Brincidofovir (CMX001) Dose and Plasma Exposure Correlates with Serum Alanine Aminotransferase Elevations

Tom Brundage1, Hervé Mommeja-Marin1, Marion Morrison1, Katherine Van Sickle1
1Clinical Research, Chimerix, Inc. Durham, NC

AASLD 2014
Boston, Massachusetts, November 2014

Introduction

Brincidofovir (BCV, CMX001) is an orally administered lipid conjugate nucleotide in Phase 3 clinical development for the prevention of cytomegalovirus (CMV) infection in hematopoietic stem cell transplant (HCT) recipients and for the treatment of adenovirus (AdV) infection. A database of ~1000 exposed patients supports the safety profile. Mild to moderate alanine aminotransferase (ALT) elevations have been observed in BCV clinical trials. Similar elevations occurred in toxicology studies but were without histopathological correlate. The relationship of BCV dose and BCV plasma concentrations to ALT concentrations were evaluated using data from two single-dose healthy volunteer studies, a food effect and bioavailability study and a thorough QTc study. Data were pooled across studies based on BCV treatment (placebo, 200 mg of BCV, and 350 mg of BCV).

Methods

• ALT concentrations were collected in all subjects prior to receiving a BCV dose and at regular intervals (Days -1, 1, 2, 4, 7, 14, 17, and as needed) for up to a median of 17 days following BCV dose.
• ALT values by day were analyzed for each individual subject using a standard PK software, WinNonLin, to assess time of max ALT (Tmax), maximum ALT (ALTmax). As a surrogate for total magnitude of ALT increase over time, an AUC from Day 0 to Day 14 was calculated (ALT AUC14) for each subject. In situations where a subject’s ALT increase resolved prior to Day 14, ALT AUC14 was imputed with AUCLast calculated from Day 0 to last ALT measurement.
• Subjects were sorted by BCV dose, and ALT parameters were compared using mixed effect models. Least square mean differences and ratios, with corresponding 90% confidence intervals, were calculated. Model details are as follows:
  • SAS 9.3, Proc Mixed
  • All models had treatment group as a fixed effect and subject as a random effect
  • All models were fitted using R-squared comparing model with and without covariates
  • ALT max and ALT AUC14 were compared using linear regression. BCV PK parameters were calculated using standard software, WinNonLin.
• A ratio of ALTmax versus ALTBaseline (ALT prior to dose) was calculated for each subject and summarized by BCV dose.

Results

The maximum ALT concentration that occurred in any individual subject was 96 IU/L in a placebo subject, 203 IU/L in a 200 mg subject, and 270 IU/L in a 350 mg subject. Elevations in both BCV groups were Grade 2 (>3× – 5× ULN). One 200 mg BCV subject with ALT increase showed initial improvement by Day 28, followed by recurrent ALT elevation, making attribution to BCV unlikely.

ALT Concentrations Post Placebo or BCV Dose

ALT max by Treatment Group

ALT AUC 14 by Treatment Group

ALT max Compared with BCV Cmax and BCV AUC

ALT AUC Compared with BCV Cmax and BCV AUC

Conclusions

• Brincidofovir treatment is associated with ALT elevations that occur at a median of 7 days post dose and are associated with BCV dose and BCV plasma exposure.
• Even at single doses 2-3.5× higher than the proposed therapeutic dose (100 mg), which is dosed twice weekly for the prevention of CMV infection, ALT elevations were typically ≤ Grade 2, asymptomatic, not associated with hyperbilirubinemia, and improved after BCV discontinuation.
• These observations are consistent with the lack histopathological findings in toxicology studies and are likely to indicate a pharmacological effect of BCV on ALT concentrations, instead of hepatocellular injury.

Acknowledgements

The authors gratefully acknowledge Maggie Anderson and Aaron Hanson for their management of the studies, Laurie Kielholz for management of bioanalytical and Tandem-RTP for conducting bioanalytical analysis.

Financial Disclosure

Tom Brundage, Hervé Mommeja-Marin, Marion Morrison, and Katherine Van Sickle are employees and share-holders of Chimerix, Inc.