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REVIEW

Oral Peptide Therapeutics as an Emerging Treatment Modality in Immune-Mediated Inflammatory Diseases: A Narrative Review

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ABSTRACT

Immune-mediated inflammatory diseases (IMIDs), such as psoriasis, psoriatic arthritis, and inflammatory bowel disease, encompass a heterogenous group of conditions associated with chronic inflammation. Systemic treatments for patients with IMIDs include parenterally delivered monoclonal antibodies (mAbs) that disrupt specific cytokine and cytokine receptor binding interactions, and orally delivered small molecules that inhibit certain enzymes involved in the regulation of inflammatory signaling. Many patients prefer oral alternatives to injectables, but currently available oral advanced therapies are less effective than mAbs and/or have tolerability concerns. Thus, an unmet need exists for additional oral treatment options for patients with IMIDs. Therapeutic peptides can be designed to possess characteristics that provide both the target selectivity typically associated with parenterally delivered mAbs and an oral route of administration. Oral peptide therapeutics are an area of intense research in several therapeutic areas, and, although some oral peptides are available for certain indications, such as diabetes, there are currently no targeted oral peptides available for the treatment of patients with IMIDs. Icotrokinra (JNJ-77242113), which is currently in development to treat patients with various IMIDs, is the first targeted oral

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peptide designed to selectively inhibit interleukin (IL)-23 signaling by blocking the IL-23 receptor on human immune cells. In a phase 2b study in adults with moderate-to-severe psoriasis, icotrokinra showed a significant dose–response effect versus placebo, and a tolerable safety profile at Week 16. Sustained skin clearance and no safety signals were observed through Week 52 in the extension study to the phase 2b study. Ongoing phase 2 and phase 3 clinical studies in patients with psoriasis, psoriatic arthritis, and ulcerative colitis will provide data to inform the therapeutic potential of icotrokinra to address the unmet need in these diseases.

Keywords: Icotrokinra; Immune-mediated inflammatory disease; Interleukin-23; Oral peptide delivery; Oral systemic peptide; Peptide therapeutics

Key Summary Points

Patients with moderate-to-severe immune-mediated inflammatory diseases are generally treated with monoclonal antibodies or small-molecule therapeutics.
Peptides may provide the target selectivity typically associated with parenterally delivered monoclonal antibodies and the oral route of administration of small molecules.
Oral peptide therapeutics are an area of intense research in several therapeutic areas, but none are yet available for the treatment of patients with immune-mediated inflammatory diseases.
Icotrokinra (JNJ-77242113) is the first targeted oral peptide under investigation in patients with immune-mediated inflammatory diseases.

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs), such as psoriasis, psoriatic arthritis, and inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, encompass a heterogenous group of conditions associated with chronic inflammation [1]. Although they affect different organs and tissues, these diseases share some common pathogenic mechanisms and can be treated with targeted treatments against pro-inflammatory cytokines, such as tumor necrosis factor alpha, interleukin (IL)-17, and IL-23 [2]. The IL-23/IL-23 receptor (IL-23R) signaling pathway in particular plays a critical role in the pathogenesis of psoriasis and psoriatic arthritis, as well as IBD, and is a well-established therapeutic target for the treatment of these conditions [3–6]. To date, several monoclonal antibodies (mAbs) targeting the IL-23 p19 or p40 subunit, which is also present in IL-12, have been approved for the treatment of one or more of these disorders; however, these therapies can only be administered parenterally [7–11]. Although oral dosing may be a more appealing option versus parenteral administration for many patients and prescribing physicians [12–16], mAbs are not amenable to oral dosing because they are prone to proteolysis and denaturation by gastrointestinal (GI) enzymes and generally have limited membrane permeability due to their large molecular weight (approximately 150 kDa) [17–19].

