•Montelukast Sodium Enhances Fracture Repair: Is There a Dose Response?

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Purpose: Previous studies have demonstrated that leukotrienes can act as negative regulators of chondrocyte activity, and that selective blockade through the use of leukotriene inhibitors can enhance chondrocyte activity and fracture repair. In this study, we sought to confirm these findings and determine if this effect was dose responsive. We hypothesized that the effect of cysteinyl leukotriene receptor blockade with montelukast sodium would demonstrate dose responsiveness and that increasing doses of the drug would demonstrate improved efficacy.

Methods: 451 animals were enrolled in an IACUC (Institutional Animal Care and Use Committee)-approved study. Animals underwent open retrograde nailing of the right femur followed by midshaft femoral guillotine fracture by standardized weight drop. Animals were divided into four treatment arms and received daily gavage with montelukast sodium at the following doses: control (carrier alone), 0.15 mg/kg once daily, 0.15 mg/kg twice daily, 1.5 mg/kg daily, and 1.5 mg/kg twice daily. Animals were sacrificed at day 7, 10, 14, and 21 post-fracture and underwent analysis by qtPCR (quantitative polymerase chain reaction) for gene expression, micro-CT, histology/immunohistochemistry, and mechanical testing.

Results: *Histomorphometry*: We performed histomorphometry on fracture callus sections from a total of 10 histological sections from each dose and time. We are able to demonstrate a clear, albeit small, effect of dose response from low to intermediate group, and a dramatic decline at the highest doses, suggesting potential inhibitory dose effect at the 1.5 mg/kg twice daily levels. *Mechanical Testing (day 21):* These data are largely consistent with our histomorphometry data showing larger callus size in the 1.5 mg/kg daily dosing, and this larger callus translated in this study to a more mechanically robust response by day 21. *Micro-CT:* For the overall bone volume and density, a tight contour around the entire ROI (region of interest) was utilized with no delineation between cortical or trabecular bone. Micro-CT data demonstrate an increased effect at 1.5 mg/kg daily dosing at specific time points, but no difference to control and a decline from 1.5 mg/kg daily was seen with 1.5 mg/kg twice daily dosing. *Gene Expression:* Aggrecan core protein expression levels and others are consistent with data demonstrating an increase to 1.5 mg/kg daily dosing and potential inhibitory dose effect at the highest levels.

Conclusion: Treatment of murine femoral fractures with oral montelukast sodium demonstrated increased callus size and gene expression profiles consistent with enhanced chondrogenesis at early time points, and this effect showed modest increases with escalating drug dosing. However, the highest dose appeared to exhibit potential inhibitory dose effect, with a drop off of nearly every parameter including mechanical testing, micro-CT parameters, and histomorphometry. This has important implications when considering the potential translation of leukotriene blockade for fracture treatments in humans.

• The FDA has not cleared this drug and/or medical device for the use described in this presentation (i.e., the drug or medical device is being discussed for an "off label" use). For full information, refer to page 600.