A Review of the Clinical Trial Landscape in Psoriasis: An Update for Clinicians

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ABSTRACT

As our understanding of the pathogenesis of psoriasis has evolved over the past two decades, so has the number of treatment options. The introduction of biologic agents targeting specific cytokines in the interleukin (IL)-23/IL-17 pathway has proven successful in promoting skin clearance among patients. However, their use is often limited owing to cost, parenteral administration, and possible reduced efficacy over time. Topical therapies have also seen limited advancement, with agents such as corticosteroids and vitamin D derivatives remaining the mainstay of treatment, despite side effects limiting their long-term use. New therapeutic agents are needed to improve disease management for patients. In this review, we summarize pipeline and recently approved therapies undergoing clinical trials for psoriasis during a 12-month search period (30 June 2021 to 30 June 2022) using ClinicalTrials.gov. New-generation biologics and oral small molecules in phase II or III development were included, and pivotal data identified through various search modalities (PubMed, conference presentations, etc.) evaluating each drug candidate will be discussed. Topical therapies will also be discussed in line with recent US Food and Drug Administration approvals. As new therapies continue to enter the treatment landscape, long-term data and comparative trials will be needed to better understand their place among existing therapeutic agents.

Keywords: Psoriasis; Biologic therapies; Oral small molecules; Topical therapies; Interleukin (IL)-17, IL-23, IL-36; Janus kinases; Phosphodiesterase-4; Aryl hydrocarbon receptor

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INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory condition that has a significant impact on quality of life [1, 2]. The disease manifests as erythematous scaling plaques on the skin and is associated with several comorbid conditions including obesity, cardiovascular disease, Crohn’s disease, and psoriatic arthritis [3]. Approximately 2–3% of the world’s population is affected by psoriasis, with plaque psoriasis being the most common subtype [1, 4].

Research investigating the pathogenesis of psoriasis has advanced substantially over the past two decades, as evidenced by the rapidly changing landscape for treatment [5]. Identification of the interleukin (IL)-23/IL-17 axis as the driving force of psoriatic inflammation has led to the development of more targeted systemic therapies, including tumor necrosis factor (TNF)-α, IL-12/23, IL-23, and IL-17 inhibitors [6–8]. These biologics have revolutionized the treatment of moderate-to-severe disease, demonstrating superior efficacy and safety profiles to conventional oral therapies (i.e., methotrexate, cyclosporine, acitretin) [9]. For patients, this has made the achievement of complete or almost complete skin clearance possible, translating to significant improvements in quality of life. [2, 10]

Despite these advances, several gaps in psoriasis treatment remain. Many patients fail to respond to biologic therapies, while others experience a loss of efficacy over time [11, 12]. These medications also require a parenteral route of administration and are often costly for patients, posing several patient-level barriers to care [13]. The treatment of mild disease has also not received the same attention with topical agents, most commonly corticosteroids and vitamin D derivatives, remaining the mainstay of treatment despite potential adverse effects often limiting their long-term use [14].

The need for new therapeutic agents for the treatment of psoriasis is clear. The purpose of this study is to review the clinical trial landscape in psoriasis over the past 12 months, highlighting pipeline therapies and recent drug approvals.

METHODS

This review is based on previously published literature and does not include any new unpublished studies conducted by the authors. To identify pipeline agents, ClinicalTrials.gov was searched using the term “psoriasis” for newly initiated, ongoing, and recently completed trials between 30 June 2021 and 30 June 2022. New-generation biologics and oral small molecules in phase II or III development were included. Topical agents were also reviewed in-line with recent US Food and Drug Administration (FDA) approvals. Additional searches for published literature (PubMed was searched using the following methods for each agent “Common Name” OR “Alternative Name”), conference presentations, abstracts, and press releases were performed to identify the most...
recent updates and available data for each therapeutic agent.

PIPETLINE THERAPIES

Interleukin-23 Inhibitors

IL-23 is a heterodimeric cytokine composed of two subunits, p19 which is specific to IL-23, and p40 which is shared with IL-12 [15]. The cytokine is overexpressed in psoriatic plaques and plays a central role in the pathogenesis of disease, driving the differentiation of naïve T helper (Th) cells into Th17 cells, which produce proinflammatory cytokines such as IL-17, IL-22, and TNF-α [16–18]. Specific inhibition of this cytokine has proven to be successful in clearing psoriatic plaques, accounting for the mechanism of action of several approved and pipeline therapies [19].

At present, there are two IL-23 inhibitors in phase II development for psoriasis (Table 1). These include IBI112 (Innovent Biologics), a selective inhibitor of the IL-23p19 subunit, and PN-235 (JNJ-77242113; Protagonist Therapeutics and Janssen Biotech) an investigational peptide targeting the IL-23 receptor. With respect to IBI112, preclinical data published by Li et al. concluded that the drug shares similar blocking activity to guselkumab with regards to its ability to inhibit the p19 subunit, signal transducer and activator of transcription (STAT) 3 phosphorylation, and subsequent IL-17 production [20]. The study also highlighted that subcutaneous injection of IBI112 significantly reduced skin thickness and inflammation in a “psoriasis-like epidermal-hyperplasia mouse model challenged by continuous hIL-23 injection.” [20] PN-235 is unique in that it offers an oral route of administration as compared with the subcutaneous injections required by the aforementioned biologics [21]. As of October 2021, PN-235 completed a phase I trial (NCT04621630) in healthy participants, however results have not yet been posted.

Interleukin-17 Inhibitors

The IL-17 family of effectors consists of six distinct subunits (IL-17A-F), forming functional homodimers of each subtype and the IL-17A/F heterodimer [22]. In psoriasis, IL-17 is considered one of the main effector cytokines contributing to disease pathogenesis, with levels of IL-17A and IL-17F found to be overexpressed in lesional skin [23, 24]. The cytokine is produced by Th17 cells, and upon production, exerts its effects on keratinocytes, promoting their proliferation as well as the release of inflammatory cytokines, chemokines, and antimicrobial peptides that contribute to the formation of psoriatic plaques [24–28].

