Worldwide Clinical Trials

Case Study

Operational & Strategic Excellence in the Delivery of a Global Phase III Trial

Outcome: FDA Approval

Executing With Speed and Quality

As a full-service, midsize CRO, Worldwide Clinical Trials executes global studies while maintaining a proactive and responsive approach for our clients and providing rigorous attention to clinical sites.

In a recent large Phase III study focusing on early Alzheimer's Disease (AD), Worldwide managed more than 230 sites across 14 countries in North America, Europe, and the Asia-Pacific region. We completed recruitment within 22 months, randomizing close to 1,800 subjects after screening more than 6,700 patients. The global pandemic introduced unanticipated disruption to recruitment, study visits, onsite monitoring, and more. **Despite facing challenges, we completed the study on time and on budget, generating statistically significant results in the primary outcome and all secondary outcome measures.**

The Study at a Glance

3 Regions
NA/EU/APAC

14 Countries
235 Sites

6,707 Patients
Screened

1,795 Patients
Randomized

ApoE4 +ve rate of 69%; stratification protocol requirement of 70%

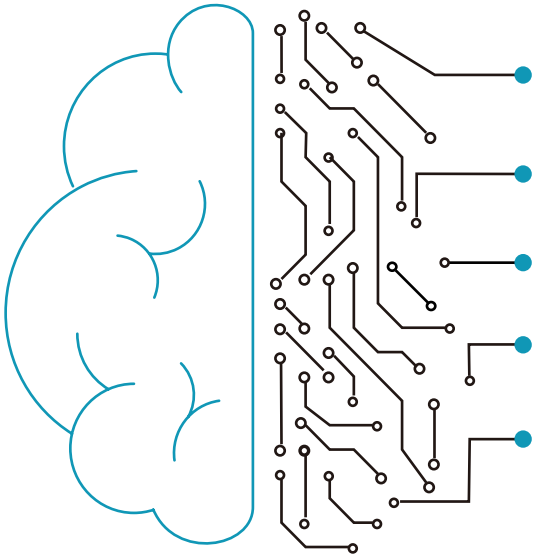
18 Months, Double-Blind

Primary Endpoint:
CDR-SB

Secondary Endpoint:
(i) Reduction in brain amyloid levels measured by amyloid PET (ii) ADCOMS (iii) ADAS-cog14

Biomarkers:
Measured by amyloid PET; tau PET; CSF; vMRI

Key Inclusion Criteria



- MCI due to AD/mild AD – NIA-AA criteria
- Amnestic memory impairment indicated by poor performance on an episodic memory test
- Amyloid + by PET or CSF
- Age: 50-90 inclusive; MMSE ≥22; CDR 0.5 or 1.0
- Stable anti-AD treatment ≥12 weeks

Striking the Balance: Localized Attention and Global Oversight

The study faced challenges that are common to large, global clinical trials. Working toward aggressive timeline expectations, Worldwide needed to activate sites across multiple regions and manage any variations in assessments, tools, and training levels. Where site budgets were more complex, negotiation timelines were protracted. Operationally, multiple protocol amendments added complexity, and an unusual adverse event profile necessitated precautions to prevent rater and study team bias.

To meet the protocol needs of the study and to satisfy preferences of our sponsor, it was imperative to pay meticulous attention to detail at a local level while providing strong global oversight to ensure alignment across all sites and geographic regions.

Localized Attention

- **Site selection:** We compressed start-up timelines by engaging sites that had already worked on earlier phases of the study with this investigational product or sites that Worldwide had previous experience with.
- **Recruitment:** A small team of experts in neuropsychology and cognitive assessments provided clinical guidance to the sites, increasing recruitment efficiency and volume. This Cognitive Task Force **reduced the overall screen-failure rate by about 27.5%** over six months through individual site outreach and training, offering significant cost efficiencies.
- **Monitoring:** To mitigate risk at the site level, we developed ad hoc central monitoring tools and metrics. These bespoke solutions enabled faster query resolution, **reducing the time to close queries by more than 70%** over one year.
- **Vendors:** The requirement of specific PET tracers and a complex vendor start-up process necessitated quick problem-solving and partnership with multiple providers.
- **Site support:** A team of nearly 20 in-house CRAs tracked and monitored the five-tiered screening process for every subject in the study. These in-house CRAs contacted sites at least weekly to discuss subject status and progress and to identify pain points and potential efficiencies to share with the client.

