

Mechanisms Underlying the Clinical Effects of Apremilast for Psoriasis

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ABSTRACT

Psoriasis is a chronic, systemic, inflammatory disease with manifestations resulting from a dysregulated immune response. In psoriatic skin, expression of all phosphodiesterase 4 (PDE4) isoforms (A-D), part of a family of enzymes known to regulate cyclic adenosine monophosphate levels and immune homeostasis, is elevated compared with healthy controls. Agents that inhibit the enzymatic activity of PDE4, the predominant PDE in most immune cells, exert well-recognized anti-inflammatory effects. Apremilast is a selective PDE4 inhibitor approved for the treatment of adults with moderate to severe plaque psoriasis and/or psoriatic arthritis. In vitro and in vivo investigations have demonstrated the beneficial impact of apremilast treatment on PDE4 activity, inflammatory signal expression, and dermal psoriasiform signs. In patients with moderate to severe psoriasis, treatment with apremilast is associated with significant reductions in plasma levels of interleukin (IL)-17F, IL-17A, IL-22, and tumor necrosis factor-α compared with placebo as early as week 4; decreases in cytokine levels were sustained with continued treatment. Multivariate analyses demonstrated that while changes in IL-17F are the most important predictor of improvement in Psoriasis Area and Severity Index scores, apremilast exerts synergistic attenuating effects among a key group of cytokines involved in the pathology of psoriasis, and these effects correlate with improved skin symptoms. These in vitro and clinical data demonstrate that the beneficial effects of apremilast on known inflammatory mediators are associated with its clinical efficacy.

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INTRODUCTION

Psoriasis is a chronic, systemic, inflammatory disease that affects 1% to 4% of the population worldwide,[1] including an estimated 7.4 million US adults.[2,3] Many patients report that psoriasis has a substantial impact on their quality of life (QOL) because of visible plaques that may be embarrassing, as well as bothersome symptoms, such as itching, flaking, and pain.[4] Skin manifestations result from a dysregulated immune response, characterized by an ongoing imbalance in the production of pro-inflammatory and anti-inflammatory cytokines.[5,6] Although the initial cause(s) of inflammatory reactivity and imbalance is still not well understood, among the first known disease-related events is keratinocyte recruitment of inflammatory myeloid dendritic cells to the skin, where they release interleukin (IL)-23 and IL-12 to activate IL-17–producing T helper (Th) 17 cells (Th17), Th1 cells, and Th22 cells to produce abundant psoriatic cytokines, including IL-17, tumor necrosis factor (TNF)-α, and IL-22.[5-7] These substances, in turn, drive the proliferation and differentiation of keratinocytes associated with epidermal thickening, which underlies skin plaque and nail disease.[6] Activated keratinocytes also produce a host of effector substances that recruit other immune cells to the affected skin, establish a positive feedback loop, and exhibit synergistic effects that amplify the inflammatory disease process.[5-7]

With an improved understanding of the complex nature of psoriasis pathophysiology, a range of new therapeutic agents have become available that selectively target and inhibit the activity of pro-inflammatory cytokines such as IL-17 and IL-23, the cell-signaling protein TNF-α, or the phosphodiesterase (PDE) 4 enzyme.[8-11] PDEs are the primary means of degrading cyclic adenosine monophosphate (cAMP), an intracellular secondary messenger that regulates inflammatory responses and maintains immune homeostasis; PDEs regulate cAMP concentrations in inflammatory cells, endothelial cells, and keratinocytes.[12]

Agents that inhibit the enzymatic activity of PDE4, the predominant PDE in most immune cells,[12] are known to exert anti-inflammatory effects.[13,14] Apremilast, a selective PDE4 inhibitor, is approved by the US Food and Drug Administration

for the treatment of adult patients with moderate to severe plaque psoriasis, as well as patients with psoriatic arthritis.[15] With apremilast-mediated inhibition of PDE4, cAMP levels become elevated, causing reduced expression of inflammatory signals central to the psoriatic disease process, such as IL-17, IL-23, and TNF-α, while at the same time causing increased expression of anti-inflammatory cytokines, such as IL-10.[16,17] The current review provides an overview of physiological mechanisms by which apremilast works to interrupt the psoriatic inflammatory cascade and helps to reduce the clinical signs and symptoms of disease activity.

