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BRINGING CLINICAL TRIALS TO LIFE

Leukemia Drug
Fast Track Drug Approval for Leukemia

Highlights

- Synteract was responsible for site qualification, training, regulatory support.
- With changes at the sponsor, an ill patient population, and numerous sites involved—Synteract was instrumental in ensuring a smooth study.
- Results for the drug were positive; the sponsor received FDA approval nearly six months early.

Introduction

When there are few efficacious drugs for any given illness or disease, companies with promising technologies may pursue expedited drug approvals. The case study ensuing is one example of

supporting a FastTrack designation for expedited drug approval that was handled by Synteract with a client that was working on a drug for leukemia.

The drug, now FDA-approved and available, is a monoclonal antibody for acute lymphocytic leukemia (ALL). Limited treatment options are available for this type of leukemia; therefore, the sponsor was able to get agreement from FDA authorities to fast track the study, using data from Phase II studies for filing. The FDA indicated that if the drug proved to be as promising as it originally appeared, they might be able to get an expedited marketing approval as well.

The Phase II study began in July of 2011 and won't actually complete until 2018. As ALL is a chronic long-term illness, participants will be studied for several years to see how long the drug continues to extend survival. It's important to note that this study was available only for the large universe of patients for whom other ALL drugs are not working well. It is not a frontline treatment but rather a treatment for those who are relapsed or refractory.

In light of these conditions, the study is also larger than is typical, and has been expanded by more than 100 people. Some characteristics of a Phase III study were included in the protocol development. The study included rigorous inclusion and exclusion criteria; most patients were quite ill.

A dose depth study, rather than an escalation study, meant that most of the patients started at about the same time. Since there were no approved drugs really competing – and this one was working to extend survival rates – the study enrolled faster than expected. In fact, many doctors were clamoring to

get their patients included. The goal and hope was to get them clear of the disease so they could receive stem cell transplants. (The good news is that some are doing well enough that they have opted not to even get stem cell transplants.) Two studies were being handled with this client, with the first ahead by about 3 months; the studies are comprised of slightly different patient populations.

Challenges

The small European biotech sponsor had innovative scientists and researchers on staff, however, they were naïve to research standards in the US. Study managers were unfamiliar with US regulatory requirements, site differences, and other geographic variances. Synteract project managers provided education on SOPs for sites, visits, monitoring, timing, and other differences between US and EU study standards. Synteract's team made the sponsor aware of study challenges and offered solutions enabling the sponsor to make the best decisions.

Less than nine months after the study began, the small biotech was acquired by a large multinational biotech company. Although the original group still functioned relatively autonomously, this acquisition resulted in a significant rescaling of the project – an increased budget extended it in both size and time, as well as increasing site visits and study procedures. The unmet medical need and high investigator interest led to several increases in target recruitment as well, finally resulting in 225 subjects treated, with 185 evaluable. This large number is not typical for a Phase II study and it became very complicated due to the large number of samples to be collected and analyzed.

With a very ill patient population and the large number of sites/countries included–about 40 sites in the US, UK, France, Germany, Italy, Spain–it was important that no study disruptions occur despite the acquisition changes underway. **Synteract was responsible for site qualification, training and coaching.**

Study logistics were complicated as well. Treatment was given by continuous infusion using pumps carried by the subject; this involved homecare nurses to change each bag before it ran out. Patients carried a small purse with their pump but they had to be checked frequently to prevent problems. Bags were prepared in hospital and shipped to the person's home. Although patients were a bit nervous about this, most were happier to be home rather than in a hospital.