Small molecules, which comprise the vast majority of pharmaceutical drugs [20], are ideally suited for oral delivery because of their low molecular weight (typically ≤ 500 Da) and oral bioavailability. However, compared with mAbs, they often have low target selectivity and specificity, which can lead to off-target effects. For instance, the development of LY3509754, an oral small-molecule inhibitor of IL-17A, was terminated in 2024 due to hepatotoxicity that was hypothesized to be due to an off-target effect [21].

Currently, there are several oral small-molecule drugs targeting specific enzymes involved in the regulation of inflammatory processes available for patients with psoriasis, psoriatic arthritis,

IBD, or other IMIDs. These include small-molecule inhibitors of Janus family kinases (JAKs), such as tofacitinib, baricitinib, upadacitinib, deucravacitinib, and the phosphodiesterase 4 inhibitor, apremilast. However, these therapies have tolerability concerns that limit their clinical use, in particular JAK inhibitors, which include safety warnings in their product labels [22–24]. Therefore, there is a high unmet need for orally administered targeted therapies that are well tolerated and provide clinical benefits for patients with IMIDs.

Icotrokinra (JNJ-77242113), a first-in-class targeted oral peptide that inhibits the binding of IL-23 with IL-23R, is currently under investigation for several IMIDs. This review will discuss key aspects of therapeutic oral peptides and provide an overview of the preclinical and clinical data for this investigational agent. Literature searches performed during the development of this narrative review covered topics and keywords, such as: oral peptides, IMIDs, therapeutic peptides, protein–protein interactions, cytokine–receptor interactions, small molecules, advantages/disadvantages of therapeutic modalities for IMIDs, patient preference for oral administration, barriers to oral formulations of mAbs/peptides, and the IL-23 signaling pathway. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DISCUSSION

Patient Preference for Oral Therapies

Due to patient preference, convenience, and noninvasiveness, oral administration is often the preferred route of delivery for treatment where possible during drug development [17–19]. This may be a particularly important consideration among people with a fear of needles, which affects 20–50% of adolescents and 20–30% of adults aged 20–40 years, and needle fear can lead to the avoidance of preventive care (e.g., vaccines) and reduce patient treatment compliance [25]. Preference studies have revealed that many patients with IBD, psoriatic arthritis, or psoriasis and their prescribing physicians prefer oral therapies over injectable or intravenous therapies [12–16]. However, patient preference can be influenced by the frequency of administration and other factors, such as convenience, and several studies have also shown that some patients prefer an injectable option, administered monthly or less frequently if available, versus a daily pill [26–28].

Targeted Oral Therapies for Immune-Mediated Inflammatory Diseases

While many patients may prefer oral therapies, the current small-molecule drugs available for patients with IMIDs are less effective than mAbs and/or have tolerability concerns. For example, apremilast and deucravacitinib have demonstrated lower levels of skin clearance relative to biologics for the treatment of plaque psoriasis [29–32]. Apremilast has also demonstrated less effectiveness than biologics for treating psoriatic arthritis [33, 34]; phase 3 studies of deucravacitinib in patients with psoriatic arthritis are ongoing (NCT04908202; NCT04908189). Additionally, GI adverse events (AEs), such as diarrhea and nausea, have been reported at higher rates with apremilast than placebo among clinical trial participants with psoriasis and psoriatic arthritis [35–38]. These GI AEs were typically mild and occurred within the first month of treatment, but GI intolerability is a potential factor in the high rates of discontinuation that have been observed for apremilast in retrospective cohort studies [39, 40].

While JAK inhibitors are effective in treating patients with IBD, psoriasis, and psoriatic arthritis [41, 42], this drug class is generally associated with an increased risk of mortality, serious infections, malignancy, and major adverse cardiovascular events, which limit their use in certain populations [22–24, 42–44]. It is currently unknown if selective tyrosine kinase 2 inhibitors like deucravacitinib have a similar risk profile as other JAK inhibitors, but serious infections, reactivation of herpes zoster, and malignancy were reported in phase 3 clinical trials of deucravacitinib in participants with psoriasis [45, 46].