PDE4 in Psoriasis and Effects of Apremilast-mediated PDE4 Inhibition

Because psoriasis is characterized by an intense inflammatory infiltrate in the dermis, it is relevant to evaluate the expression of PDE4 in psoriatic dermis. In a recent set of experiments, PDE4 isoforms were shown to be expressed more in diseased skin (including psoriasis, atopic dermatitis, and discoid lupus erythematosus) than in normal skin; in psoriatic skin, the largest consistent increases were observed in the endothelium (PDE4A and PDE4D) and fibroblasts (PDE4A, PDE4B, and PDE4D).[18] PDE4B expression was prominently greater in the vessels of the superficial dermis of patients with psoriasis compared with healthy controls, as well as in inflammatory cells, which were more abundant in psoriatic skin.[18] In vitro, PDE4B and PDE4D expression were significantly upregulated (5.4-fold higher and 2.2-fold higher, respectively) in peripheral blood mononuclear cells (PBMCs) in patients with psoriasis compared with healthy controls.[18] Fibroblasts and, to a greater extent, the more differentiated myofibroblasts, express all PDE4 isoforms at the mRNA and protein level.[18] The elevated PDE4 levels observed in psoriatic blood and tissues strongly suggest that the pro-inflammatory, PDE4-mediated degradation of cAMP likely plays a role in psoriasis pathology.

T cells are central mediators of the systemic and local inflammation in psoriasis and psoriatic arthritis.[19] Apremilast was shown in T-cell cultures to inhibit a number of Th1, Th2, and Th17 cytokines to differing degrees. Apremilast most potently inhibited IL-17, recognized as a cornerstone of the Th17 response that is characteristic of psoriasis and psoriatic arthritis.[20] Also inhibited were the Th2 cytokines IL-5, IL-10, and IL-13, and less potently, TNF-α and the Th1 cytokines granulocyte-macrophage colony-stimulating factor and interferon-γ.[16] These results indicate that IL-17 production by T cells is quite dependent upon PDE4 enzymatic activity and is very sensitive to PDE4 inhibition by apremilast.

Neutrophils are another component of psoriatic inflammatory cell infiltrates, and one of the main downstream responders to the IL-17 produced by T cells. Apremilast treatment was found to directly inhibit neutrophil responses, including the reduced production of various chemoattractant molecules such as IL-8, CD18, CD11b, and leukotriene B4, and decreased neutrophil chemotaxis and adhesion to endothelial cells.[17]

Recent studies have uncovered a functional role for PDE4 in differentiated myofibroblasts. Of interest, PDE4 co-immunoprecipitates with the nerve growth factor (NGF) receptor CD271, while apremilast inhibits cell death induced by β-amyloid, a ligand of CD271, in these cells.[18,21] In addition, apremilast decreases NGF-induced fibroblast migration and significantly reduces cAMP degradation induced by β-amyloid.[18] PDE4s therefore have a key role in the pathophysiology of psoriasis, and PDE4/CD271 plays an important role in modulating fibroblast functions, including fibrotic processes and wound healing.[18]

A functional role for PDE4 has also been observed in keratinocytes. Firstly, PDE4 isoforms are expressed in all keratinocyte subpopulations (stem, transit amplifying, and post-mitotic), while CD271 is only detected in transit amplifying cells.[21] Secondly, all PDE4 isoforms co-immunoprecipitate with CD271 in keratinocytes (most likely transit amplifying cells).[21] Apremilast inhibits NGF-induced proliferation and reduces growth arrest and apoptosis induced by the CD271 ligand β-amyloid in human keratinocytes.[21] cAMP degradation is prevented by the addition of a PDE4 inhibitor alone or in combination with an NGF receptor, as shown in cell culture supernatants (enzyme-linked immunosorbent assay).[21] Apremilast also counteracts cAMP degradation induced by β-amyloid.[21] Furthermore, PDE4 inhibition induces upregulation of IL-10 and normalizes IL-10 levels reduced by β-amyloid.[21] On the other hand, apremilast decreases β-amyloid-induced upregulation of IL-8 and IL-1β levels.[21] With apremilast treatment, normal human epidermal keratinocytes exhibit decreased expression of TNF-α while continuing to show cell viability and proliferation.[17] Schafer et al also recently showed that apremilast modulates inflammatory gene expression in normal human keratinocytes stimulated by IL-17, marked by reductions in expression of gene encoding the cytokines IL-12/IL-23p40, IL-19, IL-31, and IL-33, as well as the alarmins S100A7, S100A8, and S100A12 (Celgene, data on file). Collectively, these data suggest that PDE4 regulates keratinocyte functions via signaling pathways involving receptors such as CD271[21] and IL-17 (Celgene, data on file).

