The available treatments for chronic hepatitis B infections include nucleoside/tide analogs (NAs) and pegylated interferon-alpha (PegIFN-alpha). The inability of these approved treatments to achieve a functional cure for HBV infection warrants the discovery of antivirals with novel mechanisms. We believe that the combination of novel agents with different mechanisms of action will result in increased HBV cure rates with reduced duration of therapy. AB-452 is a HBV RNA destabilizer that promotes vRNA degradation and thus affects production of HBV proteins, encapsidation of pgRNA, viral DNA replication and virion release. It also shows additive to synergistic effects in inhibiting HBV DNA replication when combined with other anti-HBV agents in vitro and in vivo. AB-452 is specific to HBV as evidenced by its inactivity against a panel of RNA and DNA viruses. AB-452 significantly inhibits both HBV replication and antigenemia in an immunocompetent AAV based mouse HBV model (1-2).

**Background**

**Objectives**

To demonstrate AB-452: i) antiviral activities in vitro, ii) mechanism in the promotion of HBV RNA degradation, iii) antiviral selectivity and iv) complementary mechanism with capsid inhibitors.

**Results**

1. AB-452 has broad anti-HBV profile relative to ETV

   In HepG2.2.15 cells, AB-452 inhibits HBsAg, HBeAg and HBV DNA production with EC50 values ranging from 0.3 to 2.9 nM.

2. AB-452 affects multiple stages of viral life cycle

   Distinct from NA and Capsid inhibitors, AB-452 affects production of HBV proteins, encapsidation of pgRNA and viral DNA replication.

3. AB-452 reduces viral RNAs dose dependently

   AB-452 (nM) translates to pgRNA degradation.

4. HBV RNA degradation by AB-452 observed at 8 hours and beyond

   RNA shortening is observed at 2hrs and beyond, RNA body degradation becomes more apparent at 8hrs and beyond.

5. AB-452 treatment leads to RNA shortening and RNA body degradation

   pgRNA T1/2 is reduced from 4.5hr to 2.4hr (via qRT-PCR).

6. AB-452 shortens the poly (A) tail of HBV RNA prior to the RNA body degradation

   More than 80% of HBV RNA ends at nucleotides 1935-1937 (TA/C).

7. AB-452 inhibits HBV HBsAg derived from integrated HBV DNA

   HBV patient-derived Alexander cells with multiple copies of integrated HBV genome that secrete functional HBsAg (4-6).

8. Stem loop alpha (SLα) of HBV post-transcriptional element (PRE) is required for AB-452 activity, but HBV protein is not required for AB-452 activity

9. AB-452 appears to reduce HBV RNA in the cytosol and nucleus simultaneously

   pgRNA and sRNA are degraded in both cytoplasm and nucleus (70 nM AB-452).

10. AB-452 in combination with capsid inhibitor enhances pgRNA degradation

**Conclusions**

- AB-452 represents a novel class of antivirals with broad, potent anti-HBV effects.
- AB-452 is a HBV RNA destabilizer, promoting vRNA degradation and thus affecting production of HBV proteins, encapsidation of pgRNA, viral DNA replication and virion release.
- AB-452 can inhibit HBsAg derived from both integrated HBV DNA and cccDNA.
- AB-452 induces HBV RNA shortening and RNA body degradation.
- HBV PRE, but not HBV protein, is essential to AB-452 activity.
- AB-452 mediated HBV RNA degradation occurs in both the nucleus and cytosol.
- AB-452 treatment combined with capsid inhibitor(s) promotes the degradation of HBV pgRNA and splicing RNAs.
- Combining AB-452 with other anti-HBV agents, especially capsid inhibitors and NAs, may further inhibit HBV DNA replication and viral antigen production to achieve a higher cure rate with a defined and shortened treatment duration.

**References**