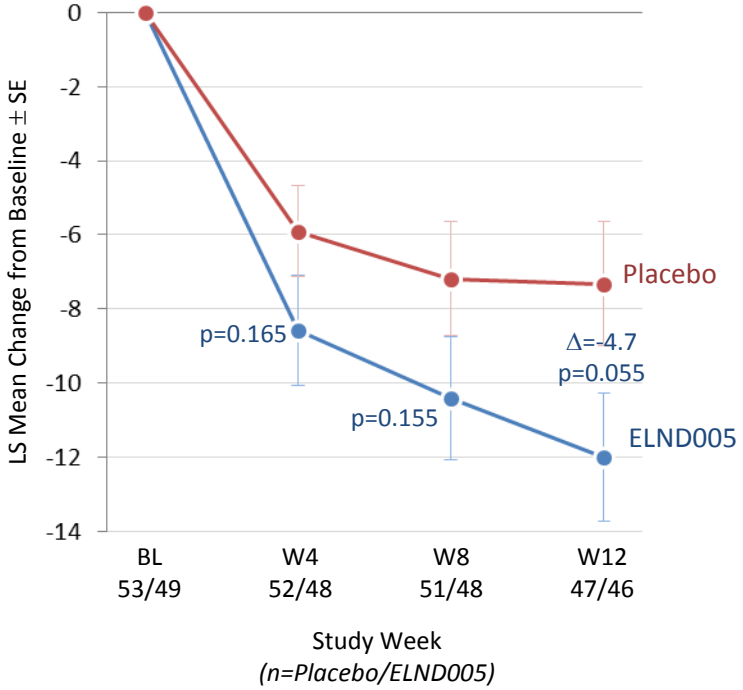
- The study did not meet the primary endpoint, NPI-C A+A change from baseline at week 12
- Secondary endpoints, NPI Agit/Agg and mADCS-CGIC, were not significant

