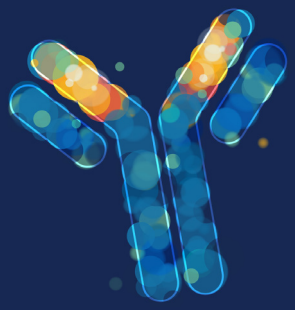

Article:

ADVANCING MAST CELL INHIBITOR DEVELOPMENT: PROTOCOL STRATEGY, ENDPOINT SELECTION, AND THE ROLE OF EXPERIENCED CROS

Authors: Kelly Metz, MD, Maxime Jeljeli, MD, PhD, Ashley Best, PhD, Nick Ackley

THE ROLE OF MAST CELLS IN HUMAN HEALTH AND DISEASE

Mast cells were first observed by Friedrich von Recklinhausen in 1863 in the connective tissue of tadpoles.[1] In 1877, Paul Ehrlich named these cells "mastzellen," meaning well-fed cells, as staining showed granulated cells that were thought to have ingested nutrients.[2,3] Several decades later, Heinz Küstner passively sensitized Carl Prausnitz to fish allergen, resulting in what is now recognized as anaphylaxis.[4] However, it was not until the 1960s that IgE, the critical immunoglobulin in the pathophysiology of allergy, was discovered and the relationship between mast cells, IgE, and hypersensitivity was unraveled.[5]

Mast cells are immune cells distributed throughout nearly all mucosal and epithelial tissues, mainly at sites of entry where the external environment meets the host in the skin, respiratory tract, gastrointestinal tract, as well as deeper connective tissues. The role of mast cells has been further defined as multifunctional inflammatory cells, serving as effector cells in allergy as well as regulators of both innate and adaptive immune function.

In the innate phase, mast cells trigger immediate inflammation by releasing preformed mediators like histamine, tryptase, and the pro-inflammatory cytokine TNF-α, which recruit neutrophils and other immune cells to the site of injury. Additionally, mast cells modulate the activation and migration of dendritic cells to lymph nodes and can even act as antigen-presenting cells themselves, directly influencing T-cell priming and B-cell antibody production. While essential for clearing infections and wound healing, their regulatory power can also drive chronic pathological conditions like allergy or autoimmunity if not properly controlled.

Mast cells' role in the allergic process begins when the adaptive immune system becomes sensitized to a harmless substance (allergen), leading B cells to produce IgE antibodies. These IgE molecules bind to high-affinity FcεRI receptors on the mast cell surface, effectively "arming" the cell. The primary trigger for degranulation occurs during a subsequent exposure, when the allergen cross-links these surface-bound IgE antibodies, causing an explosive release of internal granules. This rapid innate-style response directly causes clinical symptoms: histamine dilates blood vessels and increases permeability (leading to redness, swelling, and hives), while also stimulating sensory nerves (causing itching). In the airways, mediators like leukotrienes cause smooth muscle contraction and mucus overproduction (resulting in wheezing and congestion). If this regulation fails systemically, the massive, simultaneous recruitment of fluids into tissues can lead to a life-threatening drop in blood pressure, known as anaphylaxis.[6]

Mast cells' role in autoimmune diseases is still being explored, but studies have shown their involvement in conditions like multiple sclerosis, rheumatoid arthritis, and type 1 diabetes through the release of inflammatory mediators and the modulation of immune self-tolerance.[7]

As such, mast cell diseases affect many end organs and therefore cross multiple therapeutic areas. For instance, mast cells engaged in the gut can contribute to conditions such as eosinophilic esophagitis (EoE) and mast cell activation syndrome; in the skin to urticaria; in the eye to conjunctivitis; in the nose to rhinitis; and in the lung to asthma.