Netakimab (BCD-085; BIOCAD) is a humanized IgG1 monoclonal antibody that targets IL-17A, approved for use in Russia and Belarus for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis [29, 30]. Preliminary results from the phase III PLANETA trial revealed that 77.7% and 83.3% of patients receiving netakimab 120 mg every 2 or 4 weeks, respectively (following 3 weeks of induction), achieved a 75% reduction in the Psoriasis Area and Severity Index (PASI) score at 12 weeks compared with placebo (0%; \(p < 0.0001\)) [31]. Effects were maintained through 12 months, and the authors concluded that subcutaneous dosing every 4 weeks was non-inferior to dosing every 2 weeks. As per previously completed phase II trials, netakimab was well tolerated by participants, reporting a similar safety profile to existing IL-17 inhibitors and no discontinuations due to treatment emergent adverse events (TEAEs) [31, 32]. The PLANETA trial’s 3-year open-label extension period was recently completed and is currently awaiting results [33].

Vunakizumab (SHR-1314; Jiangsu Hengrui Medicine Co., Ltd) is a humanized IgGκ monoclonal antibody that binds to and inhibits IL-17A [34]. Zhang et al. investigated the efficacy and safety of monthly subcutaneous doses of
### Table 1 Reviewed IL-23, IL-17, and IL-36 inhibitors for psoriasis

| Name        | Target          | Route of administration | Overall stage | Ongoing trials in psoriasis | Primary endpoint | Comments                                                                                                                                 |
|-------------|-----------------|--------------------------|---------------|-----------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| IBI112      | IL-23p19        | SQ                       | Phase 2       | NCT05003531                | PASI 90 at 16 weeks | Trial investigating multiple dosing strategies of PN-235 in a delayed-release tablet formulation versus placebo                           |
| PN-235      | IL-23 Receptor  | Oral                     | Phase 2       | NCT05357755                | PASI 75 at 16 weeks | Multicenter, long-term extension, dose-ranging trial. Preceding study: NCT05223868                                                |
| Netakimab   | IL-17A          | SQ                       | Phase 3       | NCT04839016                | PASI 90 or sPGA of 0/1 at 12 weeks | Phase III trial (NCT03390101) completed in January 2022                                                                                   |
| Vunakizumab | IL-17A          | SQ                       | Phase 3       | NCT04399837                | Time to first flare (up to 48 weeks) | Aims to determine the efficacy and safety of multiple spesolimab SQ dosing regimens versus placebo in preventing GPP flares            |
| Izkibep     | IL-17A          | SQ                       | Phase 2       | NCT05096364                | PASI 90 at 12 weeks | Phase II trial (NCT03591887) completed in November 2021                                                                                   |
| Gumokimab   | IL-17A          | SQ                       | Phase 2       | NCT05352893                | GPPPGA score of 0/1 at 4 weeks | Patients with GPP experiencing an active flare randomized to receive a single IV dose of insidolimab (high dose/low dose) or placebo |
| Spesolimab  | IL-36 Receptor  | IV, SQ maintenance       | Phase 3       | NCT03886246                | TEAEs up to 252 weeks | Long-term extension of the phase II Effisayil-1 trial (NCT03782792)                                                                     |
|            |                 |                          |               | NCT05239039                | TEAEs up to 17 weeks | Phase 3 expanded access program in China enrolling participants experiencing an active GPP flare                                      |
|            |                 |                          |               | NCT05200247                | TEAEs up to 17 weeks | Phase 3 expanded access program in Japan enrolling participants experiencing an active GPP flare                                      |
|            |                 |                          |               | NCT04399837                | Time to first flare (up to 48 weeks) | Aims to determine the efficacy and safety of multiple spesolimab SQ dosing regimens versus placebo in preventing GPP flares            |
|            |                 |                          |               | NCT04493424                | TEAEs up to 260 weeks | 5-year open-label, long-term safety trial enrolling patients with palmoplantar pustulosis                                             |
| Imsidolimab | IL-36 Receptor  | IV, SQ maintenance       | Phase 3       | NCT05352893                | Incidence of AEs up to 24 weeks | Phase 3 long-term extension trial (preceding study: NCT05352893)                                                                     |

*SQ subcutaneous, IV intravenous, QD once daily, BID twice daily, wks weeks, IL interleukin, PASI Psoriasis Area and Severity Index, sPGA Static Physician’s Global Assessment, TEAEs treatment emergent adverse events, AE adverse events, GPPPGA Generalized Pustular Psoriasis Physician’s Global Assessment, GPP generalized pustular psoriasis

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vunakizumab in a phase II clinical trial and reported that a significantly greater proportion of participants in each of the treatment groups (40 mg, 80 mg, 160 mg, 240 mg) achieved a PASI 75 response at 12 weeks compared with placebo [34]. Response rates were maintained through to week 36, with additional administrations given at weeks 16 and 20. Vunakizumab was well tolerated by participants with the majority of adverse events being of mild-to-moderate severity [34]. The drug is currently being investigated in an ongoing phase III trial to evaluate its long-term safety and efficacy in patients with moderate-to-severe plaque psoriasis (Table 1).

Other pipeline IL-17A inhibitors with no published clinical trial data are summarized in Table 1.

**Interleukin-36 Inhibitors**

IL-36 is central to the pathogenesis of generalized pustular psoriasis (GPP), a subtype of pustular psoriasis with no universally recognized treatment options [35, 36]. Upon binding to its receptor, IL-36 stimulates downstream activation of the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, promoting the release of chemokines that recruit neutrophils, macrophages, and T cells to the epidermis [37, 38]. IL-36 is overexpressed in GPP and loss-of-function mutations in the gene coding for the IL-36 receptor antagonist can be linked to 10–82% of cases, leading to unopposed IL-36 activity and an accelerated inflammatory response [38]. Mutations in the CARD14, APS1S3, and SERPINA3 genes have also been identified in patients with GPP, all of which have a functional connection to the IL-36 pathway [39].

**Imsidolimab** (ANBO19; AnaptysBio Inc.) is a humanized, monoclonal IL-36 receptor antagonist, currently under investigation in two phase III trials [GEMINI-1 (NCT05352893) and GEMINI-2 (NCT05366855)] [40]. Recently, a phase II trial administering a single dose of imsidolimab to eight participants was presented at the 2021 European Academy of Dermatology and Venereology Congress [41]. The authors reported that 75% of participants achieved the primary outcome at 4- and 16-weeks follow-up. Decreases in the Modified Japanese Dermatology Association severity index (mJDA-SI) total score (29%, 54%, and 58% at weeks 1, 4, and 16, respectively) and percent body surface area with erythema and pustules (60%, 94%, 98% at weeks 1, 4, and 16, respectively) were also reported among participants over the course of the trial. The drug was well tolerated with most adverse events being mild-to-moderate in severity [41].