Global Oversight

- **Start-up:** Worldwide coordinated alignment of start-up timelines, vendor readiness, and training across all geographic regions. With a complex protocol and therapeutic area, we coordinated region- and country-specific training webinars.
- **Mitigating risk of unblinding:** Two high-risk adverse events (infusion reaction and amyloid-related imaging abnormality), inherent to monoclonal antibodies used in this therapeutic area, posed a risk for "effective unblinding." To mitigate this risk, standard study processes were siloed into two teams or workflows.
- **Managing pandemic disruption:** The COVID-19 pandemic led to patient attrition and increased frequency of missed site visits. To offset these disruptions and maintain adequate power across all endpoints, the sponsor increased the desired sample size. Despite widespread, ongoing safety restrictions, **an additional 200 subjects were enrolled within only three months.**
- **Risk-based quality management:** Worldwide held monthly calls with the sponsor to ensure routine discussion of new risks and changes to existing risks. Together, lessons learned were shared and important decisions were centralized for consistency and accountability.

Cognitive Task Force

The Cognitive Task Force helps minimize screen-failures due to cognitive assessment results and consults with sites on protocol and operational improvements, specifically with an eye toward efficient recruitment. The team comprises skilled clinicians focused on data-driven, site-level monitoring and intervention to ensure subjects with the right cognitive phenotype are enrolled into the study.

Beyond the Study Protocol

In addition to the core study, sub-studies were undertaken: CSF, amyloid PET, tau PET, and volumetric MRI. Of particular note, the results of the tau PET sub-study were vital to understanding the impact of an amyloid-modifying compound on tau load, significantly contributing to the scientific and pharmaceutical communities.

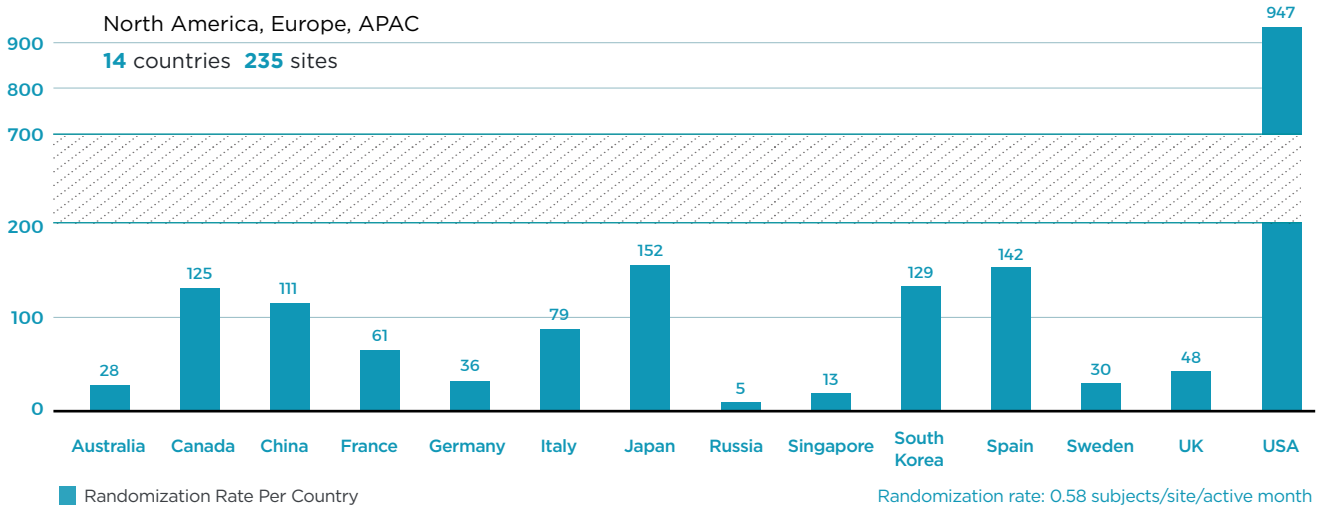
- All three sub-studies were sufficiently enrolled to meet biostatistical requirements.
- We dramatically exceeded enrollment expectations for the amyloid PET sub-study.
- **The tau PET sub-study saw the highest number of enrollees across all known Alzheimer's programs and had strong patient retention.**

Continued participation via an open-label extension study remains excellent, **with patient participation holding at about 95%.**

Key Successes

- Increase in randomization volume, as training and tools that supported sites in their pre-screening practices resulted in a 27.5% reduction in screen failures
- Excellent relationships, operational management, and oversight of sponsor-contracted vendors
- Increased site engagement and recruitment strategies tailored to individual site requirements
- Low patient discontinuation rate, despite the impact of COVID-19
- Reduction in study costs during screening period due to site-level intervention by Worldwide's Cognitive Task Force

Country Performance



A Significant Breakthrough in Alzheimer's Research

This seminal trial sets a precedence for methodology, design, and operational delivery in AD research. In collaboration with the sponsor and investigators, Worldwide delivered this complex, global study on time, rigorously applying quality measures to ensure data integrity. Primary and all key secondary endpoints were statistically significant.

The data generated from this study was the basis for an sBLA approved in early July 2023 in the United States and will be used to submit to regulatory bodies outside the United States.

Worldwide is proud to have contributed to the completion of this pivotal study which will bring hope to people with early AD and their families.

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About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.