Exposure-Response Relationship of Cenicriviroc with Week 24 Virologic Outcomes in Treatment-Naïve HIV-1-Infected Adults with CCR5-Tropic Virus

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Background

- CCR5 (CCR5) is a novel, once-daily, potent, CCR5 and CCR2 antagonist that has recently completed Phase Ib evaluation for the treatment of HIV-1 infection in treatment-naïve adults (Study 202; NCT01338883).7
- The Week 4 virologic findings comparing CVC 100 mg and 200 mg with efavirenz (EFV), in combination with entecavir/tenofovir (FTC/TDF), demonstrated feasible tolerability for CVC and comparable virologic success (91.4% vs. 84.6%, FTC/TDF). CVC 150 mg and 200 mg with efavirenz (EFV), in combination with entecavir/tenofovir (FTC/TDF), demonstrated feasible tolerability for CVC and comparable virologic success (92.0% vs. 92.1%, FTC/TDF). Efavirenz (EFV), in combination with emtricitabine/tenofovir (FTC/TDF), was selected for CVC (75-76%) and FTC/TDF (71%).
- Virologic non-response was higher with CVC (52-54%) than with EFV (4%).

Methods

Study Design

- In Study 202, a double-blind, double-dummy study in HIV-1-infected, treatment-naïve adults with CCR5-tropic virus, subjects were randomized to receive CVC 100 mg or 200 mg daily, plus oral/emtricitabine/tenofovir (FTC/TDF) for 24 weeks.
- In conclusion, the Study 202 data suggest an exposure-response relationship with virologic outcomes, with

PK/PD Analyses

- A more pronounced trend toward improved virologic outcomes was observed with higher concentrations.
- When given with FTC/TDF in treatment-naïve HIV-1-infected adults, CVC was effective at daily doses of 100 mg and 200 mg.8
- A 2-compartmental population PK model was derived from the rich samples and subsequently used to predict individual CVC exposures from the sparse samples.
- To assess the relationship between CVC exposure parameters and Week 24 virologic outcomes (FDA Snapshot algorithm), individual average Caverage and minimum Cmin plasma CVC concentrations were predicted with the model and used to conduct PK/PD analyses.
- Cmin over 24 weeks of treatment (or for a shorter duration in the event of premature withdrawal).
- Cmin at Week 24 if no PK data were available at Week 24, the last predicted Cmin was carried forward.
- Virologic success was defined as a last on-treatment HIV-1 RNA value in the Week 24 window (between study days 158-182 inclusive) of <400 copies/ml, and no observed change in antiretroviral therapy prior to that time point.
- Exposures among responders were assessed in 110 subjects: CVC-treated subjects who prematurely discontinued the study for non-virologic reasons were excluded.

Results

- Summary of plasma CVC concentrations showed that steady-state concentrations were reached by Day 14 (in the subjects with rich sampling), and that levels were relatively constant through 24 weeks (in the subjects with sparse sampling data not read). Plasma CVC concentrations were generally data-dependent.

Predicted Cmin and Cavg vs Week 24 Virologic Outcomes

- CVC 100 mg and CVC 200 mg virologic response is shown in Figure 1. The median Cmin was slightly greater in subjects with virologic success compared to those with virologic non-success at Week 24 (55.6 vs. 39.2 ng/mL, respectively). (Table 1).
- The relationship between CVC 100 mg and Week 24 virologic response is shown in Figure 2. The median Cmin in virologic responders at Week 24 was approximately 35% lower than in subjects who experienced virologic success at Week 24 (46.3 vs. 74.9 ng/mL, respectively). (Figure 2; Table 1).
- A more pronounced trend toward improved virologic outcomes was observed with higher concentrations. Exposure.
- In conclusion, the Study 202 data suggest an exposure-response relationship with virologic outcomes, with predicted Week 24 virologic success rates were increased with higher concentrations from the sparse samples.
- A more pronounced trend toward improved virologic outcomes was observed with higher concentrations.
- Prevalence of virologic outcomes, again exposure-response assessments.
- Cmin Breakpoint

Classification and Regression Tree (CART) Analysis

- A CART analysis was performed to further investigate the association between Cmin, and virologic outcomes, again exposure-response.
- A statistically significant split occurred at a Cmin value of 47.8 ng/mL. (Figure 3). (Table 1).
- 67 subjects had Cmin values ≥47.8 ng/mL, and the proportion of virologic non-responders in this subset was 7.5%.
- 34 subjects had Cmin values <47.8 ng/mL, and the proportion of virologic non-responders in this subset was 29.4%.

