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NEW PERSPECTIVES IN THE TREATMENT OF ULCERATIVE COLITIS IN ADULTS - IL-23 INHIBITORS: EFFICACY AND SAFETY

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ABSTRACT

Introduction: Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by recurrent inflammation of the colon resulting from immune dysregulation. Despite the availability of multiple therapeutic options, a substantial proportion of patients fail to achieve sustained remission or develop loss of response to existing therapies. Increasing evidence has identified the interleukin-23 (IL-23)/Th17 pathway as a key mechanism involved in the pathogenesis of UC, leading to the development of selective IL-23 inhibitors as novel therapeutic agents.

Purpose: The aim of this study was to review and summarize current evidence regarding the efficacy and safety of IL-23 inhibitors, particularly mirikizumab, risankizumab and guselkumab, in the treatment of moderate-to-severe ulcerative colitis.

Methodology: A narrative literature review was performed using PubMed and ClinicalTrials.gov to identify relevant studies investigating IL-23 inhibitors in the treatment of ulcerative colitis. The review included phase II and phase III randomized controlled trials, long term extension studies, real-world observational cohorts, systematic reviews and meta-analyses. Data were extracted and synthesized to provide a comprehensive assessment of the efficacy, safety and evolving therapeutic role of IL-23 inhibitors in ulcerative colitis.

Conclusions: Available evidence indicates that IL-23 inhibitors are effective therapeutic options for patients with moderate-to-severe ulcerative colitis. Mirikizumab, risankizumab and guselkumab demonstrated significant improvements in clinical remission, endoscopic healing, histologic outcomes and quality of life. Among these agents, mirikizumab currently has the strongest evidence supporting long-term efficacy and durability of response. IL-23 inhibitors also demonstrated favorable safety profiles, with low rates of serious adverse events and treatment discontinuation. Although further real-world data and head-to-head comparative studies are still needed, selective IL-23 blockade represents a promising advancement in personalized UC treatment strategies.

KEYWORDS

Ulcerative Colitis, Inflammatory Bowel Disease, IL-23 Inhibitors, Mirikizumab, Risankizumab, Guselkumab, Review

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease driven by immune dysregulation, in which an abnormal immune response leads to persistent inflammation of the colon (Chu et al., 2023; Parisio et al., 2025). It is characterised by gastrointestinal symptoms, most commonly including persistent diarrhea, rectal bleeding, stool urgency and abdominal pain. Patients may also experience systemic symptoms such as weight loss and fatigue. Ulcerative colitis significantly impacts patients' daily functioning and overall well-being, often contributing to reduced quality of life (Chu et al., 2023). The etiopathogenesis of UC is multifactorial and involves genetic predisposition, environmental factors, dysregulation of innate and adaptive immune responses, dysbiosis of the gut microbiota and impairment of the intestinal epithelial barrier (Porter et al., 2020; Świrkosz et al., 2023). Assessment of disease activity in UC is essential for both clinical management and the evaluation of the therapeutic outcomes in research settings. One of the most widely used tools is the modified Mayo score (mMS). mMS is based on three key components: stool frequency, rectal bleeding and endoscopic findings. Each of these subscores is graded on a scale from 0 to 3, where higher values indicate more severe disease activity, resulting in a total score ranging from 0 to 9. This allows for categorization of disease severity, with scores of 5-6 reflecting moderate activity and 7-9 indicating severe disease (B. Abraham et al., 2025).

2. Current Pharmacologic Strategies in Ulcerative Colitis

The treatment of ulcerative colitis is based on a multidimensional and individualized therapeutic approach aimed at controlling symptoms, preventing relapses and improving patients' quality of life (D'Amico et al., 2024; Turner et al., 2021; Ungaro et al., 2019).

