WORLDWIDE CLINICAL TRIALS

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EXPLORING THE FUTURE OF CLINICAL RESEARCH FOR IMMUNE-MEDIATED INFLAMMATORY DISEASES

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Immune-mediated inflammatory diseases (IMID) encompass a wide range of disorders. This includes multiple sclerosis, rheumatology disorders, psoriasis, inflammatory bowel diseases, COPD, pulmonary fibrosis and asthma, as well as immunosuppression within transplantation and other minor therapies and pathologies, and also some rare diseases. Significant and ongoing research into IMID pathology and genetic links have led to the knowledge that underpinning these diseases is the dysregulation of the immune system, which leads to widespread and chronic inflammation. These discoveries have delivered a more comprehensive understanding of immune-mediated mechanisms, and the promise for more effective treatments and possibly even cures for a range of IMID disorders.

IMID CLINICAL TRIAL CHALLENGES

In the search for more effective treatments and cures, there are challenges that sponsors and contract research organizations (CROs) must confront when conducting IMID clinical trials.

- **Conducting research around the world.** Today, many sponsors and CROs are considering IMID clinical trial sites in nontraditional countries, due to lower costs, competition for investigator sites, and the search for treatment naïve patients.

  While conducting clinical research in these countries can present real opportunities in the identification of these patients, they also can pose challenges when using less experienced investigator sites. To ensure success, CROs must conduct extensive investigator site training and deploy experts to adequately control and monitor the research program.

- **Standadized protocols.** Some clinical trial protocols are not consistent with clinical practice, making it difficult for investigators to comply. For instance, in rheumatology clinical practice, individual rheumatologists may use a subset of joints to assess joint function in a particular patient as part of a global evaluation of the patient's condition. However, in a clinical trial, investigators must use a specific, prescribed series of joint assessments for all patients, and usually are required to be blind to other clinical information regarding the patient. Additionally, patients with no or limited previous exposure to biologics are typically to be recruited, making achievement of recruitment goals very challenging as well as leading to a potentially important discrepancy between the patient population enrolled in clinical trials and the one that most likely will receive the drug once available on the market.

  Perhaps more so with IMID trials than other research programs, it may be time to move away from using standardized protocols and study designs. Instead, adaptive clinical trial designs or different study end points should be explored to align with changes and advancements in the clinical management of a disease and its course.

- **Utilization of the full therpaeutic armamentarium.** There is evidence that in some developing countries clinicians may jump from traditional yet relatively dated treatments directly to the latest investigational drug, without exploring the full scope of other available treatments. This approach is one that wouldn't be used in clinical practice and may have significant effects on the efficacy and safety of an investigational drug.

  When conducting trials in developing countries, proper vetting of investigator sites and extensive training when a site is selected can help to ensure that correct steps are being taken for the care and management of patients.

- **Patient recruitment.** Against the competitive landscape that you find in research and development of IMID drugs, participating in these trials requires a significant commitment on the part of the patients and investigator sites, involves complex protocols, and can compete with a wide range of currently available treatments, which means that the supply of investigator sites and willing patients can be quickly exhausted.

In addition to exploring locations around the world to identify naïve patient populations, a CRO should have existing relationships with research networks, specialized treatment centers, and academic institutions. Additionally, connecting with patient organizations and engaging key opinion leaders can assist in site identification and patient recruitment. Having local resources that are updated on local regulation and reimbursement policies for supplying patients with RA therapies can help in selecting the most appropriate countries.

FUTURE FEATURES OF IMID CLINICAL TRIALS

Over the last 20 years, biological therapies have revolutionized the treatment of immune-mediated inflammatory diseases. More recently, while the development of new IMID drugs may have slowed, clinical trials exploring the potential of existing drugs, including changes in dosing regimens, drug withdrawal, drug combination, or self-administration, have become more common.

In parallel, due to patent expiration, clinical development of biosimilars has been increasing. Such clinical programs, although less complex than those of originators, are still demanding in terms of cost and need for patients, while also presenting new challenges, especially from a regulatory point of view.

Conversely, the bar for development of new biologics has been raised, with regulators requiring demonstration of clinical benefit in terms of efficacy or safety of the new drug in comparison to already approved biological therapies.

IMID indications that have always proved more challenging for drug development, such as lupus erythematosus, are also being more frequently pursued, with increasing evidence of the inadequacy of current study designs and clinical end points.

These complexities contribute to increased competition for investigator sites and patients, but also can create different and new types of target patient populations, outside of those that have previously been considered.

THE NEED FOR EXPERTISE

There continues to be significant interest in the field of IMID research, especially with ongoing research advances, including those referenced above. Investigator sites that have traditionally participated in IMID trials are increasing their research activity, which is further increasing the competition for patients at those sites. This underscores the importance of identifying and engaging not just today's investigators, but the investigators of the future. Successful CROs will develop and nurture relationships with emerging investigator sites around the world, and provide them with the proper guidance and training to ensure adequate bandwidth for future IMID drug development. Additionally, the ability to offer "on the ground" global capabilities through a broad geographic footprint—combined with expertise in regulatory start-up processes, clinical management and project management across a wide range of countries—will be required for the successful execution of IMID clinical trials in the years ahead.

Finally, when embarking upon any research program, it's critical to stay focused on the needs of patients, both for those who will participate in the trial and those who may be impacted by the future potential of new drugs under development. Thoughtful study design should consider the challenges a patient may have throughout a clinical trial, whether it be access to the investigator site, complexity of the various measures, or need for self-monitoring and reporting. By targeting appropriate patient populations, developing well thought-out study designs, and providing comprehensive training and support to investigator sites, clinical research programs can benefit the patient and accomplish the goals of the study sponsor. The future success of IMID drug development is reliant upon the close collaboration between the sponsor companies that are uncovering new compounds for study, and the CROs that often lead the execution of these important clinical research programs. Since finding a new treatment for an IMID can definitely modulate the course of the disease, regulatory agencies have developed specific criteria for approvals of such treatments. Hence, understanding and experience with such guidelines are key factors to ensure an effective strategy for the approvals of these treatments.