CASE STUDY

EMERALD CLINICAL TRIALS

Global and National Scientific Leadership Helps Move Potential Breakthrough CKD Anemia Treatment Forward

Exceptional kidney and metabolic scientific leadership network provides continuity, communication and cultural expertise in long-term global trial program.

BACKGROUND

The National Institute of Diabetes and Digestive and Kidney Diseases (NIH) estimates that more than one in seven people with kidney disease have anemia, increasing their chance of developing heart problems and strokes. The prevalence of anemia increases as chronic kidney disease (CKD) progresses and is associated with an increased risk of hospitalization, cardiovascular complications and death. CKD is a significant global burden with more than 700 million people worldwide living with CKD. Current common treatments for CKD anemia include Erythropoiesis-Stimulating Agents (ESAs) and intravenous iron. However, there are safety concerns around both.

In 2011, the FDA began recommending more conservative dosing of ESAs because of data showing increased risks of cardiovascular events. KDIGO guidelines also suggest a conservative use of ESAs and express concern over the use of intravenous iron. These facts indicate the importance of finding new treatments for the millions of patients globally with CKD related anemia.

Hypoxia-inducible factor (HIF) prolyl hydroxylase enzyme inhibitors (PHI) are a new class of agents that could potentially play an important role in the treatment of renal anemia and have shown enough promise in clinical trials to warrant significant attention. HIF-PHIs would avoid injections and may also reduce the tendency to raise blood pressure. Clinical trials are underway to determine if HIF-PHIs are associated with fewer adverse cardiovascular effects at comparable hemoglobin levels.

SITUATION

ASCEND Program Evaluates HIF-PHI in 41 Countries
GlaxoSmithKline has conducted multiple studies under the Phase III ASCEND program to evaluate the efficacy and safety profile of daprodustat, an investigational HIF-PIH for CKD patients with anemia. The program enrolled more than 8,000 patients in 41 countries who were treated for up to 4.26 years.

"This is an exciting time because typically nephrology has been seen as a specialty using traditional treatments not well supported by strong evidence-based practices. That is because most clinical trials exclude patients with kidney disease due to concerns over their risk factors. The ASCEND trials will provide more insights on the safety and efficacy of HIF-PHI in treatment of anemia in CKD. It will also address their role in cardiovascular—even in pre-dialysis and patients receiving dialysis," stated **Muh Geot Wong, Emerald Clinical scientific leader, Sydney, Australia and ASCEND team's Regional Scientific Lead – APAC.**

ASCEND-D, an event-driven, open label, randomized, active-controlled, parallel-group, multicenter Phase III trial, conducted in 41 countries worldwide, was one of the largest anemia studies in dialysis patients (2964 patients), performed across Europe, North America, Latin America and Asia Pacific.

ASCEND-ND trial randomized 3,872 non-dialysis dependent patients spanning more than 40 countries and evaluated the efficacy and safety of daprodustat when compared with darbepoetin alfa in CKD patients with anemia not requiring dialysis.

In addition to the ASCEND-D and ASCEND-ND studies, the program also included studies focused on incident dialysis for patients just starting dialysis (ASCEND-ID); quality of life measures (ASCEND-NHQ); as well as three-times weekly dosing regimens (ASCEND-TD). Each of the studies from the program met its respective primary or co-primary endpoint(s).

Emerald Clinical was involved in steering committee management for the studies since the beginning of the program which included the major effort of organizing all steering committee meetings for the duration of the program and managing their logistics, members and oversight responsibilities.

Global and national scientific leadership from Emerald Clinical participated across the many countries involved in this enormous program. These committees were led by Zuhaib Baig of project operations as the global project lead with support from several Emerald Clinical operations team members as well as fellow scientific leaders Dr. Muh Geot Wong and Dr. Inna Kolesnyk.