THERAPEUTIC APPROACHES TARGETING MAST CELL ABERRANT FUNCTION AND HYPERPLASIA

Mast cell disorders occur when the mast cells are increased in number, are normal in number but overly reactive, or both. Mast cell dysfunction is fundamentally driven by dysregulated tyrosine kinase signaling, where enzymes like Syk and KIT act as critical molecular switches for degranulation and survival. Aberrant function, such as the KIT D816V mutation, leads to pathological mast cell accumulation or hyper-responsiveness in diseases like systemic mastocytosis, asthma, and irritable bowel syndrome. Clinical monitoring of these conditions relies heavily on serum tryptase as a primary biomarker for cell burden and activation, supplemented by others like histamine metabolites, prostaglandin D2, and heparin.

While current reactive therapies like antihistamines and corticosteroids offer symptomatic relief, they fail to address the underlying cellular "engine" or reduce the total cell population. This creates an urgent need for targeted approaches that go beyond surface-level symptoms. In addition to potent tyrosine kinase inhibitors (TKIs), like avapritinib and midostaurin, which shut down survival signaling, newer strategies target diverse pathways: omalizumab acts as an anti-IgE antibody, preventing the "arming" of mast cells by sequestering IgE before it can bind to the FcεRI receptor. Mast cell stabilizers, like cromolyn sodium, work by inhibiting the influx of calcium ions necessary for degranulation, while Siglec-8 agonists represent innovative depletion strategies that trigger programmed cell death specifically in mast cells and eosinophils. Furthermore, BTK inhibitors, such as ibrutinib, are being explored to block the signaling cascade immediately downstream of the IgE receptor. Together, these targeted therapies aim to achieve long-term remission and precise disease control by physically reducing the mast cell "army" or permanently silencing its internal triggers.

Despite meaningful advances and increased understanding of mast cells, a substantial unmet medical need remains across mast cell diseases. Many patients continue to experience incomplete symptom control, disease flares, and impaired quality of life (QoL) with limited targeted treatment options available. There is a critical need to optimize how mast cell inhibitor trials are designed and executed. In the following sections, we will explore the clinical and operational challenges that can impact development in this space, and how addressing these barriers is essential to improving treatment options and ultimately delivering better outcomes for patients.

STRATEGIES FOR CONDUCTING MAST CELL INHIBITOR TRIALS

Due to the complexities of mast cell inhibitor trials, robust protocol development is essential and must navigate the clinical complexity of background therapy management and the physiological challenge of biomarker-driven precision.

Enrollment and Data Integrity

Many patients manage mast cell diseases with antihistamines, steroids, or both, which directly impacts baseline mast cell activity. To effectively evaluate the on-target efficacy of new therapies, participants must either maintain a stable background regimen or undergo a washout period. However, discontinuing these medications presents significant barriers, primarily due to a pervasive 'flare fear' among patients who struggle daily with unpredictable, severe symptoms. This anxiety, coupled with the practical burden of long washouts, creates a major challenge for recruitment and retention. To lower these barriers, cross-over designs and clear, protocol-driven rescue medication allowances can mitigate the placebo-arm resistance common in this population.[8]

To overcome recruitment challenges, robust site education is critical. Principle investigators must be equipped to clearly communicate the potential benefits of participation and advantages of biologic treatments. Highlighting improved administration profiles, such as reduced dosing frequency with long-acting biologics or the convenience of targeted oral therapies, can help alleviate patient concerns and increase interest.

Beyond convenience, investigators should emphasize that participants gain access to novel mechanisms that target the root cause of mast cell activation and receive expert specialized care with comprehensive monitoring often unavailable in standard clinical practice. Furthermore, participation allows patients to make a meaningful contribution to research while benefiting from a reduced financial burden, as most trials cover the cost of study medications and specialized diagnostic testing. Tools to support the investigators' discussions with potential participants should cover all of these talking points and more.

Given the complexity of mast cell inhibitor trials, innovative engagement strategies are required. Since many patients remain symptomatic or undertreated, they often explore alternative options online, making a strong digital presence and targeted study branding vital for connection. As the approval landscape varies across the globe, it is important to consider gaps in treatment availability and insurance coverage as drivers for participation; in areas where newly approved medications may not yet be available, or not covered, there is additional motivation for those patients to be seeking additional information online and connection with regional advocacy groups.

