Study Design: Single center, randomized, double-blind, placebo-controlled, two period cross-over study.

Subjects: 14 healthy male and female subjects, aged between 18 and 65 years with a BMI of 18.0 – 30 kg/m², were enrolled.

Treatment A: 30 min iv infusion of placebo (100 mL) followed by a 3 h infusion of clazosentan (15 mg/h) 15 mg/h

Treatment B: 30 min iv infusion of rifampin (600 mg/100 mL) followed by a 3 h infusion of clazosentan (15 mg/h)

PK blood sampling: Blood samples were collected at pre-dose and every 30 min from the start of clazosentan infusion and 2, 5, 10, 15, 30, 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 21 h after the stop of clazosentan infusion.

RESULTS – SAFETY AND TOLERABILITY

Overall, 13 of 14 exposed subjects reported 44 treatment-emergent AEs. The incidence of AEs was higher following treatment B (12 subjects, 29 AEs) compared to treatment A (7 subjects, 15 AEs).

Following i.v. infusion of clazosentan, the most common AE was headache (10 out of 14 subjects, 14 AEs) with a higher incidence in treatment B (8 subjects, 9 AEs) compared to treatment A (5 subjects, 5 AEs). The incidence and frequency of AEs commonly reported after clazosentan infusion, i.e., nausea and vomiting, were also higher following treatment B compared to treatment A. All AEs resolved without sequelae.

No clinically relevant changes in clinical laboratory, vital signs, and body weight were determined.

CONCLUSIONS

- Following administration of a single i.v. dose of rifampin, exposure to clazosentan was increased by 3 – 4 fold and Vss and CL were decreased by 2.4– and 3.9 fold, respectively. The t1/2 of clazosentan was not affected by rifampin.
- Clazosentan is a substrate of the OATP1B1/1B3 transporters
- Clazosentan (15 mg for 3h) administered after rifampin or its matching placebo was safe and tolerated.