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Global Full-service CRO

STUDY INSIGHTS

From Study Execution to EMA Success:

A Global Phase III Program for Ranibizumab - Ophthalmic Biosimilar

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Study Objective

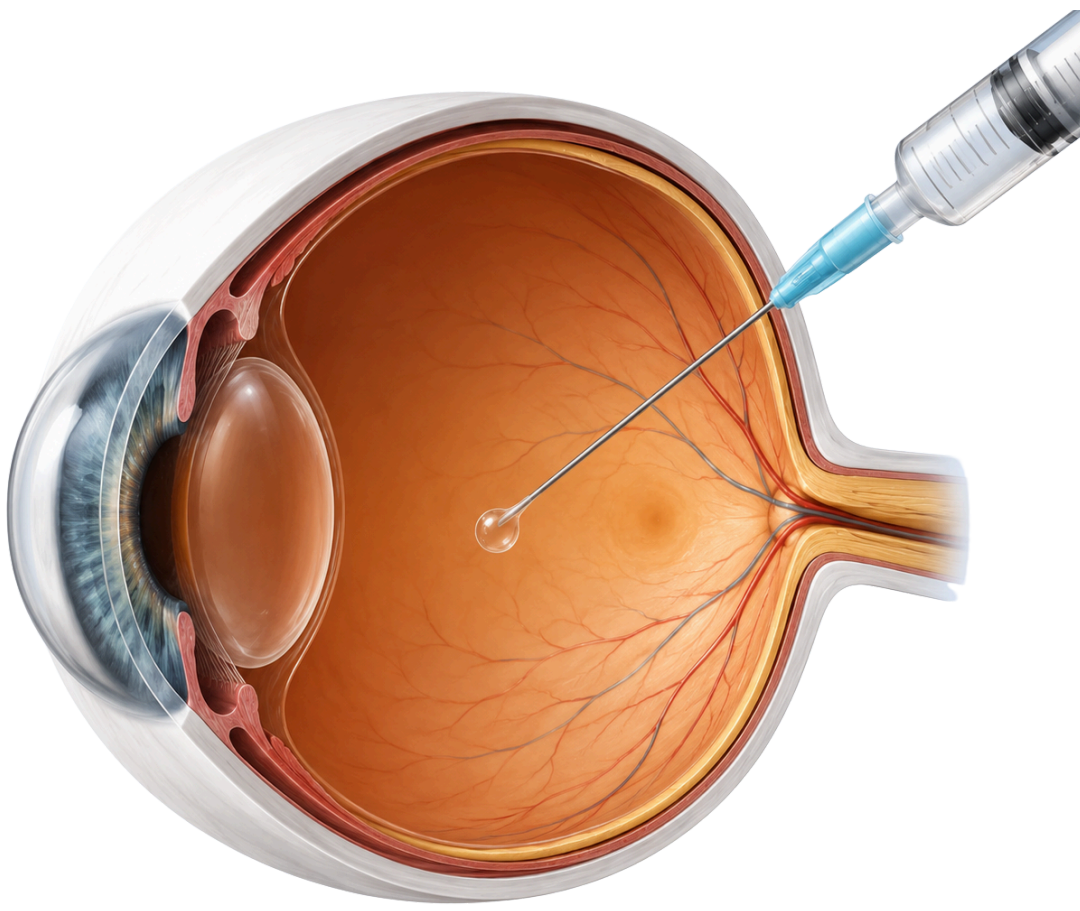
To compare the efficacy and safety of biosimilar Ranibizumab with the reference product in patients with neovascular (wet) Age Related Macular Degeneration (AMD).

The primary objective was to establish therapeutic equivalence between the biosimilar and reference product with respect to change in Best Corrected Visual Acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in adult patients with wet AMD.

Molecule Overview

Ranibizumab is an anti VEGF monoclonal antibody fragment indicated for the treatment of neovascular (wet) Age Related Macular Degeneration and other retinal vascular disorders.

It inhibits vascular endothelial growth factor (VEGF), reducing abnormal blood vessel growth and retinal fluid leakage associated with wet AMD.



Scope of work delivered by Lambda

A global pharmaceutical company engaged Lambda Therapeutic Research to support a large scale Phase III ophthalmic biosimilar study intended for regulatory submissions in highly regulated markets, including the European Union.

The study required coordination across multiple geographies, centralized ophthalmic imaging review, integration with partner CROs, and long term operational oversight over a five year study duration. The programme was designed to meet stringent regulatory and GCP expectations while maintaining consistency in imaging, safety, and efficacy evaluations across sites.

Services provided by Lambda:

- Protocol development support
- Regulatory obligations and submission support
- IWRS setup and implementation
- Central Reading Centre and Medical Imaging management
- Investigational Product (IP) and blinding management
- Trial Master File (TMF) management
- Clinical data management
- Safety reporting and pharmacovigilance support
- Large molecule bioanalysis and logistics coordination
- Clinical Study Report (CSR) preparation
- Operational conduct and clinical trial management across India
- Quality assurance and audit support
- Vendor qualification and management
- Support for software systems integrated with partner CRO operations

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Study Overview

Study Design	• Double masked, parallel group, randomized, multicentre Phase III study
Study Scale	• 546 patients enrolled • 959 patients screened • 75 sites across Europe and Asia, including 51 sites in India
Study Duration	• Approximately 5 years
Major Milestones	• Randomization Phase: 03 years (2021 to 2024) • Interim Analysis: 2024 • Database Lock: 2025 • CSR Release: 2025

Endpoint	• Primary: Mean change in BCVA in the study eye from baseline using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.
	