With our more than 20 years of global kidney and metabolic experience and our network of recognized and influential kidney and metabolic scientific leaders, Emerald Clinical was a good fit for the job and was present and accounted for in every "corner" of the **ASCEND program.**

CHALLENGES

Long-term global trials face challenges including recruitment and retention. And in the case where a long-running trial involves patients with poor health conditions, such as CKD anemia, these issues become even more critical.

ASCEND was a multi-trial, multi-year program spanning more than 40 countries creating many logistical challenges and a high risk of dropouts. In addition, there were language and cultural issues as well as nuances in treatments and clinical practices from country to country and even site to site. Challenges included proper messaging and communications specific to each country/patient population.

It must also be noted that much of the program was conducted during the pandemic, adding further challenges and stresses to all involved.

SOLUTIONS

Our scientific leadership team has clinical, research and trial experience and a peer-to-peer network with a track record of involvement in the development of new treatment strategies across diverse populations. As members of the steering committee, they ensured that ASCEND answered the fundamental scientific questions aiming to address key clinical needs and that all stakeholders were engaged and focused.

Our team managed communications, meeting agendas and all face-to-face and virtual meetings. This ensured that everyone was "sitting in the room" for decisions affecting the trials, as well as updates, scrutiny of current operations and discussions over challenge resolutions.

National leaders, chosen because of their expertise and local influence, have knowledge of local clinical practices and patients. They have previously worked with many of the sites and know how to tailor messaging for each particular audience. As a conduit between principal investigators and study committees, they led routine, interactive webinars where teams shared and learned from each other. **This created a true value exchange that benefited the sponsor, the trial and ultimately the patients and future clinical practice.**

In order to give continuity throughout the extended multi-year study, Emerald Clinical maintained the same team from start to finish. Regular communications helped build team experience and allowed pro-active attention to any arising issues. **National leaders know their sites and understand that one blanket approach doesn't always work for all countries—ensuring that the study was suited to all countries involved at every step of the way.**

Recruitment challenges were met with an energized and dynamic environment of recruitment and constant communication of metrics between countries, inspiring all teams by sharing strategies.

Emerald Clinical's team experience in previous global trials resulted in the ability to formulate effective retention policies focused on patients and communicated directly to sites. **Our scientific leaders have developed relationships with sites and investigators and, if necessary, can step in and personally help solve any issues with patient retention.** They also made sure that our studies didn't "fall off the radar" of sites that might be conducting other studies simultaneously.

In addition, Emerald Clinical in collaboration with Duke Clinical Research Institute was in charge of adjudicating pre-defined events as the Clinical Events Classification (CEC) group.

RESULTS

Because of Emerald Clinical's strong peer-to-peer network of therapeutic specialists familiar with clinical practice, research and clinical trial operations, challenges in ASCEND were handled proactively and with the scientific aims always top of mind.

Emerald Clinical teams were integral in assuring that recruitment and retention of the ASCEND trials stayed on track across multiple countries and sites over the 3- to 4-year period of the trials. Patients benefited from the involvement of our kidney and metabolic scientific leaders who have worked together on multiple global trials and who understand the nuances in cultural differences and clinical practices.

The ASCEND program showed that daprodustat met its primary efficacy endpoint in each study.

"The positive results from these long and complex ASCEND studies, with which Emerald Clinical teams have been involved for the past several years, are important for our industry, kidney and metabolic practitioners and those suffering from CKD around the world," said **Chief Medical Officer Maria Ali.**

GlaxoSmithKline announced late-breaking data from the daprodustat ASCEND-D and ASCEND-ND trials at the American Society of Nephrology's Kidney Week 2021. Results of the study have now been published in two New England Journal of Medicine articles:

ASCEND-D:
https://www.nejm.org/doi/full/10.1056/NEJMoa2113379

ASCEND-ND:
https://www.nejm.org/doi/full/10.1056/NEJMoa2113380

Also, check out more from Emerald Clinical's ASCEND team members here: https://www.georgeclinical.com/george-clinical-case-studies/insight-ascend-program

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