Despite the availability of various treatments, lack or loss of response, intolerability, nontreatment, and undertreatment of patients with psoriatic disease or IBD, coupled with the high disease burden experienced by patients, remain a substantial problem [47, 48]. Thus, an unmet need exists for well-tolerated, targeted oral therapies, either as monotherapies or in combination with other therapies [49, 50], for the treatment of IMIDs. Oral peptides represent a group of therapeutic options well positioned to meet this unmet need. Oral peptide inhibitor candidates of IL-23R and IL-17 are under preclinical investigation [51, 52], with icotrokinra under clinical investigation for psoriasis, psoriatic arthritis, and IBD.

Peptide Therapeutics: Overview and Comparison With Small Molecules and mAbs

Therapeutic peptides, typically composed of 5–50 amino acids and having a molecular weight of ≤ 5000 Da, have been an area of intensive research in recent years. There are currently > 80 approved peptide products worldwide and many more in clinical development [53–55]. These peptide products cover myriad disease areas, including oncology, endocrinology, gastroenterology, and infectious diseases, as well as metabolic and cardiovascular indications [53–57].

Table 1 shows an overview of the key clinical advantages and challenging aspects of small molecules, peptide therapeutics, and mAbs. Typically, small molecules have higher oral bioavailability and membrane permeability compared with peptides and mAbs, but often have lower target selectivity and specificity. Conversely, peptides generally have higher specificity versus small molecules, leading to fewer off-target effects [17–19, 53, 56, 58, 59]. Additionally, peptides typically have better tissue penetration and biodistribution than mAbs because of their smaller size and other features, such as their charge and hydrophobicity profile, which can improve cell permeability [53, 55, 60].

Table 1 Comparison of small-molecule drugs, peptide therapeutics, and monoclonal antibodies

	Small-molecule drugs 	Peptide therapeutics 	Monoclonal antibodies 
Advantages	High membrane permeability High oral bioavailability Wide range of targets	High selectivity High potency Wide range of targets Low risk of drug–drug interactions Effective at blocking protein–protein interactions	High specificity High potency Low risk of drug–drug interactions Effective at blocking protein–protein interactions
Challenges	Low selectivity and specificity Off-target effects/toxicity High risk of drug–drug interactions Less effective at blocking protein–protein interactions	Low oral bioavailability Low GI stability Low membrane permeability Potential for development of anti-drug antibodies/immunogenicity	No oral bioavailability Low GI stability Potential for development of anti-drug antibodies/immunogenicity Poor membrane permeability

GI gastrointestinal

Peptides and mAbs also tend to have a better safety profile, and a minimal risk of drug–drug interactions compared with small molecules. Oral small molecules are typically subject to first-pass clearance by the liver, and subsequent hepatic elimination involving cytochrome P450 (CYP) enzymes and drug transporters, and can therefore be substrates, inhibitors, or inducers of CYP enzymes or transporters [61]. Conversely, the main route of clearance for most oral peptides is degradation by peptidases followed by renal elimination [62–65]. However, some oral peptides, such as cyclosporin, voclosporin, and octreotide, are subject to first-pass metabolism, which is primarily mediated by CYP3A4 [66–68]. Metabolism of mAbs occurs primarily in the liver via proteases rather than by CYP enzymes [69, 70].

Orally administered peptide therapeutics are subject to the harsh acidic environment of the stomach and undergo enzymatic breakdown along the GI tract. Systemically active peptides must also overcome physical barriers like intestinal mucus, which is thick and rich in proteolytic enzymes, to reach systemic circulation [17, 71, 72]. Epithelial membrane permeability and intestinal absorption can also be challenging for peptide therapeutics, but several technical strategies have been developed to improve the permeability and absorption of oral peptides, which have been the subject of several prior review articles [17–19, 58, 71–73]. These technical interventions include structural modifications, such as cyclization, and formulation optimizations, including micro-emulsions, absorption enhancers, enteric coatings, and the inclusion of peptidase inhibitors (excipients and direct-acting inhibitors) in the formulation. Such innovations in peptide chemistry and delivery have facilitated the development of therapeutic oral peptides that provide a patient-focused treatment option for several conditions.