In the U.S., the pool of eligible patients is often limited by a few approved medications for conditions like Systemic Mastocytosis or Chronic Spontaneous Urticaria (CSU). Outside of the U.S., patient eligibility depends on the use of currently approved drugs and treatment access varies greatly by country. Local, on-the-ground expertise from a Contract Research Organization (CRO) is vital. It informs feasibility assessments and optimizes country selection. This expertise ensures a deep understanding of local prescribing practices and healthcare coverage.

This pool is further narrowed by stepwise treatment requirements that must be exhausted before experimental biologics. Furthermore, patient hesitancy toward subcutaneous (SC) injections can pose a barrier, particularly for those who prefer or now have access to oral treatment options. Finally, enrolling patients with a precise, documented diagnosis, such as Hereditary Alpha-Tryptasemia (HaT) or Mast Cell Activation Syndrome (MCAS), requires close collaboration with specialized diagnostic centers to ensure protocol compliance.

Strategic collaboration with patient advocacy groups can bridge the trust gap, as these organizations provide a credible platform to educate the community on the importance of clinical research and the safety measures in place to mitigate risks like rebound flares. Medpace can support a well-vetted feasibility and recruitment strategy through targeted outreach, patient-centric trial design, digital engagement tools, and strong partnerships with experienced sites, investigators, and patient advocacy networks to accelerate enrollment and reduce attrition. This approach is reinforced by dedicated recruitment teams and site support services, including feasibility assistance, training resources, and study team support where needed.

Site Selection, Feasibility, and Training

Selecting the right clinical sites is critical to the success of mast cell inhibitor trials. Given the complexity of these trials, sites should have extensive experience in conducting allergic and inflammatory disease trials. Because mast cell diseases span multiple therapeutic areas including gastroenterology, allergy, immunology, pulmonary, ophthalmology, ENT, and/or dermatology, ideal sites should demonstrate interdisciplinary expertise or robust cross-departmental involvement, where necessary. Prioritizing sites with existing referral networks, particularly those involving all targeted specialties for the trial, can significantly facilitate more efficient recruitment.

Lastly, sites must have the necessary capabilities and resources, including specialized diagnostic equipment (such as refrigerated centrifuges for mediator processing), access to specialized procedural suites for biopsies, staff trained in standardized skin photography, and ePRO administration and oversight. These factors should be primary considerations during feasibility assessments.

Medpace recommends that patient pathways be clearly defined during feasibility, alongside a thorough understanding of the site's cross-therapeutic experience, referral networks, prior enrollment performance, patient identification workflows, and local patient landscape. During start-up, this evaluation should extend to the site's planned recruitment approach, database and chart review processes, staffing model, competing studies, and operational readiness to support study-specific procedures, patient education, and follow-up.

This assessment is strengthened by centralized support from Medpace's Patient Recruitment and Retention team, which partners with sites early to refine recruitment plans, identify appropriate outreach tactics, develop tailored site and patient engagement strategies, provide IRB-approved educational and recruitment materials, and equip site staff with practical tools and training to support consistent execution. Together, these feasibility and start-up activities help reduce site and patient burden, support timely activation, and improve enrollment and retention performance.

Endpoint Selection and Hierarchy

To ensure clinical success, protocols must strategically define primary and secondary endpoints that satisfy both regulatory requirements and scientific depth. The primary endpoint should focus on a clinically meaningful, validated measure of disease activity, such as a significant reduction in baseline serum tryptase for mastocytosis or the Urticaria Activity Score (UAS7) for chronic spontaneous urticaria. Conversely, secondary endpoints should be designed to capture the broader systemic and physiological impact of the drug. These should include pharmacodynamic markers like the reduction of urinary N-methylhistamine or PGD2, as well as patient-reported outcomes (PROs) that quantify improvements in QoL and "flare" frequency.

