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

Digestive Disease Week. San Diego: 2008.

Kunwar Shailubhai, Ph.D., William Gerson, D.O., Craig Talluto, Ph.D., Gary Jacob, Ph.D.

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 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. 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

Uroguanylin Natural Hormone

NDDCELCVNVACTGCL

- 16-mer analog of uroguanylin
  - Single key amino acid change
  - Locked into stable active conformer

SP-304 Uroguanylin Analog

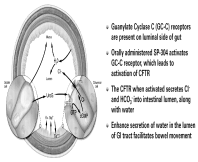
ND□CELCVNVACTGCL

- Compact stable molecule
  - Thermo and acid stable (100 C, pH 2), high resistance to proteases
  - Behaves like a small molecule drug
  - More potent than the natural hormone

GC-C Receptor

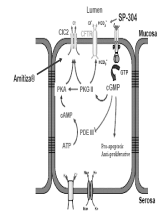
Single letters denote different amino acids. Colored lines denote disulphide bonds

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 HCO_3 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

- 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
- 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 and have no 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 From Scale (BSFS) used to asses 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 I unit staff
  - Consistency of the stool was graded by the Phase I unit staff using BSFS and was recorded in a diary

Treatment Groups

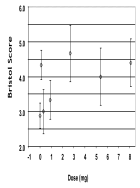
- Cohort 1: SP-304 0.1 mg once or matching placebo
- Cohort 2: SP-304 0.3 mg once or matching placebo
- Cohort 3: SP-304 0.9 mg once or matching placebo
- Cohort 4: SP-304 2.7 mg once or matching placebo
- Cohort 5: SP-304 5.4 mg once or matching placebo
- Cohort 6: SP-304 8.1 mg once or matching placebo
- 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

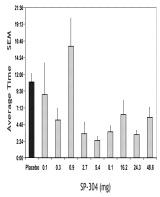
Age (years)	
Mean ± SD	44.4 ± 11.46
Min, Max	20, 62
Gender	
Male	29 (40.8%)
Female	42 (59.2%)
Race	
White	68 (95.8%)
African American	3 (4.2%)
Ethnicity	
Hispanic or Latino	68 (95.8%)
Non Hispanic or Latino	3 (4.2%)

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



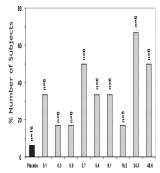
SP-304 Single-dose data in volunteers

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



SP-304 improves stool consistency

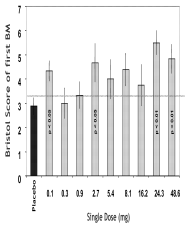
SP-304 Single-Dose Data



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), 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	12.70%
Abdominal Discomfort	3	4.76%
Nausea	2	3.17%
Emesis	1	1.59%
Headache	1	1.59%

* 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