Table 2 provides an overview of locally acting (within the GI tract) and systemic oral peptide therapeutics that have been approved by the US Food and Drug Administration. For example, semaglutide, a glucagon-like peptide-1 receptor agonist, is approved in both injectable and oral formulations for the management of type 2 diabetes mellitus (T2DM) [74]. The oral form of semaglutide, which includes an absorption enhancer to increase bioavailability [75], has demonstrated similar reductions in glycated hemoglobin as the injectable form [76, 77]. Oral semaglutide is also under investigation for treating overweight or obesity in adults without T2DM [78]. An investigational oral peptide inhibitor of proprotein convertase subtilisin/kexin type 9 (MK-0616) was well tolerated and demonstrated greater reductions in low-density lipoprotein cholesterol than placebo in a phase 2b trial [79]. However, to date, oral peptides have not been approved for IMIDs despite their potential as an effective and well-tolerated treatment modality.

Icotrokinra Description and Review of Available Data

Icotrokinra is a chemically synthesized cyclic peptide (molecular weight, 1.9 kDa) that binds selectively to the IL-23R, thereby blocking IL-23 signaling and the subsequent production of downstream cytokines, including IL-17A, IL-17F, and IL-22 [80] (Fig. 1). The cyclic structure of icotrokinra is important for its stability, and, in humans, icotrokinra has an estimated terminal elimination half-life of 9–16 h [80]. Icotrokinra is the first selective IL-23 pathway inhibitor that can be delivered orally, which is notable considering that blocking cytokine–receptor interactions has historically been targeted with mAbs due to the difficulties of accomplishing this with small molecules [81–85].

In preclinical experiments, icotrokinra bound to the IL-23R with high affinity (K_D = 7.1 pM) and demonstrated exquisite potency and selective inhibition of proximal IL-23 signaling (IC_{50} = 5.6 pM) in human peripheral blood mononuclear cells without affecting IL-12 signaling [80]. Additionally, icotrokinra inhibited IL-23–induced interferon-γ (IFNγ) production in natural killer cells, and in blood from healthy donors and patients with psoriasis [80]. Prophylactic treatment with orally administered icotrokinra in a rat skin inflammation model prevented IL-23–induced ear erythema and ear thickening, and attenuated the expression of IL-23 pathway genes in a dose-dependent

Table 2 Examples of approved oral peptide therapeutics

Peptide	Trade name	Molecular weight	Description	Formulation approach to increase oral bioavailability	Indication[a]	Manufacturer
Systemically active oral peptides						
Voclosporin	Lupkynis	1.2 kDa	Calcineurin inhibitor	Cyclization	Lupus nephritis	Novartis
Cyclosporin A	Neoral	1.2 kDa	Calcineurin inhibitor	Formulated with a self-nano-emulsifying drug delivery system	Rheumatoid arthritis; psoriasis; prophylaxis of organ rejection	Novartis
Desmopressin acetate	DDAVP	1.1 kDa	Vasopressin V2 receptor agonist	Chemical modification (cyclic synthetic analog of vasopressin)	Central diabetes insipidus; nocturnal enuresis	Apotex
Octreotide	Mycapssa	1.0 kDa	Somatostatin receptor agonist	Enteric coating; proprietary Transient Permeation Enhancer® technology	Long-term maintenance treatment of acromegaly	Chiesi Farmaceutici
Semaglutide	Rybelsus	4.1 kDa	Glucagon-like peptide-1 receptor agonist	Permeation enhancer; formulation includes Eligen® SNAC to help increase gastric/intestinal membrane permeability	Type 2 diabetes	Novo Nordisk
Gut-restricted oral peptides						
Linaclotide	Linzess	1.5 kDa	Guanylate cyclase-C receptor agonist	N/A (acts locally in the GI tract with negligible systemic bioavailability)	Irritable bowel syndrome; chronic idiopathic constipation	Ironwood Pharmaceuticals
Plecanatide	Trulance	1.7 kDa	Guanylate cyclase-C receptor agonist	N/A (acts locally in the GI tract with negligible systemic bioavailability)	Irritable bowel syndrome; chronic idiopathic constipation	Salix Pharmaceuticals