First line therapy for mild-to-moderate UC consists of 5-aminosalicylic acid (5-ASA) compounds, including mesalazine, which remains the foundation of treatment. These agents are recommended for both induction and maintenance of remission due to their efficacy and favorable safety profile. Their mechanism of action involves local anti-inflammatory effects in the colonic mucosa, including inhibition of prostaglandin and leukotriene synthesis and modulation of epithelial immune responses. However, a subset of patients fails to achieve adequate disease control, requiring treatment escalation (D'Amico et al., 2024; Paridaens et al., 2024)

In cases of moderate-to-severe disease or inadequate response to 5-ASA, systemic corticosteroids are used. Corticosteroids, such as prednisone and budesonide, act by broadly suppressing immune response, leading to symptom improvement. However, their use is limited to short-term periods due to significant adverse effects. They are not recommended for maintenance therapy and prolonged use leads to steroid dependence, which is a key indication for escalation of therapy (Paridaens et al., 2024; Rubin et al., 2019)

For patients who are steroid-dependent or refractory, immunosuppressive agents are commonly introduced. Thiopurines, such as azathioprine and 6-mercaptopurine, inhibit purine synthesis and reduce lymphocyte proliferation, thereby modulating chronic inflammation. These drugs are mainly used for maintenance of remission rather than induction due to their delayed onset of action. Despite their efficacy, their use is limited by potential toxicity, including bone marrow suppression, hepatotoxicity and increased risk of infections and malignancies, requiring regular monitoring (Harbord et al., 2017)

Over the past decade, biologic therapies have significantly changed the treatment of UC. Anti-tumor necrosis factor (anti-TNF) agents, including infliximab and adalimumab, were the first biologics introduced and remain widely used. They neutralize TNF-α, a key pro-inflammatory cytokine involved in UC pathogenesis and have demonstrated efficacy in inducing and maintaining remission as well as promoting mucosal healing (Ungaro et al., 2019). However, limitations such as primary non-response and secondary loss of response have led to the development of therapies with alternative mechanisms of action (Marsal et al., 2022).

Vedolizumab, an anti-integrin agent, selectively inhibits α4β7 integrin, preventing lymphocyte migration to the gastrointestinal tract. This gut-selective mechanism reduces systemic immunosuppression and is associated with a favorable safety profile (Feagan et al., 2013). Ustekinumab, which targets the shared p40 subunit of interleukin-12 and interleukin-23, has also shown efficacy in UC, particularly in patients who have failed previous biologic therapies (Sands et al., 2019). These agents have expanded therapeutic options and improved outcomes in difficult-to-treat patients.

In parallel, small-molecule therapies have further expanded treatment options. Jakus kinase (JAK) inhibitors, such as tofacitinib and upadacitinib, block intracellular signaling pathways involved in cytokine activity. By inhibiting multiple cytokines simultaneously, they provide rapid onset of action and high efficacy in inducing remission (Danese et al., 2022; Sandborn et al., 2017). Another class, sphingosine-1-phoshate (S1P) receptor modulators, such as ozanimod, reduce lymphocyte egress from lymph nodes, thereby decreasing inflammatory infiltration in the colon. These oral agents are particularly useful in patients who have failed biologic therapies or prefer no-injectable treatment options (Sandborn et al., 2021).

3. Interleukin-23 as a therapeutic target

Interleukin-23 (IL-23) is one of the key mediators in the pathogenesis of UC, making it an important target for novel therapeutic strategies. IL-23 is a heterodimeric cytokine composed of two subunits, p19 and p40, and plays a central role in both innate and adaptive immune responses (Chua et al., 2023; Steere et al., 2023). It takes part in differentiation, maintenance and expansion of T helper 17 (Th17) cells, a subset of T lymphocytes that are critically involved in the process of chronic inflammation. The IL-23/Th17 axis is particularly relevant in ulcerative colitis, as it regulates the production of pro-inflammatory cytokines and drives sustained immune activation within the intestinal mucosa. In addition to its effects on adaptive immunity, IL-23 also stimulates various innate immune cells, further amplifying inflammatory pathways (Steere et al., 2023). Dysregulation of IL-23 signaling has been associated with multiple autoimmune and inflammatory conditions, including diseases affecting the gastrointestinal tract (C. Abraham & Cho, 2009). Given its central role in promoting and maintaining inflammation, inhibition of IL-23 presents a promising therapeutic approach for patients with moderate-to-severe UC. Targeting this pathway has been shown to reduce inflammatory activity, promote mucosal healing and support epithelial barrier restoration (Hart et al., 2026). As a result, IL-23 inhibitors are increasingly becoming incorporated into treatment strategies and are the focus of ongoing clinical research aimed at improving outcomes in patients with UC (Verstockt et al., 2023).

