A Randomized, Double-blind, Placebo-Controlled, Single-, Ascending-, Oral-Dose Safety, Tolerability and Pharmacokinetic Study of SP-304 in Healthy Adult Male and Female Volunteers

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ABSTRACT

Purpose: SP-304 is a synthetic analog of uroguanylin, a natriuretic hormone that regulates ion and fluid transport in the GI tract. The compound is a new member of a novel class of non-systemic drugs for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C) and other GI diseases. Orally administered SP-304 binds to and activates guanylate cyclase C (GC-C), expressed on the epithelial cells lining the GI mucosa. Activation of GC-C stimulates intracellular cyclic GMP synthesis, resulting in activation of cystic fibrosis transmembrane conductance regulator (CFTR), which leads to fluid secretion into the GI lumen.

Methods: A double-blind, placebo-controlled, randomized single, oral, ascending dose (0.1 mg to 48.6 mg) study was performed in 71 healthy volunteers. Subjects were evaluated for safety, tolerability, PK and PD effects of SP-304 in healthy volunteers.

Results: SP-304 was well-tolerated at all doses and no SAEs were observed throughout the study. No measurable systemic absorption of orally administered SP-304 occurred at all dose levels studied (0.1 mg to 48.6 mg; validated SP-304 serum assay sensitive down to 10 ng/ml). Although this trial was not powered for statistical significance, SP-304 appeared to decrease the time to first bowel movement and elicited an increase in the post-dose BSFS versus placebo.

Conclusions: SP-304 was well-tolerated at all doses studied (0.1 mg to 48.6 mg) and exhibited pharmacodynamic activity in healthy volunteers with no detectable systemic absorption. These clinical data support advancing this novel analog of uroguanylin for further clinical development to treat patients with CC and IBS-C.

Purpose: The purpose of this was to characterize the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of SP-304 in healthy volunteers.

Inclusion Criteria:
- Healthy male or female, between 18 and 64 years of age with a body mass index (BMI) between 18 and 29 kg/m²
- Able to understand and give written informed consent
- Willing to abstain from and have no need for supplemental fiber 30 days prior to study entry

Exclusion Criteria:
- Any pre-existing medical condition considered clinically significant by the Principal Investigator (PI)
- Any significant abnormal laboratory results at Screening
- Participation in a clinical trial using an investigational drug within a period of 36 hours pre-dose through 48-hours post-dose
- Taken any class of phosphodiesterase inhibitors within 3 days prior to Day 1 dosing
- Any episode of abnormal bowel habit (e.g., constipation or diarrhea) within 30 days prior to study entry

Methods:
- Subjects completed a 7-day bowel movement diary during the 14-day screening period
- 7 consecutive days post-dose
- Bristol Stool From Scale (BSFS) used to assess consistency of bowel movements

Conclusions:
- SP-304 was safe and well-tolerated across all doses
- No SAEs
- No severe diarrhea even at very high doses
- No systemic absorption of orally administered SP-304
- SP-304 decreased the time to first bowel movement and increased the Bristol (BSFS) score