	• Secondary endpoints:
	  ◦ Evaluation of long term visual acuity outcomes using the ETDRS protocol
	  ◦ Changes in choroidal neovascularization and retinal thickness through fluorescein angiography and SD OCT imaging
	  ◦ Assessment of ocular and non ocular safety
	  ◦ Systemic exposure to ranibizumab and incidence of anti drug antibodies

Systems and Platforms	• Electronic Data Capture (EDC) • Clinical Trial Management System (CTMS) • Central Medical Imaging platform • Pharmacovigilance systems • Integrated Web Response System
Regulatory Standards	• EMA and FDA submission support

Challenges & Solutions

Challenges	Solutions Implemented
Clinical Operations & Study Management	
High enrollment target	• Expanded site network and strong protocol and eligibility training for study teams.
COVID-19 pandemic related challenges: • Disruption in CRA visits • Recruitment slowdown • Exposure risk for elderly patients • Sustaining patients over the 52 week study duration • Continuous IP supply to sites	Mitigation Strategies Implemented • Remote monitoring implemented across sites • Remote support provided to sites and vendors • Continuous oversight and communication maintained with trial sites • Remote and home visits implemented where feasible to minimize patient exposure and reduce site visits • Robust mitigation strategies implemented to maintain study continuity, patient retention, and uninterrupted study endpoints
Sustaining **elderly patients** for 52 weeks in the trial and ensuring adherence to protocol defined visit schedules	• Strong and consistent communication maintained with sites along with regular monitoring of patient visits and study data • Continuous and risk based monitoring with targeted review by Quality and Medical SMEs
Consistent and periodic calibration of **Visual Acuity (VA) assessments** across personnel, equipment, methodology, and designated areas during **extended study duration and COVID period,** including high staff turnover and administrative challenges	• Vendor supported qualification and certification of VA equipment along with frequent targeted retraining • Periodic and robust monitoring of certification and recertification status of equipment and personnel • Strong communication channels maintained by LTR across all participating sites • Tracking and oversight of validation status across 60+ sites

Challenges & Solutions

Challenges	Solutions Implemented
Clinical Operations & Study Management	
Maintaining **blinding integrity** throughout the **3 year study duration**, including during the **COVID period**	Training on IWRS usage, periodic monitoring of sites, and strong project management oversight from Lambda.
Coordination with partner CROs across **multiple geographies** with varying operational practices and cultural barriers	Regular meetings, status updates, aligned communication processes, operational manuals, and sponsor aligned oversight supported workflow standardization and seamless coordination.
Long duration study management	Rigorous oversight, targeted site monitoring, and continuous review by Quality and Medical SMEs.
Government institutions operating under **varied medical practices**	Continuous and risk based monitoring to align study conduct with GCP requirements.
Central bioanalytical **cold chain shipment coordination across Europe with partner CRO**	Shipment vendor qualification, periodic oversight, and review of shipment documentation.
Tracking active **ophthalmic disease parameters**	Centralized ophthalmic imaging platform for assessment of central foveal thickness, area of choroidal neovascularization, and lesion leakage.

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Challenges & Solutions

Challenges	Solutions Implemented
Bioanalytical & Immunogenicity Challenges	
Maintaining Ranibizumab (Fab fragment) **stability** in serum during PK sample handling and analysis	• PK method development and validation were aligned with ICH M10 principles. • Stability preserving controls were incorporated across pre analytical and analytical phases, including standardized conditions for sample collection, processing, storage, and analysis, to maintain ranibizumab stability in serum throughout the sample to result workflow.
PK sample handling and stability: Small antibody fragments susceptible to degradation (e.g., proteolysis) and inconsistent handling can introduce variability	• Temperature controlled collection, rapid processing, and validated storage/shipment conditions implemented throughout the study • Controlled sample handling minimized degradation risk and maintained analyte integrity from sample collection through PK result reporting
Immunogenicity (ADA assay): Different baseline reactivity across Indian and European populations affecting cut point assessment and ADA reporting	• Population specific cut point strategy implemented instead of relying on a single pre study cut point • Separate statistical cut point evaluations performed to support true immunogenicity assessment while minimizing population driven background variability
Variability associated with cell based **Neutralizing Antibody (NAb) assays**	• Competitive ligand binding NAb assay developed to improve sensitivity and reduce run-to-run variability. Robust assay format supported reliable NAb testing and clinically meaningful NAb assessment
Ensuring bioanalytical data comparability across regions, sites, and long study timelines in **a global multicentre study**	• Standardized and harmonized procedures implemented across participating sites and regions • Centralized testing strategy, critical reagent management, and aligned validation/performance monitoring supported globally comparable and regulator ready data

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Key Findings

- Study successfully demonstrated the primary efficacy outcome
- Favorable safety profile observed throughout the study
- Centralized imaging platform supported consistency in assessments across global sites
- Integrated operational approach supported execution across multiple geographies
- Major study milestones achieved within planned timelines
- PK, ADA, and NAb assessments supported reliable immunogenicity evaluation
- Standardized bioanalytical approach supported globally comparable data
- Data supported FDA and EMA submissions

Conclusion

Lambda successfully conducted and supported the execution of a large scale Phase III ophthalmic biosimilar study for wet Age Related Macular Degeneration across multiple geographies. Through integrated clinical operations, centralized medical imaging capabilities, strong quality oversight, and effective coordination with global stakeholders, Lambda enabled consistent study execution over a five year period, including during the COVID-19 pandemic. A harmonized bioanalytical and immunogenicity strategy supported robust PK, ADA, and NAb assessments while maintaining globally comparable and regulator ready data across regions and study timelines. The study met its primary efficacy and safety objectives and supported regulatory review requirements.

The program subsequently achieved successful EMA inspection outcomes, contributing to marketing authorization in the European Union.

Connect with us to explore how we can accelerate your clinical development programs.

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