

Repetitive Rapid Delivery of Pharmacologically-Active hPTH 1-34 Across Human Skin Without Injection

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TransPharma has developed a system for transdermal delivery of hPTH 1-34 (TD) to alleviate the discomfort of injections (SC) and improve patient acceptance of and compliance with hPTH 1-34 therapy. The system utilizes RF ablation to create MicroChannels in the upper skin, allowing rapid diffusion of peptide from a subsequently-applied drug patch into the inner skin and systemic circulation. We compared the safety, tolerability, pharmacokinetics (PK), and type I procollagen N-terminal propeptide (PINP) based pharmacodynamic (PD) profile of TD vs. SC hPTH 1-34 administered once-daily for 7 days. 48 healthy post-menopausal women, age 65 ± 4 years, were randomly allocated in 3 blocks of 16 to a daily TD dose of 50, 70, or 90 μg or a daily SC dose of 20 μg (FORTEO[®]). On days 1 and 7 we measured fasting serum PINP 1 hour before dosing (after which participants ate breakfast), and measured serum hPTH 1-34 15 minutes before and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 14 and 24 hours after TD or SC administration of the peptide. To minimize assay-related bias, all sera for a woman were measured in the same hPTH 1-34 or PINP assay. In each treatment group the mean PK profile on day 7 (presented in the Table below) did not differ significantly from that on day 1, indicating reproducible peptide delivery and no peptide accumulation.

Treatment	Cmax (pg/ml) mean \pm SD	Tmax (h) mean \pm SD (range)	AUC _{0-t} (hr*pg/ml) mean \pm SD	P1NP absolute change from baseline ($\mu\text{g/L}$) (% Change) mean \pm SD
TD 50 μg (n = 12)	53 \pm 16	2.0 \pm 0.5 (1.5-2.5)	135 \pm 48	13 \pm 7 (28 \pm 15)
TD 70 μg (n = 12)	68 \pm 28	2.3 \pm 0.3 (1.5-2.5)	162 \pm 73	13 \pm 9 (26 \pm 15)
TD 90 μg (n = 12)	90 \pm 37	2.5 \pm 0.6 (1.5-4.0)	250 \pm 116	12 \pm 9 (22 \pm 15)
SC 20 μg (n= 10-12)	72 \pm 21	0.6 \pm 0.4 (0.25-1.0)	117 \pm 45	8 \pm 17 (20 \pm 29)

Cmax occurred approximately 2 hours after TD application and 0.6 h after SC injection. Serum hPTH 1-34 was quantifiable 1.5-3.5 hours longer after TD dosing than after 20 μg SC dosing. The bioavailability of TD hPTH 1-34, calculated from the area under the time-concentration curves, was ~40% of SC injection. Following 6 days of hPTH 1-34 treatment, serum PINP increased significantly in each treatment group by paired t-test (*p< 0.0001- 0.05). Transdermal therapy was well-tolerated; application sites showed only very minor and transient erythema and edema, and no infections. These safety, tolerability, PK and early PD data demonstrate that TD hPTH 1-34 is a promising alternative to the currently-marketed injections.

* P values are based on percent changes.