Table 2 continued

Peptide	Trade name	Molecular weight	Description	Formulation approach to increase oral bioavailability	Indication[a]	Manufacturer
Vancomycin	Vancocin	1.4 kDa	Glycopeptide bactericidal antibiotic	N/A (acts locally in the GI tract with negligible systemic bioavailability)	*C. difficile*-associated diarrhea; staphylococcal enterocolitis	ViroPharma

FDA Food and Drug Administration, *GI* gastrointestinal, *N/A* not applicable, *SNAC* sodium N-(8-[2-hydroxylbenzoyl] amino) caprylate
[a]Indications and approval are per United States FDA

manner. Additionally, in a rat model of trinitrobenzene sulfonic acid–induced colitis, oral administration of icotrokinra significantly inhibited colon tissue inflammation and attenuated weight loss [80]. In healthy human volunteers, oral dosing of icotrokinra inhibited ex vivo IL-23–stimulated IFNγ production in the blood [80]. Together, these data provide evidence of systemic activity as well as activity in skin for orally administered icotrokinra.

The completed and ongoing clinical trials for icotrokinra are shown in Table 3. In a phase 2b dose-ranging trial [FRONTIER 1 (NCT05223868)], adult participants with moderate-to-severe plaque psoriasis (n = 255) were randomized to receive five different doses of oral icotrokinra (25 mg daily, 25 mg twice daily, 50 mg daily, 100 mg daily, or 100 mg twice daily) or placebo for 16 weeks [86]. The primary endpoint, ≥ 75% reduction from baseline in the Psoriasis Area and Severity Index (PASI 75) at Week 16, was met by all icotrokinra treatment groups compared with placebo. At Week 16, a PASI 90 response occurred in 26–60% of participants in the icotrokinra treatment groups, compared with 2% of participants in the placebo group; a PASI 100 response was also observed in 12–40% of participants treated with icotrokinra versus 0% for placebo. Response rates were highest in the 100-mg twice-daily icotrokinra group, in which PASI 90 and PASI 100 responses at Week 16 were achieved in 60% and 40% of participants, respectively. Response rates for scalp-specific psoriasis were also higher for all icotrokinra doses versus placebo at Week 16 [87]. In the long-term extension study [FRONTIER 2 (NCT05364554)], sustained skin clearance was demonstrated through 52 weeks, including for scalp-specific psoriasis. Across endpoints, response rates at Week 52 were highest in the 100-mg twice-daily icotrokinra group, with 76%, 64%, and 40% of participants in this group achieving PASI 75, PASI 90, and PASI 100 responses, respectively [87]. Although head-to-head comparisons are not available, the response rates observed with the 100-mg twice-daily dose in the phase 2 FRONTIER studies were similar in magnitude to those observed in phase 3 studies of mAbs that target IL-23 [88–92].