POST-HOC ANALYSIS: NPI-C A+A CHANGE FROM BASELINE

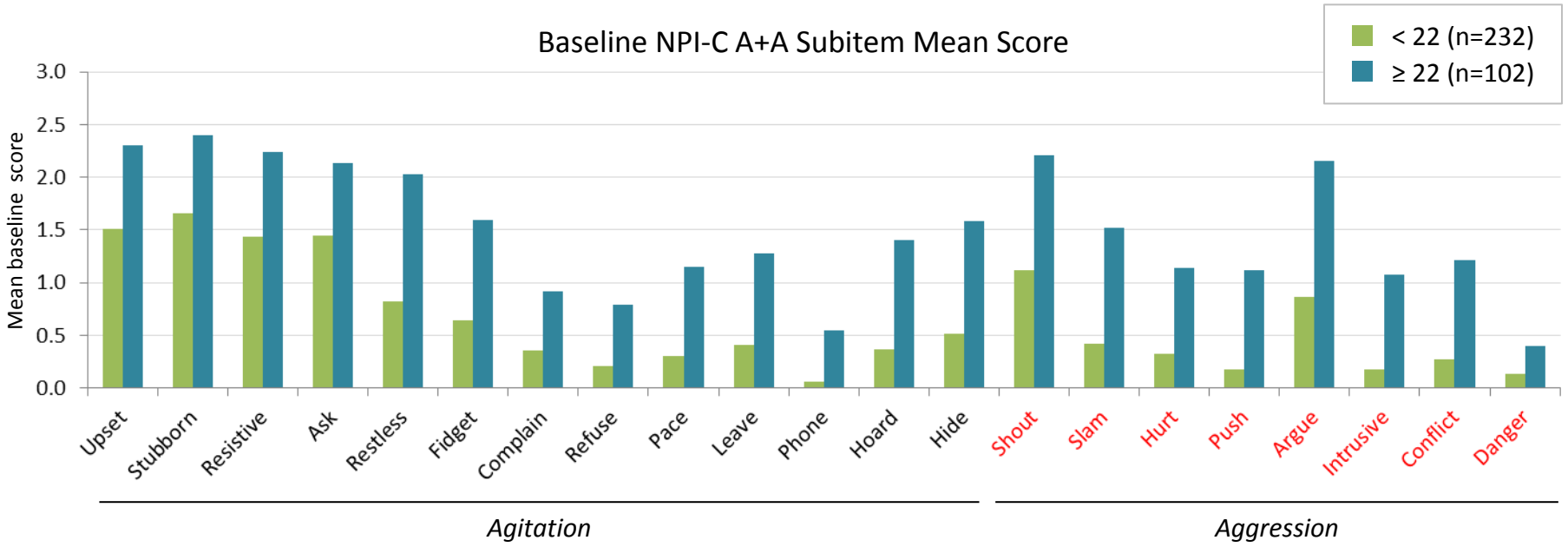
CORRELATION BETWEEN NPI-C A+A CUTOFF and WEEK 12 CHANGE FROM BASELINE



BL NPI-C A+A ≥ 22



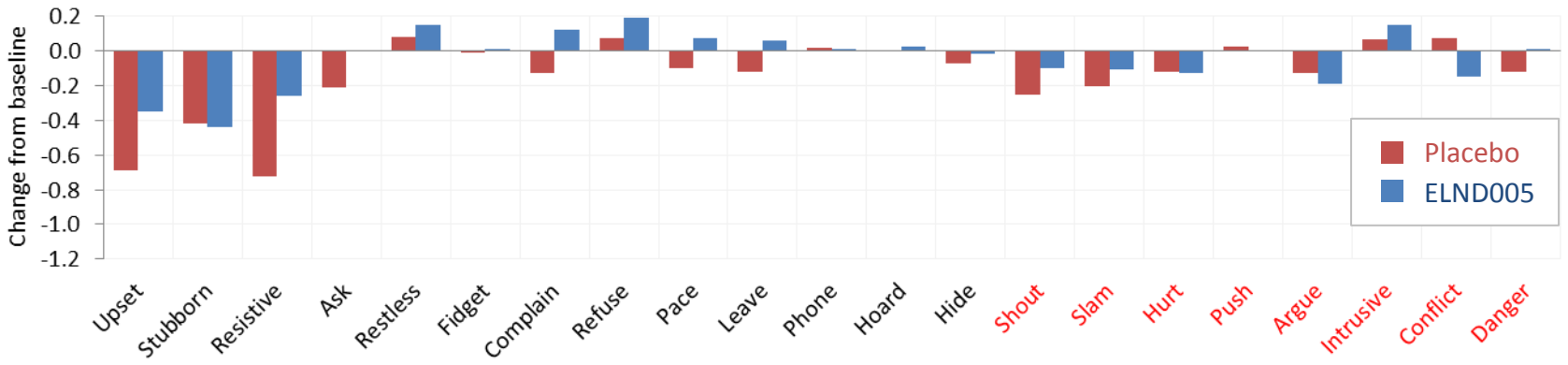
NPI-C A+A SUBITEM MEAN BASELINE SCORES (ALL SUBJECTS)



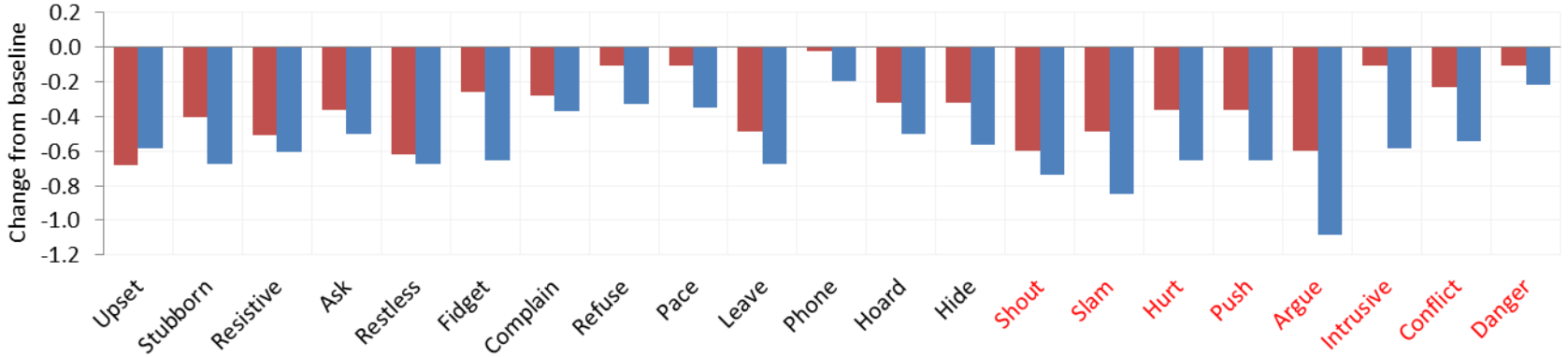
- Most prevalent agitation/aggression behaviors in patients with NPI-C < 22 include *UPSET, STUBBORN, RESISTIVE, ASK, and SHOUT*
- In more severe patients (NPI-C A+A ≥ 22), behaviors such as *RESTLESS, FIDGET, PACE, REFUSE, COMPLAIN, HOARD, HIDE, SLAM, HURT, PUSH, ARGUE, INTRUSIVE, CONFLICT, and DANGER* become prevalent/severe