Predicted Cmin Data for CVC 100 mg and 200 mg Doses

- When the PK model was used to predict Cmin data for both doses of CVC, it was shown that 50% of subjects receiving CVC 100 mg had a Cmin value of 50 ng/mL, compared to only 10% of subjects receiving CVC 200 mg (Figure 4).

CVC Exposure in Subjects with Emerging NRTI Resistance-Associated Mutations

- An exploratory pharmacological assessment was conducted in the CVC-treated subjects who met protocol-defined antiretroviral failure at any time during the study. Subjects who had borderline virologic response to nucleoside reverse transcriptase inhibitor (NRTI) resistance-associated mutations.
- All emerging primary NRTI mutations occurred at codon 184. In 4 of 5 subjects with emerging substitutions at codon 184, predicted Cmin values were below 50 ng/mL.

Conclusions

- When given with FTC/TDF in treatment-naïve HIV-1-infected adults, CVC was effective at daily doses of 100 mg and 200 mg.8
- PK/PD analysis of the Week 24 virologic findings comparing CVC 100 mg and 200 mg with efavirenz (EFV), in combination with entecavir/tenofovir (FTC/TDF), demonstrated feasible tolerability for CVC and comparable virologic success (91.4% vs. 84.6%, FTC/TDF).
- Four of the five CVC-treated subjects with protocol-defined virologic failure (34%) at any time during the study) and emerging NRTI resistance-associated mutations had Cmin ≤50 ng/mL.
- Predictions of Cmin for the two CVC dose levels showed that there were fewer subjects with Cmin ≤50 ng/mL at the 200 mg dose level than at the 100 mg dose level.
- Allopregest is a novel, once-daily, potent, CCR5 and CCR2 antagonist that has recently completed Phase Ib evaluation for the treatment of HIV-1 infection in treatment-naïve adults (Study 202; NCT01338883).7
- The Week 4 virologic findings comparing CVC 100 mg and 200 mg with efavirenz (EFV), in combination with entecavir/tenofovir (FTC/TDF), demonstrated feasible tolerability for CVC and comparable virologic success (91.4% vs. 84.6%, FTC/TDF). CVC 150 mg and 200 mg with efavirenz (EFV), in combination with entecavir/tenofovir (FTC/TDF), demonstrated feasible tolerability for CVC and comparable virologic success (92.0% vs. 92.1%, FTC/TDF). Efavirenz (EFV), in combination with emtricitabine/tenofovir (FTC/TDF), was selected for CVC (75-76%) and FTC/TDF (71%).
- Virologic non-response was higher with CVC (52-54%) than with EFV (4%).
- The current preclinical pharmacokinetics/pharmacodynamics (PK/PD) analysis of the Phase 2b study was carried out to assess the PK of CVC, using a population approach, and to determine the relationship between CVC exposure and virologic outcomes at Week 24.

Note: The Week 24 virologic findings from the Phase 2b study will be presented at the conference (Paredes et al., Abstract P147).

References:

1. Allopregest. Alloquie Therapeutics, Inc., San Francisco, CA, USA, 2013.2. Paredes et al. Preclinical Pharmacokinetics/pharmacodynamics (PK/PD) analysis of the Phase 2b study was carried out to assess the PK of CVC, using a population approach, and to determine the relationship between CVC exposure and virologic outcomes at Week 24.

Figure 4. Predicted Minimum Plasma CVC Concentrations (predicted Cmin) vs Week 24 Virologic Outcomes.