Review Article

Stapokibart for Moderate-to-Severe Seasonal Allergic Rhinitis: A Comprehensive Review of a Randomized Phase 3 Trial

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Abstract: This review critically evaluates the efficacy, safety, and therapeutic potential of stapokibart, a novel monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα), for the management of moderate-to-severe seasonal allergic rhinitis (SAR). Evidence synthesized from a recent phase 3 randomized, double-blind, placebo-controlled trial demonstrates that stapokibart, when administered as an adjunct to standard therapy, produced a rapid, significant, and durable reduction in both nasal and ocular symptoms, as assessed by reflective Total Nasal Symptom Score (r TNSS) and reflective Total Ocular Symptom Score (r TOSS). Importantly, the safety profile of stapokibart was favorable, with adverse events comparable to placebo and no serious treatment-related events reported. Mechanistically, stapokibart exerts therapeutic benefit through dual inhibition of IL-4 and IL-13 signaling, key drivers of type 2 inflammation. By targeting these pathways, stapokibart addresses an unmet clinical need in patients with SAR who remain symptomatic despite conventional pharmacologic options. Within the broader context of emerging biologic therapies, stapokibart represents a promising candidate for disease modification and may help redefine treatment paradigms in allergic rhinitis.

Keywords: moderate-to-severe, seasonal allergic rhinitis, randomized phase 3 trial

1. INTRODUCTION

Seasonal allergic rhinitis (SAR), a widespread and globally recognized condition, is characterized by a sudden, recurring onset of symptoms that closely coincides with periods of pollen exposure [4]. The clinical manifestations of SAR include a range of bothersome nasal and ocular symptoms, such as nasal congestion, rhinorrhea (runny nose), itching, and sneezing, as well as itchy, watery, and red eyes [1]. The impact of these symptoms on daily life and overall quality of life is significant, contributing to a substantial global health burden. A notable distinction exists between SAR and perennial allergic rhinitis (PAR), with SAR often presenting with more severe and intense symptoms due to its concentrated exposure to high allergen loads during specific seasons [4]. The increasing prevalence of SAR, a trend projected to become a more widespread global health issue, underscores the urgent need for more effective management strategies [5]. Current standard-of-care (SoC) treatments for SAR typically include pharmacotherapies such as oral H1-antihistamines and intranasal corticosteroids (INCS) [4]. While these conventional therapies offer effective symptomatic relief for a large portion of the patient population, they are often insufficient for individuals with moderate-to-severe SAR.1 A significant number of patients, with some studies citing up to 62%, have expressed dissatisfaction with their existing long-term therapeutic options, pointing to insufficient efficacy and the persistence of troublesome residual symptoms. This therapeutic gap represents a substantial unmet medical need for a novel class of treatments that can provide more comprehensive and sustained symptom control, particularly for patients whose lives are significantly affected by the condition [1]. The search for new treatments has thus shifted towards agents that can address the root cause of the allergic response

rather than merely mitigating its symptoms. The fundamental pathophysiology of allergic rhinitis is driven by an amplified type 2 inflammatory cascade. This immune response involves a complex interplay of cytokines, cellular activation, and immunoglobulin synthesis. Biologics, specifically monoclonal antibodies, offer a targeted approach to therapy by interfering with a precise, upstream component of these immune pathways [7]. This is in stark contrast to traditional pharmacotherapies, which often provide broad, symptomatic relief without modifying the core inflammatory process. The use of biologics in allergic diseases holds the potential to offer a more profound and sustained therapeutic effect by addressing the underlying immune mechanisms responsible for the condition. The purpose of this review is to provide an in-depth, expert-level analysis of a recent randomized phase 3 trial for stapokibart, an anti-IL-4Rα monoclonal antibody. This review will detail the trial's methodology, critically evaluate its efficacy and safety outcomes, and discuss the clinical implications of its findings. The objective is to inform healthcare professionals and researchers about the potential role of stapokibart in filling the current therapeutic gap for patients with moderate-to-severe SAR whose symptoms remain inadequately controlled by existing treatments.