**Spesolimab** (BI 655,130; Boehringer Ingelheim) is a humanized, anti-IL-36R monoclonal antibody, recently approved by the FDA for the treatment of GPP flares (1 September 2022) [42]. The approval was based on the completion of the phase II Effisayil-1 trial, results of which were recently published [43]. The trial enrolled 53 patients experiencing an active GPP flare, and participants were randomized 2:1 to receive a single dose of 900 mg spesolimab intravenously or placebo. By the end of the first week, a significantly greater proportion of participants in the spesolimab group achieved the primary outcome of a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 compared with placebo (54% versus 6%; \( p < 0.001 \)). Additionally, 43% of participants randomized to the spesolimab group and 11% of participants randomized to placebo achieved a GPPGA total score of 0 or 1 at 1 week follow-up (\( p = 0.02 \)). Infections were more common among patients who received spesolimab over the course of the trial. Two participants that received spesolimab also experienced drug reactions with eosinophilia and systemic symptoms, one of which occurred concurrently with a case of drug-induced hepatic injury [43].

Ongoing trials with spesolimab are summarized in Table 1. Of note, spesolimab is currently being investigated in a 5-year long-term safety trial enrolling patients with palmoplantar pustulosis (PPP). Results from a preceding phase I/II trial were previously published and reported that the trial failed to reach its primary endpoint [44].
Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE4) is the primary PDE expressed in immune cells and keratinocytes [45]. The enzyme mediates inflammatory responses through hydrolyzing cyclic adenosine monophosphate (cAMP), a second messenger involved in the regulation of several normal cellular metabolisms [46–48]. Inhibition of PDE4 increases intracellular concentrations of cAMP, activating several downstream pathways that hamper the inflammatory response, suppressing inflammatory cytokine generation and elevating the production of anti-inflammatory mediators [45].

Several oral PDE4 inhibitors are currently under investigation for psoriasis with limited data available on their efficacy. These include ME3183 (Meiji Seika Pharma Co., Ltd.), Mufemilast (Hemay005; Tianjin Hemay Pharmaceutical Co., Ltd.), and Orismilast (LEO-32731; UNION Therapeutics), ongoing trials of which are summarized in Table 2.

**PF-07038124** (Pfizer) is a topical PDE4 inhibitor currently under investigation in a phase IIb trial for psoriasis and atopic dermatitis (NCT05375955). The drug was designed using the previously investigated and successful topical PDE4 inhibitor crisaborole as a model [49, 50]. It also includes boron in its structure, hypothesized to alter the conformation of the drug in a way that improves its combinability with antibody therapies [49]. A phase IIa trial (EMPORIA; NCT04664153) investigating the mean change in PASI response at 6 weeks among participants randomized to receive once daily PF-07038124 ointment or vehicle was completed in August 2021. Recently posted results revealed that the percent change in PASI score from baseline to 6 weeks was significantly greater among those receiving PF-07038124 compared with placebo (raw data, not yet published) [51].

**Roflumilast** (ARQ-151; Arcutis Biotherapeutics) is a topical PDE4 inhibitor that was recently approved by the FDA (29 July 2022) for the treatment of plaque psoriasis in patients ≥ 12 years of age, following the completion of two identical phase III trials [DERMIS-1 (NCT04211363) and DERMIS-2 (NCT04211389)] [52–54]. Together, these trials enrolled over 800 participants, randomized to receive roflumilast cream or vehicle cream once daily for 8 weeks. Top-line results were presented and revealed that 42.4% and 37% of patients randomized to the roflumilast groups, and 6.1% and 6.9% of patients randomized to the vehicle groups achieved Investigator’s Global Assessment (IGA) score success (defined as an IGA score of 0/1 and a ≥ 2-grade improvement from baseline) at 8 weeks in the DERMIS-1 and DERMIS-2 trials, respectively [54]. Participants in the roflumilast groups also reported significant improvements in key secondary endpoints, including intertriginous-area IGA success rate, PASI 75 response, and itch severity (as measured by the Worst Itching Intensity Numerical Rating Scale) over the course of the trial. The authors reported low rates of application site reactions among those treated with roflumilast, and the most commonly reported TEAEs included hypertension, headache, diarrhea, and nasopharyngitis [54]. Ongoing trials with roflumilast are summarized in Table 2.

Janus Kinase Inhibitors

Several cytokines involved in the pathogenesis of psoriasis bind to type I and II receptors, which rely on Janus kinases (JAKs) for signal transduction [55]. Examples include IL-6, IL-22, IL-12, IL-23, and several interferons [55]. When a cytokine binds to its receptor, the receptor undergoes a conformational change, activating and recruiting two JAK proteins [56, 57]. The activated JAKs alter the receptor, allowing two STAT proteins to bind, which then become phosphorylated, dimerize, and translocate to the nucleus where they alter gene expression [56]. There are four JAKs [JAK1-3 and tyrosine kinase 2 (TYK2)] and seven STAT proteins (STAT1-4, STAT5a, STAT5b, STAT6) [55]. Different cytokine receptors signal through different combinations of JAKs [55, 56]. Therefore, inhibition of each subtype of JAK can interfere with various downstream signaling pathways, acting as a powerful treatment for limiting inflammation in psoriasis [57].
| Name         | Target | Route of administration | Overall stage | Ongoing trials in psoriasis | Primary endpoint | Comments                                                                                           |
|--------------|--------|-------------------------|---------------|-----------------------------|-----------------|---------------------------------------------------------------------------------------------------|
| Mufemilast   | PDE4   | Oral                    | Phase 3       | NCT04839328                 | PASI 75 at 16 weeks | 60 mg BID selected as the phase 3 dosing strategy                                                 |
| ME3183       | PDE4   | Oral                    | Phase 2       | NCT05268016                 | PASI 75 at 16 weeks |                                                                                                   |
| Orismilast   | PDE4   | Oral                    | Phase 2       | NCT05190419                 | % change in PASI score from baseline to 16 weeks |                                                                                                   |
| Jaktinib     | JAK1/2 | Oral                    | Phase 2       | NCT04612699                 | PASI 75 at 12 weeks |                                                                                                   |
| Deucravacitinib | TYK2 | Oral            | Phase 3       | NCT04036435                 | AEs and SAEs up to 244 weeks | Long-term extension trial (POETYK PSO-LTE). Preceding studies: POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751). Participants receiving 6 mg deucravacitinib QD administered orally |

