

Novel Psoriasis Therapies and Patient Outcomes, Part 3: Systemic Medications

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PRACTICE POINTS

- A wide spectrum of promising nonbiologic systemic medications presently are in development or were recently approved for the management of moderate to severe psoriasis and psoriatic arthritis (PsA).
- Systemic medications broaden the therapeutic armamentarium for patients with psoriasis and PsA, offering targeted therapeutic regimens that afford enhanced clinical outcomes with favorable side-effect profiles.

The therapeutic armamentarium for patients with psoriasis and psoriatic arthritis (PsA) has been strengthened by research affording more individualized treatment regimens with new therapeutic targets. In this article, new systemic therapies for psoriasis are discussed, including a review of the relevant clinical trials for novel therapeutics and their respective mechanisms of action, patient outcomes, and safety profiles. This article is the final installment in a 3-part series on agents in the pipeline for the management of psoriasis and PsA including topical agents, biologic treatments, and systemic therapies in phase 2 through phase 4 clinical trials. These systemic agents offer patients more targeted treatment regimens with the prospect of enhanced therapeutic efficacy and more favorable side-effect profiles with better tolerability.

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This article is the third of a 3-part series.

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Evolving knowledge of the underlying pathogenesis of psoriasis has afforded the development of a broad spectrum of nonbiologic systemic medications with therapeutic potential in moderate to severe psoriasis and psoriatic arthritis (PsA). The targets for these medications are antagonists of proinflammatory mediators such as tyrosine kinase, protein kinase, Janus kinase (JAK), p38 α mitogen-activated protein (MAP) kinase, phosphodiesterase 4 (PDE-4), calcineurin, Rho-associated kinase (ROCK) 2, cytochrome P450 26 (CYP26), and purine nucleoside phosphorylase (PNP); agonists of anti-inflammatory mediators such as sphingosine-1-phosphate receptor 1 (S1P₁) and adenosine A₃ receptor; and myriad other mechanisms. A brief introduction to some of these therapies presently in phase 2 and phase 3 clinical trials are presented (Table).¹

Masitinib (Tyrosine Kinase Inhibitor)

Masitinib (formerly known as AB1010)(AB Sciences) is a tyrosine kinase inhibitor that is purported to decrease inflammation by inhibiting stem cell factor receptor (c-kit) and consequently limiting mast cell degranulation.² A randomized, placebo-controlled, double-blind phase 3 study evaluating its efficacy as an oral formulation was completed, but the results were not available at the time of publication (registered at www.clinicaltrials.gov with the identifier NCT01045577).

Ponesimod (S1P₁ Receptor Agonist)

Ponesimod (formerly known as ACT-128800) (Actelion Pharmaceuticals US, Inc) is an orally formulated S1P₁ receptor agonist. Sphingosine-1-phosphate receptor 1 is necessary for lymphoid chemotaxis.³

Novel Systemic Therapies for Psoriasis Currently in Development or Recently Approved^{1,a}