2. PATHOPHYSIOLOGY OF SAR AND STAPOKIBART'S MECHANISM OF ACTION

The pathogenesis of allergic rhinitis is intrinsically linked to a Type 2 immune response.8 At the center of this inflammatory response are the cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13), which are key drivers of the allergic cascade.8 These cytokines exert their effects by binding to a shared receptor subunit, the IL-4 receptor alpha (IL-4Rα), on the surface of various immune cells [2]. The binding event activates a complex downstream signaling cascade, most notably the Janus kinase (JAK)/STAT signaling pathway.8 The activation of this pathway orchestrates critical inflammatory processes, including the class switching of immunoglobulins to Ig E in B-cells, the production of pro-inflammatory chemokines, and the recruitment of inflammatory cells such as eosinophils to the site of allergic reaction [8]. This molecular and cellular cascade ultimately culminates in the clinical manifestations of SAR, such as nasal congestion, rhinorrhea, and ocular symptoms. Stapokibart is a humanized IgG4 monoclonal antibody that is specifically designed to target and bind with high affinity to the IL-4Rα subunit [2]. By binding to IL-4Rα, stapokibart effectively dual-blocks the signaling pathways of both IL-4 and IL-13, preventing these cytokines from engaging with their receptor [4]. This blockade disrupts the JAK/STAT signaling cascade, leading to the downregulation of genes involved in inflammation. The mechanism results in a multi-pronged therapeutic approach, encompassing the inhibition of T-cell activation, the suppression of B-cell activation and Ig E synthesis, and a reduction in the infiltration of inflammatory cells [1]. This targeted molecular intervention underpins the clinical efficacy of the drug and positions it as a disease-modifying agent rather than a purely symptomatic treatment [1]. The research provides a clear cause-and-effect relationship between the drug's mechanism and its clinical benefit. The specific blockade of the IL-4Rα subunit is a foundational element of the drug's action [8]. This molecular intervention is directly responsible for the observed pharmacodynamic effects, which include a significant reduction in total serum Ig E levels and allergen-specific Ig E levels, as well as a decrease in inflammatory biomarkers like cystatin SN and eotaxin-3 in nasal secretions. These molecular and cellular changes then directly correlate with the clinical efficacy observed in the trial, which is the reduction of nasal and ocular symptoms and the improvement of quality of life [1]. This strong internal consistency between the drug's intended action, its measurable impact on key biomarkers, and its ultimate clinical outcome provides a robust foundation for its therapeutic rationale. The data demonstrates a well-validated therapeutic hypothesis where the molecular blockade leads to biomarker changes, which in turn produce the clinical benefit.

3. METHODOLOGY AND DESIGN OF THE PHASE 3 TRIAL

The study was conducted as a multicenter, randomized, double-blind, placebo-controlled clinical trial with the goal of confirming the efficacy and safety of stapokibart in a defined patient population [7]. The patient cohort comprised adults aged 18 to 65 years with a documented history of moderate-to-severe SAR [7]. A key inclusion criterion for participants was that their symptoms remained inadequately controlled despite the use of standard-of-care therapies, such as nasal corticosteroids and antihistamines [1]. A particularly important aspect of the patient selection was the inclusion criterion of a baseline blood eosinophil (EOS) count of at least 300 cells per microliter [4]. Participants were randomized in a 1:1 ratio to receive either stapokibart or a placebo [7]. The stapokibart group received an initial 600 mg loading dose followed by a 300 mg dose administered subcutaneously every 2 weeks (Q2W) for a total of two administrations over a 4-week treatment period. The placebo group was administered a matching regimen of an indistinguishable placebo [12]. A crucial element of the trial design was that both groups continued to receive concomitant standard therapies, such as nasal corticosteroids (e.g., mometasone furoate nasal spray) and oral antihistamines (e.g., loratadine) [4]. This design effectively evaluated stapokibart as an add-on therapy, reflecting how it would likely be used in a real-world clinical setting. The primary efficacy endpoint of the trial was the mean change from baseline in the daily reflective Total Nasal Symptom Score (r TNSS) over the first 2 weeks of treatment [2]. The r TNSS is a composite score of four symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, with each symptom scored on a scale of 0 to 3.13 Secondary efficacy endpoints included changes in r TNSS over 4 weeks, the daily reflective Total Ocular Symptom Score (r TOSS), and the Rhino conjunctivitis Quality of Life Questionnaire (RQLQ) scores at 2 and 4 weeks [2]. The design of this trial demonstrates an intelligent, data-driven approach to drug development. A prior phase 2 trial (the MERAK trial) had previously shown that stapokibart's efficacy was not statistically significant in the overall SAR population but was significant within a specific subgroup of patients who had a high blood eosinophil count (≥300 cells per microliter) [4]. Instead of abandoning the drug, the Phase 3 trial was specifically designed to enroll this high-eosinophil patient cohort, thereby maximizing the likelihood of a positive outcome [7]. The success of this Phase 3 trial is a testament to this strategic, iterative trial design, which built directly upon the lessons learned from the earlier study and focused the investigation on the patient population most likely to benefit. This approach is instrumental for advancing precision medicine in allergic diseases.

