Poster Abstract P2

Long-acting entecavir prodrugs for HBV treatment

Anil K. Gupta, Anders M. Eliasen, Arnab K. Chatterjee
Calibr at Scripps Research, California, USA

Background
Hepatitis B virus (HBV) is a hepatotropic virus that can establish persistent, chronic infection through immune anergy, affecting >250 million people globally. Current first-line therapies require lifelong, daily administration, making patients susceptible to missed treatments and disease relapse. As adherence to therapy is imperative to achieve and maintain viral suppression, a long-acting HBV therapy with minimal dosing requirements would significantly improve treatment outcomes.

Methods
We applied our LAI platform to develop a LAI based on prodrugs of an approved NARTI i.e. Entecavir (ETV) to improve adherence and limit viral breakthrough and disease progression in patients with HBV. More than 30 prodrugs were synthesized and subjected to formulation development and subsequent rodent and non-rodent PK studies.

Results
ETV prodrug mCEC540 identified as early lead for solution-based depot strategy, with lower Cmax and favorable IM release in rats relative to parent entecavir. On the aqueous suspension front, lead prodrug mCMQ657 provided differentiated PK profile in dogs with extended duration of therapeutic exposure relative to parent entecavir for more than 3 months after a single intramuscular injection dose.

Conclusions
Lead Prodrugs of ETV have been determined to provide plasma levels higher than therapeutic levels for more than 3 months, thereby providing exciting opportunities for improving adherence via LAI approach.