Product Name	Manufacturer	Mechanism of Action	Indication(s)	Stage of Development
AB1010 (masitinib)	AB Sciences	Tyrosine kinase inhibitor	Psoriasis	Phase 3
ACT-128800 (ponesimod)	Actelion Pharmaceuticals US, Inc	S1P ₁ receptor agonist	Psoriasis	Phase 2
AEB071 (sotrastaurin)	Novartis AG	Protein kinase C inhibitor	Psoriasis	Phase 2
Alitretinoin (9- <i>cis</i> -retinoic acid)	Stiefel, a GSK company	Retinoid	Palmoplantar pustular psoriasis	Phase 2
Apo805K1	ApoPharma Inc	Unknown	Psoriasis	Phase 2
ASP015K	Astellas Pharma US, Inc	JAK 1 and JAK 3 inhibitor	Psoriasis	Phase 2
BMS-582949	Bristol-Myers Squibb Company	p38 α MAP kinase inhibitor	Psoriasis	Phase 2
CC-10004 (apremilast)	Celgene Corporation	PDE-4 inhibitor	Psoriasis, PsA	Phase 3
CEP-701 (lestaurtinib)	Teva Pharmaceutical Industries	Multikinase inhibitor	Psoriasis	Phase 2
CF101 (IB-MECA)	Can-Fite BioPharma Ltd	Adenosine A ₃ receptor agonist	Psoriasis	Phase 2/ phase 3
CP-690550 (tofacitinib)	Pfizer, Inc	JAK 1 and JAK 3 inhibitor	Psoriasis, PsA	Phase 3
FP187	Forward Pharma A/S	Fumaric acid ester	Psoriasis	Phase 3
Doxercalciferol	Genzyme Corporation, a Sanofi company	Vitamin D ₂ analogue	Psoriasis	Phase 2
GSK2586184 ^b	GlaxoSmithKline	JAK 1 inhibitor	Psoriasis	Phase 2
ISA247 (voclosporin)	Aurinia Pharmaceuticals Inc	Calcineurin inhibitor	Psoriasis	Phase 3
KD025	Kadmon Corporation, LLC	ROCK 2 inhibitor	Psoriasis	Phase 2
LAS41008	Almirall, S.A.	Fumaric acid ester	Psoriasis	Phase 3
LEO 22811	LEO Pharma	Anti-inflammatory	Psoriasis	Phase 2
LY3009104 or INCB28050 (baricitinib)	Eli Lilly and Company	JAK 1 and JAK 2 inhibitor	Psoriasis	Phase 2
R115866 (talarozole)	GlaxoSmithKline	CYP26 inhibitor	Psoriasis	Phase 2
R3421 or BCX-4208	BioCryst Pharmaceuticals, Inc/Hoffman-La Roche	PNP inhibitor	Psoriasis	Phase 2
RWJ-445380	Alza Corporation, DE	Cathepsin S inhibitor	Psoriasis	Phase 2
SRT2104	GlaxoSmithKline	Sirtuin 1 activator	Psoriasis	Phase 2
VB-201	VBL Therapeutics	Oxidized phospholipid	Psoriasis	Phase 2

Abbreviations: S1P₁, sphingosine-1-phosphate receptor 1; JAK, Janus kinase; MAP, mitogen-activated protein; PDE-4, phosphodiesterase 4; PsA, psoriatic arthritis; ROCK, Rho-associated kinase; CYP26, cytochrome P450 26; PNP, purine nucleoside phosphorylase.

^aAs of publication in July 2015.

^bWithdrawn by manufacturer.

A randomized, placebo-controlled, double-blind phase 2 trial of 326 patients demonstrated 75% improvement in psoriasis area and severity index (PASI) score at week 16 in 13.4%, 46.0%, and 48.1% of participants receiving placebo, ponesimod 20 mg, and ponesimod 40 mg, respectively.⁴ At week 28, PASI 75 scores for participants transitioned from ponesimod 40 mg to placebo or ponesimod 20 mg to placebo and those maintained on ponesimod 20 mg and 40 mg were 40.4%, 42.2%, 77.4%, and 71.4%, respectively. This study demonstrated benefit of treatment with ponesimod versus placebo with increased efficacy using maintenance therapy.⁴

Sotrastaurin (Protein Kinase C Inhibitor)

Sotrastaurin (formerly known as AEB071) (Novartis AG) is an oral medication that inhibits protein kinase C, thereby limiting CD28-induced activation of T cells. Furthermore, it increases forkhead box P3 expression, which is important, as proinflammatory IL-17 production is stimulated in regulatory T cells with lost forkhead box P3 expression.⁵ In a study of 32 patients who received placebo or sotrastaurin 25, 100, 200, or 300 mg twice daily for 2 weeks, the mean PASI score was reduced by 69% for the 300-mg group versus 5.3% for placebo.⁶ A randomized, placebo-controlled, double-blind phase 2 study was completed for patients with moderate to severe psoriasis, but the results were not available at the time of publication (NCT00885196).

Alitretinoin (Retinoid)

Alitretinoin (9-*cis*-retinoic acid; Stiefel, a GSK company) is an oral retinoid with purported promise for patients with palmoplantar pustular psoriasis recalcitrant to conventional therapies. In one study, 7 participants with palmoplantar psoriasis received alitretinoin 30 mg daily for 12 weeks with 60% to 90% clinical improvement noted using the visual analog scale and palmoplantar pustular PASI to assess response.⁷ A randomized, placebo-controlled, double-blind phase 2 trial of alitretinoin assessing the success of alitretinoin in patients with palmoplantar psoriasis recalcitrant to topical treatments was completed, but the results were not available at the time of publication (NCT01245140).