4. Efficacy of IL-23 inhibitors

Interleukin-23 inhibitors represent an emerging and increasingly important therapeutic class in the management of moderate-to-severe active UC. By selectively targeting the p19 subunit of IL-23, these agents modulate the IL-17/Th17 pathway, which plays a key role in the maintenance of chronic intestinal inflammation (Parisio et al., 2025; Verstockt et al., 2023). Recent clinical studies evaluating mirikizumab, risankizumab and guselkumab have shown encouraging efficacy during both induction and maintenance phases of the treatment. Across multiple studies, IL-23 inhibitors demonstrated the ability to induce clinical remission, endoscopic healing, reduce symptoms and enhance quality of life in patients with moderate-to-severe disease (Ananthakrishnan et al., 2024; Dai et al., 2025). The following sections summarise the available evidence regarding the efficacy of mirikizumab, risankizumab and guselkumab in UC, focusing on key clinical trials, maintenance outcomes and emerging real-world data.

4.1. Efficacy of Mirikizumab

Mirikizumab is a humanized monoclonal antibody targeting the p19 subunit of IL-23, thereby inhibiting the IL23/Th17 inflammatory pathway involved in the pathogenesis of ulcerative colitis. Over recent years, it has become one of the most extensively investigated IL-23 inhibitors in UC, with evidence derived from phase 2 and face 3 clinical trials, long-term extension studies and real-world observational analyses.

Evidence of efficacy was demonstrated in a phase 2 randomised clinical trial in which mirikizumab achieved significantly higher rates of clinical remission, clinical response and endoscopic improvement compared with placebo in patients with moderate-to-severe active UC. Notably, extended induction with mirikizumab induced a clinical response in up to 50% of patients who did not respond to the initial 12-week treatment. Most of these patients maintained a clinical response through week 52, supporting the durability of mirikizumab efficacy (Sandborn et al., 2022)

Further studies demonstrated that mirikizumab modulates genes associated with inflammatory activity and anti-TNF resistance, indicating that IL-23 inhibition remains effective even in biologically experienced patients. Transcriptomic analyses additionally showed that molecular changes induced during induction therapy persisted through week 52, supporting sustained suppression of inflammatory pathways (Johnson et al., 2023; Steere et al., 2023).

The phase 3 LUCENT clinical trial program confirmed the efficacy of mirikizumab. Rapid improvements in rectal bleeding, stool frequency, bowel urgency and symptomatic remission were observed during induction therapy and maintained throughout long-term treatment. Mirikizumab also demonstrated significant rates of histologic remission and endoscopic mucosal healing, indicating deeper disease control beyond symptom improvement (Danese et al., 2022; Magro et al., 2023).

Patient-reported outcomes further supported the clinical benefits of treatment. Mirikizumab significantly improved health-related quality of life, bowel function, fatigue, emotional well-being and social functioning. Improvements and bowel urgency, an increasingly recognised therapeutic target in UC, were also associated with higher remission rates and better patient outcomes (Dubinsky et al., 2023; Sands et al., 2023).

In a prespecified subpopulation analysis of the phase 3 LUCENT-1 and LUCENT-2 trials, mirikizumab demonstrated efficacy and a favourable safety profile in Chinese patients with moderate-to-severe active UC. During induction therapy (LUCENT-1) clinical remission at week 12 was achieved in 18.6% of patients treated with mirikizumab compared with 7.0% of those receiving placebo. During maintenance therapy (LUCENT-2) clinical remission at week 40 was observed in 50.0% of patients receiving mirikizumab versus 12.5% in the placebo group, while the incidence of adverse events was comparable between treatment groups (Ran et al., 2026).

Emerging real-world studies in biologic-experienced and therapy-refractory patients reported clinical response and remission rates consistent with randomised clinical trials, supporting the effectiveness of mirikizumab in routine clinical practice (Levartovsky et al., 2025; Takagi et al., 2025). Recent systematic reviews and meta-analysis additionally confirm that mirikizumab significantly improves clinical remission, endoscopic response and maintenance remission compared with placebo, reinforcing its therapeutic value in moderate-to-severe active UC (X. Chen et al., 2025; Khan et al., 2026).

