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

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## ABSTRACT

**Purpose:** SP-304 is a synthetic analog of uroguanylin, a natriuretic hormonethat regulates ionand fluid transport in the GI tract. The compound is a new member of a novel class of non-systemic drug s for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C) and otherGI diseases Orally administered SP-304 binds to and activatesguanylate cyclase C (GC-C) , expressed onthe epithelial cellslining the GI mucosa. Activation of GC-C stimulates intracellular cyclic GMP synthesis, resulting inactivationof cystic fibrosis transmembrane conductance reg ulator (CFTR), whi ch leads to an augmented flow of chloride and water into the lumen of the gut to facilitate bowel movement. In animal models, oral administration of SP-304 promotes intestinal secretion and ameliorates g astrointestinal inf lammation. The purpose of this studywasto characterizethe safety, tolerability, pharmacokinetic (PK) andpharmacodynamic (PD) effects of SP-304 inhealthy volunteers.

**Methods:** A double-blind, placebo-controlled, randomized single, oral, ascending dose (0.1 mg to 48.6 mg) study was performed in 71 healthyvolunteers. Subjects were evaluatedfor safety, tolerability, PKand PDeffects of SP-304. Adverse events (AE) were evaluated using Common Terminology Criteria for Adverse Events (CTCAE), version 3. Pharmacodynamic effects were evaluated by the time to first stool and by the 7 -point Bristol Stool Form Scale ( BSFS) to monitor stool consistency.

**Results:** SP-304 waswell-tolerated at all doselevels and no SAEs were observed throughout the study. No measurable systemic absorption of orally administered SP-304 occurred at all dose levelsstudied (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 sig nificance, SP-304 appeared to decrease the time to first bowel movement and elicited anincrease inthe post-dose BSFSversus 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 datasupportadvancingthisnovel analog of uroguanylin for further clinicaldevelopment to treat patients with CC and IBS-C.

## SP-304

Uroguanylin Natural Hormone

NDDCELCVNVACTGCL

- 16-meranalog of urogu anylin
  - Single key a mino acid change
  - Locked intostable active conformer

SP-304 Uroguanylin Analog

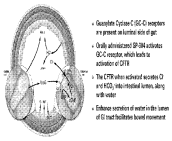
NDECELCVNVACTGCL

- Compact stable molecule
  - Thermo and aci d stable (100 C, pH 2), high resistance to pro teases
  - Be haves like asmal molecule drug
  - More potent thanthe natural hormone

GC-C Receptor

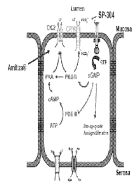
Single letters denote different amino acids. Colored lines denote disulphide bonds

## Physiological Mechanism of GC-C Agonists



- Guanylate Cyclase C (GC-C) receptors are present on luminal side of gut
- Orally administered SP-304 activates GC-C receptor, which leads to activation of CFTR
- The CFTR when activated secretes Cl and HCO3 into intestinal lumen, along with water
- Enhance secretion of water in the lumen of GI tract facilitates bowel movement

## Activation of chloride channels increases fluid secretion into the GI lumen




## Purpose

- Thepurposeof thiswas to characterize thesafety, 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
- Neg ative testfor drugs of abuse, hepatitis B and C and HIV
- Abstainfrom caffeinated beverag es, alcohol and nicotine for a period of 36 hours pre-dosethrough48-hours post-dose
- Abstain f rom and haveno clinical needfor supplemental fiber 30days priorto study entry

## Exclusion Criteria

- Any pre-existing medical condition considered clinically significant by the Principal Investigator (PI)
- Clinicallysignificant abnormallaboratoryresultsat Screening
- Participation in a clinical trial usingan investigational drugwithin30days of the Screening visit
- Ingested, injected, or applied any prescription, OTC, or herbal medications within 30 days prior to Day 1 dosing
- Receivedany treatment agents, herbs, or foods (eg., grapefruit juice) known to inhibit or induce enzymes withinthe cytochromeP450 system, within 7 daysprior to Day 1 dosing
- Takenanyclass of phosphodiesterase inhibitors within 3 dayspriorto Day 1 dosing
- Any episode of abnormal bowel habit (e.g., constipation or diarrhea) within 30 daysof Day 1
- Failure to complete the Screening bowel movement diary accuratelyand completely for 7 consecutivedays (during the 1 4 day Screening period) prior to Day 1 dosing
- Donation of blood (≥1 pint) within 8 weeks, donation of plasma within 2 weeks prior to the Screening visit, or receipt of blood products within 8 weeks prior to Day 1