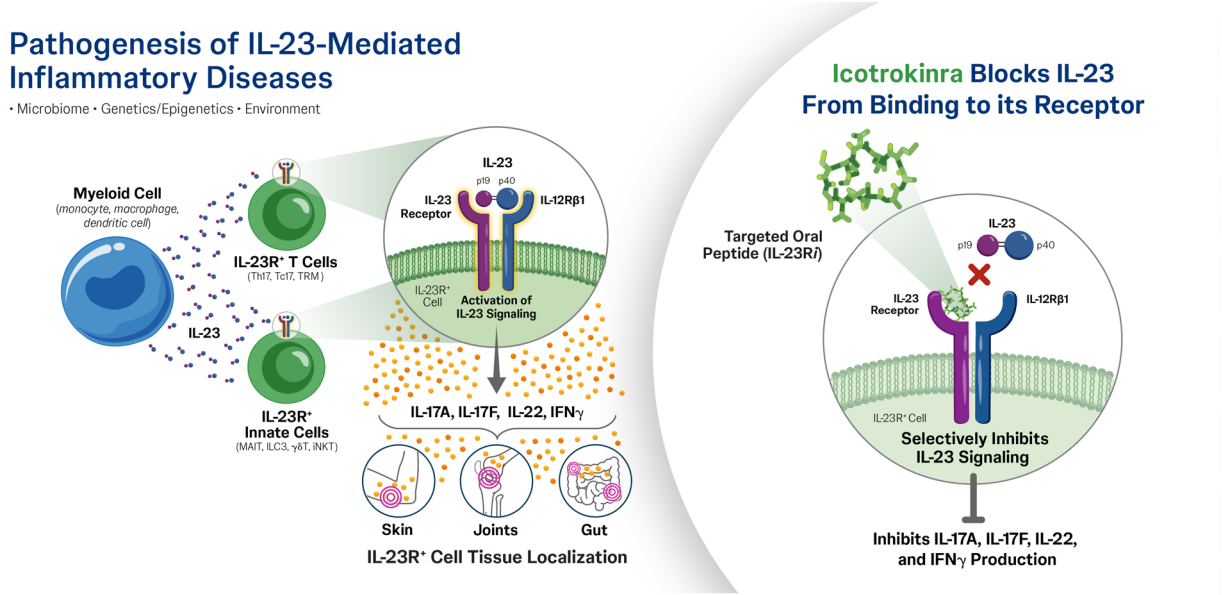

Fig. 1 Mechanism of action of icotrokinra. *CD* cluster of differentiation, *IFNγ* interferon-γ, *IL* interleukin, *ILC3* type 3 innate lymphoid cell, *iNKT* invariant natural killer T cell, *MAIT* mucosal-associated invariant T cell, *R* receptor, *Tc17* CD8+ cells that produce IL-17, *Th17* CD4+ T helper cells that produce IL-17, *TRM* tissue resident memory T cell

In FRONTIER 1 and FRONTIER 2, there was no evidence of dose-related increases in AEs across the icotrokinra dosing groups. In FRONTIER 1, the most common AEs reported in the placebo group and the combined icotrokinra dose group were COVID-19 (12% and 11%, respectively) and nasopharyngitis (5% and 7%, respectively) through Week 16. GI-related AEs were also comparable through Week 16 in the combined icotrokinra dose group (11%) and the placebo group (12%). Safety results in FRONTIER 2 were consistent with those from FRONTIER 1, and rates of GI-related AEs did not increase in participants receiving icotrokinra through 52 weeks (6% in the combined icotrokinra group) [87].

Based on these data, pivotal phase 3 trials comparing icotrokinra with placebo in participants aged 12 years and older with moderate-to-severe plaque psoriasis [ICONIC-LEAD (NCT06095115)] and plaque psoriasis involving difficult-to-treat high-impact sites including scalp, genitals, and hands/feet [ICONIC-TOTAL (NCT06095102)], have been initiated (Table 3). Head-to-head phase 3 trials comparing icotrokinra against deucravacitinib and placebo [ICONIC-ADVANCE 1 (NCT06143878) and ICONIC-ADVANCE 2 (NCT06220604)] in adults with moderate-to-severe plaque psoriasis are ongoing. A phase 2b dose-ranging trial comparing icotrokinra with placebo in adults with moderately to severely active ulcerative colitis [ANTHEM-UC (NCT06049017)] and phase 3 trials in adults with psoriatic arthritis [ICONIC-PsA 1 (NCT06878404) and ICONIC-PsA 2 (NCT06807424)] have also been initiated. The results from these ongoing studies will provide further data on the efficacy and tolerability of the investigational targeted oral peptide, icotrokinra in psoriasis, psoriatic arthritis, and IBD.

