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Chemical compatibility of calcipotriene 0.005% foam in combination with topical steroids

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Objectives: Combination therapy is an effective approach to the treatment of skin disease, and studies have shown that topical combination therapy with a vitamin D3 analogue and a corticosteroid are an effective approach for treating mild to moderate psoriasis. It is believed that this combination approach enhances the efficacy of the vitamin D analogue and limits the toxicity of the corticosteroid. A new calcipotriene foam formulation has been developed using a novel vehicle technology that collapses to deliver calcipotriene through the skin. Because the compatibility of products not only depends on the active ingredients, but also the inactive ingredients present in the respective products, it is critical to understand whether a vehicle influences the chemical stability of the active ingredients. The objective of these studies was to evaluate the chemical compatibility of calcipotriene 0.005% foam (CAL foam) with available corticosteroid products: desonide 0.05% foam (DES foam), clobetasol propionate 0.05% EF foam (CP foam)m and clobetasol propionate 0.05% spray (CP spray).

Methods: Equal amounts (400-500 mg) of CAL foam and [DES foam, CP foam, or CP spray] were mixed in a glass container and stored at 40°C for 6, 15, 24, 32, and 48 hours. Concentrations of calcipotriene, desonide, and clobetasol propionate were determined by ultra performance liquid chromatography (UPLC) after each time-point and compared to that of an unstressed freshly mixed sample (control).

Results: The potencies of calcipotriene remained at >97% relative to control samples, thus calcipotriene is chemically stable for up to 48 hours at 40°C after CAL foam is mixed with either DES foam, CP foam or CP spray. Likewise, the potency of desonide and clobetasol propionate remained at >97% relative to control samples, thus desonide and clobetasol propionate are also chemically stable for up to 48 hours at 40°C after CAL foam is mixed with either DES foam, CP foam, or CP spray.

Conclusion: These results show that calcipotriene foam is chemically compatible when used concomitantly with either desonide foam or with clobetasol propionate in either a spray or EF foam formulation. This provides the clinician with the confidence to use this new calcipotriene foam formulation in combination with available topical steroid foams and sprays.

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The long-term safety of adalimumab: An analysis of all adalimumab exposure in all moderate to severe psoriasis clinical trials

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Objective: To assess the long-term safety data of all adalimumab-treated patients in all phase II, II/III, III, IIIb, and IV clinical trials in moderate to severe psoriasis.

Methods: Safety data from all patients treated with at least 1 dose of adalimumab in any of the 13 clinical trials in moderate to severe psoriasis were pooled through November 6, 2008, and through November 6, 2009, respectively, to create two overlapping datasets. Most patients received 40 mg adalimumab every other week, begun either 1 week after an initial dose of 80 mg or after a period of placebo treatment. Adverse events (AEs) that occurred up to 70 days after the final dose of adalimumab were analyzed. Standardized incidence ratios (SIR) were determined using the SEER database for comparison.

Results: Patient numbers and adalimumab exposure increased by 20.8% (n = 378) and 79.5% (1,927.2 PYs), respectively, between April 15, 2007, and November 6, 2008, as previously reported. The relatively large increases in the percentages of patients (37.0%; n = 813), versus adalimumab exposure (11.3%; 492.8 PYs), between the 2008 (N = 2197; 4,351.9 PYs) and 2009 (N = 3010; 4,844.7 PYs) datasets reflects the relatively brief duration of the two most recent studies. Overall adverse event (AE) incidence rates (events per PY) for the 2008 and 2009 data sets were 2.757 and 3.133, with serious AE rates of 0.072 and 0.084, respectively. Rates of other types of AEs for the 2008 and 2009 data sets, respectively, were: infections, 0.802/0.888; serious infections, 0.014/0.017; opportunistic infections, 0.003/0.004; and malignancies (excluding NMSC), 0.006/0.007. The 2008 and 2009 incidence rates were identical for nonmelanoma skin cancer (NMSC) (0.007), demyelinating disorders (<0.001), CHF (0.002), lupus-like syndrome (<0.001), and tuberculosis (<0.001). There were no events of hepatitis B reactivation, 1 lymphoma, and no new events of demyelinating disease in the 2009 data set. SIR (95% CI) for malignancies (excluding NMSC) were 0.89 (0.57-1.32) and 0.90 (95% CI, 0.60-1.29), respectively, for 2008 and 2009. These results are consistent with earlier findings that at least some AE incidence rates decrease with increased adalimumab exposure.

Conclusion: AE rates from pooled results for all adalimumab-treated patients in all psoriasis clinical trials were low and generally stable over time.

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Improved quality of life with apremilast (APR) in the treatment of psoriasis: Results from a phase IIb randomized controlled study

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Purpose: Psoriasis is a chronic inflammatory skin disorder that negatively impacts health-related quality of life (HRQOL). We evaluated the effect of APR, a novel oral pluripotent immunomodulator that specifically inhibits phosphodiesterase-4 (PDE4), on patient-reported outcomes (PROs).