Apo805K1 (Unknown Mechanism of Action)

Apo805K1 (ApoPharma Inc) is an oral agent whose mechanism of action has not been disclosed. A randomized, placebo-controlled, double-blind phase 2 trial in patients with moderate to severe psoriasis with a treatment duration of 14 days has been completed. For 12 weeks there was a daily dosing regimen of

Apo805K1 10, 30, 60, or 100 mg or placebo, with 12 patients in each treatment group. The proportion of patients achieving PASI 75 was 16.7%, 0%, 0%, 8.3%, and 16.7%, respectively ($P=.1975$). The number of participants with adverse events reported ranged between 4 to 7, with the greatest number of adverse events reported in the 30-mg subset.⁸ It may be of interest to repeat the study with a larger sample size.

ASP015K (JAK 1 and JAK 3 Inhibitor)

ASP015K (Astellas Pharma US, Inc) is the first of the JAK inhibitors that will be discussed in this section. Janus kinase inhibitors represent a group of tyrosine kinases that regulate cytokine-mediated signaling pathways through the activation of signal transducer and activator of transcription proteins via phosphorylation in the cytoplasm, which in turn control the transcription of genes that generate inflammation. ASP015K and tofacitinib (formerly known as CP-690550)(Pfizer, Inc) inhibit JAK 1 and JAK 3, whereas GSK2586184 (GlaxoSmithKline) inhibits JAK 1 and baricitinib (formerly known as LY3009104 or INCB28050)(Eli Lilly and Company) inhibits JAK 1 and JAK 2.⁹ In a 6-week, dose-escalation phase 2 trial in patients with moderate to severe psoriasis, ASP015K showed a dose-dependent decline in PASI, psoriasis static global assessment, and body surface area.¹⁰

BMS-582949 (p38 α MAP Kinase Inhibitor)

BMS-582949 (Bristol-Myers Squibb Company) is an oral p38 α MAP kinase inhibitor.¹¹ Along with c-Jun N-terminal kinase and extracellular signal-regulated protein kinases 1 and 2, MAP kinase plays a role in the pathogenesis of psoriasis.¹² A randomized, placebo-controlled, double-blind, 12-week phase 2a study of placebo versus BMS-582949 dosed at 10, 30, and 100 mg has been completed, but the results were not available at the time of publication (NCT00399906).

Apremilast (PDE-4 Inhibitor)

Apremilast (formerly known as CC-10004)(Celgene Corporation) is an oral PDE-4 inhibitor that acts to inhibit the degradation of cyclic adenosine monophosphate. It is approved by the US Food and Drug Administration for moderate to severe plaque psoriasis¹³ and is a particularly good treatment for patients with recalcitrant disease.¹⁴ Several studies on apremilast have been published, including a phase 2 trial of 204 participants receiving placebo or apremilast 20 mg or 40 mg twice daily with American College of Rheumatology (ACR) 20% improvement response of 11.8%, 35.8%, and 43.5%, respectively.¹⁵ The phase 3 PALACE 1, 2, 3, and 4 trials also

demonstrated therapeutic efficacy.¹⁶ In PALACE 1, 504 patients receiving placebo or apremilast 20 mg and 30 mg twice daily had an ACR20 of 19%, 31%, and 40%, respectively. In the PALACE 4 study, ACR20 was achieved by 58% of participants at week 52, but the ACR50 and ACR70 rates were less impressive.¹⁶

Lestaurtinib (Multikinase Inhibitor)

Lestaurtinib (formerly known as CEP-701) (Teva Pharmaceutical Industries) is an oral multi-kinase inhibitor for which a 12-week, nonrandomized, dose-escalation phase 2 study was completed, but the results were not available at the time of publication (NCT00236119).