4. EFFICACY FINDINGS: SYMPTOM REDUCTION AND QUALITY OF LIFE

The phase 3 trial demonstrated compelling efficacy for stapokibart, with significant and rapid improvements observed across multiple key endpoints. The results validated the drug's potential as a powerful add-on therapy for moderate-to-severe SAR. The trial successfully met its primary endpoint, with stapokibart demonstrating a significant improvement in the mean change from baseline in daily r TNSS over the 2-week treatment period compared with placebo [5]. The least-squares (LS) mean difference between the stapokibart and placebo groups was -1.3 points (95% CI, -2.0 to -0.6; P=0.0008), a difference that far exceeded the minimal clinically important difference (MCID) of 0.23.3 This finding signifies not only a statistically significant effect but also a clinically meaningful one. An additional finding was the rapid onset of action, with a significant improvement in nasal congestion symptom reported as early as Day 2.1 The overall r TNSS showed a 2.7-point reduction from baseline by Day 4, an improvement that was significantly greater than that observed in the placebo group [1]. The efficacy of stapokibart was not only rapid but also sustained. Over the entire 4-week treatment period, the drug maintained its significant effect on nasal symptoms, with an LS mean difference of -1.7 points for r TNSS (95% CI, -2.5 to -0.8; P=0.0002) [1]. This sustained control was also reflected in the proportion of patients who achieved a state of "mild or no nasal symptoms" (defined as r TNSS ≤1 for each symptom), which reached an impressive 84% by Week 4 [1]. Stapokibart provided comprehensive relief across all major symptom domains, including a significant impact on ocular symptoms. The drug demonstrated

clinically significant reductions in the daily reflective Total Ocular Symptom Score (r TOSS) from baseline.1 Improvements of 2.6 points at Week 2 and 3.7 points at Week 4 were both statistically superior to placebo.1 By Week 4, an impressive 94% of patients in the stapokibart group achieved a state of mild or no ocular symptoms [1]. The data highlights that stapokibart does not just provide relief for a single symptom. The rapid and sustained relief for both nasal and ocular symptoms is a key factor in the drug's clinical value, as many patients suffer from both types of symptoms, and traditional therapies may not be as effective at providing integrated relief. The significant improvement across both symptom sets directly translates to a marked improvement in patients' overall quality of life [1]. The patient-reported quality of life improvements are a direct reflection of this comprehensive efficacy and a powerful differentiator from other therapies that may only focus on one aspect of the condition. The table below provides a summary of the key efficacy endpoints.

Table 01: Key Efficacy Endpoints of the Stapokibart Phase 3 Trial

Endpoint	Timepoint	Stapokibart (LS Mean Change)	Placebo (LS Mean Change)	LS Mean Difference (95% CI)	P-Value
Daily r TNSS	2 weeks	-3.6 points (from baseline)	-2.3 points (from baseline)	-1.3 (-2.0 to -0.6)	0.0008
Daily r TNSS	4 weeks	-4.9 points (from baseline)	-3.2 points (from baseline)	-1.7 (-2.5 to -0.8)	0.0002
Daily r TOSS	2 weeks	-2.6 points (from baseline)	N/A	-0.7 (-1.3 to 0.0)	0.039
Daily r TOSS	4 weeks	-3.7 points (from baseline)	N/A	-0.8 (-1.4 to -0.2)	0.016

LS Mean Difference reflects stapokibart vs. placebo. The Minimal Clinically Important Difference (MCID) for r TNSS is 0.23.3

5. SAFETY AND TOLERABILITY PROFILE

Stapokibart demonstrated a favorable safety profile in the clinical trial [1]. The incidence of treatment-emergent adverse events (TEAEs) was found to be comparable to that of the placebo group, suggesting that the drug is well-tolerated and does not present a substantial increase in common side effects.1 Importantly, the trial reported that no serious adverse events (SAEs) occurred in any of the stapokibart-treated patients. As with all biologic treatments, a crucial consideration is the long-term safety and tolerability profile, as these therapies are often intended for chronic or repeated use. The favorable safety data from this short-term phase 3 trial, along with a consistent track record of good tolerability in previous clinical investigations, provides a strong initial signal for the drug's safety [7]. The absence of SAEs and the comparable rates of TEAEs to placebo are not merely positive results; they are a critical prerequisite for a biologic designed to treat a chronic, but non-life-threatening, condition like SAR. A favorable safety profile de-risks the drug and makes it a much more attractive option for patients and clinicians. This is particularly important when considering that other drug classes, such as triptans for migraine, can carry a risk of cardiovascular events, which is not a concern with stapokibart's mechanism of action. The low incidence of adverse events with stapokibart suggests it could be a valuable and well-tolerated addition to the therapeutic landscape for allergic diseases.

