BACKGROUND: The delta opioid receptor (DOR) has long been of interest as a target for potentially non-addictive treatments for a variety of CNS disorders. Recent evidence suggests that DOR activation may be beneficial in the treatment of migraine. However, DOR agonists have caused seizure in preclinical species, hindering the development of selective drugs targeting the DOR. We sought to harness ligand bias at the DOR to discover a DOR modulator with efficacy in animal models of migraine and other CNS disorders while minimizing seizure liability.
METHODS: Based on data suggesting that G protein coupling without beta-arrestin2 engagement at the DOR would reduce seizure liability, we identified TRV250, a novel small molecule targeting the DOR. Rat and mouse models of migraine pain, and seizure liability were used to assess the potential therapeutic index of TRV250.
RESULTS: Compared to unbiased agonists AZD2327 and SNC80, TRV250 has potent, full efficacy for G protein coupling, but much weaker engagement of beta-arrestin2. TRV250 is highly selective for the DOR over the mu and kappa opioid receptors. In rodent nitroglycerin-induced hyperalgesia models of migraine, TRV250 showed robust efficacy after both subcutaneous and oral dosing. TRV250 was also active in models of nociception, depression, and anxiety. Compared to AZD2327, TRV250 showed a markedly improved margin between efficacious doses and doses associated with seizure.
CONCLUSION: TRV250 shows promise as a potential new class of therapy for the treatment of migraine, as well as other CNS disorders. Preclinical development to support future clinical trials of TRV250 is underway. Data submitted will be disclosed in an oral presentation prior to the AHS meeting at the 17th Congress of the International Headache Society in Valencia, Spain (May 14-17th, 2015).

LBP18
TEV-48125 for the Preventive Treatment of Chronic Migraine – Efficacy at Early Time Points
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BACKGROUND: TEV-48125 is a monoclonal antibody against CGRP that was recently shown to be effective and tolerable for the preventive treatment of chronic migraine and high frequency episodic migraine. Efficacy was achieved as early as 1 month after therapy was initiated. Herein we evaluate the efficacy and safety of two doses of subcutaneous TEV-48125 during the first month of therapy in patients with chronic migraine.
METHODS: This was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study. Following a 28 day run-in period, participants were randomized and treated for three months with subcutaneous once monthly injections of TEV-48125 675/225 mg or 900 mg, or placebo. Headache information was captured daily using an electronic headache diary. The primary endpoint was change from baseline in the number of hours with headache in month 3; the secondary endpoint was change from baseline in number of headache days of moderate or severe intensity in month 3. Herein we assess the efficacy of each dose at earlier time-points.
RESULTS: The sample consisted of 261 subjects. Compared to placebo, significant decreases in the number of hours with headache were seen after 1 week of therapy for both doses (low dose: $p < 0.05$; high dose, $p < 0.01$). These benefits were maintained through the second and third weeks of therapy. Both doses significantly decreased the number of hours with headache relative to placebo in month 1($p< 0.01$ and $p< 0.0001$), month 2 ($p =< 0.05$ and $p= < 0.0001$) and month 3 of therapy ($p < 0.05$ and $p= < 0.01$). In the analysis of change from baseline in weekly headache days of at least moderate or severe intensity, both doses were superior to placebo at week 2 ($p < 0.05$ and $p < 0.01$).Treatment was well tolerated and no treatment-related serious adverse events were reported.
CONCLUSION: Both doses of TEV-48125 resulted in the rapid onset of a preventive response in subjects with CM. To the best of our knowledge, this is the first preventive migraine medication demonstrating significant improvement within 1 week of the initiation of therapy.