

# 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

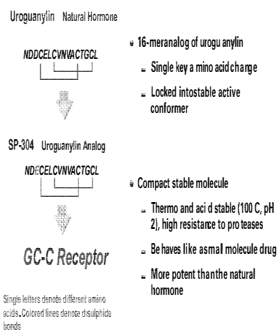
**Purpose:** SP-304 is a synthetic analog of uroguanylin, a natriuretic hormone that regulates ion and fluid transport in the GI tract. The compound is a new member of a novel class of non-systemic drugs for treatment of chronic constipation (CC), irritable bowel syndrome with constipation (IBS-C) and 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 inactivation of cystic fibrosis transmembrane conductance regulator (CFTR), which 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 gastrointestinal inflammation. The purpose of this study was to characterize the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of SP-304 in healthy volunteers.

**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. Adverse events (AE) were evaluated using Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Pharmacodynamic effects were evaluated by the time to first stool and by the 7-point Bristol Stool Form Scale (BSFS) to monitor stool consistency.

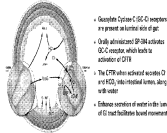
**Results:** SP-304 was well-tolerated at all dose levels and no SAEs were observed throughout the study. No measurable systemic absorption of orally administered SP-304 occurred at all dose levels studied (0.1 mg to 48.6 mg; validated SP-304 serum assay sensitive down to 10 ng/ml). Although this trial 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.

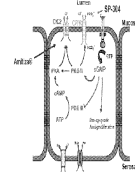
### SP-304



### Physiological Mechanism of GC-C Agonists



Activation of chloride channels increases fluid secretion into the GI lumen



### 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/m<sup>2</sup>
- Negative test for drugs of abuse, hepatitis B and C and HIV
- Abstain from caffeinated beverages, alcohol and nicotine for a period of 36 hours pre-dose through 48 hours post-dose
- Abstain from having clinical 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)
- Clinically significant abnormal laboratory results at Screening
- Participation in a clinical trial using an investigational drug within 30 days of the Screening visit
- Ingested, injected, or applied any prescription, OTC, or herbal medications within 30 days prior to Day 1 dosing
- Received any treatment agents, herbs, or foods (e.g., grapefruit juice) known to inhibit or induce enzymes within the cytochrome P450 system, within 7 days prior to Day 1 dosing
- 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 of Day 1
- Failure to complete the Screening bowel movement diary accurately and completely for 7 consecutive days (during the 14 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-day bowel movement diary during the 14-day screening period
- 7 consecutive days
- Bristol Stool Form Scale (BSFS) used to assess consistency of bowel movements
- Subjects checked into the Phase 1 unit 1 day prior to dosing
- Pre-dose lab tests were performed to confirm eligibility (hematology, blood chemistry, urinalysis, fecal occult blood exam, drugs of abuse)
- Randomized 6:2 (active:placebo)
- Subjects were dosed at 9:00am (fasting)
- PK blood draws were taken pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours post-dose
- All post-dose bowel movements were reported to Phase 1 unit staff
- Consistency of the stool was graded by the Phase 1 unit staff using BSFS and was recorded in a diary

### Treatment Groups

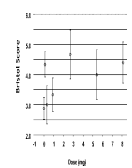
- Cohort 1: SP-304 0.1 mg once or matching placebo
- Cohort 2: SP-304 0.3 mg once or matching placebo
- Cohort 3: SP-304 0.9 mg once or matching placebo
- Cohort 4: SP-304 2.7 mg once or matching placebo
- Cohort 5: SP-304 5.4 mg once or matching placebo
- Cohort 6: SP-304 8.1 mg once or matching placebo
- Cohort 7: SP-304 16.2 mg once or matching placebo
- Cohort 8: SP-304 24.3 mg once or matching placebo
- Cohort 9: SP-304 48.6 mg once or matching placebo

### Results

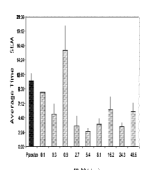
#### Subject Characteristics

Characteristic	Mean (SD)	Range
Age (years)	44.4 (11.4)	20-67
Weight (kg)	70.6 (17.1)	50-107
Gender		
Male	51 (48.2%)	
Female	42 (91.8%)	
Race		
White	65 (91.5%)	
Asian American	3 (4.2%)	
Ethnicity		
Hispanic or Latino	62 (95.3%)	
Non-Hispanic or Latino	7 (9.7%)	

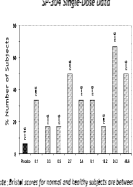
#### Bristol Score of First Bowel Movement Following a Single Dose of SP-304



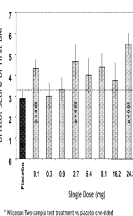
#### SP-304 Single-dose PK in Volunteers



#### SP-304 Improves stool consistency



#### SP-304 Improves stool consistency



### Adverse Event (AE) Profile

- Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, was used to assess all adverse events
- 12 out of 63 subjects (19%) reported mild AEs
- All AEs resolved 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 in consistency as per the Bristol Stool Form Scale (BSFS)

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

Adverse Event Term	Number Reported	%
Diarrhea	8	12.7%
Abdominal Discomfort	1	1.6%
Nausea	1	1.6%
Headache	1	1.6%
Headache	1	1.6%

\* Diarrhea is defined 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 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