Development of a novel Drug Delivery System (DDS) to deliver drugs directly to the colonic mucosa to improve efficacy and reduce systemic exposure for the treatment of ulcerative colitis (UC)

Shaoying Nikki Lee[1], Erik Sandefer[2], Walter Doll[2], Richard Page[2], Cheryl Stork[1], Ghesal Razag[1], Kathleen Martin[3], Nelson Quintana[1], Chris Wahl[1], and Sharat Singh[1]

1. Biora Therapeutics, Inc., 2. Scintipharma Inc. 3. CHI Saint Joseph Medical Group

INTRODUCTION

Despite multiple approved and novel therapies for the management of moderate to severe ulcerative colitis (UC), outcomes remain sub-optimal, with clinical remission rates between 15-30% after induction. Research has shown that an inadequate amount of drug at the disease site may be responsible for limited clinical benefit.

The Drug Delivery System (DDS) is an ingestible electronic targeted delivery device containing a localization system to autonomously identify colon entry based on gastrointestinal (GI) anatomy, independent of variable GI physiological conditions. The DDS is designed to deliver a bolus dose of a liquid drug formulation to the colon mucosa to improve efficacy and reduce systemic toxicity. In these two device function studies, we evaluated the safety, tolerability, and functionality of a single dose of the DDS device using gamma scintigraphy images as a reference for the location and delivery of radioactive payload in the GI tract in both normal healthy volunteers (NHV) (PM-601) and in patients with active UC (PM-602) in a fasted state.

THE DDS DEVICE

- The DDS device comprises a drug reservoir that houses a liquid formulation of the therapeutic compound and an electronic module **(Figure 1A)**.
- The electronic module houses the localization system, electronics, and the gas cell required for the drug displacing reservoir from the device at the target location **(Figure 1A)**.

Autonomous Localization

- The proprietary autonomous localization system identifies different anatomical regions by emitting colored light that interacts with the local GI environment and returns to spatially separated detectors. Measured light levels are analyzed by the algorithm to detect changes associated with different anatomical features **(Figure 1B)**.
- Upon detection of entry into the colon (S4), the device initiates the gas cell actuator for drug release **(Figure 1B)**.

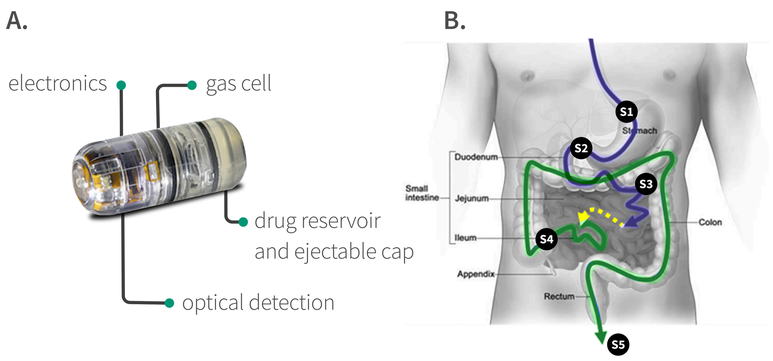

FIGURE 1. DDS with autonomous localization technology enables targeted delivery of therapeutics. (A) Photograph of DDS device; B) The internal algorithm can detect five major anatomical locations: (S1) entry to stomach, (S2) pylorus (gastric emptying), (S3) small intestine, (S4) colon, and (S5) exit from body.

OBJECTIVE

- To assess the safety and tolerability of DDS devices in both NHV and active UC patients in a fasted state by measuring the number, severity, expectedness, and type of device-related adverse events (AE).
- To evaluate the localization and delivery function of DDS devices using gamma scintigraphy in both NHV and active UC patients in a fasted state.

METHODS

Clinical Study Designs and Intervention

- Each study participant fasted overnight for a minimum of 8 hours and was dosed with a single DDS device before resuming normal diet at 4 hours post-dose.
- Each device was filled with radioactive marker indium-111 DTPA (^{111}In-DTPA) to identify DDS localization and to visualize payload release in the GI tract. Water radiolabeled with technetium-99m DTPA (^{99}mTc-DTPA) was co-administered with the device to help delineate GI landmarks by gamma scintigraphy.
- The GI transit of the device and its delivery location was confirmed by serial scintigraphy imaging and compared with the localization data in the recovered device.

Main Inclusion and Exclusion Criteria

- Male and non-pregnant female subjects between ≥ 18 and ≤ 75 years of age who were willing to adhere to contraception and sperm donation criteria.
- Subjects who could swallow 000 size capsule.
- Normal heathy volunteers or subjects with a documented diagnosis of UC confirmed by endoscopy and histology and have active UC within one (1) month of screening; defined as:
  - Mayo score ≥ 2 or elevated Fecal Calprotectin Protein or high sensitivity C-reactive protein within one month of the screening visit.
- Subjects diagnosed with Crohn's disease, indeterminate colitis, or clinical findings suggestive of CD (e.g., stricture, fistula, or granulomas on biopsy) were excluded.
- Subjects who had fulminant colitis (e.g., toxic megacolon or bowel perforation), evidence or history of colonic dysplasia, needed to undergo surgery, or other histories of increased risk of bowel obstruction were excluded.

