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TARGETING IL23p19 USING RISANKIZUMAB FOR THE MANAGEMENT OF MODERATE-TO-SEVERELY ACTIVE CROHN'S DISEASE: THE NEXT FRONTIER?

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Introduction

Targeting Th17-mediated inflammatory pathways through inhibition of interleukin (IL)-23 has emerged as an important therapeutic mechanism for patients with inflammatory bowel disease. Ustekinumab, a monoclonal antibody blocking both IL-12 and IL-23, was the first agent approved by Health Canada with this mechanism of action, initially for Crohn's disease (CD) in 2016 and subsequently for ulcerative colitis (UC) in 2020. Over the past decade, there has been increasing attention focused on selectively blocking IL-23, as the key activator of pathogenic Th17 inflammatory cells. Several monoclonal antibodies that target the unique p19 subunit of IL-23 (IL23p19 antagonists) have been developed for psoriasis and psoriatic arthritis, where IL-23 specific blockade results in substantially greater efficacy compared to targeting IL-12/23.[1] The first IL23p19 antagonist, risankizumab, has recently been approved in Canada for the treatment of moderate-to-severely active CD. Here, we describe the mechanism of action of risankizumab and how it differentiates from ustekinumab; review the pivotal clinical trial data that demonstrates the ability of risankizumab to achieve relevant clinical and endoscopic endpoints in both biologic treatment naïve and exposed patients; and summarize key safety data that helps inform decisions about the benefit-risk profile of this novel therapy.

Th17 Immune Responses and the Mechanism of Action of Risankizumab

IL-12 and IL-23 are heterodimeric cytokines that play important roles in both innate immunity and pathogenic inflammation, as master cytokines in the Th1 and Th17 pathways, respectively. IL-12 consists of two disulfide-bound subunits, p35 and p40, that bind to the IL12 receptor to induce downstream signalling.[2] IL-12 is predominantly secreted by antigen presenting cells, dendritic cells and macrophages, in response to microbial products such as lipopolysaccharide. IL-12 secretion activates natural killer (NK) cells and stimulates differentiation of naïve T-cells to interferon (IFN)-γ producing

cytotoxic CD8+ T-cells.[3] These IL-12 mediated Th1 responses are critical for regulating host mucosal defences and clearance of intracellular bacteria, as supported by clinical observations that subjects with genetic deficiencies in IL-12 have an increased susceptibility to salmonella and mycobacterial infections.[4]

IL-23 also consists of two subunits: the p40 subunit is shared with IL-12, however, the p19 subunit is unique to IL-23 (**Figure 1**). IL-23 is secreted predominantly by macrophages, and drives T-cell activation through Th17-mediated proliferation and stimulation of memory T cells.[5] Patients with CD demonstrate pathogenic activation and over-expression of IL-23 with a highly potent inflammatory response.[6] Receptor binding of IL-23 activates master transcription factors responsible for IL-17 gene transcription in CD4+ T-cells, and downstream production of IL-6; granulocyte monocyte colony stimulating factor (GM-CSF); IL-22; IL-17; IL-17F; and IFNγ.[7] This subsequently potentiates and maintains pathogenic Th17 responses through stimulation of NK cells, innate lymphoid cells and Th17 T-cells to produce more IL-6 and TGF-β that stimulate naïve T-cells to undergo Th17 differentiation. Finally, IL-23 may play a key role in "overriding" immunosuppressive pathways in the bowel by inhibiting the function of regulatory T cells (T_{reg}).[8]

Several lines of evidence suggest that IL-23 is the predominant cytokine responsible for inflammation in patients with CD. First, murine models with IL-12 specific deficiencies in IL12p35 are *not* protected against development of autoimmune colitis; conversely, mice models with deficiencies in IL-23 (either IL-23p19 or through the shared p40 subunit) are protected.[9-12] Second, while both IL-12 and IL-23 are constitutively expressed in normal healthy gut mucosa, inflamed tissue from patients with active CD demonstrates markedly increased expression of IL-23 on immunohistochemistry.[13] Third, multiple polymorphisms in the IL-23 pathway have now been identified in genome wide association studies to confer susceptibility to the development of IBD.[14] Fourth, mucosal IL-23p19, IL23R, and IL-17 and apoptosis-resistant intestinal IL23R+ T cells have been demonstrated to be significantly upregulated in CD patients who are non-responsive to biologic treatment with anti-tumour necrosis factor (TNF) therapy, suggesting that IL-23 is potentially a predominant driver of treatment-resistant CD.[15]