- NCT04167462 PASI 75 or sPGA 0/1 at 16 weeks
- NCT05478499 ss-PGA score of 0/1 + a > / = 2-point dec. from baseline at 16 weeks
- NCT05124080 Change in mNAPSI score at 24 weeks compared to baseline
- NCT04772079 Multiple (i.e., PASI 75 at 16 weeks, sPGA score of 0/1 + a > / = 2-point dec. from baseline at 16 weeks)
| Name         | Target | Route of administration | Overall stage | Ongoing trials in psoriasis | Primary endpoint | Comments                                                                 |
|--------------|--------|--------------------------|---------------|-----------------------------|------------------|--------------------------------------------------------------------------|
| NDI-034858   | TYK2   | Oral                     | Phase 2       | NCT04999839                 | PASI 75 at 12 weeks |                                                                          |
| AUR101       | RORγt  | Oral                     | Phase 2       | NCT04855721                 | PASI 75 at 12 weeks |                                                                          |
| Cedirogant   | RORγt  | Oral                     | Phase 2       | NCT05044234                 | PASI 75 at 16 weeks |                                                                          |
| BI 730,357   | RORγt  | Oral                     | Phase 2       |                             | –                 | Phase 2 trial (NCT03835481) completed in July 2021                      |
| GSK2982772   | RIPK1  | Oral                     | Phase 2       |                             | –                 | Phase 1 trial (NCT04316585) completed in October 2021. Sought to investigate the efficacy and safety of a once-daily modified release tablet formulation of GSK2982772 versus placebo |
| Piclodenoson | A3AR   | Oral                     | Phase 3       |                             | –                 | Phase 3 trial (NCT03168256) completed in April 2022                     |
| RIST4721     | CXCR2  | Oral                     | Phase 2       | NCT05194839                 | PPPASI 50 at 12 weeks | Enrolling patients with palmoplantar pustulosis                           |
| SCD-044      | SIPR1  | Oral                     | Phase 2       | NCT04566666                 | PASI 75 at 16 weeks | Phase 2 trial (NCT04908514) completed in January 2022                   |
| ADX-629      | RASP   | Oral                     | Phase 2       |                             |                   |                                                                          |
| Rimegepant   | CGRP   | Oral                     | Phase 2       | NCT04629950                 | Change in PASI score from baseline to 16 weeks |                                                                          |
| Roflumilast  | PDE4   | Topical                  | Phase 3       | NCT04286607                 | TEAEs up to 24 weeks | Multicenter, open-label extension study. Participants to apply roflumilast cream 0.3% QD for 24 weeks |
| PF-07038124  | PDE4   | Topical                  | Phase 2       | NCT05375955                 | Patient Global Assessment score of 0/1 + a > / = 2-point reduction from baseline at 12 weeks |                                                                          |
Deucravacitinib (BMS-986165, Sotyktu; Bristol-Myers Squib) is a highly selective once-daily oral TYK2 inhibitor, recently approved by the FDA (9 September 2022) for the treatment of moderate-to-severe plaque psoriasis [49, 58]. Avoiding the enzyme’s catalytic domain, which is highly conserved between JAKs, deucravacitinib instead binds to its regulatory/pseudokinase (JH2) domain, allowing for more potent blocking of downstream IL-12, IL-23, and type-1 interferon signaling [58]. Results from the 52-week phase III POETYK PSO-1 trial were recently published (pre-proof) [59]. The trial enrolled 666 participants, and patients were randomized 2:1:1 to receive deucravacitinib 6 mg once daily, apremilast 30 mg twice daily, or placebo. At 16 weeks, a significantly greater proportion of participants in the deucravacitinib group achieved a PASI 75 response compared with apremilast and placebo (58.4% versus 35.1% versus 12.7%; \( p < 0.0001 \)). A total of 53.6% of participants in the deucravacitinib group also achieved a static Physician’s Global Assessment (sPGA) score of 0/1 at 16 weeks compared with 32.1% and 7.2% in the apremilast and placebo groups, respectively (\( p < 0.0001 \)). Responses among the deucravacitinib group were maintained through week 52. The most commonly reported adverse events among those who received deucravacitinib were upper respiratory tract infections (URTIs) and nasopharyngitis. The frequency of serious adverse events was lowest among the deucravacitinib group compared with placebo and apremilast at 16 weeks. The same held true with respect to trial discontinuations due to adverse events at 52 weeks. The incidence of herpes zoster infections and acne cases were also low among patients receiving deucravacitinib [59]. The POETYK PSO-2 trial, another 52-week phase III study sharing the same primary outcome, published consistent results [60]. Ongoing trials investigating deucravacitinib in plaque psoriasis, as well as in nail psoriasis, scalp psoriasis, and among adolescents are summarized in Table 2.

Jakatinib (Suzhou Zelgen Biopharmaceuticals Co., Ltd.) is a twice-daily, oral selective JAK1/2 inhibitor currently in phase II development for psoriasis (Table 2) [61]. The drug was
investigated in a phase I single ascending dose (SAD), multiple ascending dose (MAD), and food effect study and was found to be well tolerated among healthy Chinese participants [61]. The most common adverse events reported were neutropenia, diarrhea, dizziness, and headache and no serious or grade 4 adverse events were reported. Only one case of grade 3 varicella was reported in the SAD cohort that was believed to be treatment-related. In the MAD cohort, the incidence of neutropenia appeared to be dose-dependent, limiting the maximum tolerated dose to 200 mg once daily [61].

NDI-034858 is another allosteric TYK2 inhibitor developed by Nimbus Therapeutics [62, 63]. In preclinical modeling studies, the drug was found to be $1.3 \times 10^4$-fold more selective for the TYK2-JH2 domain than deucravacitinib, owing to a single amino acid difference in the enzyme’s allosteric binding pocket [62, 63]. Results of a phase Ib trial for moderate-to-severe plaque psoriasis (unlisted) were recently presented and revealed a dose-dependent trend in PASI 50 responses between the treatment groups (5 mg, 10 mg, 30 mg, placebo) at 28 days [63]. The most commonly reported adverse events were diarrhea and infections, all of which were grade 1 or 2 severity except for one grade 3 case of neutropenia in the 30 mg group that led to trial discontinuation. Lesional biopsies taken at day 28 revealed decreased epidermal thickness and keratin-16 expression compared with baseline [63]. NDI-034858 is currently being investigated in a phase IIb trial for moderate-to-severe plaque psoriasis (NCT04999839).

