

Cabotegravir Stearate (XVIR-110) an Integrase Strand Transfer Inhibitor (InSTI) Prodrug Provides Ultra-Long-Acting Cabotegravir Exposures

656

Brian P. Kearney¹, Brady Sillman², Howard E. Gendelman², Benson Edagwa², Leigh Ann Burns-Naas³, Alborz Yazdi¹

¹Exavir Therapeutics, Inc., Omaha, NE, USA; ²University of Nebraska Medical Center, Omaha, NE, USA; ³Magnolia Toxicology Consulting, LLC, Traverse City, MI, USA.

BACKGROUND

- Adherence is a major factor for the success of treatment with highly effective antiretroviral (ARV) therapies (HAART) or the long-term success of pre-exposure prophylaxis (PrEP)
- Recent ARV development efforts have focused on creating long-acting (LA) agents and include use of parenteral (i.e., intramuscular (IM) or subcutaneous (SQ)) dosing
- Currently available agents have limitations due to suboptimal dosing frequency and both acute & long-lived injection site reactions (ISRs) that adversely impact tolerability and reduce patient acceptability
- Cabotegravir (CAB) is a potent HIV integrase inhibitor (InSTI) currently available as cabotegravir extended-release injectable suspension (CAB-LA), administered IM by healthcare providers monthly or bi-monthly as monotherapy for PrEP or as part of a combination treatment for HAART
- XVIR-110 is a nanocrystalline formulation of the novel CAB prodrug cabotegravir stearate (NM2CAB) with unique physicochemical properties designed to achieve an ultra-long-acting CAB PK profile to enable less frequent dosing

OBJECTIVE

- To evaluate the non-clinical pharmacokinetic (PK) profile of NM2CAB and/or CAB from XVIR-110 in rats & dogs and to comparatively assess the acute ISR & PK profile of XVIR-110 versus commercially available CAB-LA in rats

METHODS

Pharmacokinetic Study of XVIR-110 in Rats & Dogs

- Male Sprague-Dawley rats (N=4 to 6/cohort) and beagle dogs (N=3/cohort) were administered a single dose of XVIR-110 IM (thigh muscle(s) of hind limb) at NM2CAB doses of 75, 185 (single & 2-split inj.) and 638 mg/kg as 2-split inj. (representing 45, 110, & 382 mg/kg-eq. of CAB) in rats and at 40 & 151 mg/kg (representing 24 & 90 mg/kg-eq. of CAB) in dogs
- PK (CAB in rats, NM2CAB & CAB in dogs) were assessed at multiple timepoints up to 12 months or until CAB concentrations fell to less than the protein binding-adjusted IC₉₀ (PB-IC₉₀) of 166 ng/mL using validated UPLC-MS/MS methods

Comparative ISR & PK Study of XVIR-110 vs. CAB-LA in Rats

- Male Sprague-Dawley rats (N=15/cohort) were administered, via the caudal thigh muscle: XVIR-110 at a dose of 75 mg/kg (representing 45 mg/kg-eq. of CAB), vehicle control, or CAB-LA at a dose of 45 mg/kg on Day 1 of study
- Animals (N=3/day) were euthanized & necropsied on Day 3, 7, 14, 28 & 86 of study; collected tissues were embedded in paraffin, processed by routine histologic methods, and stained with hematoxylin & eosin
- Visual & histopathologic assessments were conducted at all necropsy timepoints by a board-certified veterinary pathologist
- PK of the prodrug NM2CAB & CAB were evaluated at all necropsy timepoints for comparative assessment of CAB from XVIR-110 vs. CAB-LA at an equivalent CAB dose

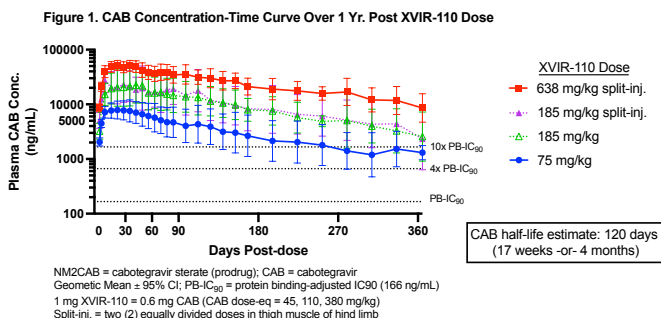
XVIR-110 is a novel cabotegravir prodrug that achieves and maintains sustained cabotegravir exposures which support its ongoing development as a potential ultra-long-acting InSTI for use in PrEP and HIV treatment