Table 3 Completed and ongoing clinical trials for icotrokinra

Study population	Study acronym (NCT number)	Trial phase	Comparator	Status[a]	Enrollment	Estimated primary completion date[b]
Healthy Chinese adult participants (18–55 y)	N/A (NCT05703841)	1	N/A	Completed	30	N/A
Healthy Japanese and Chinese adult participants (20–60 y)	N/A (NCT05062200)	1	PBO	Completed	36	N/A
Adult participants (≥ 18 y) with moderate-to-severe plaque psoriasis	FRONTIER 1 (NCT05223868)	2b	PBO	Completed	255	N/A
FRONTIER 1 long-term extension	FRONTIER 2 (NCT05364554)	2b	N/A	Completed	227	N/A
Adult and adolescent participants (≥ 12 y) with plaque psoriasis involving high-impact sites[c]	ICONIC-TOTAL (NCT06095102)	3	PBO	Active, not recruiting	311	Jun 2024
Adult and adolescent participants (≥ 12 y) with moderate-to-severe plaque psoriasis	ICONIC-LEAD (NCT06095115)	3	PBO	Active, not recruiting	684	Jul 2024
Adult participants (≥ 18 y) with moderately to severely active ulcerative colitis	ANTHEM-UC (NCT06049017)	2b	PBO	Active, not recruiting	252	Sept 2024
Adult participants (≥ 18 y) with moderate-to-severe plaque psoriasis	ICONIC-ADVANCE 1 (NCT06143878)	3	Deucravacitinib; PBO	Active, not recruiting	774	Mar 2025
Adult participants (≥ 18 y) with moderate-to-severe plaque psoriasis	ICONIC-ADVANCE 2 (NCT06220604)	3	Deucravacitinib; PBO	Active; not recruiting	675	Jan 2025
Adult and adolescent participants (≥ 12 y) with pustular or erythrodermic psoriasis	N/A (NCT06295692)	3	N/A	Active; not recruiting	16[d]	Feb 2025

Table 3 continued

Study population	Study acronym (NCT number)	Trial phase	Comparator	Status[a]	Enrollment	Estimated primary completion date[b]
Biologic-naïve adult participants (≥ 18 y) with active psoriatic arthritis	ICONIC-PsA 1 (NCT06878404)	3	PBO Includes active reference arm (ustekinumab)	Recruiting	540	Oct 2026
Biologic-experienced adult participants (≥ 18 y) with active psoriatic arthritis	ICONIC-PsA 2 (NCT06807424)	3	PBO	Recruiting	750	Feb 2027

N/A not applicable, *PBO* placebo, *y* years

[a]Status as of March 26, 2025

[b]Not listed for completed trials

[c]Scalp, genitals, and/or palms of the hands and soles of the feet

[d]Estimated enrollment

CONCLUSION

Patients with moderate-to-severe psoriasis, psoriatic arthritis, and IBD are typically treated with injectable mAbs or a variety of small-molecule therapeutics. Oral peptides are an area of intense research in several therapeutic areas, but none are yet available for the treatment of patients with IMIDs. Icotrokinra is the first investigational orally administered peptide being tested in patients with these conditions. Due to its high affinity and potency for the IL-23R, it combines the target selectivity associated with mAbs with the simplicity of oral administration, addressing an important unmet medical need. Positive results from phase 2 studies in psoriasis have been encouraging, and phase 3 trials are underway to determine the potential of icotrokinra in the treatment of IMIDs.

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Declarations

Conflict of Interest. Linda Stein Gold is an investigator/advisor and/or speaker for AbbVie, Amgen, Arctis, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, and UCB. Kilian Eyerich has received speaker's fees from and/or served as an advisory board member for AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Hexal, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi, Sitryx, and UCB; and is a co-founder and owns shares in Dermagnostix and Dermagnostix

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