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

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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).

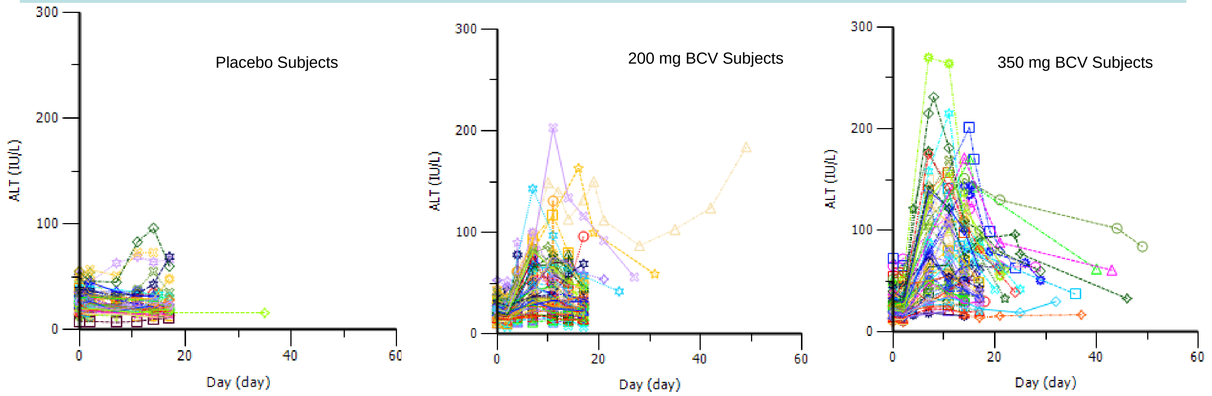
Methods

- 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 asses 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
  - 4 models are presented based upon 2 endpoints (ALTmax and ALT AUC14) and 2 scales (original and LN-transformed)
  - All models had treatment group as a fixed effect and subject as a random effect
  - A full model was run to include fixed effects for fed state and formulation; included in final model only if p<0.1 in full model
- ALT and BCV plasma exposure (Cmax and AUClast) for each subject 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.

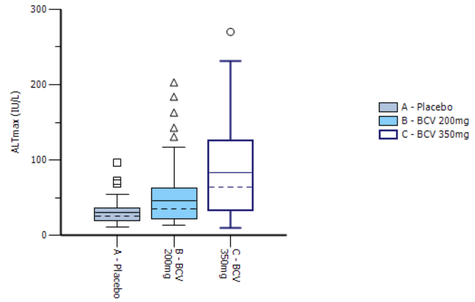
Results

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 (>3x – 5x 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.

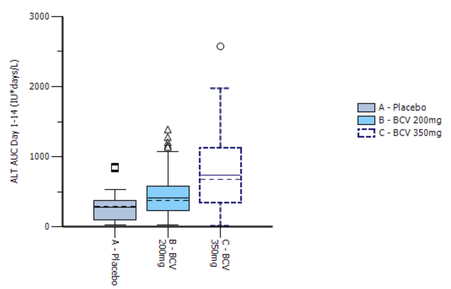
ALT Concentrations Post Placebo or BCV Dose



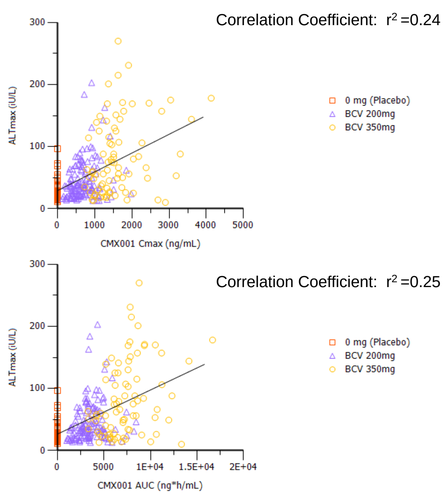
ALT max by Treatment Group



ALT AUC 14 by Treatment Group

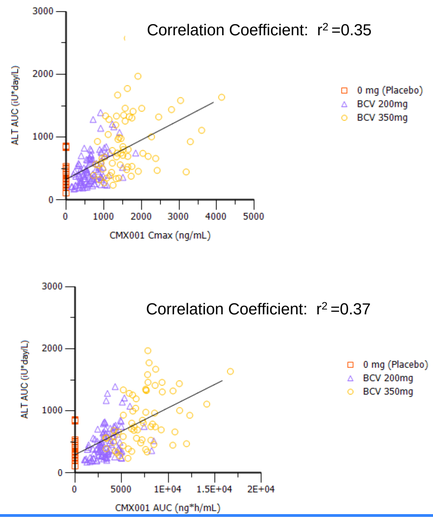


ALT max Compared with BCV Cmax and BCV AUC



A trend toward higher ALTmax and ALT AUC was observed in individual subjects with higher BCV Cmax and AUC (r^2= 0.24-0.37)

ALT AUC Compared with BCV Cmax and BCV AUC



ALT Parameters

ALT Parameter [Mean (%CV)]	Placebo	200 mg BCV	350 mg BCV
ALT baseline (IU/L)	27 (41%)	23 (35%)	26 (46%)
ALT max (IU/L)	31 (53%)	46 (72%)	83 (72%)
Ratio ALTmax / ALTbaseline	1.1 (19%)	2.0 (55%)	3.0 (62%)
ALT Tmax [1] (Days)	0 (0-17)	7 (0-49)	7 (0-18)
ALT AUC 14 (IU*Days/L)	280 (69%)	415 (67%)	737 (74%)

[1]Tmax: median (minimum – maximum)

After single dose of placebo, 200 mg BCV, and 350 mg BCV, mean ALTmax values were 31, 46, and 83 IU/L, respectively, representing mean 1.1, 2.0, and 3.0-fold increased relative to pre-dose values. Median Tmax occurred at day 7 for subjects in both BCV treatment groups.

Statistical Evaluation of ALT Values

ALT Parameter	Dose Group	Comparator Dose Group	Least Square Mean P-value	Least Square Mean (Ratio) P-Value
ALT max	350 mg BCV	200 mg BCV	<.0001	<.0001
	350 mg BCV	Placebo	<.0001	<.0001
	200 mg BCV	Placebo	0.0151	0.0007
ALT AUC14	350 mg BCV	200 mg BCV	<.0001	<.0001
	350 mg BCV	Placebo	<.0001	<.0001
	200 mg BCV	Placebo	0.0367	0.0584

ALTmax and ALT AUC14 were significantly higher following 350 mg BCV compared to 200 mg BCV or placebo (p<0.0001), and significantly higher following BCV 200 mg compared to placebo (p<0.03)

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 2-3.5x 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.

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