In immunodeficient mice xenotransplanted with normal human skin and triggered with human psoriatic natural killer (NK) cells, treatment with oral apremilast was associated with morphological normalization of the epidermis, marked histologically by significant reductions in epidermal thickness and a decreased proliferation index (versus vehicle-treated groups), and the absence of lymphocyte infiltration.[17] Findings with apremilast were generally similar to those observed

in mice that received cyclosporine treatment. Qualitative immunohistochemistry showed decreases in TNF-α, intercellular adhesion molecule-1 and human leukocyte antigen-DR labeling in the epidermal tissue.[17] In a separate study, similarly to dexamethasone, apremilast reduced ear swelling in two mouse models of dermatitis using fluorescein isothiocyanate and dinitrochlorobenzene compared with vehicle-treated mice. Apremilast also significantly decreased monocyte chemoattractant protein-1 protein levels in mouse ears (Celgene, data on file).

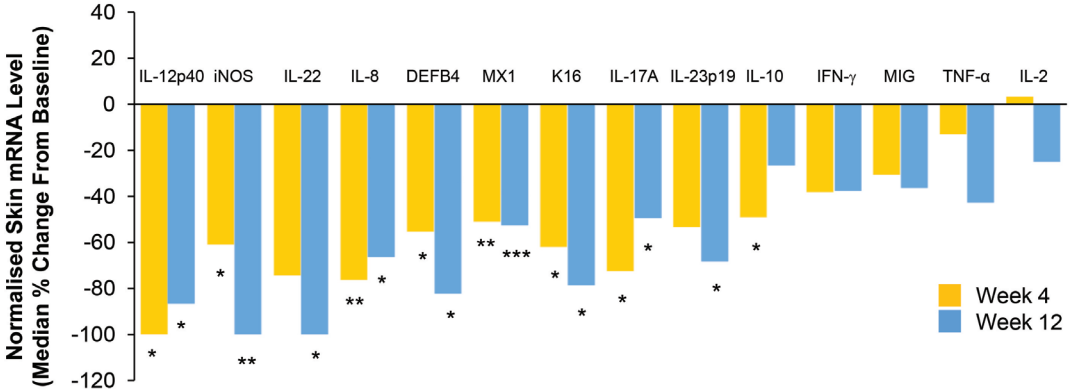
Apremilast's Mechanism of Action and Clinical Efficacy

The relationship between how apremilast works on key immune cell populations and how it alters expression of cytokines/inflammatory mediators to produce beneficial clinical effects has been explored using subanalyses of clinical trial data in patients with moderate to severe psoriasis or recalcitrant psoriasis. In the first apremilast psoriasis study, an early open-label pilot study, patients with severe psoriasis were treated with apremilast 20 mg once daily for 29 days.[22] Analysis of skin biopsies at the end of treatment (vs baseline) demonstrated that 8 of 15 (53%) patients with evaluable samples experienced a ≥20% reduction in epidermal thickness (ie, "response"); among all the patients, the mean decrease in epidermal thickness was 20.5%. Improvements were seen across most immunohistochemical parameters evaluated, including decreases in the numbers of T cells and CD11c myeloid dendritic cells in the dermis and epidermis; improvements were generally greater in patients who showed reductions in epidermal thickness.[22] Also, in this first apremilast psoriasis study, a reduction of TNF-α production was observed using a whole blood ex vivo assay, despite the very low dose administered (20 mg once daily, which is one-third the approved clinical dose of 30 mg twice daily).[15,22] Based on these favorable changes in biomarkers measured in the psoriatic skin (epidermal thickness) and blood (TNF-α production ex vivo), apremilast was advanced into further clinical development for psoriasis.

