Worldwide Clinical Trials

Case Study

Agile Mitigation for Rapid Trial Timeline Recovery in a Three Cohort Dosing Study for Primary Sclerosing Cholangitis

A three-part dosing study measuring the efficacy, safety, and tolerability of a novel therapeutic developed to treat Primary Sclerosing Cholangitis (PSC), a rare progressive liver disease that ultimately leads to cirrhosis and liver failure, encountered recruitment delays in Part Two. Recognizing this, Worldwide Clinical Trials acted and increased Part Two enrollment through strategic decisions and worked with the sponsor to modify the Part Three protocol to keep enrollment on course.

Case Details

Worldwide ran a blinded Phase IIa study evaluating a novel treatment for patients with PSC and suspected liver fibrosis. The study design included three dosing cohorts, four, 12, and 24 weeks of dosing, comprising Parts One, Two, and Three, respectively. The study's goal involved assessing a novel intervention's safety, tolerability, and pharmacokinetics. Part One went according to plan. However, Worldwide noted slow enrollment in Part Two, which threatened to delay the overall trial timeline significantly, but immediately acted alongside the sponsor to identify the causes and establish effective solutions.

Identifying the Causes

Worldwide's team identified the potential factors leading to slower enrollment, which ultimately came down to the following:

01

Increased screen failure (SF) rate. Part Two experienced a 58% SF rate compared with a standard of 33% seen in Part One. This phenomenon was likely due to strict eligibility criteria, which limited individuals from qualifying that otherwise could have enrolled. Eligibility criteria and other factors, including a smaller cohort, the COVID-19 outbreak, and site tendencies to put best-qualified subjects in their Part One group collectively contributed to the increased SF.

02

A lower percentage of active sites screening. Part Two reached only 15% active site screening compared with the 22% seen in Part One. The lower active site screening metrics indicated reduced trial awareness at the sites and insufficient site-wide education for qualified participant identification.

03

The Part Two protocol was unattractive to participants. Part Two offered 12 weeks of treatment and no open-label extension; multiple investigators communicated that this led to patients' declining study participation.

04

Regulatory approval for protocol amendments extended site activation in the E.U. Following multiple protocol amendments implemented by the sponsor in Part Two, sites in the E.U. awaited regulatory approval before starting site activation or participant screening efforts, leading to fewer site activations in Part Two than necessary.

Worldwide's Solutions

The Worldwide team and sponsor quickly recognized the challenges, implemented plans to mitigate the delays, and kept the overall study timeline intact. The solutions included the following:

1. **Identify and eliminate overly stringent eligibility criteria to reduce the SF rate.**
Worldwide reviewed common reasons for SF to identify if the sponsor could loosen any eligibility criteria without impacting study rigor. Proactively tracking reasons for SF allowed the team to work with the sponsor to create potential amendments as soon as possible.

2. **Elevate study awareness.**
The study team initiated global email distribution to all sites to increase study awareness and provide subject identification strategies. In addition, the team increased Clinical Site Liaison to PI engagement for the remaining Part Two timeline and leading into Part Three recruitment, collectively aiming to improve patient screening volume and shorten the duration of the end of Part Two and Part Three.

3. **Part Three protocol adjustment to increase trial attractiveness for current and prospective participants.**
In response to site reports suggesting that eligible patients were uninterested in participating, the sponsor and Worldwide worked to modify the Part Three protocol to include a minimum of 24 and up to 48 weeks of treatment for new patients and allowed Part Two participants the opportunity to enroll in Part Three as a surrogate treatment extension.

4. **Establish a single resource to fill both Site Activation Manager and Regulatory Lead roles.**
The resourcing model reduced the regulatory oversight time required to work with regulatory agencies and internal personnel to obtain approvals.

The Results

The sponsor and Worldwide collaborated on an approved protocol amendment that made essential eligibility requirements less stringent without impacting study rigor. These adjustments improved enrollment at the Part Two midpoint and allowed a broader subject base for Part Three. In addition to protocol amendments, optimized start-up resourcing ensured the trial stayed on track.

Together, we achieved:

- Site recruitment optimization from 15% in Part 2 to **23%** in Part Three.
- **Higher participant enrollment and retention** after participants learned they would have extended treatment opportunities beyond the initial 12 weeks.
- A more than **doubled screening rate**, from an average of seven subjects per month in Part Two to 15 subjects per month in Part Three, following increased communication to each site regarding participant screening awareness.
- **A reduced SF rate** that returned to an expected level, matching the observed rate in Part One.
- **A significantly quicker** 14-week enrollment period for Part Three compared with the slower rate in Part Two.
- Increased volume of sites with protocol approval, from 32% at the beginning of Part Two to **100%** in Part Three, after adding a Regulatory Affairs Manager to support better engagement.

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Why Worldwide?

Rare disease research is associated with significant additional challenges in participant enrollment, in part due to the lower global patient population, reflective of the rare designation, and the increased complexities across global regulatory body oversight. Worldwide has a deep history in rare and orphan indications and commits to providing hands-on, team-based approaches to facilitate trial success and high-quality data. Our experts bring decades of collective expertise and provide custom-tailored approaches to each trial, ensuring adequate and specialized attention from start to finish. We maintain vigilance over trial timelines and act quickly whenever potential delays or hurdles arise.

Contact us for more information on how our experts can help you with your current or upcoming rare disease clinical trials.

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