GALIDESIVIR, A BROAD-SPECTRUM ADENOSINE ANALOG DIRECT-ACTING ANTIVIRAL DRUG, ABROGATES VIREMIA IN RHESUS MACAQUES CHALLENGED WITH ZIKA VIRUS

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Background: Zika virus (ZIKV) was first isolated from a sentinel rhesus monkey in 1947. ZIKV infection in humans is associated with serious neurological complications. Guillain-Barré syndrome and pediatric microcephaly have been reported to overlap with ZIKV endemicity in South America. No antivirals or protective vaccines are available. Galidesivir (BCX4430) an adenosine analogue is a potent viral RNA-dependent RNA polymerase inhibitor with demonstrated broad-spectrum antiviral activity.

Methods: We have conducted a pre-clinical study in rhesus monkeys to assess the safety and efficacy of Galidesivir against ZIKV infection. Fifteen animals were subcutaneously challenged with 1x10^5 TCID50 of a Puerto Rican ZIKV isolate. Animals were distributed into 3 groups (n=5/group). Ninety minutes after challenge, group 1 received intramuscular (I.M.) doses of 100 mg/kg BCX4430 BID on Day 0 followed by 25mg/kg BID for 9 additional days. Group 2 received only 100 mg/kg BCX4430 IM BID on Day 0. Group 3 received vehicle only. We followed multiple endpoints, including ZIKV RNA levels in plasma, urine, saliva, and cerebrospinal fluid. Immune activation, complete blood counts, chemistries and BCX4430 pharmacokinetics were also monitored longitudinally throughout the study.

Results: Galidesivir administration was well-tolerated. All control animals developed high-level viremia by day 2 post infection. Monkeys in group 1 did not develop any detectable plasma viremia. Monkeys in group 2 were partially protected; two animals from this group had detectable plasma ZIKV RNA, but the onset was delayed and magnitude reduced compared to controls. All control monkeys (group 3) had readily detectable ZIKV RNA in CSF, saliva and urine. Animals in groups 2 and 3, had sporadically detectable ZIKV in CSF, urine and saliva and viral shedding was markedly reduced compared to controls. ZIKV infection elicited immune responses in BCX4430-treated monkeys; these were diminished compared to controls.

Conclusions: Galidesivir dosing in rhesus monkeys was well-tolerated and offered significant protection against ZIKV challenge. These results warrant further study. Experiments on dose optimization and potential therapeutic regimens are planned.