4.2. Efficacy of Risankizumab

The efficacy of risankizumab in UC was demonstrated in the phase 3 INSPIRE induction trial, in which patients receiving risankizumab achieved significantly higher rates of clinical remission, symptomatic improvement and endoscopy response compared with placebo. At week 12 clinical remission was achieved in 20.3% of patients treated with risankizumab versus 6.2% of those receiving placebo. Furthermore, the phase 3 COMMAND maintenance trial confirmed the durability of treatment response, with clinical remission at week 52 observed in 40.2% and 37.6% of patients receiving risankizumab 180 mg and 360 mg, respectively, compared with 25.1% in the placebo group. These findings confirmed the therapeutic relevance of selective IL-23 inhibition in reducing inflammatory reactivity and improving disease manifestations while maintaining a favourable safety profile (Louis et al., 2024a).

Subsequent analyses focused on long-term outcomes and efficacy in biologic-experienced populations. Post hoc analyses of the INSPIRE and COMMAND phase 3 studies demonstrated that risankizumab maintained efficacy in patients with prior inadequate response or intolerance to advanced therapies, including anti-TNF agents. Moreover, extended induction treatment enabled over 50% of initial non-responders to achieve clinical response by week 24, with accompanying improvements in clinical remission and endoscopic outcomes that were sustained during maintenance therapy. These findings support the potential role of risankizumab in patients with refractory disease courses and confirm its favorable safety profile (Panaccione et al., 2025).

Additional studies demonstrated a favorable effect on patient-reported outcomes and symptom burden. Risankizumab treatment resulted in meaningful improvements in bowel symptoms, daily functioning and overall health-related quality of life, with benefits observed as early as week 4 and sustained for a week 52. Comprehensive resolution of UC-related symptoms was achieved more frequently with recent risankizumab than with placebo during both induction (21.8 versus 9.5) and maintenance therapy. Symptomatic improvement was strongly associated with clinical remission and endoscopic healing, reinforcing the relationship between objective inflammatory control and patient-centered outcomes (Torres et al., 2025).

Another important aspect of risankizumab therapy is its corticosteroid-sparing potential. Treatment with risankizumab was associated with corticosteroid-free clinical and endoscopic remission in patients with moderate-to-severe active UC. Achieving steroid-free remission is considered a major therapeutic target because long-term corticosteroid exposure is associated with significant morbidity and treatment related complications (Reinisch et al., 2025).

Comparative analyses and network meta-analyses further supported the efficacy of risankizumab and other IL-23 inhibitors in moderate-to-severe UC. Evidence syntheses demonstrated favorable outcomes regarding induction remission, maintenance remission and endoscopic response compared with placebo and other advanced therapies (Ananthakrishnan et al., 2024; Dai et al., 2025). Overall, current evidence indicates that risankizumab is an effective therapeutic option for UC, demonstrating efficacy across induction and maintenance phases, including in biologic-experienced patients, while also improving quality of life and supporting corticosteroid-free remission.

4.3. Efficacy of Guselkumab

The most important evidence supporting guselkumab efficacy in UC originates from the phase 2b QUASAR induction study. In this randomized clinical trial, clinical response at week 12 was achieved in 61.4 % and 60.7% of patients receiving guselkumab 200 mg and 400 mg respectively compared with 27.6% in the placebo group (P<.001). Higher rates of clinical remission, symptomatic remission and endoscopic improvement were also observed during induction therapy, with over half of initial non-responders achieving a clinical response by week 24 following continued treatment. These results established proof of concept for selective IL-23 blockade in UC and confirmed a favorable safety profile (Peyrin-Biroulet et al., 2023).

Subgroup analyses further demonstrated consistency of efficacy across different patient populations. Evaluation of East Asian patients participating in the QUASAR induction and maintenance studies show clinical remission, endoscopic response and maintenance outcomes comparable to those observed in the overall study population. These findings suggest that guselkumab is generally consistent across ethnically diverse patient groups (B. Chen et al., 2025).

Translational and mechanistic studies have also supported the biological rationale for guselkumab therapy. Multiomic analyses demonstrated that guselkumab induction therapy was associated with modulation of inflammatory pathways, transcriptomic normalisation and biologic signatures linked to mucosal healing. These molecular findings support the clinical efficacy observed in randomized studies and suggest that guselkumab may induce deeper immunologic remission beyond symptomatic improvement alone (Hart et al., 2026).

