

**[150] - Effects of a Purine Nucleoside Phosphorylase Inhibitor, BCX4208, on the Serum Uric Acid Concentrations in Patients with Gout.**

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Purine nucleoside phosphorylase inhibitors (PNPi) are a novel approach to lowering serum uric acid (sUA) in patients with gout. The specific PNPi, BCX4208, has a 0.52 nM Ki for human PNP. This compound was studied in a randomized, placebo-controlled, double blind three week trial using oral doses of 40, 80, and 120 mg daily in 60 gout patients whose sUA was >8 mg/dL at baseline. Eligible subjects were followed weekly for sUA, safety labs (including lymphocyte subsets), and adverse events during treatment and for 4 weeks of follow-up.

56 males and 4 females (39W, 6B, 5 Pacific Islander, 4 Asian, 6 Other) meeting the ARA criteria for the diagnosis of gout completed the study. Mean (SD) age was 51 (12) years; mean weight was 108 (25) kg. Trial endpoints were: absolute reduction in sUA at 3 weeks, proportion of subjects with sUA <6.0 mg/dL, frequency of gout flares, safety, tolerability, and abbreviated first dose BCX4208 pharmacokinetics.

After 3 weeks of therapy, sUA was reduced by -2.7, -3.3, and -3.4 mg/dL in the 40, 80, and 120 mg/d dose groups of BCX4208, respectively, compared to -0.4 mg/dL in the placebo group ( $p < 0.001$ ). No placebo-treated subject achieved a sUA <6.0 mg/dL, whereas 33%, 36%, and 31% of the subjects on BCX4208 at 40, 80, and 120 mg/d, respectively, met this goal at 3 weeks ( $p < 0.05$ ). 33%, 57%, and 56% of the BCX4208-treated subjects met this goal at least once during the 3 weeks of treatment ( $p < 0.001$ ), and 38%, 60%, and 100% of subjects with baseline sUA <10 mg/dL met this goal at least once during therapy with the 3 respective dose levels ( $p < 0.001$ ). One gout flare (1/16) occurred in a subject on 120 mg/d, and two gout flares (one placebo- and one 80 mg/d-treated subject) occurred during the 4 week follow-up period. Lymphocyte subsets (CD4+, CD8+, CD20+, and CD56+ cells) were reduced 30 to 70% by all doses of BCX4208, without a clear dose-response relationship. No subject met pre-defined stopping criteria for lymphocyte subset cell counts during the treatment period. All subjects completed the study and adverse events were evenly distributed in the BCX4208 and placebo arms. There were no serious adverse events. Abbreviated pharmacokinetics on the first day of treatment with BCX4208 showed a dose-proportional increase in C<sub>max</sub> and AUC<sub>0-24</sub>.

BCX4208 at 40, 80, and 120 mg/day produced a prompt reduction in sUA in gout patients and achieved the therapeutic goal of < 6.0 mg/dL in up to one-half of the patients during a 3 week trial. The drug produced moderate reductions in lymphocyte subsets, but was well tolerated. PNP inhibition may represent a novel approach to the treatment of gout.

Keywords: gout, clinical trials, uric acid, BCX4208, Purine Nucleoside Phosphorylase Inhibition, Pharmacokinetics

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Halls B1 & B2

APS - ACR Poster Session A