Leveraging Biomarkers In Early Phase Clinical Trials To Drive Smarter Drug Development

In modern drug development, early clinical studies are under pressure to deliver more than pharmacokinetic (PK) and safety data. There is growing recognition among industry stakeholders that early, well-chosen biomarkers can reveal whether a new therapy is engaging its target, producing a biological effect, and demonstrating a signal of potential efficacy, providing insights into pharmacodynamics (PD) long before traditional endpoints are available.

Therefore, integrating biomarkers into early-phase studies, particularly within the PK/PD framework, is becoming not just advantageous but essential. This integration enables smarter, faster, and more informed go/no-go decisions, helping to reduce the risk of late-stage failures and guide development with scientific precision.

The limitations of traditional phase 1 studies

Phase 1 and early phase 2 trials are designed to provide initial data on how a drug behaves in the human body. Most often, this includes characterizing the PK and evaluating safety and tolerability. While these are essential parameters, they fall short of answering a critical question:

Is the drug doing what it's supposed to do biologically?

Traditional clinical trial designs tend to be optimized for throughput, efficiency, and standardization. In many cases, protocols are designed with minimal viable complexity, using endpoints chosen for feasibility rather than scientific relevance. This approach can overlook opportunities to gather data on target engagement or biological activity, which is particularly problematic when the drug acts on novel targets or mechanisms where validated clinical endpoints are lacking or underdeveloped.

This gap can be particularly consequential for early-stage biotech companies or programs focused on first-in-class molecules. Without compelling evidence of pharmacological activity in humans, promising compounds may struggle to secure funding or justify further development, even if they are mechanistically sound.

The growing role of biomarkers in early clinical development

Biomarkers serve as measurable indicators of a drug's biological effects. When integrated into early-phase studies, they can offer a host of benefits:

- Evidence of target engagement: Demonstrating that the compound reaches and acts on its intended target.
- Pharmacodynamic insights: Assessing downstream biological responses to drug exposure.
- Early efficacy signals: Using functional or mechanistic biomarkers that correlate with clinical benefit.
- Safety signal detection: Monitoring on- and off-target biological effects that could indicate risk.
- Data for modeling and simulation: Enabling dose optimization and population PK/PD extrapolation.

Critically, the presence (or absence) of biomarker signals in early studies supports more confident go/no-go decisions, helping developers avoid costly phase 2/3 failures or accelerate programs with clear mechanistic rationale.

A case example: from method validation to therapeutic impact

A recent example highlights how a biomarker-driven approach can shape the trajectory of a novel therapeutic.

A biotechnology company was developing a first-in-class inhibitor targeting ClC-1 channels, with the aim of improving muscle function in patients with myasthenia gravis (MG). ClC-1 channels are key regulators of muscle membrane excitability, a mechanism not previously targeted in clinical trials. Standard endpoints such as muscle strength or symptom scales were considered too downstream and variable to demonstrate early proof-of-mechanism.

To bridge this gap, researchers focused on validating a functional electrophysiological biomarker called muscle velocity recovery cycles (MVRC). MVRC measures the rate at which muscles recover following electrical stimulation and is sensitive to changes in membrane excitability, making it a plausible readout for ClC-1 inhibition. The following steps outline the process the company's researchers followed to validate the MVRC biomarker and integrate it into the development of a new CIC-1 inhibitor.

Step 1: Biomarker validation in healthy volunteers

Before clinical trials of the new compound began, an investigator-initiated study was conducted using registered compounds to explore whether MVRC could serve as a PD biomarker. This study, performed in healthy participants, established baseline characteristics and confirmed that MVRC responded predictably to pharmacological modulation of muscle excitability. It provided critical data on the biomarker's variability and sensitivity, allowing for realistic sample size calculations in future trials.

Step 2: First-in-human study with integrated biomarkers

With MVRC validated, the first-in-human (FIH) trial for the ClC-1 inhibitor was launched. Beyond the standard safety and PK measurements, the study was designed to assess MVRC changes across multiple doses.

The results were compelling: the compound produced statistically significant, dose-dependent changes in MVRC parameters, providing clear proof-of-pharmacology. In addition to confirming target engagement, these data gave early indications of dose responsiveness and therapeutic potential.

Step 3: Translational patient study

Building on the results in healthy subjects, the next phase involved a translational study in patients with MG. Here, MVRC was again used as a pharmacodynamic biomarker, alongside established clinical endpoints such as the quantitative MG (QMG) score.

The study showed that the drug was well tolerated and led to clinically meaningful improvements in muscle function, supported by aligned changes in both MVRC and QMG scores. The biomarker had served its purpose: guiding dose selection, confirming target activity, and connecting mechanism to clinical outcome.

Key enablers for biomarker integration

Integrating biomarkers into early PK/PD studies goes beyond scientific curiosity; it requires a foundation of strong infrastructure, specialized knowledge, and thoughtfully designed protocols. A critical first step is ensuring biomarkers are validated for their intended use, ideally under conditions that reflect the planned clinical intervention. This typically involves preliminary research well before any clinical drug trial.

Equally important is access to reliable and sensitive assays. Whether based on for example biochemical, physiological or imaging techniques, these assays must be capable of consistently and precisely detecting relevant biological changes. The study design itself should also incorporate an integrated PK/PD approach, aligning biomarker sampling with expected drug exposure based on preclinical data and pharmacological modeling.

Interpreting biomarker data requires multidisciplinary expertise. Accurately assessing what a change in a biomarker signifies in terms of drug action, dose response, and biological variability requires collaboration between pharmacologists, clinicians, and data scientists. Finally, productive collaboration between clinical teams, academic institutions, and industry stakeholders is essential to the successful development and application of innovative biomarker strategies.

Impact on drug development decisions

Incorporating validated biomarkers into early-phase studies delivers value across the development ecosystem:

- Smarter investment and development choices: When early studies confirm mechanistic action, sponsors and investors can move forward with confidence. Conversely, absence of effect under the right conditions may signal that a program should be deprioritized.
- Faster, more efficient progression: Early confirmation of biological activity helps streamline subsequent trial designs, inform patient selection, and reduce redundancy in later stages.
- Improved regulatory engagement: Regulators increasingly expect mechanistic data to accompany novel drug applications, particularly for innovative targets. Biomarkers can support rationale for dosing, safety margins, and surrogate endpoints.
- Reduced clinical risk: Safety biomarkers and functional readouts can detect off-target effects before adverse events occur, improving patient safety and preserving compound value.

Looking ahead

As drug development shifts toward precision therapies, complex mechanisms, and data-driven decision-making, the importance of biomarker integration will only grow. Early-phase studies are no longer just about safety, they are a proving ground for therapeutic hypothesis.

The case example described above shows that when biomarker science is aligned with clinical execution, it transforms early trials into powerful engines of insight. Whether measuring receptor occupancy, downstream signaling, functional performance, or safety thresholds, the goal remains the same: to bring better therapies to patients, faster and more confidently.

For development teams willing to embrace this approach, the payoff is substantial: smarter studies, stronger signals, and more sustainable success.