6. DISCUSSION: CLINICAL IMPLICATIONS AND THERAPEUTIC POSITIONING

Stapokibart represents a significant advancement in the treatment of SAR. It is the first biologic to be assessed as an add-on therapy during pollen exposure for patients with uncontrolled SAR, establishing a new therapeutic niche [11]. Unlike standard pharmacotherapies that often provide incomplete or transient relief, stapokibart's targeted, disease-modifying mechanism provides a "transformative solution" that comprehensively addresses the underlying inflammatory cascade and the resulting symptoms [1]. For patients who are dissatisfied with the limited efficacy of conventional treatments, stapokibart offers a potent new option that addresses the root cause of their condition. The introduction of stapokibart into the biologic landscape necessitates a comparison with other available options. Omalizumab, an anti-Ig E monoclonal antibody, has also demonstrated efficacy in alleviating SAR symptoms. However, omalizumab is a costly treatment, with a price range that can be "economically impractical" for widespread use, limiting its broader utilization [4]. The development and approval of stapokibart as the "first domestically manufactured IL-4Rα monoclonal antibody" in China is a noteworthy event [3]. This may signal a strategic effort to address the cost barrier that has historically limited access to biologics for large patient populations. The potential for a more accessible and affordable alternative could democratize advanced SAR therapy and significantly impact global pharmaceutical market dynamics.

Table 02: Comparative Overview of Stapokibart and Existing SAR Therapies

Therapeutic Class	Example Agent	Mechanism of Action	Efficacy	Onset of Action	Route	Key Advantages / Disadvantages
Biologic (IL-4Rα m Ab)	Stapokibart	Blocks IL-4 and IL-13 signaling pathways 8	High efficacy in moderate-to-severe SAR with high eosinophils 7	Rapid (Day 2 for congestion) 1	Subcutaneous injection	Targeted, disease-modifying, good safety profile. Currently limited to a specific patient phenotype.11
Oral Antihistamine	Loratadine	H1-receptor antagonism 4	Effective for mild symptoms, less so for congestion 6	30-90 minutes 6	Oral tablet	Readily available, inexpensive. Can be insufficient for moderate-to-severe symptoms.4
Intranasal Corticosteroid	Mometasone	Reduces local inflammation 10	High efficacy, considered standard-of-care 6	1-12 hours 6	Nasal spray	Highly effective, well-tolerated. Can cause local irritation and dryness.6

Biologic (Anti-Ig E mAb)	Omalizumab	Binds and deactivates Ig E 4	Efficacious for severe SAR 4	Weeks-months	Subcutaneous injection	Highly effective, but expensive and economically impractical for widespread use.5

The primary strength of the study is its robust design as a randomized, double-blind, placebo-controlled trial, which provides high-quality evidence regarding the drug's efficacy and safety [7]. The trial's success in a specific patient cohort (high eosinophils) further suggests that stapokibart could be positioned as a personalized medicine approach, best suited for patients with a specific inflammatory phenotype. A limitation of the data is the short-term nature of the trial (4 weeks), which highlights the need for long-term data on the drug's sustained efficacy, safety, and potential for immunogenicity [4]. Long-term studies would be essential to confirm the drug's role in chronic management and its overall impact on disease progression.

7. CONCLUSION

The phase 3 clinical trial data for stapokibart provides compelling evidence of its efficacy and safety for the treatment of moderate-to-severe seasonal allergic rhinitis. By providing rapid and sustained relief of both nasal and ocular symptoms and demonstrating a favorable safety profile with no serious adverse events, stapokibart offers a promising new therapeutic option for patients who are inadequately controlled by standard pharmacotherapies. Its targeted mechanism of action, validated by a reduction in key inflammatory biomarkers, positions it as a significant advancement in the management of allergic rhinitis. While further research is needed to confirm its long-term safety and efficacy, the current data strongly support stapokibart as a clinically valuable addition to the therapeutic armamentarium, particularly for patients with a high eosinophil inflammatory phenotype. The development of this biologic also suggests a broader trend towards more targeted, and potentially more accessible, treatments for chronic inflammatory diseases.

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