In a phase II open-label, single-arm trial in patients with recalcitrant psoriasis, 12 weeks of treatment with apremilast 20 mg twice daily reduced infiltration of myeloid dendritic cells, T cells, and NK cells into the dermis and epidermis.[23] In real-time reverse transcriptase polymerase chain reaction analyses of skin biopsy specimens, significant reductions in gene expression were observed for IL-12/IL-23p40, IL-23p19, IL-17A, IL-22, IL-8, and defensin beta 4 (DEFB4), all of which are considered part of the Th17 pathway (Figure 1).[23] Among these genes, the reduction in IL-17A and DEFB4 significantly correlated with the reduction in the Psoriasis Area and Severity Index (PASI) score at week 12.[23] For example, there was a median –46.7% change from baseline IL-17A gene expression and a median –46.5% change from baseline PASI score at week 12 (n=10, P=0.030).[23] Thus, the magnitude of the decreased IL-17A gene expression in the lesional skin was quite similar to the magnitude of the decrease in PASI score at the low apremilast dose of 20 mg twice daily. In general, the inhibition of pro-inflammatory genes was greater in patients with a clear beneficial clinical response (eg, ≥75% reduction from baseline PASI [PASI-75]).[23] Notably, there was an increase in IL-10 gene expression in the skin of responders, but a decrease in the non-responders, indicating that apremilast mediates an increase in this anti-inflammatory gene in some but not all patients.

Comprehensive analyses of the relationship between normalized cytokine profiles and clinical improvement during apremilast treatment in patients with moderate to severe plaque psoriasis have been performed in randomized, placebo-controlled trials. An analysis was conducted using data

FIGURE 1. Effects of apremilast 20 mg twice daily on gene expression in lesional skin biopsies from the recalcitrant psoriasis phase II study (PSOR-004).[23] DEFB4, defensin beta 4; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; MIG, monokine induced by IFN-γ; PASI, Psoriasis Area and Severity Index; TNF-α, tumor necrosis factor-α. *P≤0.05, **P≤0.01, ***P≤0.001 by two-sided Wilcoxon signed rank test.



from a subset of patients from the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM 2), a phase III study in North America and Europe, as well as from patients in a separate phase IIb study conducted in Japan (PSOR-011).[24] In ESTEEM 2, treatment with apremilast 30 mg twice daily was associated with significant reductions in plasma levels of IL-17F, IL-17A, IL-22, and TNF-α compared with placebo as early as week 4 and decreases in cytokine levels were sustained through week 44 (Figure 2).[24,25] Similar reductions emerged in patients who were initially randomized to receive placebo and were switched to apremilast treatment at week 16. Findings were generally similar in PSOR-011 (Figure 2).[24,25] The rapid, substantial reduction in systemic IL-17 protein levels should be highlighted: In these two studies, the median reduction was approximately –43% to –44% for IL-17A and –50% to –57% for IL-17F at week 4. The median reductions in systemic IL-22 and TNF-α protein levels were significant, although more modest (–27% to –36% for IL-22 and –3% to –9% for TNF-α at week 4).[24,25] Further analysis of the ESTEEM subset of patients showed positive correlations between changes from baseline in IL-17A, IL-17F, and IL-22 levels at week 4 and PASI improvement at week 16; only weak correlations were observed between the change in TNF-α and PASI at week 16.[24,26] It should be noted that the decrease in IL-17A plasma protein levels in phase IIb and phase III (median –42 to –44% at week 16[24,25]) is very similar to the observed decrease in IL-17A gene expression in the lesional skin (median –46.7% at week 12) observed in a separate phase II study of apremilast in patients with recalcitrant plaque psoriasis in the United States.[23] Therefore, these findings of IL-17 inhibition are consistent and reproducible across multiple studies, are in line with those of previous in vitro investigations, and demonstrate that inhibition of IL-17 is an important mechanism through which apremilast exerts its anti-inflammatory effects in patients with psoriasis.

