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A novel intracutaneous microneedle delivery system for the treatment of acute migraine

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Introduction:
A Novel Intracutaneous Microneedle Delivery System for zolmitriptan has been developed by Zosano. This delivery system provides: Rapid non oral delivery and pulsatile PK profile, Room temperature stable formulations, Patient friendly alternative to injection,Versatile delivery platform capable of delivering large and small molecules, and vaccines. In a recent clinical trial zolmitriptan intracutaneous microneedle delivery system was highly effective for the treatment of migraine, with statistical significance compared to placebo achieved for the two co-primary endpoints of pain freedom at 2 hours and most bothersome symptom absence at 2 hours.

Objectives:
ADAM is a novel patient- administered system for intracutaneous drug administration. In a Phase I pharmacokinetic study, Zolmitriptan administered using ADAM had much faster absorption than oral administration with higher exposure in the first two hours. During a 28- to 56-day run-in period to determine eligibility, patients recorded daily headache and migraine symptoms using an e-diary. On the first day of the run-in period, patients declared their most bothersome migraine symptom (MBS) other than pain (nausea [with or without vomiting], photophobia, or phonophobia, which is most bothersome most of the time with their migraine headaches). Eligible patients had experienced two to eight migraine headaches per 28-day period and were randomly assigned in a 2:2:1:2:1 ratio to receive one 1 mg ADAM zolmitriptan, one 1.9 mg ADAM zolmitriptan, one ADAM placebo, two 1.9 mg ADAM zolmitriptan (3.8 mg total), or two ADAM placebo, to treat a single qualifying migraine headache (pain of moderate or severe intensity and presence of MBS). Uncoated titanium microprojections were used in the placebo. A central, permuted block randomization scheme stratified by MBS was generated by an independent statistician. The primary analysis method was a Cochran Mantel-Haenszel (CMH) test controlling for the ran domization stratification by MBS. Each individual active treatment group was compared to the pooled placebo group in a pairwise manner. Pooling of the placebo groups was planned a priori for statistical simplicity. Post hoc analyses showed no significant dif ferences in outcomes in the 1- or 2-patch placebo groups, supporting the decision to pool these groups. In addition, the Breslow-Day test was performed to assess the homogeneity of the odds ratios across MBS. A fixed sequential testing methodology was applied to control the overall type 1 error. A test was considered statistically significant only if the corresponding CMH test had a p value < 0.05 and all previous tests had a p value < 0.05. Last observation carried forward (LOCF) was used to impute missing data.

Results:
The results in our clinical study show the usefulness of intracutaneous microneedle delivery system for delivering zolmitriptan rapidly and yielding pharmacologic effects quickly which may be a significant advantage compared to nasal and oral formulations of zolmitriptan. In combination with our ongoing long-term safety study we believe this trial will form the basis for approval. In addition, patients have demonstrated that they are able to reliably apply the intracutaneous patches and find the product convenient and easy to use. Of patients treated with ADAM zolmitriptan 3.8 mg or placebo, 41.5% and 14.2%, respectively were pain-free 2 hours post-dose (p ¼ 0.0001) and 68.3% and 42.9% were free from their most bothersome other symptom (p ¼ 0.0009). Due to the fixed sequential testing methodology, formal statistical significance was not established for secondary endpoints. However, the proportion of patients who were photophobia-free, phonophobia-free, and nausea-free at 2 hours post-dose was higher in the ADAM zolmitriptan 3.8 mg group compared with placebo, as were the percentages of patients who were pain-free, and who experienced pain relief up to 48 hours post-dose. Systemic adverse events were consistent with previous triptan trials, and included dizziness, paresthesia, muscle tightness, and nausea, all of which occurred in < 5% of patients in any group. Application site reactions were generally mild and resolved within 48 hours,although erythema and bruising persisted for longer periods in some patients.

Conclusions:
In this randomized, double-blind, placebo-controlled study, ADAM zolmitriptan 3.8 mg was effective andwell-tolerated for the acute treatment of migraine.Nearly 42% of patients treated with ADAM zolmitriptan 3.8 mg were pain-free 2 hours after treatment and nearly 70% were free from their most bothersome headache-associated migraine symptom. Efficacy was dose dependent, with the 3.8 mg dose providing a better response than the 1.9 mg and 1 mg doses.

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