Update on Safety and Efficacy in the REP 401 Protocol: REP 2139-Mg or REP 2165-Mg Used in Combination with Tenofovir Disoproxil Fumarate and Pegylated Interferon Alpha-2A in Treatment Naïve Caucasian Patients with Chronic HBeAg Negative HBV Infection

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INTRODUCTION

The nucleic acid polymer (NAP) REP 2139 clears serum HBsAg and improves the efficacy of immunotherapy to establish functional control of chronic HBV infection and HBV / HDV co-infection. The REP 401 protocol (NCT02565719) is a randomized controlled trial assessing the safety and efficacy of REP 2139 and a REP 2139 derivative with improved tissue clearance (REP 2165) in combination with tenofovir disoproxil (TDF) and pegylated interferon-alpha-2a (pegIFN) in treatment naïve patients with chronic HBeAg negative HBV infection.

RESULTS

Twenty weeks of lead-in TDF (300mg PO qD) is followed by randomization (1:1) into experimental and control groups (Table 1). The experimental group will receive 24 weeks of TDF (300mg PO qD), peg-IFN (180μg SC qW) and REP 2139 or REP 2165-Mg (1:1, 250 mg IV infusion qW) (Table 2). The control group will receive 24 weeks of TDF + peg-IFN but will crossover to 48 weeks of experimental therapy in the absence of any, in a 3 by 2 array. HBV RNA and HBsAg (Fujiprot Lumipulse®) were determined from frozen serum samples at DDL Diagnostic Laboratory (Rijswijk, The Netherlands) were determined from frozen serum samples at DDL Diagnostic Laboratory (Rijswijk, The Netherlands). Table 1: Pre-treatment demographics in the REP 401 protocol.

Table 2: REP 2139 versus REP 2165.

Table 3: Serum transaminase flares (A) and liver synthetic function (B) in the REP 401 protocol.

Table 4: Pre-exposure to pegIFN suppresses evolution of transaminase flares with NAP-mediated HBsAg reduction.

Table 5: Analysis of changes in HBV RNA and HBcAg.

CONCLUSIONS

• REP 2139 and REP 2165 continue to demonstrate well tolerated elimination of HBsAg in most patients.

• PegIFN therapy is associated with dramatic elevations in anti-HBs and transaminase flares only in the absence of HBsAg.

• Transaminase flares occur in the absence of altered liver synthetic function, suggesting these flares are therapeutic in nature and reflect elimination of infected hepatocytes and/or hepatocytes harbouring integrated HBsAg.

• Pre-exposure to pegIFN does not affect clearance of HBsAg by NAPs or evolution of anti-HBs but transaminase flares are substantially reduced, suggesting that suppression of the immune response in the liver may become more pronounced with continued pegIFN exposure.

• Pre-treatment levels of HBsAg are not related to HBV DNA, HBV RNA or HBsAg levels. Moreover, HBsAg levels do not change during TDF/pegIFN treatment when significant reductions in HBV RNA and HBcrAg do occur, suggesting the bulk of circulating HBsAg is derived from integrated HBsAg in HBsAg negative patients.

• TDF may also suppress cccDNA activity, either by preventing replenishment of cccDNA or via a direct immunostimulatory activity.

ACKNOWLEDGEMENTS

This work was supported by Replicor Inc.

REFERENCES


ACKNOWLEDGEMENTS


DISCLOSURES

MB and AV are employees of and shareholders in Replicor Inc. The other authors have nothing to disclose.

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