Methods: A phase IIb, randomized, double-blind, placebo (PBO)-controlled, dose-ranging multicenter study was conducted in the US and Canada in subjects with moderate to severe plaque psoriasis (PASI $\geq$ 12; BSA $\geq$ 10%) randomized equally to oral APR (BID: 10, 20, or 30 mg) or PBO for 16 weeks. PROs included the Dermatology Life Quality Index (DLQI), pruritus visual analog scale (VAS), the physical (PCS) and mental (MCS) component summaries and individual domain scores of the short-form 36 (SF-36), and the SF-6D health utilities. Minimum clinically important differences (MCID) are 5.0 points for DLQI, 10.0 for pruritus VAS, 2.5 to 5.0 for PCS and MCS, and 5.0 to 10.0 for SF-36 domain scores. Minimally important differences (MID) for SF-6D are >0.041.

Results: Three hundred fifty-two subjects enrolled (63% males; mean age, 44 years; mean BMI, 31). Baseline scores approached age/gender-matched US norms, indicating potential ceiling effects. Nonetheless, at 16 weeks, statistically significant ($P < .01$) treatment-associated improvements in MCS scores $\geq$MCID in all active treatment groups were reported: 3.0, 3.3, and 2.8 for 30, 20, and 10 mg groups, respectively, versus PBO -0.5. Changes in SF-36 domain scores were statistically significant and clinically meaningful for 30 mg (bodily pain [BP], social functioning [SF], role emotional [RE], mental health [MH]; statistically significant for 20 mg (BP, SF, RE, MH, physical functioning [PF]); and statistically significant and clinically meaningful for 10 mg (BP, RE, and MH). These improvements in the 30- and 10-mg groups resulted in mean increases of 0.058 and 0.046 in SF-6D scores, exceeding MID. More subjects in the 20- and 30-mg groups had improvement in DLQI and pruritus VAS scores $\geq$MCID versus subjects in PBO group, with moderate and statistically significant correlations between DLQI and pruritus VAS scores and SF-36. The number needed to treat to obtain improvement in all 3 PROs ranged from 8 to 9 in the 30- and 20-mg groups.

Conclusion: Despite high scores at baseline, APR treatment, especially 30 mg BID, was generally associated with statistically significant and/or clinically meaningful mean improvements in PROs including DLQI, pruritus VAS, and SF-36 MCS and domain scores.

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ESPRIT: Interim results from a 10-year postmarketing surveillance registry of adalimumab treatment for moderate to severe psoriasis

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Background: ESPRIT is a phase IV, prospective, multicenter, 10-year observational registry study of the long-term safety and efficacy of adalimumab (ADA) as used in routine clinical practice in adult patients with moderate to severe chronic plaque psoriasis (NCT00799877).

Methods: ESPRIT is enrolling 5000 chronic plaque psoriasis patients in the United States and Canada, and $\leq$1000 patients in participating European countries. Enrolled patients have been newly initiated on ADA, previously on ADA treatment or were rolled over from previous ADA psoriasis trials. Patients are evaluated 3 and 6 months after enrollment, then every 6 months for up to 10 years, including patients who discontinue ADA. Data collection includes medical history, baseline demographics, disease characteristics, serious adverse events (SAEs), AEs of special interest and patient reported outcomes (US sites only). Efficacy parameters include Physician's Global Assessment (PGA) and DLQI (US sites only).

Results: One thousand three hundred ten patients were enrolled from September 26, 2008 to November 30, 2009, of which 1235 have received $\geq$1 dose of ADA. Baseline demographics included: 58% male; median age 46 (range, 18-91); median weight 86.2 kg (range, 43.1-193.0). Median registry exposure is 174 days (range, 14-676). Of dosed patients, eight (0.6%) have discontinued the registry, most frequently because of withdrawal of consent. A total of 1.2% (15/1235) of patients reported $\geq$1 SAE. One patient died after experiencing systemic inflammatory response syndrome, aspiration pneumonia, and congestive cardiac failure. Serious infections of special interest occurred in two patients (candidiasis and urosepsis). One patient, who at enrollment had a negative purified protein derivative test, developed disseminated TB after 16 weeks of treatment. Malignancies were reported in nine patients (0.7%): seven were nonmelanoma skin cancer and two were melanomas (1 melanoma in situ and 1 invasive melanoma). One patient each reported lupus-like syndrome, allergic reaction, demyelinating disorder, congestive heart failure, and stroke. For this interim analysis, 49.6% of 1235 patients had reached 3 months in the registry; of observed patients, 46.6% (284/610) had a PGA of 'clear or minimal,' and mean change from baseline DLQI was -5.1 $\pm$ 6.8.

Conclusion: ESPRIT will provide data complementary to those from the preregistration studies of ADA in psoriasis. No new safety signals were observed in ESPRIT as of the data cut-off date of November 30, 2009.

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