## Methods

- Subjects completed a 7-daybowel movement diary during the 14-dayscreening period
  - 7 consecutive days
  - Bristol Stool From Scale (BSFS) usedto asses consistency of bowel movements
- Subjects checked intothe Phase 1 unit 1 day priorto dosing
- Pre-dose lab tests were performed to confirm eligibility (hematolog y, blood chemistry, urinalysis, fecal occult blood exam, drugs of abuse)
- Randomized 6:2 (activeplacebo)
- Subjectswere dosed at 9:00am (f asting )
- PK blood draws were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and48 hours post-dose
- All post-dose bowel movements were report ed to Phase I unit staff
  - Consistency of the stool was graded bythe Phase I unit staff using BSFS andwas recorded in a diary

## Treatment Groups

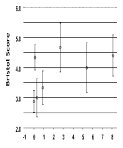
- Cohort 1: SP-304 0. 1 mg once or matching placebo
- Cohort2: SP-3040.3 mg onceor matching placebo
- Cohort 3: SP-3040.9 mg onceor matching placebo
- Cohort4: SP-304 27 mg once or matching placebo
- Cohort5: SP-304 5.4 mgonceor matchingplacebo
- Cohort 6: SP-304 8.1 mg onceor matching placebo
- Cohort 7: SP-304 16.2 mg onceor matching placebo
- Cohort 8: SP-304 24.3 mg onceor matching placebo
- Cohort 9: SP-304 48.6 mg onceor matching placebo

## Results

Subject Characteristics

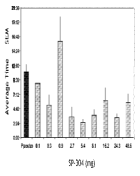
| | |
|---|---|
| Age (years) | |
| Mean + SD | 44.4 + 11.46 |
| Min, Max | 20, 63 |
| Gender | |
| Male | 29 (40.8%) |
| Female | 42 (59.2%) |
| Race | |
| White | 68 (95.8%) |
| African American | 3 (4.2%) |
| Ethnicity | |
| Hispanic or Latino | 68 (95.8%) |
| Non-Hispanic or Latino | 3 (4.2%) |

Bristol Score of First Bowel Movement Following a Single Dose of SP-304



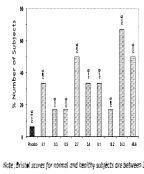

SP-304 Single-dose data In volunte ers

Average time to first bowel movement through 24 hr post-dose




SP-304 improves stool consistency

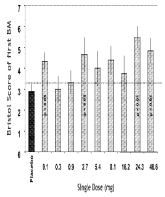
*SP-304 Single-Dose Data*




Note: Bristol scores for normal and healthy subjects are between 3 and 4

SP-304 improves stool consistency

*SP-304 Single-Dose Data*




* Wilcoxon Two-sample test treatment vs placebo one-sided

## Adverse Event (AE) Profile

- Common Terminology Criteria for Adverse Events (CTCAE), ver ion 3.0, was used to assess all adverse events
- 12 out of 6 3 subjects (19%) reportedmild AEs
  - All AEsresolved within 2 hours of dosing
- All AEs resolved within 24 hours of being reported
- Per CTCAE criteria, diarrhea is defined as an increase in the number of bowel movements per day compared to baseline
  - Not based on changes inconsistency asperthe Bristol Stoolform Scale ( BSFS)

Number of AEs Reported with an Assigned Relationship to SP-304

| Adverse Event Term | Number Reported | % |
|---|---|---|
| Diarrhea * | 8 | 12.70% |
| Abdominal Discomfort | 3 | 4.76% |
| Nausea | 2 | 3.17% |
| Bruising | 1 | 1.59% |
| Headache | 1 | 1.59% |

* Diarrhea is def ined as an increase in the number of bowel movements per day compared to baseline

## Conclusions

- SP-304 was safe and well-tolerated across all doses
- No SAEs
- No severe diarrhea evenatvery hig h doses
- No systemic absorption of orally administered SP-304
- SP-304 decreased the time to first bowel movement and increased the Bristol ( BSFS) score