Risankizumab is a fully human IgG monoclonal antibody that binds to the p19 subunit of IL-23.[16] Key characteristics of this molecule that differentiate it from ustekinumab include: 1) High degree of specificity for IL-23p19 subunit blockade with no binding of the shared IL-12/23p40 subunit, up to

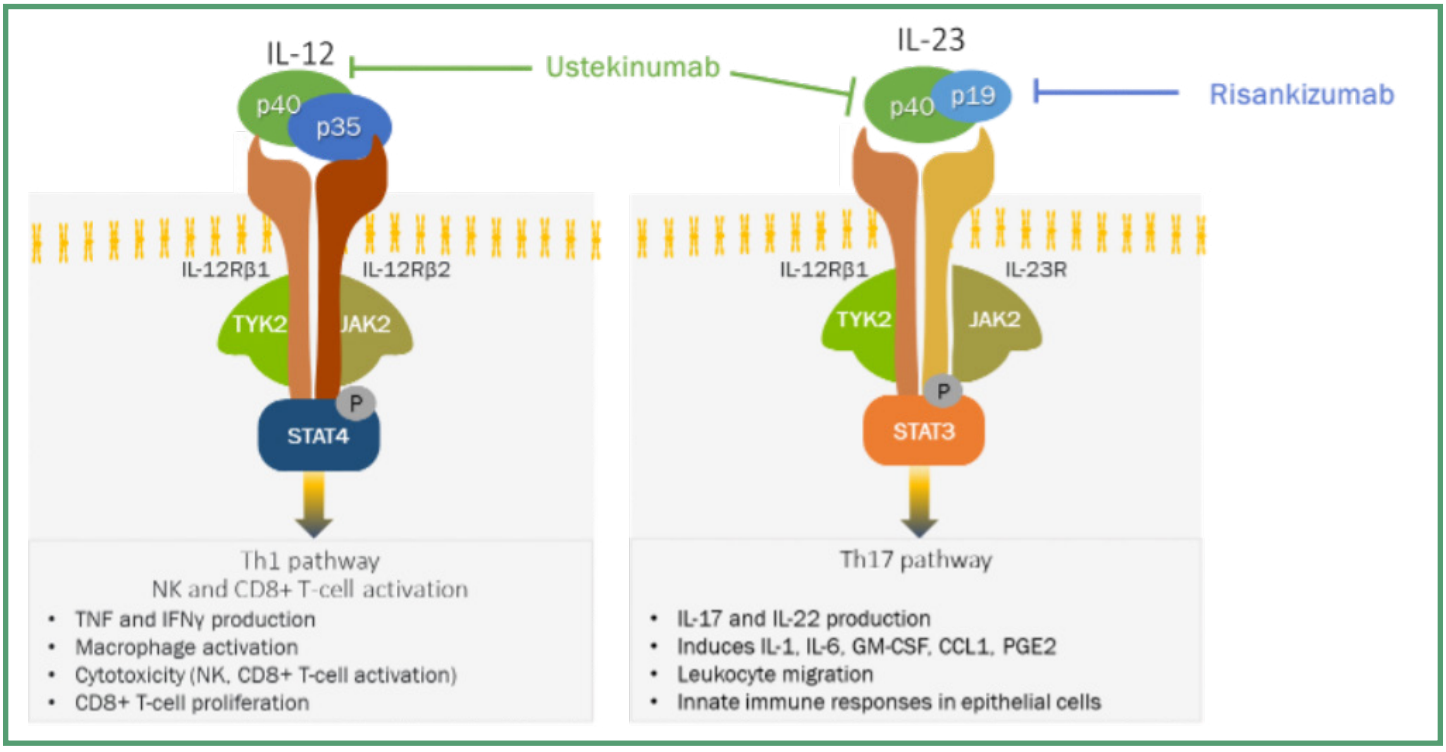

Figure 1. *Effect of ustekinumab (anti-IL-12/23p40) vs that of risankizumab (anti-IL-23p19) on inflammatory signalling.*
Abbreviations: CCL, C-C ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; JAK, Janus kinase; NK, natural killer; PGE, prostaglandin; pSTAT, signal transducer and activator of transcription protein; R, receptor; Th, T helper cell; TNF, tumour necrosis factor; TYK, tyrosine kinase.