RESULTS

Pharmacokinetic Study of XVIR-110 in Rats & Dogs

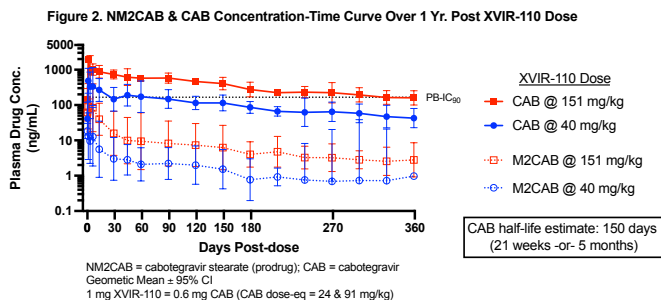
In S-D Rats (Figure 1)

- CAB achieved peak (C_{max}) conc. within 21 to 42 days (observed T_{max})
- Split- vs. single-injection site (180 mg/kg XVIR-110 dose) cohorts resulted in modestly (20-30%) higher CAB C_{max} & early area under the curve (AUC_{0-28 days}) but a similar extended CAB concentration-time profile
- The estimated elimination half-life of CAB from XVIR-110 is ~120 days (~17 weeks or ~4 months) and provided mean CAB concentrations greater than 10x & 4x the PB-IC₉₀ for more than 6 months & 1 year at all dose levels



In Beagle Dogs (Figure 2)

- Both the prodrug NM2CAB & CAB achieved C_{max} on Day 1 following injection (observed T_{max}); NM2CAB prodrug was present at low concentrations (mean value < 10 ng/mL) 2 to 6 weeks post-dose at XVIR-110 doses of 40 & 151 mg/kg, respectively
- The estimated elimination half-life of CAB was ~150 days (~21 weeks or ~5 months) and maintained mean CAB concentrations above the PB-IC₉₀ for 3 & 6 months following XVIR-110 doses of 40 & 151 mg/kg, respectively



RESULTS (continued)

Comparative ISR & PK Study of XVIR-110 vs. CAB-LA in S-D Rats

- Test article was visible in the injection site of all or most animals that received XVIR-110 or CAB-LA on Days 3, 7, 14, & 28 of study; no test article was grossly visible of any animal on Day 86
- Day 3: Microscopic findings in XVIR-110 treated animals consisted only of hemorrhage at the injection site; CAB-LA treated showed hemorrhage, necrosis, mixed cell inflammation, neutrophilic inflammation, and foreign material accumulation
- Day 7: No microscopic findings at the injection site for XVIR-110 vs. necrosis, mixed cell inflammation, granulomatous inflammation, foreign material accumulation, and multinucleated giant cell infiltration in animals treated with CAB-LA
- Day 14: Microscopic findings of granulomatous inflammation, foreign material accumulation, and multinucleated giant cell infiltration in 1 of 3 animals dosed with XVIR-110; in rats treated with CAB-LA necrosis, mononuclear cell inflammation, granulomatous inflammation, foreign material accumulation, and multinucleated giant cell infiltration observed
- Day 28: Microscopic findings in both XVIR-110 or CAB-LA consisted of necrosis, granulomatous inflammation, foreign material accumulation, and multinucleated giant cell infiltration
- Day 86: No microscopic findings were seen of any animal treated with XVIR-110 or CAB-LA
- In summary, XVIR-110 was associated with fewer acute microscopic changes at the injection site than CAB-LA; changes were generally similar at Day 28, were reversible and were no longer observed in either group at Day 86 of study

PK Assessment

- XVIR-110 resulted in lower C_{max} & AUC_{0-85days} but achieved substantially prolonged CAB concentrations vs. CAB-LA at an equivalent CAB dose
- C_{max} ratio: 13% (8.33 vs. 63.6 mcg/mL); AUC_{0-85days} ratio: 25% (11,500 vs. 46,200 mcg*hr/mL)
- Estimated elimination half-life ratio: 400% (1340 vs. 329 hr)

CONCLUSIONS

- XVIR-110 (cabotegravir stearate (NM2CAB) nanocrystal formulation), a novel prodrug of CAB results in an ultra-long-acting PK profile of CAB following a single IM injection
- XVIR-110 demonstrated sustained CAB exposures when compared to commercially available CAB-LA and evidence of less acute ISRs at an equivalent IM CAB dose
- Less frequent administration of XVIR-110 may offer an improved CAB PK profile over CAB-LA that would be desirable for pre-exposure prophylaxis (PrEP) or in treating patients with known adherence challenges

ADDITIONAL KEY INFORMATION

Author Contact Information: brian@exavirtx.com

Acknowledgments & Disclosures

- Funded in part by NIH SBIR grant 1R44AI179564-01
- These studies were funded by Exavir Therapeutics, Inc.
- Kearney & Yazdi are employees, Gendelman & Edagwa are co-founders & Burns-Naas is a consultant to Exavir Therapeutics, Inc