Since mast cells are locally active, biopsies and standardized skin photography serve as vital exploratory endpoints; however, because these procedures are not routine in standard clinical practice, comprehensive manuals, site-staff training, and appropriate patient stipends are essential to support participation and ensure high-quality, reproducible results.

Beyond localized assessment, objective pharmacodynamic endpoints, such as serum tryptase, total IgE, and stem cell factor, are critical for tracking the kinetics of cell depletion. Because these specific biomarkers can be potentially unblinding, laboratory data must be strictly masked to maintain study integrity.

To capture the full systemic impact of inhibition, researchers should monitor a diverse cytokine profile; prioritizing IL-6 and TNF-α offers insight into the immediate-early innate inflammatory response, while tracking IL-4, IL-13, and IL-10 helps evaluate the modulation of adaptive immunity.

Ultimately, integrating these markers allows trials to move beyond simple cell counts to evaluate the actual reduction in pathogenic signaling and tissue-wide inflammation.

Patient-Reported Outcomes & Clinician-Reported Outcomes

Patients with mast cell diseases often experience a high disease burden and reduced QoL due to insufficient or poorly managed treatment, making symptom improvement and QoL measures critical study endpoints.[9] Regulatory agencies, including the FDA and EMA, place significant value on the patient perspective, which is commonly done through the use of PROs.

To generate meaningful data and capture the patient's perspective, PROs should be carefully selected to align with study objectives while balancing assessment volume and frequency relative to the overall study duration to minimize PRO completion fatigue. Transparent communication and patient education increase patient compliance and engagement to ensure that questionnaire-based endpoints are met. Participants are more likely to remain engaged in clinical trials when the process is transparent, when they understand their role in advancing treatments, and when it is easy to submit their data.

Site training is equally important, as patients may underreport symptoms due to adaptation of their disease burden. Investigators and study staff should be equipped to educate patients on the importance of accurate and timely PRO completion. When using PRO scores as a study entry requirement, protocols should allow for occasional missed entries, targeting a completion rate of ≥75% to avoid excessively high screen-failure rates. Incorporating this compliance into inclusion criteria helps select participants who are more likely to remain diligent throughout the study.

Medpace supports patient engagement through the TrialPACE® ePRO/eCOA/eDiary system, which streamlines patient-reported data collection and analysis, enables real-time site support, and provides reminders to participants and site study teams on missing questionnaires.

Clinician-Reported Outcomes (ClinRO) complement PROs by providing an objective and standardized approach that helps minimize participant bias. Electronic completion of ClinROs can be set up within the TrialPACE® system to streamline reporting and reduce data entry errors. To minimize variability, sites should maintain the same assessor throughout the study when possible. Validated ClinROs provide universal guidance to ensure uniform interpretation of questions and aligned responses.

While ClinROs and PROs are essential to mast cell inhibitor trials, their successful implementation requires comprehensive training and standardized materials (e.g., manuals and guides). Medpace has extensive experience supporting the selection and implementation of appropriate questionnaire(s) for each study, helping to balance data collection needs with participant burden while maximizing data quality and study compliance.

Managing Adverse Events

Another important consideration across mast cell trials is the management of side effects, including the risk of anaphylaxis. Consequently, sites must be trained to recognize and manage anaphylaxis, while understanding the rationale behind risk-mitigation strategies. Because some sites may express discomfort with protocol requirements like mandatory epinephrine autoinjectors (EpiPens), providing a clear explanation of the strategy is vital. When presented as a measure of extreme caution rather than expectation of harm, most sites accept the strategy. Medpace develops comprehensive materials and training that explain the safety profile of the investigational product, supported by clinical data to contextualize potential adverse events.