concentrations of 1.2 µM (highest concentration tested); 2) High affinity for binding to IL-23 (dissociation constant K_d <10 pM); and 3) High degree of potency for functional inhibition of IL-23 induced Th17 responses, with sparing of the IL-12 mediated Th1 pathway.[16]

Overview of the ADVAVNCE, MOTIVATE, and FORTIFY Clinical Trials

The efficacy and safety of risankizumab for the treatment of CD was evaluated in the Phase 3 ADVANCE (NCT03105128), MOTIVATE (NCT03104413), and FORTIFY (NCT03105102) randomized controlled trials (RCTs) (**Figure 2**).[17, 18] ADVANCE and MOTIVATE were placebo-controlled, double-blinded induction studies. Participants were randomized to receive risankizumab 600 mg, 1200 mg or placebo intravenously at weeks 0, 4 and 8. The ADVANCE trial (n=931) recruited participants who had failed either conventional or biologic therapy. The MOTIVATE trial (n=618) enrolled exclusively a refractory population with prior biologic failure. Responders to induction therapy were re-randomized into the 52-week maintenance FORTIFY study, and then received subcutaneous (SC) risankizumab 180 mg, 360 mg or placebo (i.e., risankizumab was withdrawn following induction) every 8 weeks. In Canada, the approved dosing is risankizumab 600 mg IV induction at Week 0, 4 and 8, followed by 360 mg SC injection maintenance therapy at week 12 and every 8 weeks thereafter. The clinical data supporting this dosing will be summarized below.

Several key features of these RCTs should be noted, as they represent a substantial advance in trial methodology for the field. First, this was the first Phase 3 CD program to enroll patients not only on the basis of clinical symptoms (Crohn's disease activity index [CDAI] 220-450 at baseline), but also patient-reported outcomes (PRO) (average daily stool frequency (SF) ≥4 or average daily abdominal pain (AP) score ≥2), and centrally-evaluated confirmation of endoscopic evidence of mucosal inflammation at baseline (defined by a Simple Endoscopic Score for Crohn's Disease [SES-CD] ≥6 or ≥4 for isolated ileal disease). Requiring endoscopic confirmation of disease activity has important implications for defining the study population, as symptoms in CD are poorly correlated with objective measures. Correspondingly, participants in ADVANCE and MOTIVATE had clinically meaningful disease activity: One in three patients in ADVANCE and half of patients in MOTIVATE had failed multiple biologics, and the mean baseline SES-CD ranged from 13.4-15.1, indicating severely active endoscopic activity. For reference, the mean baseline SES-CD in the head-to-head SEAVUE trial comparing adalimumab to ustekinumab was only approximately half of that observed in the ADVANCE and MOTIVATE studies.[19]

Second, the risankizumab Phase 3 RCTs were the first to evaluate the co-primary endpoint of clinical remission (CDAI <150 or daily SF ≤2.8 and daily AP ≤1 and not worse than baseline) *and* endoscopic response (defined by 50% reduction in SES-CD). Previously, registrational Phase 3 programs had used clinical remission alone as the primary endpoint. Requiring both symptomatic and endoscopic response to therapy not only increases the stringency of the primary readout, but also brings the findings of these clinical trials in line with clinical practice guidelines from the STRIDE-II consensus, which recommends targeting early achievement of symptomatic response and long-term endoscopic

