One month GLP toxicology study in cynomolgus monkeys

The objectives of this GLP study were to determine the maximum tolerated dose of SZN-043 and to identify any potential toxicity of SZN-043 in cynomolgus monkeys. A single IV bolus injection twice weekly for 29 days to cynomolgus monkeys, but did not decompensation of alcoholic liver disease that develops in alcoholic hepatitis (AH) is a serious form of acute inflammation and is characterized by a severe form of liver failure. This disease is often fatal, with a mortality rate of up to 50% within the first year. The pathogenesis of AH is complex, involving a variety of factors, including genetic predisposition, metabolic perturbations, and exposure to alcohol. Alcoholic hepatitis is characterized by a proinflammatory and prothrombotic state, which leads to injury and necrosis of hepatic cells. This results in the release of DAMPs (damage-associated molecular patterns) and ATP, which activate immune cells and promote hepatic injury.

In the current study, the focus was on the evaluation of the safety and pharmacology of SZN-043 in cynomolgus monkeys. The study was conducted in accordance with the GLP guidelines and was designed to determine the maximum tolerated dose (MTD) of SZN-043. The study was conducted in three phases: a pretreatment phase, a dosing phase, and a recovery phase.

**Methods**

- **Animals**: Cynomolgus monkeys, aged 23–90 months, were allocated to study groups as shown in Table 1. The animals were dosed with SZN-043 twice weekly via IV injection for a total of 9 doses. The dosing regimen was based on the results of a GLP study conducted in mice.
- **Dosing Regimen**: The dose was adjusted based on the results of a GLP study conducted in mice. The maximum tolerated dose was determined based on the results of this study.
- **Clinical Pathology**: The increase in ALP that was attributed to binding of SZN-043 to ASGR1 was largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Toxicokinetics**: The increase in ALP was an expected observation based on the binding of SZN-043 to ASGR1, which is largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Immunogenicity (anti-drug antibody)**: No anti-drug antibodies were observed in the cynomolgus monkeys following the IV injection of SZN-043.

**Results**

- **Clinical Pathology**: The increase in ALP was an expected observation based on the binding of SZN-043 to ASGR1, which is largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Toxicokinetics**: The increase in ALP was an expected observation based on the binding of SZN-043 to ASGR1, which is largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Immunogenicity (anti-drug antibody)**: No anti-drug antibodies were observed in the cynomolgus monkeys following the IV injection of SZN-043.

**Conclusions**

- **Clinical Pathology**: The increase in ALP was an expected observation based on the binding of SZN-043 to ASGR1, which is largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Toxicokinetics**: The increase in ALP was an expected observation based on the binding of SZN-043 to ASGR1, which is largely responsible for the elimination of ALP from serum; thus, depletion of ASGR1 by SZN-043 prevents ALP clearance.
- **Immunogenicity (anti-drug antibody)**: No anti-drug antibodies were observed in the cynomolgus monkeys following the IV injection of SZN-043.

**Based on the results of the studies, the NOAEL was 125 mg/kg which was the highest administered dose tested**