CF101 (Adenosine A₃ Receptor Agonist)

CF101 (IB-MECA; Can-Fite BioPharma Ltd) is an oral adenosine A₃ receptor agonist. Adenosine A₃ is a G protein-coupled receptor that has an anti-inflammatory role, which lends itself to the treatment of inflammatory conditions such as rheumatoid arthritis.¹⁷ In a randomized, placebo-controlled, double-blind phase 2 trial of 75 patients who received placebo or CF101 1, 2, or 4 mg twice daily for 12 weeks, PASI 50 or greater was reported in 35.3% of participants in the 2-mg group, which was statistically significant at weeks 8 ($P=.047$) and 12 ($P=.031$).¹⁸ A randomized, placebo-controlled, double-blind, 16-week phase 2/phase 3 trial in patients with moderate to severe psoriasis treated with CF101 2 mg twice daily versus placebo is ongoing but not recruiting participants (NCT01265667).

Tofacitinib (JAK 1 and JAK 3 Inhibitor)

Tofacitinib is a JAK 1 and JAK 3 inhibitor that is available in both topical and oral formulations. Many studies have been published on tofacitinib, including a dose-ranging phase 2b trial of 197 patients randomized to placebo or tofacitinib 2, 5, or 15 mg daily in which 2.0%, 25.0% ($P<.001$), 40.8% ($P<.0001$), and 66.7% ($P<.0001$) of participants in each treatment group, respectively, achieved PASI 75 at week 12.¹⁹ Another 12-week phase 2b trial in patients with moderate to severe psoriasis explored the effectiveness of oral formulations of tofacitinib based on body location, namely the head and neck, arms, trunk, and legs.²⁰ Designed with twice-daily placebo and tofacitinib 2-, 5-, and 15-mg treatment arms, the target plaque severity score demonstrated a statistically significant dose-responsive improvement in each of the 4 anatomic regions ($P<.01$).

Two randomized, double-blinded, placebo-controlled phase 3 trials of tofacitinib have been completed. One trial compared the safety and effectiveness of tofacitinib and etanercept in patients with moderate to severe psoriasis.²¹ The 329 participants were randomized to

treatment with oral tofacitinib 5 mg or 10 mg twice daily with placebo subcutaneous (SQ) injections twice weekly; oral placebo twice daily with etanercept 50-mg SQ injections twice weekly; or oral placebo twice daily with placebo SQ injection twice weekly. At week 12, PASI 75 was achieved in 39.51%, 63.64%, 58.81%, and 5.61% of participants in each treatment group, respectively. Thus, tofacitinib 10 mg and etanercept 50 mg were the first and second best performers in this study design.²¹

In the other phase 3 trial, the efficacy and safety of treatment, treatment withdrawal, and subsequent resumption of treatment with tofacitinib was examined in 290 patients who received either tofacitinib 5 mg or 10 mg or placebo twice daily for 24 weeks.²² In the withdrawal period, the percentage of patients who maintained a PASI 75 response in the tofacitinib 5-mg group was 56.2% versus 23.3% in the placebo group at week 16 ($P<.0008$). In the 10-mg group, 62.3% of participants maintained PASI 75 at week 16 versus 26.1% in the placebo group ($P<.0001$). During the re-treatment period for those who showed a greater than 50% reduction in week 24 PASI during treatment withdrawal (N=102), 50.0% of the tofacitinib 5-mg group showed PASI 75 versus 31.58% of the placebo group at week 16. In the tofacitinib 10-mg group, PASI 75 was seen in 0% versus 50.85% in the placebo group. Of note, only 5 participants who demonstrated a greater than 50% reduction in week 24 PASI response following withdrawal of therapy were in the tofacitinib 5- or 10-mg groups, as the rest were in the placebo group.²²

FP187 (Fumaric Acid Ester)

FP187 (Forward Pharma A/S) is an oral fumaric acid ester whose underlying mechanism is thought to be elevation of glutathione levels that decreases the amount of inflammatory cytokines by blocking the translocation of nuclear factor κ B. Other fumaric acid esters such as monoethyl fumarate and dimethyl fumarate have been used in Europe for the management of psoriasis.²³ A phase 2 study of the safety and effectiveness of FP187 for moderate to severe psoriasis has been completed, but the results were not available at the time of publication (NCT01230138). A phase 3 trial examining the efficacy of FP187 in managing moderate to severe psoriasis was not yet open for participant recruitment at the time of publication (NCT01815723).

