

## **Analyses of Markers of Liver Injury in Phase 2 and 3 Controlled Clinical Trials of Peramivir in Subjects with Influenza Infection.**

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**Abstract: BACKGROUND:** Bystander hepatitis is described in influenza patients, and liver enzyme abnormalities are reported with neuraminidase inhibitor (NAI) therapy. We evaluated the possible association of NAI therapy with hepatotoxicity in adult influenza patients.

**METHODS:** Multinational, blinded, placebo (Pbo)- or oseltamivir (OSE)-controlled studies evaluated the safety and efficacy of peramivir (PVR); adults with influenza received single IM (Studies BCX1812-211 and BCX1812-212) or IV (Studies 0722T0621 and 0815T0631) doses, or multiple daily (5 days) IV (Study BCX1812-201) doses. ALT, AST, bilirubin (BIL) and alkaline phosphatase (AP) levels were measured at baseline (BL) and up to 14 days post therapy. Descriptive statistics and change in DAIDS toxicity grades were tabulated. Multiple logistic regression analyses with stepwise selection were performed to identify potential predictors of increases of markers of liver injury.

**RESULTS:** Five randomized trials (2006 – 2009) enrolled 2119 adults with confirmed influenza. Within 48 hr of influenza symptom onset (72 hr in BCX1812-201, n=91), subjects received PVR (n=1346), Pbo (n=383), or OSE 75 mg BID (n=390). Pre-therapy median (range) ALTs were 20 (1, 415) U/L; median (range) ASTs were 22 (9, 410) U/L, median (range) BIL levels were 0.4 (0, 3.4) mg/dL and median (range) AP were 67 (21,410). Median changes from BL to 48 hour post therapy were similar among the three groups for ALT, AST, BIL and AP. Increases of AST were somewhat higher in the peramivir group at this timepoint; however, AST elevations in IM peramivir studies correlated with elevations in creatine kinase, suggesting muscle injury ( $r=0.75$ ,  $p<0.001$ ). Forty eight hour post therapy, most increases in ALT, AST, BIL and AP were grade 2. Grade 2 (42, 87.5%) or higher (6, 12.5%) ALT ( $> 2.5*ULN$ ) with at least a 1 grade increase from BL was seen in 1.8% of placebo subjects, 2.7% of peramivir subjects (2.4% in IV studies and 3.5% in IM studies), and 1.3% of oseltamivir subjects. Grade 2 (33, 86.8%) or higher (5, 13.2%) AST ( $> 2.5*ULN$ ) with at least a 1 grade increase from BL was seen in 2.3% of placebo subjects, 1.9% of peramivir subjects (1.0% in IV studies and 4.1% in IM studies), and 1% of oseltamivir subjects. Grade 2 (8, 88.9%) or higher (1, 11.1%) BIL ( $> 1.5*ULN$ ) with at least a 1 grade increase from BL was seen in 0.5% of placebo subjects, 0.5% of peramivir subjects, and 0% of oseltamivir subjects. At 14 days post therapy, the proportions with increases had declined to: for ALT: 0.5% of Pbo subjects, 0.6% of PVR subjects and 0.3% of OSE subjects, for AST: 0.3% of Pbo subjects, 0.1% of PVR subjects and 0 of OSE subjects, and for BIL: 0.3% of Pbo subjects, 0.2% of PVR subjects and 0 of OSE subjects. No grade 2 or higher AP with at least one grade increase from BL was observed. No differences in reporting rates of hepatic adverse events were observed. The only consistent significant predictors of Grade 2 or higher ALT, AST or BIL levels were their corresponding baseline levels.