Retinoic Acid Receptor-Related Orphan Receptor γt Inhibitors

Retinoic acid receptor-related orphan receptor γt (RORγt) is a ligand-dependent transcription factor that is critical for Th17 cell differentiation [64]. Its expression is stimulated upon IL-23 signaling, and its inhibition may be beneficial in treating psoriasis [65].

AUR101 (Aurigene Discovery Technologies Limited), Cedirogant (ABBV-157; AbbVie and Inventiva), and BI 730,357 (Boehringer Ingelheim) are oral RORγt inhibitors that have either recently completed or are currently undergoing phase II trials for psoriasis (Table 2). The results of a phase I SAD and MAD trial (unlisted) with AUR101 were presented and reported that the drug was well tolerated by healthy participants with no withdrawals due to adverse events or reported lab abnormalities [66]. Results from previously completed phase I trials investigating cedirogant and BI 730,357 in healthy participants or in patients with plaque psoriasis have not yet been published.

Receptor-Interacting Serine Protein-Kinase 1 Inhibitors

Necroptosis, or programmed cell necrosis, is a newly recognized form of cell death mediated by receptor-interacting serine protein-kinase 1 (RIPK1) [67]. In psoriasis, necroptosis of keratinocytes in response to TNF signaling contributes to the inflammatory cascade [67]. Thus, RIPK1 inhibitors have emerged as potential therapeutic agents for treatment [68].

GSK2982772 is an oral, mono selective, RIPK1 inhibitor developed by GSK plc [69]. In a previously published phase II trial, participants were randomized to receive an oral dose of GSK2982772 60 mg twice or thrice daily or placebo [70]. Participants were followed for 84 days, and the most common TEAEs were headaches, diarrhea, and nausea. No apparent differences in adverse effects were noted between the treatment and control groups and no severe TEAEs were reported. Lesional biopsies taken on day 43 showed improvements in epidermal thickness and lymphocyte infiltration (CD3+ T cell) relative to baseline and placebo [70]. A modified release-formulation of the drug is currently under development to compensate for the drug’s short half-life and allow for a once-daily dosing option for patients [71, 72]. This new formulation proved successful in preclinical trials and was recently investigated in a phase I trial (NCT04316585) for psoriasis [71]. Results from this study have not yet been published.
A3 Adenosine Receptor Agonists

The A3 adenosine receptor (A3AR) is a Gi-associated protein coupled receptor found to be overexpressed on peripheral blood mononuclear cells in patients with psoriasis [73]. Upon activation, the receptor mediates pathways that downregulate NF-κB, reducing the expression of TNF-α and eliciting an anti-inflammatory effect that may be beneficial for treatment [73].

Piclidenoson (CF101, IB-MECA; Can-Fite BioPharma) is an A3AR agonist currently in phase III development for psoriasis (Table 2). Its efficacy was demonstrated in a previously completed phase II trial, which enrolled 75 participants, randomized to receive oral piclidenoson 1 mg, 2 mg, or 4 mg twice daily or placebo [74]. At 12 weeks follow-up, a significantly greater change in mean PASI score was noted among the 2 mg piclidenoson group compared with placebo. The same result was not seen in the 1 mg and 4 mg groups. All TEAEs were mild-to-moderate in severity, aside from one severe psoriasis exacerbation reported in the 1 mg group [74].

CXC Chemokine Receptor 2 Antagonists

IL-8 plays a central role in the pathogenesis of PPP, acting in the recruitment and activation of neutrophils [75]. The CXC chemokine receptor 2 (CXCR2) mediates IL-8 signalling and may act as an attractive target for the treatment of the disease [75].

RIST4721 is a small molecule CXCR2 antagonist developed by Aristea Therapeutics (Table 2). Bissonnette et al. investigated the drug in a phase IIa trial for PPP and reported that once-daily treatment with RIST4721 300 mg was not superior to placebo in reducing fresh and total pustule count among participants at 4 weeks [76]. The most frequently reported TEAEs were gastrointestinal disorders, the majority of which were mild in severity. A post hoc analysis excluding patients that experienced spontaneous remission prior to randomization reported that a significantly greater proportion of participants in the treatment group achieved a 50% reduction in the Palmoplantar Pustulosis Area and Severity Index score at 4 weeks compared with placebo [76].

Aryl Hydrocarbon Receptor Modulators

The aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that is highly expressed in keratinocytes [77]. It can be activated by a variety of ligands and regulates processes that maintain skin homeostasis including keratinocyte differentiation, skin barrier function, and responses to oxidative stress [77, 78].

Tapinarof cream 1% (Vtama; Dermavant Sciences Inc.) is an AhR modulator, recently approved by the FDA (24 May 2022) for the treatment of plaque psoriasis in adults [79]. The approval was based on the findings of two identical phase III trials [PSOARING-1 (NCT03956355) and PSORAING-2 (NCT03983980)], which concluded that a significantly greater proportion of participants receiving tapinarof cream once daily achieved treatment success, defined as a Physician Global Assessment (PGA) score of 0 or 1 and a ≥2-grade improvement from baseline, at 12 weeks compared with vehicle [79, 80]. The drug was well tolerated among participants, with folliculitis, contact dermatitis, and headache among the most commonly reported adverse events [80]. Long-term data from the PSOARING-3 trial, a 40-week open-label extension study, further supported these findings, reporting no new safety signals [81].

Tapinarof is currently being investigated for use in pediatric patients in a phase III, single-arm, multi-center trial (NCT05172726).

Other Agents

Several other therapies are also under investigation in early-stage clinical trials for psoriasis, with limited data available on their efficacy (Table 2).

ADX-629 (Aldeyra Therapeutics, Inc.) is a reactive aldehyde species inhibitor that recently completed a phase II multi-center, open-label trial for psoriasis (NCT04908514) [82]. The trial enrolled 10 participants with moderate-to-severe disease, all of whom received 250 mg oral
ADX-629 twice daily for 12 weeks. A significant reduction in mean PASI score was seen among participants over the course of the trial, and peak PASI 50 and PASI 75 responses were 57% \( (p = 0.001) \) and 25% \( (p = 0.051) \), respectively \[82\]. Trial results have not yet been published.