THE FUTURE OF MAST CELL INHIBITORS IN CLINICAL DEVELOPMENT

Mast cell inhibitor trials are rapidly evolving, reshaping how the industry views immunology and inflammation. Once viewed primarily through the lens of allergy and anaphylaxis, mast cells are now recognized as key drivers in a broad range of conditions, including EoE, urticaria, conjunctivitis, rhinitis, asthma, and more. This expanding understanding is accelerating therapeutic innovations, offering new treatment options that are safer, more effective, and more targeted. With these advances comes the need for high-caliber CRO partners.

IMPORTANCE OF AN EXPERIENCED CRO PARTNER TO ACCELERATE MAST CELL INHIBITOR TRIALS

Successful mast cell inhibitor trials require deep scientific expertise and operational excellence. As the field rapidly expands beyond traditional areas, the value of partnering with an experienced CRO partner has never been greater.

A modern mast cell program cannot be siloed within a single specialty. Mast cells play important roles across a wide range of diseases, and a CRO with broad therapeutic intelligence is better equipped to support Sponsors as mast cells expand into new clinical areas. Medpace has extensive experience not only in immunology and allergy, but also other therapeutic areas seeing recent advances in mast cells, including ophthalmology, GI, oncology, pulmonology, and dermatology. This breadth of expertise enables a more nuanced approach to trial design, endpoint selection, patient recruitment and retention, and safety oversight.

As mast cell research advances beyond conventional routes, Medpace helps Sponsors navigate complex development challenges across cell and gene therapies, biologics, combination therapies, and other emerging approaches. Our integrated teams include more than 70 physicians—including allergists and clinical immunologists—spanning a wide range of specialties, alongside operational experts and a global regulatory affairs team that provide comprehensive support from study design through closeout. Combined with long-standing relationships across allergy and immunology networks and key opinion leaders (KOLs), Medpace delivers the scientific leadership, operational agility, and strategic execution needed to advance mast cell inhibitor trials efficiently and successfully.

Trial execution is further strengthened by Medpace's full-service, single-vendor outsourcing strategy. Our comprehensive CRO services are supported by our wholly-owned Central Laboratories, Core Labs, and a proprietary Clinical Trial Management System that integrates all study data together onto a single platform.

Interested in learning more about how Medpace can accelerate your mast cell inhibitor trial? Contact our experts today.

REFERENCES

1. 1von Recklinghausen F. Über Eiter und Bindegewebskörperchen. Virchows Arch Pathol Anat Physiol Klin Med 1863; **28**: 157–197.
2. Ehrlich P. Beiträge zur Theorie und Praxis der histologischen Färbung. Test (Hrsg.), I. Teil: Die chemische Auffassung der Färbung. II. Teil: Die Anilinfarben in chemischer, technologischer und histologischer Beziehung. Leipzig, 1878. 65 S. Zgl.: Leipzig, Univ., Diss., 1878.
3. Prausnitz C, Küstner H. Studien über die Ueberempfindlichkei. Zentralbl Bakteriol 1921; **86**: 160–169.
4. Prausnitz C, Küstner H. Studien über die Ueberempfindlichkei. Zentralbl Bakteriol 1921; **86**: 160–169.
5. 24Bennich HH, Ishizaka K, Johansson SGO, Rowe DS, Stanworth DR, Terry WD. Immunoglobulin E, a new class of Immunoglobulin. Bull World Health Organ 1968; **38**: 151–152.
6. Amin K. (2012). The role of mast cells in allergic inflammation. *Respiratory medicine*, *106*(1), 9–14. https://doi.org/10.1016/j.rmed.2011.09.007
7. Xu, Yunzhi, Chen, Guangjie, Mast Cell and Autoimmune Diseases, *Mediators of Inflammation*, 2015, 246126, 8 pages, 2015. https://doi.org/10.1155/2015/246126
8. Chis Ster A, Cornelius V, Cro S. Current approaches to handling rescue medication in asthma and eczema randomized controlled trials are inadequate: a systematic review
Journal of Clinical Epidemiology, 2020; 125, 148-157
9. Goncalo M, Gimenez-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein J, Ensina L, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol. 2021;184(2):22636.