Because apremilast modulates the expression of a number of cytokines involved in the pathogenesis of psoriasis (ie, IL-17A/F, IL-22, and TNF-α), nonlinear, multivariate algorithms were used in ESTEEM 2 to examine potential interactions and synergies between cytokine levels at week 4 and PASI improvement at week 16. The inclusion of nonlinearities, interactions, and synergies resulted in a greater ability to predict week 16 PASI improvement than was found with linear univariate models. These analyses revealed that IL-17F is the most important predictor of PASI improvement but that synergies between IL-17A/F, IL-22, and TNF- α clearly exist.[24] Therefore, the well-characterized pleiotropic effects of apremilast appear to create a unique therapeutic milieu, in which decreases in multiple cytokines are not simply additive, but feed into one another, resulting in observed clinical improvements (Figure 3A and 3B).

Clinical Profile of Apremilast

The efficacy and safety of apremilast in the treatment of moderate to severe psoriasis have been demonstrated in the comprehensive global ESTEEM phase III trial program and the LIBERATE phase IIIb trial.[27-29] In the ESTEEM and LIBERATE trials, adult patients with moderate to severe psoriasis receiving apremilast demonstrated statistically significant and clinically meaningful improvement, as measured by PASI-75 response at week 16, the primary end point.[27-29] Other analyses from the ESTEEM trials showed that apremilast treatment significantly reduces pruritus,[30] a symptom reported as highly bothersome.[4] QOL also significantly improved in the ESTEEM trials, with significant improvements from baseline at week 16 in mean Dermatology Life Quality Index scores in patients treated with apremilast versus placebo.[27,28] At week 16, the most commonly occurring adverse events in ESTEEM patients taking apremilast were diarrhea, nausea, upper respiratory tract infection, and headache.[27,28] Apremilast demonstrated

FIGURE 2. Effects of apremilast 30 mg twice daily on plasma cytokine levels in phase III (ESTEEM 2) and phase IIb (PSOR-011) studies. *$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ vs. placebo, based on 2-sided Wilcoxon signed rank test. ESTEEM 2: placebo N=46; apremilast N=83. PSOR-011: placebo N=23; apremilast N=24. IL, interleukin; TNF, tumor necrosis factor.

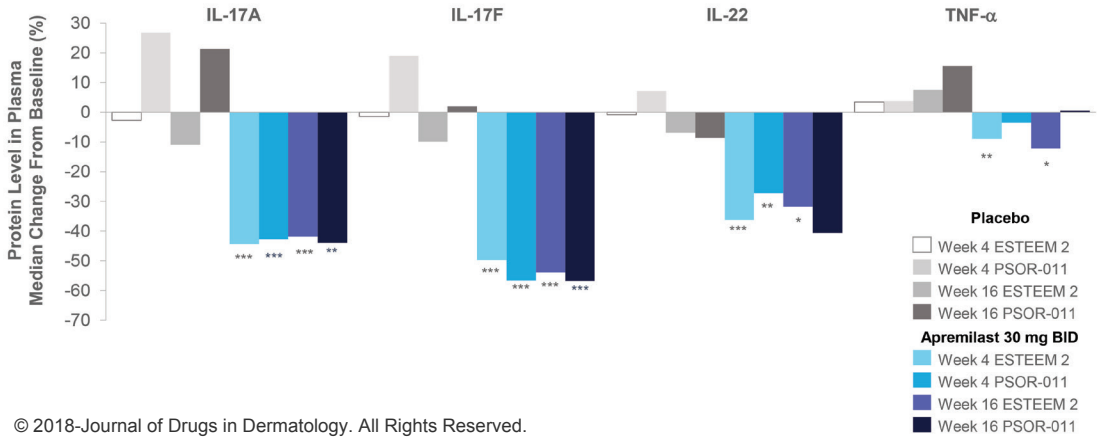
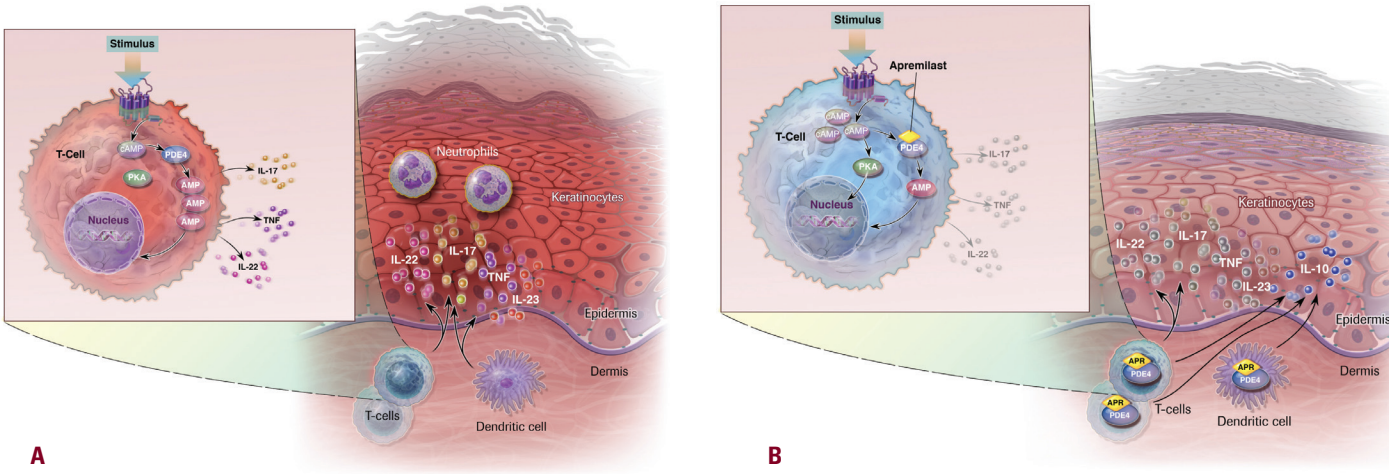


