Comparing recruitment among geographic regions in multinational Alzheimer's disease clinical trials.

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Introduction

Alzheimer's disease (AD) clinical trials frequently struggle to enroll. To address this consistent challenge, most AD clinical trials now recruit multinationally.

Methods

We combined demographic and clinical measures for participants and their study partners from four similarly-designed, randomized, double-blind, placebo-controlled trials with nearly identical entry criteria enrolled patients aged ≥55 years with mild-to-moderate probable AD, based on the National Institute of Neurological and Communicative Disorders and Stroke /AD and Related Disorders Association (NINCDS/ADRDA) criteria

- Two 76-week semagacestat (IDENTITY) studies[1]
- Two 80-week solanezumab (EXPEDITION) studies[2]

We assigned participating countries to 7 global regions:

North America (NA)
US
Canada

Western Europe (WE)
Belgium
Denmark
Finland
France
Germany
Israel
Italy
Spain
Sweden
UK

Eastern Europe (EE)
Bulgaria
Hungary
Poland
Romania
Russia
Serbia
Turkey
Ukraine

Australia/ S. Africa (AU)
Australia
South Africa

South America (SA)
Argentina
Brazil
Chile
Mexico

Japan (JP)

Asia (AS)
China
India
Korea
Taiwan

For all outcomes, we tested the hypothesis that global regions do not differ from each other. Analysis of variance (ANOVA) and Levene's tests (for continuous variables with normal distributions); Kruskal-Wallis tests (non-normal continuous); and Chi-square tests (X^2, categorical data) were used to examine overall effects of geographic region. Pair-wise comparisons between regions were performed using Tukey's HSD test (with the ANOVA), Wilcoxon Rank sum tests with Holm's adjustment for multiple comparisons (with the Kruskal-Wallis), and X^2 using Holm's adjustment for multiple comparisons (with the X^2 test). All statistical analyses were conducted using R, version 2.14.0 (www.r-project.org).

Results

- We examined data from 4694 participants. More participants were enrolled in North America than any other region.
- We observed significant effects of global region ($p<0.01$) for every variable we examined (Table; Figure 1; Figure 2).

Table 1. Regional demographic and disease-related summaries of the participants at baseline (*p<0.01 vs South America; #p<0.01 vs Eastern Europe; &p<0.01 vs Asia; @p<0.01 vs Japan; Ωp<0.01 vs Australia/South Africa; Ψp<0.01 vs Western Europe; θp<0.01 vs North America).

	North America	Western Europe	Australia/South Africa	Japan	Asia	Eastern Europe	South America
N (%)	1884 (40.1)	981 (20.9)	237 (5.1)	435 (9.3)	339 (7.2)	408 (8.7)	410 (8.7)
Age, mean ± SD	75.1 ±8.3#&@Ωψ	71.9 ± 7.8*@	72.9 ± 7.4*#θ	73.4 ± 7.6*θ	72.1 ± 7.6*θ	70.7 ± 7.8*Ωθ	75.4 ± 7.7#&@Ωψ
Female gender, n (%)	986 (52.3)*#@	503 (51.3)#@	128 (54.0)*	276 (63.5)ψθ	191 (56.3)	255 (62.5)ψθ	279 (68.1)Ωψθ
Height (cm), mean ± SD	166.5 ± 10.7*#&@	166.1 ± 9.8*#&@	166.8 ± 9.7*#&@	154.6 ± 8.9*#&Ωψθ	158.2 ± 8.6*#@Ωψθ	163.4 ± 9.1*&@Ωψθ	160.0 ± 9.1#@Ωψθ
Weight (kg), mean ± SD	73.2 ± 15.7*#&@ψ	70.2 ± 12.7*&@θ	70.7 ± 13.1*&@	53.1 ± 10.0*#&Ωψθ	58.4 ± 9.7*#@Ωψθ	68.7 ± 12.6&@θ	66.6 ± 12.5&@Ωψθ
Body mass index, mean ± SD	26.3 ± 4.7&@ψ	25.4 ± 3.8&@θ	25.4 ± 4.1&@	22.1 ± 3.1*#&Ωψθ	23.3 ± 3.1*#@Ωψθ	25.4 ± 3.8&@	26.0 ± 4.2&@
Years education, mean ± SD	14.1 ± 3.3*#&@Ωψ	11.2 ± 4.2*#&θ	12.1 ± 3.5*&ψθ	11.7 ± 2.7*&θ	9.5 ± 4.7#@Ωψθ	11.9 ± 3.8*&ψθ	8.9 ± 4.5#@Ωψθ
APOE ε4 carriers, n (%)	1086 (63.2)*#&@	494 (63.3)*#&@	149 (63.7)*	220 (51.9)ψθ	93 (48.4)ψθ	191 (51.1)ψθ	189 (49.5)Ωψθ
Years since symptom onset, mean ± SD	4.8 ± 2.6#&@	4.6 ± 2.5#@	4.7 ± 2.8#@	3.7 ± 2.3*&Ωψθ	4.2 ± 2.4@θ	3.9 ± 2.2*Ωψθ	4.5 ± 2.4#@
Years since diagnosis, mean ± SD	2.5 ± 2.1#&@Ωψ	2.1 ± 1.8#@θ	2.0 ± 1.8#θ	1.7 ± 1.5*ψθ	2.0 ± 1.9*#θ	1.5 ± 1.5*&Ωψθ	2.4 ± 1.9#&@
Taking any anti-AD medication, n (%)	1677 (89.0) #&Ω	902 (92.0) *#&Ω	172 (72.6) @ψθ	389 (89.4) &Ω	274 (80.8) ψθ	302 (74.0) @ψθ	342 (83.4) ψ
Taking dual anti-AD therapy, n (%)	894 (47.5)*#&@Ωψ	147 (15.0)*&@Ωθ	16 (6.8)*@ψθ	3 (0.7)*#&Ωψθ	21 (6.2)*#@ψθ	58 (14.2)*&@θ	117 (28.5)#&@Ωψθ
Enrolled with spouse study partner, n (%)	1318 (70.4) *#&	719 (73.7) *#&	178 (75.7) *#&	279 (64.6) *#&	172 (50.9) @Ωψθ	163 (40.1)@Ωψθ	174 (42.7) @Ωψθ
Enrolled with adult child study partner, n (%)	374 (20.0)	192 (19.7)	36 (15.3)	116 (26.9)	136 (40.2)	203 (49.9)	162 (39.7)
Enrolled with other study partner, n (%)	179 (9.6)	64 (6.6)	21 (8.9)	37 (8.6)	30 (8.9)	41 (10.0)	72 (17.7)