An additional clinically important aspect of guselkumab therapy is its impact on patients' quality of life. Improvements in symptoms such as diarrhoea, abdominal pain, stool urgency and rectal bleeding substantially enhance daily functioning and overall well-being. Effective inflammatory control achieved with IL-23 inhibition has been associated with meaningful improvements in patient-reported outcomes and quality of life measures (Dai et al., 2025)

Comparative analyses and network meta-analyses have additionally reinforced the therapeutic potential of guselkumab and IL-23 inhibitors in UC. Studies evaluating advanced therapies for moderate-to-severe ulcerative colitis demonstrated that IL-23 inhibitors achieved favorable efficacy and safety profiles across multiple clinical and endoscopic endpoints. Although direct head-to-head comparison to remain unavailable, current evidence suggest that guselkumab may represent an effective alternative within the current biologic treatment landscape (Chu et al., 2023; Dai et al., 2025; Huang et al., 2025; Sawaf et al., 2025).

Despite these encouraging findings, the current evidence base for guselkumab in UC remains more limited compared with other IL-23 inhibitors such as mirikizumab. Most available data derive from phase 2 studies and subgroup analyses, while long-term extension studies and real-world evidence remain relatively limited. Nevertheless current evidence suggests that guselkumab is a promising therapeutic option for moderate-to-severe active UC, with demonstrated efficacy in clinical remission, symptomatic improvement and endoscopic healing.

5. Safety of IL-23 inhibitors

Inhibitors of IL-23 have demonstrated a generally favorable safety profile in the treatment of UC. Across randomized controlled trials, most adverse events (AEs) associated with IL-23-targeting agents were mild, non-serious and rarely required treatment discontinuation (Verstockt et al., 2023). Importantly, the incidence of serious adverse events, infections (including serious infections) and malignancies did not significantly differ from placebo groups (B. Abraham et al., 2025; Verstockt et al., 2023). In addition to their safety, IL-23 inhibitors significantly improved clinical remission rates during both induction and maintenance phases of treatment, highlighting a favorable benefit-risk balance. These findings support IL-23 blockade as a well-tolerated and effective therapeutic strategy in chronic inflammatory conditions.

5.1. Safety profile of Mirikizumab

Mirikizumab has shown a reassuring safety profile in patients with moderate-to-severe active UC. Clinical trial data indicate that mirikizumab-treated patients experience numerically lower rates of serious adverse events and treatment discontinuations compared to placebo (B. Abraham et al., 2025; Takagi et al., 2025). The most frequently reported AEs (≥2%) included upper respiratory tract infections, arthralgia, injection-site reactions, rash, headache and herpes viral infections (B. Abraham et al., 2025). During induction therapy, adverse events occurred in the minority of patients and were predominantly mild, with no cases requiring permanent discontinuation or resulting in death. Long-term data from the LUCENT Phase 3 trial trials further confirmed sustained safety alongside increasing rates of disease clearance over time. Overall, mirikizumab combines durable efficacy with a low incidence of clinically significant adverse outcomes (Colombel et al., 2025).

5.2. Safety profile of Risankizumab

Risankizumab has demonstrated a favorable safety profile consistent with the IL-23 inhibitor class, although direct comparative data remain more limited. Available evidence suggests that most adverse events are mild to moderate in severity, with low rates of serious adverse events and treatment discontinuation. Similar to other IL-23 inhibitors, the risk of infections and other complications does not appear to be significantly increased compared to placebo. These findings position risankizumab as a generally well-tolerated therapeutic option, though further head-to-head and long-term studies are needed to better define its comparative safety profile (Louis et al., 2024a).

5.3. Safety profile of Guselkumab

Guselkumab demonstrates a strong safety profile, with nuanced findings depending on the specific safety outcome assessed. Comparative analyses indicate that guselkumab ranks favorably in terms of overall adverse events, showing the lowest incident among evaluated therapies, while also being highly effective at minimizing treatment discontinuations due to adverse events during both induction and maintenance phases (Chu et al., 2023). Additionally, guselkumab has been associated with significant improvements in quality of life, likely due to its efficacy in reducing intestinal inflammation and alleviating key symptoms such as diarrhea, abdominal pain and rectal bleeding (Dai et al., 2025). These characteristics make guselkumab a promising long-term therapeutic option for patients with UC.