Rimegepant (Nurtec ODT; Biohaven Pharmaceuticals) is a calcitonin gene-related peptide (CGRP) receptor antagonist under investigation in a phase II clinical trial (NCT04629950) for psoriasis \[84\]. Rimegepant is currently approved by the FDA for the treatment of acute migraines \[84\]. However, there is a large body of evidence suggesting that CGRP may promote keratinocyte proliferation and proinflammatory cytokine release (i.e., IL-6, IL-1b, and TNF-a), also making it an attractive target for psoriasis. \[85\].

Finally, SCD-044 is a sphingosine-1-phosphate receptor 1 (SIPR1) agonist (Sun Pharmaceutical Industries Limited) currently in phase II development for psoriasis (NCT04566666) \[86\]. The agent acts to inhibit lymphocyte migration through stimulating internalization of the SIPR1, a receptor which is normally found on the surface of lymphocytes and recognizes signals that control their egress from the secondary lymphoid organs to the blood \[87\]. According to Sun Pharma, SCD-044 successfully reduced lymphocyte counts at all investigated dosing levels in a phase I proof-of-concept study in healthy participants (unlisted) \[86\].

**CONCLUSION**

The treatment of psoriasis remains a rapidly advancing area of study with new and innovative therapies coming down the pipeline, many of which were recently approved. The FDA approval of deucravacitinib, an oral TYK2 inhibitor; spesolimab, an anti-IL-36R antibody; and several nonsteroidal topical agents are promising steps toward addressing gaps that currently limit patient care. Moving forward, head-to-head trials comparing new oral therapies and approved biologics will be required to better understand their place in the treatment landscape. Long-term efficacy and safety data are also required to better understand nuances between treatments that may aid in optimal selection for patients. As we continue to uncover the pathogenesis of disease, newer therapies will be developed to further improve quality of life for patients.

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REFERENCES

1. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA. 2020;323(19):1945–60.

2. Puig L, Thom H, Mollon P, Tian H, Ramakrishna GS. Clear or almost clear skin improves the quality of life in patients with moderate-to-severe psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2017;31(2):213–20.

3. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol. 2017;76(3):377–90.

4. Sewerin P, Brinks R, Schneider M, Haase I, Vordenburg S. Prevalence and incidence of psoriasis and psoriatic arthritis. Ann Rheum Dis. 2019;78(2):286–7.

5. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol. 2017;140(3):645–53.

6. Singh R, Koppu S, Perche PO, Feldman SR. The cytokine mediated molecular pathophysiology of psoriasis and its clinical implications. Int J Mol Sci. 2021;22(23):12793.

7. Girolomoni G, Strohal R, Puig L, et al. The role of IL-23 and the IL-23/Th17 immune axis in the pathogenesis and treatment of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(10):1616–26.

8. Sbidian E, Chaimani A, Garcia-Doval I, et al. Systematic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2022; 5(S):CD011535.

9. Dommasch ED, Kim SC, Lee MP, Gagne JJ. Risk of serious infection in patients receiving systemic medications for the treatment of psoriasis. JAMA Dermatol. 2019;155(10):1142–52.

10. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. J Eur Acad Dermatol Venereol. 2015;29(4):645–8.

11. Elberdin L, Fernández-Torres RM, Paradela S, et al. Biologic therapy for moderate to severe psoriasis. Real-world follow-up of patients who initiated biologic therapy at least 10 years ago. Dermatol Ther (Heidelb). 2022; 12(3):761–770.

12. Curmin R, Guillo S, De Rycke Y, et al. Switches between biologics in patients with moderate-to-severe psoriasis: results from the French cohort PSOBIOTEQ. J Eur Acad Dermatol Venereol. 2022.

13. Aleshaki JS, Cardwell LA, Muse ME, Feldman SR. Adherence and resource use among psoriasis patients treated with biologics. Expert Rev Pharmacoecon Outcomes Res. 2018;18(6):609–17.

14. Lé AM, Torres T. New topical therapies for psoriasis. Am J Clin Dermatol. 2022;23(1):13–24.

15. Lupardus PJ, Garcia KC. The structure of interleukin-23 reveals the molecular basis of p40 subunit sharing with interleukin-12. J Mol Biol. 2008;382(4):931–41.

16. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signalling pathway and the treatment of psoriasis. J Immunol. 2018;201(6):1605–13.

17. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. Ther Adv Chronic Dis. 2018;9(5):111–9.

18. Fotiadou C, Lazaridou E, Sotiropoulos D. Targeting IL-23 in psoriasis: current perspectives. Psoriasis (Auckl). 2018;8:1–5.

19. Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: a comprehensive review. Am J Clin Dermatol. 2021;22(2):173–92.

20. Li L, Wu Z, Wu M, et al. IBI112, a selective anti-IL23p19 monoclonal antibody, displays high efficacy in IL-23-induced psoriasiform dermatitis. Int Immunopharmacol. 2020;89(Pt B):107008.

21. Protagonist Therapeutics. Protagonist Therapeutics Announces the Selection of Oral Peptide PN-235 into Phase 2 Clinical Development Program for Multiple Indications [Internet]. 2021. Available from: https://www.prnewswire.com/news-releases/protagonist-therapeutics-announces-the-selection-of-oral-peptide-pn-235-into-phase-2-clinical-development-program-for-multiple-indications-301436694.html
22. Brembilla NC, Senra L, Boehncke WH. The IL-17 family of cytokines in psoriasis: IL-17A and beyond. Front Immunol. 2018;9:1682.

23. Soderstrom C, Berstein G, Zhang W, et al. Ultra-sensitive measurement of IL-17A and IL-17F in psoriasis patient serum and skin. AAPS J. 2017;19(4):1218–22.

24. Tollenaere MAX, Hebsgaard J, Ewald DA, et al. Signalling of multiple interleukin (IL)-17 family cytokines via IL-17 receptor A drives psoriasis-related inflammatory pathways. Br J Dermatol. 2021;185(3):585–94.

25. AbuHilal M, Walsh S, Shear N. The role of IL-17 in the pathogenesis of psoriasis and update on IL-17 inhibitors for the treatment of plaque psoriasis. J Cutan Med Surg. 2016;20(6):509–16.

26. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol. 2018;55(3):379–90.

27. Von Stebut E, Boehncke WH, Ghoreschi K, et al. IL-17A in psoriasis and beyond: cardiovascular and metabolic implications. Front Immunol. 2020;10:39;

28. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol. 2018;55(3):379–90.

29. Gisondi P, Geat D, Pizzolato M, Girolomoni G. State of the art and pharmacological pipeline of biologics for chronic plaque psoriasis. Curr Opin Pharmacol. 2019;46:90–9.

30. Gisondi P, Geat D, Pizzolato M, Girolomoni G. State of the art and pharmacological pipeline of biologics for chronic plaque psoriasis. Curr Opin Pharmacol. 2019;46:90–9.

31. Korotaeva T, Gaidukova I, Mazurov V, et al. POS1043 Netakimab reduces psoriatic arthritis activity in patients with or without axial disease: subanalysis of the PATERA study. Ann Rheum Dis. 2021;80:796–7.

32. Puig L, Bakulev AL, Kokhan MM, et al. Efficacy and safety of netakimab, a novel Anti-IL-17 monoclonal antibody, in patients with moderate to severe plaque psoriasis. Results of a 54-week randomized double-blind placebo-controlled PLANETA clinical trial. Dermatol Ther (Heidelb). 2021; 11(4):1319–1332.

33. Samtsov AV, Khairutdinov VR, Bakulev AL, Kabanov AA, Karamova AE, Artem’eva AV, Korotaeva TV: Efficacy and safety of BCD-085, a novel interleukin-17 inhibitor. Results of phase II clinical trial in patients with moderate-to-severe plaque psoriasis. Vestnik Dermatologii i Venerologii 2017:52–63.

34. Zhang C, Yan K, Diao Q, et al. A multicenter, randomized, double-blinded, placebo-controlled, dose-ranging study evaluating the efficacy and safety of vunakizumab in patients with moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2022;87(1):95–102.

35. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. Expert Rev Clin Immunol. 2019;15(9):907–19.

36. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol. 2017;140(1):109–20.

37. Marrakchi S, Puig L. Pathophysiology of generalized pustular psoriasis. Am J Clin Dermatol. 2022;23(Suppl 1):13–9.

38. Samotij D, Szczecz J, Reich A. Generalized pustular psoriasis: divergence of innate and adaptive immunity. Int J Mol Sci. 2021;22(16):9048.

39. Zhou J, Luo Q, Cheng Y, Wen X, Liu J. An update on genetic basis of generalized pustular psoriasis (Review). Int J Mol Med. 2021;47(6):118.

40. AntaptysBio Inc. Imsidolimab [Internet]. Available from: https://www.anaptysbio.com/pipeline/imsidolimab/

41. Gudjonsson J RA, Barker J, Pink A, et al. Imsidolimab, an anti-IL-36 receptor monoclonal antibody, in the treatment of generalized pustular psoriasis; results from a phase 2 trial. 30th EADV Congress; 29 September–2 October 2021.

42. Boehringer Ingelheim. FDA approves the first treatment option for generalized pustular psoriasis flares in adults [Internet]. 2022. Available from: https://www.boehringer-ingelheim.us/press-release/fda-approves-first-treatment-option-generalized-pustular-psoriasis-flares-adults

43. Bachelez H, Choon S-E, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. N Engl J Med. 2021;385(26):2431–40.

44. Mrowietz U, Burden AD, Pinter A. Spesolimab, an anti-interleukin-36 receptor monoclonal antibody, in patients with palmoplantar pustulosis: results of a phase iiia, multicenter, double-blind, randomized placebo-controlled pilot study. Dermatol Ther (Heidelb). 2021;11(2):571–85.
45. Li H, Zuoj J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. Front Pharmacol. 2018;9:1048.

46. Gerlo S, Koelman R, Beck IM, Kolmus K, Spooren A, Haegeman G. Cyclic AMP: a selective modulator of NF-κB action. Cell Mol Life Sci. 2011;68(23):3823–41.

47. Wittmann M, Helliwell PS. Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. Dermatol Ther (Heidelb). 2013;3(1):1–15.

48. Milakovic M, Gooderham MJ. Phosphodiesterase-4 inhibition in psoriasis. Psoriasis (Auckl). 2021;11:21–9.

49. Boerner LK. Hybrid meeting divulges structures of drug candidates [Internet]. Chemical & Engineering News. 2022. Available from: https://cen.acs.org/acs-news/acs-meeting-news/Hybrid-meeting-divulges-structures-drug-candidates/100/web/2022/03

50. Hashim PW, Chima M, Kim HJ, et al. Crisaborole 2% ointment for the treatment of intertriginous, anogenital, and facial psoriasis: a double-blind, randomized, vehicle-controlled trial. J Am Acad Dermatol. 2020;82(2):360–5.

51. Pfizer. Study to assess efficacy, safety, tolerability and pharmacokinetics of PF-07038124 ointment in participants with atopic dermatitis or plaque psoriasis (EMPORIA) NCT04664153. Available from: https://clinicaltrials.gov/ct2/show/NCT04664153

52. Lebwohl MG, Papp KA, Stein Gold L, et al. Trial of roflumilast cream for chronic plaque psoriasis. N Engl J Med. 2020;383(3):229–39.

53. Arcutis Biotherapeutics. FDA approves Arcutis’ ZORYVE (roflumilast) Cream 0.3% For the treatment of plaque psoriasis (EMPORIA) NCT04664153. Available from: https://clinicaltrials.gov/ct2/show/NCT04664153

54. Lebwohl M, Kirick LH, Moore AY, et al. Safety and efficacy of once-daily roflumilast Cream 0.3%, a potent phosphodiesterase-4 inhibitor for the treatment of psoriasis in the DERMIS-1 and DERMIS-2 phase 3 trials. Poster presented at: 30th EADV Congress, Sept 29–Oct 2, 2021; virtual.

55. Słuczanowska-Gła˛bowska S, Ziegler-Krawczyk A, Szumilas K, Pawlik A. Role of Janus kinase inhibitors in therapy of psoriasis. J Clin Med. 2021;10(19):4307.

56. Hsu L, Armstrong AW. JAK inhibitors: treatment efficacy and safety profile in patients with psoriasis. J Immunol Res. 2014;2014:283617.