Doxercalciferol (Vitamin D₂ Analogue)

Doxercalciferol (1 α -hydroxyvitamin D₂; Genzyme Corporation, a Sanofi company) is an oral prodrug of vitamin D.²⁴ Topical preparations of vitamin D analogues approved by the US Food and Drug Administration such as calcipotriene are mainstays in psoriasis management. Doxercalciferol has been used for other therapeutic applications such

as decreasing elevated parathyroid hormone levels.²⁵ Research has demonstrated that CYP24A1 can extrahepatically regulate the activation of vitamin D prodrugs in cutaneous tissues.²⁶ In a phase 2 study examining the efficacy and safety of doxercalciferol in patients with moderate to severe psoriasis, 111 patients were randomized to placebo or doxercalciferol 2.5, 5, or 7.5 µg daily for 24 weeks (NCT00601107). At week 12, PASI 50 was similar regardless of the treatment administered, reported at 20.0%, 20.0%, 17.9%, and 20.0%, respectively ($P=1.000$).²⁷

GSK2586184 (JAK 1 Inhibitor)

GSK2586184 is an oral JAK 1 inhibitor. A placebo-controlled, double-blind, dose-dependent phase 2 study of GSK2586184 in patients with chronic plaque psoriasis who were randomized to placebo or GSK2586184 100, 200, and 400 mg twice daily for 84 days has been completed, but the results were not available at the time of publication (NCT01782664). Of note, despite clinical promise, due to potential adverse effects of the medication that included a possible interaction with statin medication, the manufacturer decided against pursuing GSK2586184 as a treatment in the management of psoriasis.²⁸

Voclosporin (Calcineurin Inhibitor)

Voclosporin (formerly known as ISA247)(Aurinia Pharmaceuticals Inc) is an oral calcineurin inhibitor that is purported to be as effective as cyclosporine A with less associated toxicity. A 12-week randomized, placebo-controlled, double-blind phase 2 trial demonstrated PASI 75 in 0%, 18.2%, and 66.7% of 201 participants receiving placebo, voclosporin 0.5 mg/kg, and voclosporin 1.5 mg/kg twice daily, respectively ($P<.0001$). Elevated serum creatinine levels within the high range of normal were noted in the 1.5-mg/kg group.²⁹ A 12-week phase 3 study of 451 patients randomized to placebo or voclosporin 0.2-, 0.3-, or 0.4-mg/kg treatment groups similarly demonstrated a dose-responsive PASI 75 of 4%, 16%, 25%, and 47%, respectively, that was maintained at week 24. Mild to moderate decreases in glomerular filtration rates were noted in 8 patients in the 0.3- and 0.4-mg/kg subsets.³⁰ Another phase 2 study of voclosporin in patients with moderate to severe psoriasis showed improvements according to the psoriasis disability index and dermatology life quality index.³¹

Three randomized, placebo-controlled, double-blind phase 3 trials have been completed for voclosporin, but the results were not available at the time of publication. The phase 3 ESSENCE trial compared voclosporin to placebo and ciclosporin controls (NCT00408187). Two phase 3 trials known as the SPIRIT trials—one a 12-week study (NCT00244842) and the other a

36-week extension trial (NCT00258713)—compared the efficacy of placebo to voclosporin administered at 0.2-, 0.3-, and 0.4-mg/kg doses.

KD025 (ROCK 2 Inhibitor)

KD025 (Kadmon Corporation, LLC) is an oral ROCK 2 inhibitor. The inhibition of ROCK in the ras homolog gene family, member A/ROCK pathway has been targeted therapeutically for pulmonary arterial hypertension,³² glaucoma,³³ and many other uses. A phase 2a study assessing the tolerability and safety profile of KD025 in patients with moderate to severe psoriasis was completed, but the results were not available at the time of publication (NCT02106195).

LAS41008 (Fumaric Acid Ester)

LAS41008 (Almirall, S.A.) is purported to be an oral dimethyl fumarate that inhibits endothelial cell proliferation, migration, and differentiation.³⁴ A phase 3 trial comparing the safety and effectiveness of LAS41008, LASW1835 (an active comparator), and placebo in patients with moderate to severe psoriasis is ongoing but not recruiting participants (NCT01726933).

