Study of ELND005 in Agitation and Aggression of Alzheimer's Disease (HARMONY-AD): Diagnostic Criteria and Patient Characteristics

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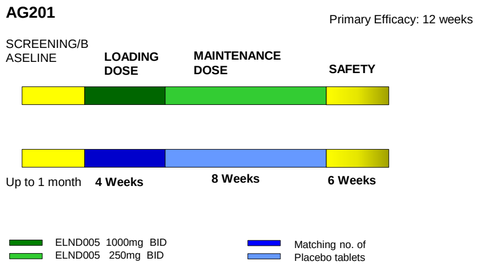
BACKGROUND & OBJECTIVES

- Agitation and Aggression are among the most disruptive neuropsychiatric symptoms (NPS) in Alzheimer's Disease (AD), and occur in up to 50% of AD dementia patients.
- They are likely related to mono-aminergic imbalance and synaptic dysfunction in limbic frontal networks (**Lyketsos, 2006; Sultzer et al. 1995**), possibly due to amyloid toxicity.
- There are no drugs approved for this indication beyond a few weeks (EU only).
- ELND005 (Scyllo-inositol, a myo-inositol isomer) is being evaluated as a potential treatment for Agitation and Aggression in AD (clintrials NCT01735630) based on data from a completed 78-week AD study ELND005 showed:
  - Amyloid lowering effects in CSF (**Salloway et al. 2011**)
  - Myo-inositol lowering effects on brain imaging (**Tariot et al. 2012**)
  - Beneficial trends on cognition in Mild AD (**Salloway et al. 2011**)
  - Beneficial effects on Agitation/Aggression in overall population (**Abushakra et al., 2012)**
- Myo-inositol reduction is thought to play a role in regulation of phosph-inositol signaling pathways, and in mood stability and behavioral control.
- We herein describe the operational diagnostic criteria and novel outcome measures utilized in this trial, and baseline characteristics of population.

METHODS

- Study ELND005-AG201 is a 12-week, 2 arm study (1 ELND005 arm and placebo), in diagnosed AD patients:
  - Probable AD diagnosed per the NIA/AA criteria (**McKhann et al. 2011**); MMSE 5-24,
  - Who have no active or untreated underlying metabolic, infectious, or medical condition causing their NPS,
  - Are on stable doses of AD drugs and/or psychotropic agents,
  - Have suboptimal or no response to non-pharmacological interventions,
  - Have Agit/Aggr of at least moderate severity at baseline:
    - NPI-Agit/Aggr score is ≥ 4 (NPI: Neuropsychiatric Inventory)
- Primary outcome measure:
  - Change from baseline for NPI-C summed agitation and aggression scores, and
  - NPI-C is an expanded and clinician rated NPI; **De Medeiros et al. 2010**)
- Secondary outcomes:
  - Clinician global impression of change (ADCS-CGIC) for agitation/aggression; NPI- Agitation/Aggression score
- CGIC supports clinical meaningfulness of NPI-C treatment effects

Study Design



Comparison of NPI-C and NPI

NPI-C Domain	# items	Score Range	NPI Domain	# items	Score Range
Delusions	8	0 - 24	Delusions	9	0 - 12
Hallucinations	7	0 – 21	Hallucinations	7	0 - 12
Agitation	13	0 – 39	Agitation/ Aggression	8	0 - 12
Aggression	8	0 – 24			
Dysphoria	13	0 – 39	Depression/ Dysphoria	8	0 - 12
Anxiety	14	0 – 42	Anxiety	7	0 - 12
Elation/Euphoria	6	0 – 18	Elation/Euphoria	7	0 - 12
Apathy/Indifference	11	0 – 33	Apathy/ Indifference	8	0 - 12
Disinhibition	16	0 – 48	Disinhibition	7	0 - 12
Irritability/Labiality	12	0 – 36	Irritability	7	0 - 12
Aberrant Motor Disturbance	9	0 – 27	Aberrant Motor Behavior	7	0 - 12
Sleep Disorders	8	0 – 24	Nighttime Behaviors	8	0 - 12
Appetite and Eating Disorders	9	0 – 27	Appetite/Eating Behaviors	8	0 - 12
Aberrant Vocalizations	8	0 – 24			
TOTAL SCORE		0 - 426			0 - 144

- *Note: NPI-C Dysphoria, Anxiety, Apathy are secondary outcomes (in red)
  - NPI-C Agitation and Aggression are separate domains on NPI-C
  - Max. score for NPI-C domain is 3 (maximal clinical severity) x no. of items in that domain
  - **Maximal summed scores for NPI-C Agitation + Aggression is 63 (39 + 24)**
  - **While maximal score for NPI-Agit/Aggression is 12**

RESULTS

Patient Demographics

	Age	Gender	Race	AD Severity
N	300	300	300	300
Mean	75.5 years	F 55% M 45%	Caucasian 89% Non Caucasian: 11%	Mild Moderate: (MMSE > 15) 48% Severe : MMSE ≤ 15 52%

Use of Psychotropic Concomitant Medications

	% Anti-psychotic	% Anti-depressant	% Anti-depressant AND Anti psychotic	% Anti-epileptics (mood stabilizers)
N (%)	77 (26%)	140 (47%)	45 (15%)	16 (5%)

Agitation/Aggression at Baseline by AD Severity

MMSE range	N	MMSE	NPI-total	NPI agit/aggr	NPI-C agit + aggr
Overall 5 -24	300	14.7	48.4	7.3	18.9
Mild/ Mod > 15	143	19.8	45.3	7.3	17.8
Severe ≤ 15	157	10.1	51.2	7.3	20.0

Baseline Scores of other NPS (12-Item NPI Domains)

N= 300	Anxiety	Apathy	Depression
Mean (SD)	**5.1 (4.0)**	**5.4 (4.1)**	**4.2 (3.7)**
	Irritability	**Aberrant motor**	Delusions
Mean (SD)	**5.7 (4.0)**	**4.7 (4.3)**	3.7 (4.4)
	Sleep behaviors	Disinhibition	Hallucination
Mean (SD)	3.0 (4.0)	2.8 (3.6)	2.0 (3.5)

- Bolded Scores > or = 4 are at least moderate severity
- At baseline:
  - Approximately 90 % have either Anxiety or Depression
  - Approximately 70% have Aberrant motor behavior

NPI-C Domain Scores by AD Severity

	NPI-C Agit	NPI-C Aggr	NPI-C Depr	NPI-C Anx	NPI-C Apathy
Overall	13.1	5.8	10.3	9.6	12.1
Mild/ Moder	12.3	5.5	10.4	8.9	11.4
Severe	13.9	6.1	10.1	10.3	12.7

CONCLUSIONS

- The NPI-C provides more details on agitated and aggressive behaviors and a wider range of scores, which may allow more sensitivity to drug effects.
- These inclusion criteria identify a population with at least moderate Agitation/Aggression, irritability and aberrant motor behavior.
- This population also has high levels of apathy, anxiety and depression
- Agitation/Aggression severity is similar between Mild/Moderate and Severe AD
- These features are consistent with the diagnostic criteria of "Agitation in Dementia" proposed by International Psychogeriatric Association (**IPGA 2014**) .

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Disclosures:
Drs. Abushakra, Liang, and Pasterak are full time Transition Therapeutics employees and stock holders; Drs Porsteinsson and Mintzer are investigators in this study and advisors to TTHI . Dr. Lyketsos is a consultant for Transition Therapeutics via Johns Hopkins University for this study.