NPI-C A+A SUBITEM CHANGE FROM BASELINE AT WEEK 12

Baseline NPI-C A+A < 22 (N=108/111)



Baseline NPI-C A+A ≥ 22 (N=47/46)



SAFETY ANALYSES

OVERVIEW OF ADVERSE EVENTS

	PLACEBO (N=175)	*ELND005 (N=175)*
Any TEAE	95 (54.3%)	99 (56.6%)
Any study drug-related TEAE	26 (14.9%)	23 (13.1%)
Serious AEs	5 (2.9%)	17 (9.7%)
Serious study drug-related AEs	0 (0.0%)	2 (1.1%)
Death	0 (0.0%)	0 (0.0%)
SUBJECTS WITHDRAWN DUE TO AN ADVERSE EVENTS		
TEAE	7 (4.0%)	8 (4.6%)
Drug-related TEAE	3 (1.7%)	5 (2.9%)
SUBJECTS WITH TEAES BY MAXIMUM SEVERITY		
Mild	37 (21.1%)	36 (20.6%)
Moderate	50 (28.6%)	48 (27.4%)
Severe	7 (4.0%)	15 (8.6%)
Life-threatening	1 (0.6%)	0 (0.0%)

SUMMARY OF TEAES INCIDENCE ≥ 2% ELND005 GROUP

PREFERRED TERM	*PLACEBO (N=175)*	*ELND005 (N=175)*
Agitation	13 (7.4%)	14 (8.0%)
Diarrhea	**5 (2.9%)**	**14 (8.0%)**
Urinary tract infection	7 (4.0%)	12 (6.9%)
Fall	9 (5.1%)	11 (6.3%)
Cough	**2 (1.1%)**	**7 (4.0%)**
Lethargy	**2 (1.1%)**	**6 (3.4%)**
Insomnia	7 (4.0%)	5 (2.9%)
Vomiting	5 (2.9%)	5 (2.9%)
Constipation	**2 (1.1%)**	**4 (2.3%)**
Gait disturbance	**1 (0.6%)**	**4 (2.3%)**
Headache	**2 (1.1%)**	**4 (2.3%)**

HARMONY AD STUDY CONCLUSION

PRIMARY ANALYSIS

- ELND005 did not meet the primary efficacy endpoint (NPI-C A+A)
- ELND005 showed an acceptable safety profile

POST HOC ANALYSIS

- ELND005 showed significant improvement in patients with more severe agitation and aggression
- Most prevalent agitation/aggression behaviors in patients with baseline NPI-C < 22 include *UPSET, STUBBORN, RESISTIVE, ASK, and SHOUT*
- In more severe patients (NPI-C A+A ≥ 22), behaviors such as *RESTLESS, FIDGET, PACE, REFUSE, COMPLAIN, HOARD, HIDE, SLAM, HURT, PUSH, ARGUE, INTRUSIVE, CONFLICT, and DANGER* become more prevalent
- ELND005 resulted in numerical benefits in 20 out of 21 A/A symptoms in severe A+A patients

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