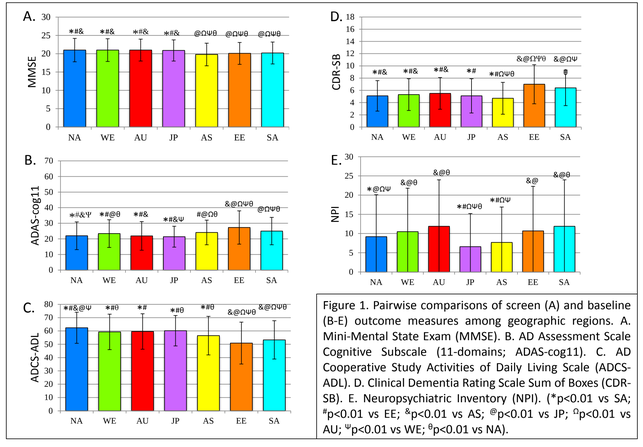
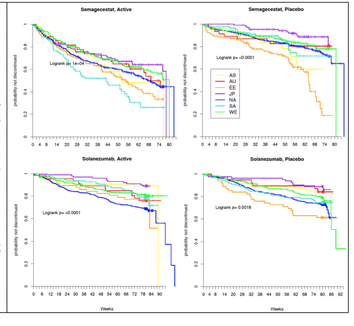


Figure 1. Pairwise comparisons of screen (A) and baseline (B-E) outcome measures among geographic regions. A. Mini-Mental State Exam (MMSE). B. AD Assessment Scale Cognitive Subscale (11-domains; ADAS-cog11). C. AD Cooperative Study Activities of Daily Living Scale (ADCS-ADL). D. Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). E. Neuropsychiatric Inventory (NPI). (*p<0.01 vs SA; #p<0.01 vs EE; &p<0.01 vs AS; @p<0.01 vs JP; Ωp<0.01 vs AU; ψp<0.01 vs WE; θp<0.01 vs NA).

Figure 2. Overall dropout rates were similar for the combined active solanezumab (24%) and both combined placebo data sets (22% for semagecestat; 25% for solanezumab). The rate of dropout for the combined active semagecestat trials was 46%. In each combined data set, the global regions differed in the rates of participant retention (X^2; p<0.01 for each data set). In a time to discontinuation model JP differed from at least one other region in each of the four data sets. JP had lower dropout than EE for the solanezumab placebo arms, than NA in the solanezumab active treatment arms, than AS and EE in the semagecestat placebo arms, and than SA in the active semagecestat arms (Log rank test; p<0.01, for all comparisons). EE had higher dropout than AU, NA, and WE in the semagecestat placebo arms (Log rank test; p<0.01). SA had higher dropout than WE in the active semagecestat arms (Log rank test; p<0.01).



Discussion

- Most (86%) participants took approved AD therapies; anti-AD drug use was highest in NA, WE, and JP. Recruiting treatment-naïve AD patients will be difficult, even if enrolling globally.
- NA, WE, and AU were similar in the proportions of male participants, apolipoprotein ε4 carriers, and participants enrolling with a spouse study partner. AS, EE, and SA had lower proportions for these variables.
- NA, WE, JP, and AU had milder scores and AS, SA, and EE had more moderate severity for the MMSE. EE had worse ADAS-cog11 scores than all other regions. EE and SA had more severe scores for the ADCS-ADL and the CDR-SB. Mean scores in AS were milder than all regions except JP for the CDR-SB. NPI scores in AS and JP were lower than all other regions.
- Several not mutually exclusive factors may contribute to the observed heterogeneity, including regional differences in overall health and health care; regional differences in the availability of experienced AD investigators; cultural differences in AD care; and ethnogenetic differences in disease.

Conclusions

- Despite strict protocols, ample site training, and substantial trial monitoring—significant heterogeneity exists among global AD trial populations.
- Consistent regional patterns were observed when comparing scores on trial outcomes at screen and baseline, but seemed dependent upon whether the outcome measure was based on informant report.
- Sponsors should consider this heterogeneity when planning multinational AD trials.

Acknowledgements & References

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(1) Doody RS, et al. 2013 NEJM 369(4):341-350.
(2) Doody RS, et al. 2014 NEJM 370(4):311-321.