57. Gómez-Garcia F, Gómez-Arias PJ, Montilla-López A, et al. A scoping review on use of drugs targeting the JAK/STAT pathway in psoriasis. Front Med (Lausanne). 2022;9:754116.

58. Chimalakonda A, Burke J, Cheng L, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with Janus kinase 1/2/3 inhibitors. Dermatol Ther (Heidelb). 2021;11(5):1763–76.

59. Armstrong AW, Gooderham M, Warren RB, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol. 2022;S0190–9622(22):02256–63.

60. Strober B, Thaci D, Sofen H, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 POETYK PSO-2 trial. J Am Acad Dermatol. 2022;S0190–9622(22):02643–53.

61. Liu J, Lv B, Yin H, Zhu X, Wei H, Ding Y. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple ascending dose and food effect study to evaluate the tolerance, pharmacokinetics of Jaktinib, a new selective Janus kinase inhibitor in healthy Chinese volunteers. Front Pharmacol. 2020;11:604314.

62. Gangolli EA, Carreiro S, Leit S, et al. Characterization of pharmacokinetics, pharmacodynamics, tolerability and clinical activity in phase I studies of the novel allosteric TYK2 inhibitor NDI-034858. Presented at: 2022 SID Annual Meeting, May 18 - 21, 2022; Portland, Oregon.

63. McElwee JJ, Garcia S, Leit S, et al. Analysis of histologic, molecular and clinical improvement in moderate-to-severe psoriasis: results from a phase 1b trial of the novel allosteric TYK2 inhibitor NDI-034858. Presented at: 2022 AAD Annual Meeting, March 25–29, 2022; Boston, Massachusetts.

64. Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell. 2006;126(6):1121–33.

65. Gege C. Retinoic acid-related orphan receptor gamma t (ROryt) inverse agonists/antagonists for the treatment of inflammatory diseases – where are we presently? Expert Opin Drug Discov. 2021;16(12):1517–35.
66. Mandavia D, Farinola N, Ramachandra M, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of AUR101, an RORγt inhibitor, in normal healthy volunteers. Presented at: EAACI Congress 2019, June 1–5, 2019; Lisbon, Portugal.

67. Duan X, Liu X, Liu N, et al. Inhibition of keratinocyte necroptosis mediated by RIPK1/RIPK3/MLKL provides a protective effect against psoriatic inflammation. Cell Death Dis. 2020;11(2):134.

68. Weisel K, Berger S, Papp K, et al. Response to inhibition of receptor-interacting protein kinase 1 (RIPK1) in active plaque psoriasis: a randomized placebo-controlled study. Clin Pharmacol Ther. 2020;108(4):808–16.

69. Harris PA, Berger SB, Jeong JU, et al. Discovery of a first-in-class receptor interacting protein 1 (RIP1) kinase specific clinical candidate (GSK2982772) for the treatment of inflammatory diseases. J Med Chem. 2017;60(4):1247–61.

70. Weisel K, Berger S, Papp K, et al. Response to inhibition of receptor-interacting protein kinase 1 (RIPK1) in active plaque psoriasis: a randomized placebo-controlled study. Clin Pharmacol Ther. 2020;1–8(4):808–16.

71. Tompson D, Whitaker M, Pan R, et al. Development of a once-daily modified-release formulation for the short half-life RIPK1 inhibitor GSK2982772 using DiffCORE technology. Pharm Res. 2022;39(1):153–65.

72. Tompson DJ, Whitaker M, Pan R, et al. Development of a prototype, once-daily, modified-release formulation for the short half-life RIPK1 inhibitor GSK2982772. Pharm Res. 2021;38(7):1235–45.

73. Fishman P. Drugs targeting the A3 adenosine receptor: human clinical study data. Molecules. 2022;27(12):3680.

74. David M, Ackerman L, Ziv M. Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial. J Eur Acad Dermatol Venereol. 2012;26(3):361–7.

75. Misiak-Galazka M, Zozula J, Rudnicka L. Palmo-plantar pustulosis: recent advances in etiopathogenesis and emerging treatments. Am J Clin Dermatol. 2020;21(3):355–70.

76. Bissonnette R, Maari C, Tsianakas A, et al. A randomized, double-blind, placebo-controlled, phase 2a study to evaluate the efficacy and safety of RIST4721 in subjects with palmoplantar pustulosis. Dermatol Ther (Heidelb). 2021;11(6):2179–93.

77. Napolitano M, Fabbrocini G, Martora F, Picone V, Morelli P, Patruno C. Role of aryl hydrocarbon receptor activation in inflammatory chronic skin diseases. Cells. 2021;10(12):3559.

78. Fernández-Gallego N, Sánchez-Madrid F, Cibrian D. Role of AHR ligands in skin homeostasis and cutaneous inflammation. Cells. 2021;10(11):3176.

79. Keam SJ. Tapinarof cream 1%: first approval. Drugs. 2022;82(11):1221–8.

80. Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. N Engl J Med. 2021;385(24):2219–29.

81. Strober B, Stein Gold L, Bissonnette R, et al. One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: results from the PSOARING 3 trial. J Am Acad Dermatol. 2022;S0190–9622(22):02219–28.

82. Aldeyra Therapeutics, Inc. Aldeyra Therapeutics to announce top-line data for systemic RASP Modulator ADX-629 at 2022 Research & Development Day [Internet]. 2022. Available From: https://www.businesswire.com/news/home/20220328005825/en/

83. Weill Medical College of Cornell University. Rimegepant in Moderate Plaque-type Psoriasis NCT04629950. Available from: https://clinicaltrials.gov/ct2/show/NCT04629950

84. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventative treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397(10268):51–60.

85. Kim YJ, Granstein RD. Roles of calcitonin gene-related peptide in the skin, and other physiological and pathophysiological functions. Brain Behav Immunol. 2021;18:100361.

86. Sun Pharmaceutical Industries Limited. Sun Pharma announces initiation of phase 2 clinical trial of SCD-044 in patients with moderate to severe plaque psoriasis [Internet]. 2021. Available From: https://sunpharma.com/wp-content/uploads/2021/01/Press-Release-Initiation-of-Phase-2-clinical-trial-of-SCD-044.pdf

87. Liu L, Wang J, Li H-J, et al. Sphingosine-1-Phosphate and its signal modulators alleviate psoriasis-like dermatitis: preclinical and clinical evidence and possible mechanisms. Front Immunol. 2021;12:759276.