FIGURE 3. A. Proinflammatory cytokines in psoriasis. B. Mechanism of action of apremilast. IL, interleukin; PDE4, phosphodiesterase 4; TNF, tumor necrosis factor.



clinical efficacy that was maintained with continued treatment for up to 52 weeks,[27-29] and some patients enrolled in the ESTEEM trials will continue to receive apremilast therapy for up to 5 years. In the more recent Evaluating Apremilast in a Phase IV Trial of Efficacy and Safety in Patients With Moderate Plaque Psoriasis (UNVEIL) study, the efficacy of apremilast was demonstrated in systemic-naive, post-topical patients with moderate plaque psoriasis (ie, 5% to 10% body surface area involvement and static Physician's Global Assessment score of 3 [moderate] on a 6-point scale) and was consistent with results from the ESTEEM trials in patients with moderate to severe plaque psoriasis.[31]

SUMMARY

Psoriasis involves chronic, systemic dysregulation of pro-inflammatory and anti-inflammatory cytokines that leads to the symptoms of psoriasis and underlying systemic inflammation. Apremilast is an oral PDE4 inhibitor that has demonstrated safety and efficacy in the treatment of moderate to severe plaque psoriasis and psoriatic arthritis. Apremilast exhibits pleiotropic, synergistic attenuating effects on a key group of cytokines involved in the pathology of psoriasis, most notably IL-17A/F, IL-22, and TNF-α, and these effects correlate with reduced skin manifestations.[24] Newly available pharmacodynamic data from clinical study patients further clarify the link between clinical efficacy and the beneficial effects of apremilast on these known inflammatory mediators.

DISCLOSURES

Dr. Pincelli reports grants from Expascience, Lilly, and Mylan; nonfinancial support from Celgene Corporation; and personal fees from Sienna. Dr. Schafer is an employee of and has stocks/stock options in Celgene Corporation. Dr. French has received a grant from Celgene Corporation and has served as a consultant for Celgene Corporation. Dr. Augustin has served as a consultant to or paid speaker for clinical trials sponsored by companies that manufacture drugs for the treatment of psoriasis, including AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene Corporation, Centocor, Eli Lilly, GSK, Janssen-Cilag, LEO Pharma, Medac, Merck, MSD, Novartis, Pfizer, UCB, and XenoPort. Dr. Krueger reports grants paid to institution and/or personal fees from AbbVie, Acros, Allergan, Amgen, Asana, Aurigne, Biogen-Idec, BiogenMA, BMS, Boehringer Ingelheim, Escalier, Innovaderm, Janssen, Kineta, LEO Pharma, Lilly, Novan, Novartis, Paraxel, Pfizer, Regeneron, Roche, Vitae, Sienna, UCB, and Valeant.

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