A Regional Gastrointestinal Absorption Study of the HCV NS3 Protease Inhibitor SCH 900518 in Healthy Volunteers


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Abstract

Background: SCH 900518, a novel orally delivered protease inhibitor, demonstrates potent antiviral activity against HCV infection in vitro and in vivo. This study investigated the relative bioavailability of SCH 900518, when delivered to the small bowel and ascending colon, in comparison to the standard oral route of administration.

Methods: This was a randomized, crossover, open-label study of SCH 900518 delivered in healthy volunteers. The study employed the Enterion™ capsule system, a unique drug delivery capsule device that delivers a capsule via its radioisotope port (receives external activation signal) to key regions of the human GI tract (Figure 1). The primary objective was to investigate the relative bioavailability of SCH 900518, when delivered to the small bowel and ascending colon. SCH 900518 was delivered to the colon using a history-based pattern of transit and activation of the Enterion™ capsules in this study.

Results: The site and extent of absorption of SCH 900518 were detected following delivery to the colon. Delivery of the micronized formulation of SCH 900518 to the colon resulted in no detectable concentrations of SCH 900518 (microemulsion) were similar following administration of an IR formulation and treatment of the AC. SCH 900518 (microemulsion) to the distal small bowel (DSB), Enterion™ delivery of SCH 900518 (microemulsion) in the AC was assessed to be the least effective site of delivery, with 99.2% absorption (proximal small bowel [PSB], distal small bowel [DSB], and ascending colon [AC]).}

Conclusions

• Efficient suppression of HCV viral replication is achieved through sustained maintenance of plasma drug levels and exposure throughout the gastrointestinal (GI) system may be beneficial.

• SCH 900518 (MMN) absorbed when administered after oral administration of an IR formulation; delivery to the PSB, DSB, and AC. SCH 900518 (MMN) was absorbed after delivery to the colon than they were after administration of IR formulation.

• Rate and extent of absorption of SCH 900518 (MMN) were lower after delivery to the DSB compared with administration of an IR formulation.

• Absorption of SCH 900518 (MMN) after delivery to the PSB was similar to that of the administration of the IR formulation. SCH 900518 (MMN) was absorbed after delivery to the colon than they were after administration of IR formulation.

• All other treatment-emergent AEs occurred in 1 or fewer subjects.

• No deaths or serious AEs and all clinically significant changes occurred in laboratory or hemoglobin parameters, vital signs, or electrocardiograms.

• SCH 900518 (MMN) absorption after delivery to the PSB was similar to that of the administration of the IR formulation. SCH 900518 (MMN) was absorbed after delivery to the colon than they were after administration of IR formulation.

• Rate and extent of absorption of SCH 900518 (MMN) were lower after delivery to the colon than they were after administration of IR formulation.

• Absorption of SCH 900518 (MMN) was slightly lower after delivery to the PSB compared with administration of the IR formulation.

• No deaths or serious AEs and all clinically significant changes occurred in laboratory or hemoglobin parameters, vital signs, or electrocardiograms.