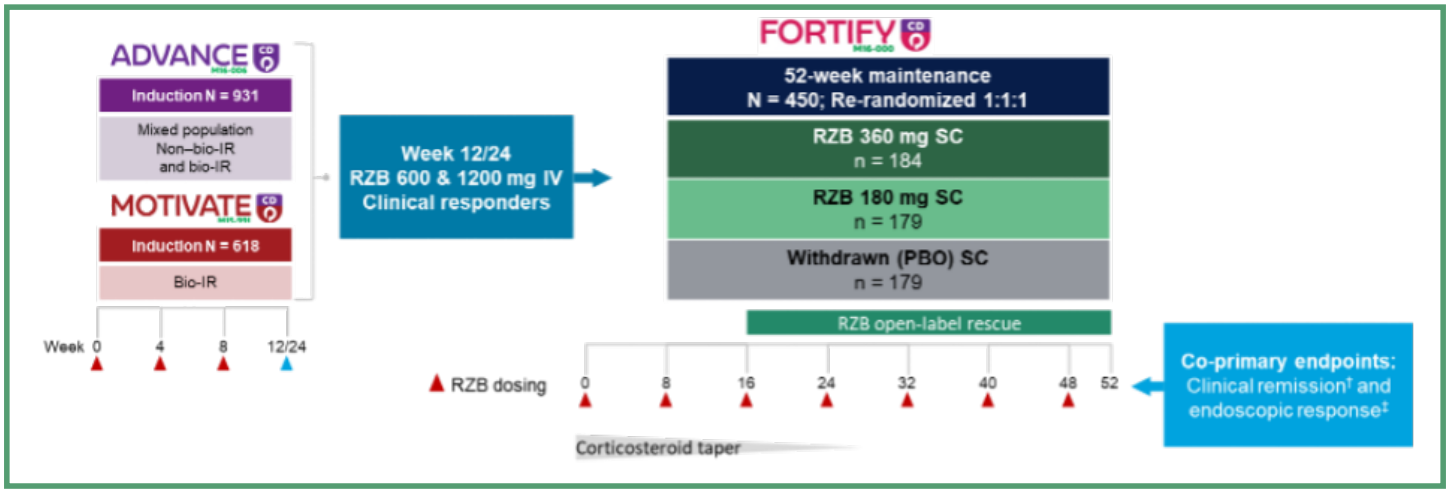

Figure 2. *Design of the ADVANCE, MOTIVATE, and FORTIFY Phase 3 clinical trials.*
Abbreviations: bio biologic; IR inadequate response; IV intravenous; RZB risankizumab; SC subcutaneous

remission.[20] Therefore, these clinical trials have raised the bar with respect to what clinicians and patients should expect to achieve with advanced therapy in CD. The results are more generalizable to clinical care, where endoscopic improvement is an important therapeutic target for ultimately altering the natural history of progressive CD.[21]

Induction Efficacy

At Week 12, risankizumab 600 mg IV was demonstrated to be significantly more effective than placebo for achieving the coprimary endpoints of clinical remission and endoscopic response. In ADVANCE, clinical remission defined by the PRO2, was achieved in 43.4% (146/336) of patients on risankizumab vs 21.7% (38/175) of patients receiving placebo (P<0.0001). In the biologic failure-only population in the MOTIVATE study, 39.8% (76/191) of patients receiving risankizumab achieved clinical remission vs 19.3% (36/187) of patients receiving placebo (P=0.0007). Similar results were observed when using a CDAI definition for clinical remission. Treatment responses were achieved rapidly: Statistically significant differences in the proportion of patients achieving endoscopic remission were observed as early as week 4.

Beyond symptoms, early endoscopic efficacy at 12 weeks was also demonstrated: 50% reductions in SES-CD from baseline were observed in 40.2% (135/336) of patients receiving risankizumab in ADVANCE vs 12.0% of patients in the placebo group (P<0.0001). Numerically, higher rates of endoscopic response were achieved in biologic naïve patients, among whom half (50.3%, 71/141) achieved week 12 endoscopic response vs 12.8% (10/78) in the placebo group. However, risankizumab was still highly effective vs placebo in achieving endoscopic response in patients with prior biologic failure: 32.8% (64/195) vs 11.3% (11/97) in ADVANCE and 28.8% (51/191) vs 11.2% (21/187) in MOTIVATE (P<0.0001). Finally, approximately 1 in 4 patients treated with risankizumab (24.1% [81/336] in ADVANCE and 19.4% [37/191] in MOTIVATE) achieved endoscopic remission by week 12, defined by an SES-CD≤4 with at least a 2-point reduction vs baseline and with no SES-CD subscore >1 (adjusted treatment vs placebo: Δ15% [95% confidence interval CI 9-21%], P<0.0001 in both trials).

The efficacy of risankizumab for inducing both clinical and endoscopic endpoints is further highlighted by the baseline characteristics of patients entering the FORTIFY maintenance trial. Whereas the baseline SES-CD was approximately 13-15 in ADVANCE/MOTIVATE, the mean SES-CD approximately halved to 7.6-8.5 in FORTIFY. Similar reductions in biomarkers, including fecal calprotectin (mean 960-1367 mg/kg in ADVANCE/MOTIVATE to 307-424 mg/kg in FORTIFY) and high-sensitivity C-reactive protein (mean 7.3-11.7 mg/L in ADVANCE/MOTIVATE to 3.7-4.1 mg/L in FORTIFY) were also observed.