Our Solutions

The Synteract team consisted of a project manager, two clinical leads, a CTA (admin who is responsible for data accuracy) and approximately 14 CRAs. The first point of contact for study coordinators were CRAs from Synteract who answered questions and worked closely with them to resolve complex study issues, bringing in the sponsor as needed for resolution. **Synteract offered intensive site support by resolving study logistics, but of equal and perhaps unexpected importance, by providing emotional support for coordinators dealing with very ill patients.**

Patients underwent a 28-day continuous IV infusion with intervals of two weeks – which could be repeated up to 5 cycles. Response was assessed after the first cycle; if the patient was worse, they were off the study. Primary response end point was after 2 cycles; if a patient had complete response

or a complete response with partial hematological response, then they could get 3 additional cycles. For CRAs it meant lots of paperwork, but the process worked well because the coordinators and nurses were well trained around complex study nuances, and perhaps most important, were compassionate and helpful.

The sponsor handled data management/biostatistics; however, Synteract was responsible for checking the cleanliness and accuracy of data during regular clinical monitoring visits and for timely delivery of data to the biostatistics group. Synteract overcame challenges of data review associated with multiple protocol revisions to meet sponsor timelines for data snapshots and database lock.

The merged sponsor company made a small change in drug formulation, working with regulatory authorities to get approval to do that. Synteract was responsible for the submission of the request to agencies and ethics committees. In all, five protocol amendments were released – about every 5-6 months – so the teams had to adapt each time, by retraining, managing any staff turnover, and looking at neurological side effects of the drug. A sixth amendment was released in November of 2014 and since the commercial drug was not yet available and they had to provide a way for patients to get the drug, entirely new patients were still being enrolled.

Everyone on the team worked shoulder-to-shoulder in problem solving with the sponsor who, like Synteract, took a collaborative approach; it proved to be a good partnership of equals. The long-term team developed good relationships, confidence, respect for each other and a common goal to meet deadlines.

Results

Synteract offered an experienced and dedicated CRA team over a long study period requiring intensive investigative site support. This workforce provided much needed communications continuity over time, in addition to longstanding expertise and historical knowledge. Good communications among the sponsor, biostats and Synteract teams were enhanced by the fact that the drug was working, so optimism prevailed as well.

Organization, communication and written standards to document and centralize information were handled by Synteract as needed for FDA audits. The Synteract project team handled three FDA audits at sites and one at the sponsor's US headquarters, where the sponsor's TMF (trial master file) was audited. We supported with documentation and knowledge on what to anticipate in audits. CRAs offered preparation support for two sites.

Results for the drug were positive; therefore, the sponsor received FDA approval for this drug nearly six months earlier than the expected approval date. The study will continue to go on as planned and teams will continue to collect data for the long-term follow-up and newlyenrolled patients.

The FDA granted Breakthrough Therapy Designation status to this leukemia drug. Notes from the December 2014 FDA document approving the drug:

> *The pivotal clinical trial upon which the drug was approved enrolled 185 adults with B-cell ALL no longer responding to previous treatments. Following treatment, 32% of patients had a complete remission, meaning there was no evidence of the cancer in their body. The median duration of response was 6.7 months.*
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> *The clinical research study manager at the original small biotech who worked closely with us, says, "Synteract was a great partner for achieving a FastTrack designation for expedited drug approval. This study was bigger, faster and more complex than originally expected. They helped us to understand US regulations and requirements of sites, in addition to managing, tracking and monitoring of data. Soft skills were also critically important in this study – to answer questions, retain patients and maintain compliance. We have solid respect for the great CRAs that helped to solve issues."*

About Synteract

Synteract is an innovative, full-service CRO supporting biopharma companies across all phases of drug development to help bring new medicines to market. Synteract has conducted 4,000 studies on six continents and in more than 60 countries, working with more than 26,000 investigative sites and 750,000 patients. It has contributed to more than 240 product approvals. Synteract offers a notable depth of expertise in oncology, general medicine, dermatology, and neuroscience indications, as well as rare and orphan, pediatric, and immunotherapy studies.

For more information on how we can support your clinical trial, please visit www.synteract.com/Therapeutic-Expertise/Oncology or ContactUs@synteract.com.

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