LEO 22811 (Anti-inflammatory)

LEO 22811 (LEO Pharma) is an oral anti-inflammatory agent for the treatment of psoriasis. Two clinical trials have been completed, the results of which have not yet been published. A phase 1 trial assessing the tolerability and safety profile of LEO 22811 (NCT00833872) and a phase 2 proof-of-concept study assessing dose response of LEO 22811 versus placebo (NCT01116895) were completed, but the results were not available at the time of publication.

Baricitinib (JAK 1 and JAK 2 Inhibitor)

As noted above, baricitinib (LY3009104 or INCB28050) is a JAK 1 and JAK 2 inhibitor. A phase 2b trial examining dose response for LY3009104 or baricitinib administration in patients with moderate to severe psoriasis has been completed, but the results were not available at the time of publication (NCT01490632).

Talarozole (CYP26 Inhibitor)

Talarozole (formerly known as R115866) (GlaxoSmithKline) is a selective oral CYP26 inhibitor that could serve to regulate the degradation of all-*trans* retinoic acid in the management of conditions such as acne and psoriasis. One phase 2 non-randomized, open-label study (NCT00725348) and another phase 2 randomized, placebo-controlled, double-blind, dose-dependent trial examining the effectiveness and safety profile of 12-week talarozole

treatment in patients with severe plaque psoriasis have been completed, but the results were not available at the time of publication (NCT00716144).

R3421 or BCX-4208 (PNP Inhibitor)

R3421 or BCX-4208 (BioCryst Pharmaceuticals, Inc/Hoffman-La Roche) is an oral PNP inhibitor that may help regulate apoptosis of T cells and B cells.³⁵ A randomized, placebo-controlled, double-blind, dose-dependent phase 2 trial in patients with moderate to severe psoriasis has been completed, but the results were not available at the time of publication (NCT00504270).

RWJ-445380 (Cathepsin S Inhibitor)

RWJ-445380 (Alza Corporation, DE) is an oral cathepsin S inhibitor. Cathepsin S is produced by antigen-presenting cells and activates CD4⁺ T cells via presentation of antigen by class II major histocompatibility complex.³⁶ A randomized, placebo-controlled, double-blind, dose-dependent phase 2 trial evaluating the tolerability, safety, pharmacodynamics, and pharmacokinetics of RWJ-445380 in patients with plaque psoriasis has been completed, but the results were not available at the time of publication (NCT00396422).

SRT2104 (Sirtuin 1 Activator)

SRT2104 (GlaxoSmithKline) is a selective oral NAD⁺-dependent deacetylase sirtuin 1 activator. Sirtuins help regulate apoptosis, inflammation, and other important cellular mechanisms.³⁷ A randomized, open-label phase 1 trial examining drug bioavailability (NCT01702493) and a randomized, placebo-controlled, double-blind, dose-dependent phase 2 trial studying the efficacy, tolerability, and safety of SRT2104 in patients with moderate to severe psoriasis have been completed (NCT01154101), but the results were not available at the time of publication.

VB-201 (Oxidized Phospholipid)

VB-201 (VBL Therapeutics) is an orally administered oxidized phospholipid analogue with anti-inflammatory effects.³⁸ Oxidized phospholipids are another element in the intricate spectrum of inflammatory mediators. A randomized, placebo-controlled, double-blind, dose-dependent phase 2 trial of VB-201 20 mg or 80 mg daily in patients with moderate to severe psoriasis was completed, but the results were not available at the time of publication (NCT01001468). Another randomized, placebo-controlled, double-blind, dose-dependent phase 2 trial of VB-201 80 mg and 160 mg twice daily in patients with moderate to severe psoriasis has been completed, but the results were not available at the time of publication (NCT01837420).

Conclusion

We are living in an exciting time in the treatment of psoriasis and PsA, with promising novel therapies afforded by the discovery of new therapeutic targets. In this 3-part series, we have reviewed topical, systemic, and biologic therapies that currently are in phase 2 through phase 4 clinical trials or have recently been approved by the US Food and Drug Administration for the management of psoriasis and PsA. These treatments offer patients and their caregivers the prospect of more targeted therapeutic regimens that offer enhanced clinical outcomes with more favorable side-effect profiles. As clinicians and researchers build upon this knowledge in the years to come, we can offer psoriasis patients an increasingly diverse and powerful therapeutic armamentarium.

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