6. Discussion

Over the last decade, the treatment of ulcerative colitis (UC) has evolved from symptom-oriented management towards achieving long-term disease control, mucosal healing and improved quality of life (Turner et al., 2021; Ungaro et al., 2019). Better understanding of UC pathogenesis has identified the IL-23/Th17 pathway as a key mechanism involved in chronic intestinal inflammation, leading to the development of selective IL-23 inhibitors as a new therapeutic strategy (Steere et al., 2023; Verstockt et al., 2023).

The present review summarizes current evidence regarding the efficacy and safety of IL-23 inhibitors in the management of moderate-to-severe active UC, with a focus on mirikizumab, risankizumab and guselkumab. Collectively, available data indicate that selective blockade of the IL-23/Th17 axis represents a clinically meaningful advancement in UC therapy, with consistent improvements in clinical remission, endoscopic healing and patient-reported outcomes across randomized controlled trials and emerging real-world studies (Ananthakrishnan et al., 2024; Dai et al., 2025).

Across all three agents, induction and maintenance studies demonstrate robust efficacy, with clinically significant rates of remission and response compared with placebo. Risankizumab and guselkumab, in particular, have shown sustained efficacy beyond induction, including in biologic-experienced populations, suggesting that IL-23 inhibition remains effective even in patients with prior exposure to advanced therapies (Louis et al., 2024; Panaccione et al., 2025). Mirikizumab has also demonstrated durable long-term outcomes, with maintenance of clinical and endoscopic response over extended follow-up periods (Sands et al., 2024, 2025). Importantly, improvements in objective inflammatory markers and histologic endpoints suggest that IL-23 inhibitors may facilitate deeper disease control beyond symptomatic relief alone.

Mechanistic and translational studies further support these clinical findings. In particular, molecular analyses have demonstrated that IL-23 blockade is associated with downregulation of inflammatory gene signatures and modulation of immune pathways involved in chronic intestinal inflammation, as well as a restoration of epithelial and mucosal repair processes (Hart et al., 2026; Johnson et al., 2023). These findings provide biological plausibility for the observed clinical benefits and suggest that IL-23 inhibition may contribute to long-term disease modification rather than transient symptom suppression.

In terms of safety, IL-23 inhibitors consistently demonstrate a favorable and class-consistent safety profile. Across clinical trials, most adverse events are mild to moderate, with low rates of serious adverse events and treatment discontinuation (Verstockt et al., 2023). Importantly, the incidence of infections, malignancies and other serious complications does not appear to differ significantly from placebo, supporting the overall tolerability of this therapeutic class (B. Abraham et al., 2025). Among individual agents, risankizumab and guselkumab, demonstrate particularly favorable safety profiles, although long-term and head-to-head comparative data remain limited (Chu et al., 2023; Louis et al., 2024).

Despite these promising results, several limitations should be acknowledged. Direct comparative trials between IL-23 inhibitors are currently lacking, making relative efficacy and safety assessment largely indirect. Additionally, long-term real-world data remain limited for newer agents, particularly guselkumab,, which is primarily supported by phase 2 evidence and sub group analyses. Further studies are therefore required to better define long-term durability, optimal positioning with treatment algorithms and competitive effectiveness against other advanced therapies.

7. Conclusions

Selective inhibition of IL-23 is becoming increasingly important in the treatment of moderate-to-severe UC, addressing therapeutic needs that remain insufficiently controlled with existing therapies. Current evidence demonstrates that mirikizumab, risankizumab and guselkumab effectively improve clinical remission, endoscopic healing, histologic outcomes and quality of life. Among these agents, mirikizumab currently has the strongest evidence supporting long-term efficacy and durability of response. Available safety data indicate a generally favourable and predictable adverse-event profile, with low rates of serious complication and treatment discontinuation. At the same time, additional research is still needed, particularly direct comparative studies, long-term real-world analyses and investigations of predictive biomarkers, to better define the optimal positioning of IL-23 inhibitors within current ulcerative colitis treatment algorithms.

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