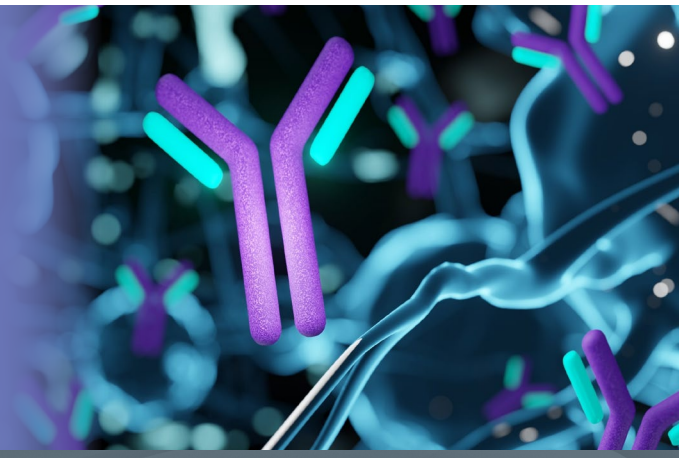
Clinical and Bioanalytical Support for Monoclonal Antibody Drugs



Biologic therapies such as monoclonal antibodies (mAb) target specific proteins or cells involved in inflammatory or immune diseases, often providing more effective treatment compared to a small molecule drug. In addition, since mAb's target a specific pathway, they tend to cause fewer side effects and have longer lasting effects. Therefore, they are often touted for requiring less frequent dose administration and better patient compliance compared to small molecule drugs.

Whether a mAb has immunosuppressive or immunostimulating properties, a First-in-Human (FIH) study in healthy volunteers can provide key information about a drug's safety and tolerability profile prior to patient drug administration. Single ascending dose (SAD) and occasionally multiple ascending dose (MAD) mAb studies can enroll healthy participants. Healthy volunteers can also be considered for bioequivalence studies when there are changes in manufacturing platforms or formulation, as well as for the development of biosimilars.

General Design Considerations for mAb Healthy Volunteer Studies:

Starting Dose Level:

– Determine the starting dose in FIH studies using the lowest value from the Minimal Anticipated Biologic Effect Level (MABEL) or Physiologically Active Dose (PAD) approaches

Sentinel Dosing:

– Initiate dosing with one active and one placebo participant
– Observe a 48-hour monitoring period before dosing the remaining cohort to ensure safety

Long Half-Life:

– Account for prolonged mAb half-lives when designing study duration and dosing intervals
– Assume 21 days for FIH studies based on IgG clearance, if unknown

Safety Profile:

– Track changes in white blood cell counts and populations
– Monitor subjects for cytokine storm, immunogenicity and injection site reactions

Pharmacodynamic Assessments

– Measure receptor occupancy, target receptor engagement, and soluble target levels
– Assess inflammatory cytokines to gauge immune response and target engagement

Celerion Differentiators:

Experience:

– Conducted 60 studies with mAbs since 2010
– Expert clinical and bioanalytical team with extensive FIH study experience

Expertise:

– Principal Investigators (PIs) and Protocol Writers with more than 20 years of biologics experience

Efficiencies:

– 650-bed capacity accommodates large cohorts and studies with multiple returns
– Co-located bioanalytical lab and clinic for immediate PBMC processing and assessment
– Turnkey clinical and bioanalytical solutions for a wide range of biosimilar products

Celerion's Approach to Participant Recruitment & Retention for mAb Studies:

- **Competitive Stipends:** Strategically structure stipends to reflect study demands, including study duration, number of overnight stays, and return visits, ensuring attractive compensation for participants.
- **Efficient Study Design:** For protocols with a favorable safety profile, employ shorter confinement periods (around 72 hours) with scheduled return visits, enhancing flexibility and participant satisfaction.
- **Protocol Flexibility:** Build adaptable recruitment and retention strategies directly into the protocol, allowing for adjustments as needed to optimize participant engagement.
- **Retention Incentives:** Integrate retention-focused incentives, such as performance-based bonus payments, to minimize dropout rates and ensure study continuity.
- **Precision in Bioequivalence Powering:** Accurately power bioequivalence studies to account for critical variances, securing reliable and meaningful data from each participant cohort.

Leverage Immune Biomarkers:

Immune cell biomarkers can be applied in a clinical trial to monitor mAb safety as well as assess early signals of efficacy and target engagement:

– **White Blood Cell Profiling:** Flow cytometry analysis of key white blood cell populations (e.g., lymphocytes, monocytes) and subsets (e.g., T cells, B cells)

– **Inflammatory Cytokines:** Ligand binding assays to assess cytokine levels to monitor immune response and inflammation

– **Chemokines:** Ligand binding assays to assess chemokines to track immune cell recruitment and activation

Key Bioanalytical Assessments:

Celerion employs a wide range of state-of-the art platforms for pharmacokinetic, anti-drug-antibody, pharmacodynamic and neutralizing antibody assessments based on assay context of use.

Assay Type	Assessment	Platforms and Techniques Applied
Pharmacokinetics	mAb concentration	Ligand binding assays (e.g. ELISA, AlphaLISA, ECLA and Gyrolab®)
Immunogenicity	Anti-Drug Antibodies (ADA) Neutralizing antibodies (nAb)	Ligand binding assays and cell- or plate-based assays
Effect monitoring	Soluble biomarkers	Clinical analyzers, immunoassays and multiplex platforms tailored to the mAb's mechanism of action
Target engagement	Receptor binding and pathway engagement	Flow cytometry, ligand binding assays, LC-MS/MS, and enzymatic assays

ECLA, electrochemiluminescence assay; **ELISA**, enzyme-linked immunosorbent assay; **LC-MS/MS**,liquid chromatography with tandem mass spectrometry

RESOURCES:

Your Partner for High-Quality PBMC Processing & Clinical Site Training

Key Clinical Pharmacology Studies to Support Biologic Drug Regulatory Submission

Leaders in Biosimilars