Bemnifosbuvir is a potent HCV NS5B inhibitor with a favorable antiviral profile and high resistance barrier
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INTRODUCTION
- Bemnifosbuvir (BEM) is an orally bioavailable, modified guanosine nucleotide produg under development for the treatment of people with COVID-19 (as monotherapy) or HCV infections (combined with razavir).
- BEM, a direct-acting antiviral (DDA), is a hemisulfate salt of AT-511, a phosphoramidate produg that is converted after multi-step activation to the active 5'-triphosphate metabolite, AT-9010.
- AT-511 selectively targets the RNA-dependent RNA polymerase (RdRp), a nonstructural protein (NS5B) essential for viral replication in flaviviruses, such as HCV.
- AT-511 is a potent inhibitor of the HCV genotype (GT)1b and high resistance barrier.

RESULTS
- Since a previous attempt to select resistance failed with AT-9010 (GT1b), only single or linked mutants that emerged during GT1a replication were used. Ten HCV GT1a replicon colonies survived, with no obvious toxicities observed at the highest dose tested.
- AT-9010 selectively targets the RNA-dependent RNA polymerase (RdRp), a nonstructural protein (NS5B) essential for viral replication in flaviviruses, such as HCV.
- The potency of BEM (AT-511) to inhibit viral replication of HCV genotypes, which is ~10- to 20-fold more active than the standard of care (SOF).
- AT-9010 is a potent inhibitor of the HCV genotype (GT)1b and high resistance barrier.

METHODS
- In vitro resistance selection was conducted in the presence of G418 and gradually increasing concentrations of AT-511, and cells may impact the efficacy of treatments for HCV infection.
- We performed pooled passage experiments for BEM (AT-511) resistance selection in HCV GT1a and GT1b replicon cells.

CONCLUSIONS
- • CC23H was found to be the primary BEM RAS in GT1b and multiple substitutions at other NS5B regions were required to confer meaningful resistance, suggesting BEM provides a very high barrier to resistance.
- • In addition, BEM and SOF did not display cross-resistance in a panel of NS5B RASSs tested in vitro.
- • BEM is currently being evaluated in combination with razavir, a highly potent pan-genotypic NS5A inhibitor, in a Phase 2 clinical trial (NCT05904470).

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Disclosures
QH, SG, DC, NA, and JS are employees of and may own stock in Atea Pharmaceuticals, Boston, MA, USA.

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