Appendix

Enrichment factors for clinical trials in mild-to-moderate Alzheimer's disease

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Statistical analysis methodology

Changes from baseline in rating scale scores were analyzed using mixed models for repeated measures with restricted maximum likelihood estimation. Such models assume a decomposition of the patient-level longitudinal profiles into patterns that can be described by fixed effects (e.g., baseline score, baseline treatment) and random patient-level variation (both correlated variation across visits within a patient and visit-to-visit variation).

The random patient-level variation was modeled using an unstructured covariance matrix across visits (3 visits, 6 covariance parameters). This allowed the maximal level of flexibility within this class of model.

The models adjusted the patient-level trajectories of longitudinal change for the following fixed effects:

- baseline score in rating scale – continuous variable
- visit – categorical variable with 3 levels (Week 4, Week 12, or Week 24 after baseline)
- country – categorical variable with 34 levels
- MMSE stratum – categorical variable with 2 levels (12–18 or 19–22)
- cholinesterase inhibitor therapy stratum – categorical variable with 2 levels (donepezil or rivastigmine/galantamine)
- study – categorical variable with 3 levels (STARSHINE, STARBEAM, or STARBRIGHT)
- treatment – categorical variable with 4 levels (placebo, idalopirdine 10 mg, idalopirdine 30 mg, or idalopirdine 60 mg)
- enrichment group – categorical variable with number of levels dependent on enrichment group (3 levels for *APOE* ε4 carrier status, 2 levels for other groups).

Furthermore, a sensitivity analysis included the following additional fixed effect:

- age – both continuous and categorical with 4 levels (<65, 65–74, 75–84, or ≥85).

Except for country, the fixed effects were allowed to vary across visits. To model this, interactions between the fixed effects and visit were included in the model.

The goal of this analysis was to explore the effect of predefined enrichment groups on the longitudinal trajectory of patients receiving placebo. To assess this, a third-order interaction term between enrichment group, treatment, and visit was added to the model. This term allowed different longitudinal trajectories for enrichment group categories within each treatment arm.

Taken together, the fixed effects model can be described as:

$$\begin{aligned} &\textit{country} + \textit{(baseline score} \times \textit{visit)} + \textit{(MMSE stratum} \times \textit{visit)} \\ &+ \textit{(cholinesterase inhibitor therapy stratum} \times \textit{visit)} + \textit{(study} \times \textit{visit)} \\ &+ \textit{(enrichment group} \times \textit{treatment} \times \textit{visit).} \end{aligned}$$

To determine if there was a difference between enrichment group categories, it was tested if the difference between the corresponding levels of the third-order interaction was equal to zero. For example, to test if there was a difference between the *APOE* ε4++ and *APOE* ε4- groups at Week 24, the difference of the estimates

$$(\varepsilon 4{+}{+} \times \textit{treatment}_{\text{placebo}} \times \textit{visit}_{24}) - (\varepsilon 4{-} \times \textit{treatment}_{\text{placebo}} \times \textit{visit}_{24})$$

was tested using a *t*-test with the Kenward–Roger approximation to calculate denominator degrees of freedom.

Note: All treatment arms were included in the analyses, but only effects for patients in the placebo arms were tested. There are two motivations for basing the analyses on all patients: 1) the estimates of fixed effects (in particular, country effects) become more stable, and 2) the estimates of variance parameters describing the patient-level random variation become more stable.

Table A.1: Data used for power modeling

Group	Proportion of Phase 3 population, %	Observed mean change in ADAS-Cog score from baseline to Week 24 in the placebo group (95% confidence limits)	Withdrawal rate in placebo group, No. (%)
Phase 3 population	100.0 (n=2,525)	0.61 (0.20, 1.02)	98/963 (10.2)
ε4+	58.3 (n=2,451)	0.95 (0.43, 1.47)	48/551 (8.7)
ε4+-	45.5 (n=2,451)	0.80 (0.24, 1.37)	37/443 (8.4)
ε4++	12.9 (n=2,451)	1.55 (0.20, 2.90)	11/108 (10.2)
FH+	27.8 (n=2,517)	1.53 (0.71, 2.35)	23/259 (8.9)
A+	9.2 (n=2,525)	2.38 (0.90, 3.85)	7/84 (8.3)
ε4+/FH+/A+	70.8 (n=2,472)	1.02 (0.54, 1.50)	62/664 (9.3)
ε4++/FH+/A+	41.8 (n=2,472)	1.61 (0.94, 2.28)	38/384 (9.9)
ε4++/A+	20.8 (n=2,454)	1.84 (0.82, 2.86)	17/181 (9.4)

A+=amyloid positive. AD=Alzheimer's disease. ADAS-Cog=AD Assessment Scale – Cognitive subscale. ε4+=*APOE* ε4 carrier. ε4++=*APOE* ε4 homozygous. ε4+-=*APOE* ε4 heterozygous. FH+=first-degree relative with AD.

Table A.2: Number of randomized patients per arm needed to detect a treatment effect

Group	80% power	85% power	90% power
Phase 3 population	1,619	1,851	2,166
ε4+	659	753	881
ε4+-	919	1,051	1,230
ε4++	251	288	336
FH+	255	291	340
A+	148	170	198
ε4+/FH+/A+	574	657	768
ε4++/FH+/A+	231	264	309
ε4++/A+	178	203	237

Number of randomized patients per arm needed to obtain 80%, 85% and 90% power to detect a 2-point difference on the ADAS-Cog at the 0.05 level. A+=amyloid positive. AD=Alzheimer's disease. ADAS-Cog=AD Assessment Scale – Cognitive subscale. ε4+=*APOE* ε4 carrier. ε4++=*APOE* ε4 homozygous. ε4+-=*APOE* ε4 heterozygous. FH+=first-degree relative with AD.