Maintenance Efficacy

The durability of treatment response to induction therapy was evaluated among risankizumab responders in the re-randomized FORTIFY trial, where participants were randomized 1:1:1 to receive risankizumab 180 mg or 360 mg SC, or withdrawal of risankizumab (placebo) for 52 weeks (**Figure 2**).

At week 52, risankizumab 360 mg SC every 8 weeks was demonstrated to be significantly more effective than withdrawal of therapy for maintaining PRO2-defined clinical remission (51.8% [73/141] vs. 39.6% [65/164], P=0.004). The remission rate in the withdrawal arm is notable: To be eligible for FORTIFY, all participants must have responded to risankizumab induction therapy; the long half-life of risankizumab (approximately 21 days) should be considered when comparing treatment efficacy in the withdrawal group. A post-hoc analysis of participants who received placebo *only* during both induction and maintenance therapy (a "true" placebo group) demonstrated that only 16.3% (17/104) of placebo participants were in clinical remission at Week 52.[22] Rates of clinical remission were highest in patients who were biologic-naïve: 61.5% (24/39) of this subgroup achieved Week 52 clinical remission with risankizumab 360 mg.

Treatment differences between risankizumab and the withdrawal group were more pronounced for evaluation of endoscopic efficacy. Nearly half (46.8% [66/141]) of participants receiving maintenance risankizumab achieved week 52 endoscopic response vs 21.9% (36/164) of participants in the withdrawal (placebo) arm (p<0.0001). Efficacy was observed in both biologic-naïve (53.9% [21/39]) and bio-failure (44.1% [45/102]) populations. At week 52, endoscopic remission was achieved in a significantly higher proportion of patients receiving risankizumab 360 mg compared to withdrawal (placebo) (adjusted treatment difference vs. placebo 28% [95% CI: 20-37%], p<0.0001), and nearly 1/3 patients achieved the STRIDE-II recommended long-term treatment target of complete ulcer-free endoscopy (defined

by an SES-CD ulcerated surface subscore of 0 in participants with ulcerations at baseline) (30.5% [43/141] vs. 10.5% [17/162], p<0.0001).

Safety

To date, ADVANCE, MOTIVATE, and FORTIFY represent the largest CD-specific Phase 3 dataset. The safety of risankizumab was consistent with that observed in plaque psoriasis and psoriatic arthritis. Treatment is generally very well tolerated, and rates of adverse events (AEs) were similar in patients who received risankizumab 360 mg (448 events per 100 person-years exposure) vs patients receiving placebo (545 events per 100 person-years exposure in FORTIFY). There were no differences in severe or serious AEs, or AEs leading to treatment discontinuation between participants receiving risankizumab vs placebo, either during induction or maintenance. Treatment discontinuation of risankizumab was rare: In FORTIFY, 144/157 in the 180 mg and 124/141 in the 360 mg risankizumab groups completed the trial to week 52.

Infections are an important potential AE for CD patients undergoing immunosuppression. Most infections occurring in the Phase 3 risankizumab program were mild; serious or opportunistic infections were rare and occurred similarly in the placebo group vs the risankizumab group. No cases of herpes zoster or active tuberculosis were observed in patients receiving risankizumab 360 mg in the FORTIFY trial. These findings highlight the favourable safety profile of risankizumab, which is consistent with integrated safety data from the psoriasis literature.[23] To date, across indications, 26 clinical trials over 7 years have been performed evaluating risankizumab, with more than 107,000 patients treated worldwide since 2019, and approximately 13,500 patient-years of exposure.

Conclusion

In summary, risankizumab is a potent novel therapy that has been added to the therapeutic armamentarium for moderate-to-severely active CD in Canada. It is the first IL-23p19 specific monoclonal antibody, with a mechanism of action distinct from IL-12/23p40 blockade. The efficacy and safety of risankizumab have been demonstrated in the largest Phase 3 CD program to date, which was the first to enroll patients based on both clinical symptoms and endoscopically confirmed inflammation at baseline, and then subsequently measure both clinical and endoscopic outcomes relevant to clinical care. Risankizumab demonstrated efficacy across both biologic treatment naïve and failure populations, with rapid induction of symptomatic and endoscopic response followed by maintenance of clinical remission and achievement of endoscopic remission and ulcer-free mucosal healing. Combined with a highly favourable safety profile, risankizumab is likely to become a dominant therapy for first- and second-line treatment of moderate-to-severely active CD.

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