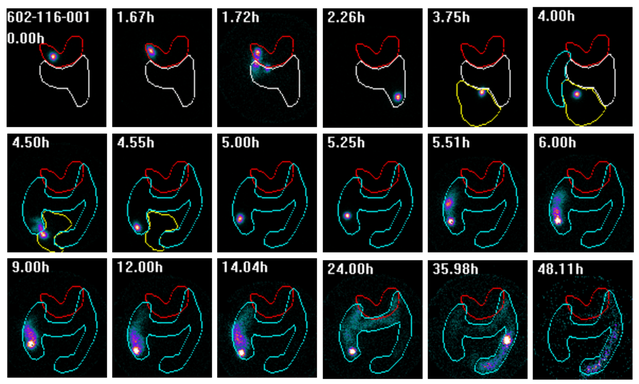

FIGURE 2: Cumulative distribution of radiotracer ^{111}In-DTPA release from device post-dose in subject with ulcerative colitis. Subject 602-116-001, who has a Mayo score of 6 and frequent bowel movements with visible blood in the stool.

RESULTS

Safety and Tolerability of DDS

- A total of twelve NHV (N=12) and seven active UC patients (N=7) (ages between 20-66 years old; BMI 22.1-41.3 kg / m2) with variable active UC disease status were enrolled and dosed in the study **(Table 1)**.
- The DDS device was well tolerated by all subjects.
- One subject with active UC experienced mild intermittent abdominal cramping that was assessed as possibly related to the device administration by the investigator and resolved on the same day. No other device-related AEs were reported.

Localization Validation and Delivery Performance

- GI transit metrics were consistent with the variable GI motility and the frequent bowel movements observed among active UC patients compared to NHV (Table 1).
- A total of 17 out of 19 DDS devices (90%) successfully identified colon entry, and 15 out of 19 DDS devices (79%) delivered the radio payload into the colon regardless of variable GI transit time, the level of inflammation, or the presence of blood in the stool **(Table 1 & 2)**.
- The dispersion of the ^{111}In-DTPA payload completely covered the colon over time and spread to match the ^{99}mTc-DTPA water coverage area from the site of the release throughout the remainder of the colon **(Figure 2)**.

SUMMARY

- **These studies demonstrated that the DDS device was well-tolerated in both NHV and active UC patients.**
- **The DDS device functioned as intended in identifying colon entry and releasing payload in the colon regardless of variable GI motility or disease status.**
- **By functioning independently of variable GI pH and motility, the DDS device has the ability to provide precise dosing with a liquid formulation to locally deliver therapeutics directly to the disease site in the colon.**

TABLE 2: Device performance in NHV and active UC patients

Parameter	PM-601 NHV (N = 12)	PM-602 Active UC (N = 7)	Combined (N = 19)
S4 Call			
Correct call (%)	10/12 (83.330%)	7/7 (100%)	17/19 (89.47%)
Wilson Score 95% CI	(55.20%, 95.30%)	(64.57%, 100%)	(68.61%, 97.06%)
Payload Release Activation			
Delivered (%)	8/12 (66.67%)	7/7 (100%)	15/19 (78.95%)
Wilson Score 95% CI	(39.06%, 86.19%)	(64.57%, 100%)	(56.67%, 91.49%)

TABLE 1: Comparison of the GI transit and motility, location of device at time of S4 call, and release of payload between PM-602 and PM-601.

Subject ID	Mayo score	Visible blood in stool	Gastric emptying time (min)	Small intestine residence time (min)	Arrival time at cecum (min)	Release time of ^{111}In-DTPA (min)	Device location at time of release	Device recovery time (hrs)	Bowel movements to recover device
602-116-001	6	Yes	104	169	273	323	Cecum	47.67	3
602-116-002	3	No	23	115	138	188	Cecum	26.50	3
602-116-003	8	Yes	38	285	323	353	Cecum	32.83	5
602-116-004	2	No	14	249	263	308	Splenic Flexure	24.25	1
602-116-005	6	Yes	9	149	158	188	Cecum	6.83	3
602-116-006	2	No	87	498	585	616	Cecum/Ascending Colon	48.67	9
602-116-007	3	No	465	105	570	638	Cecum/Ascending Colon	23.75	2
601-NHV (N=11)* Median	N/A	No	29	228	270	368	Cecum/Ascending Colon/ Splendic Flexure	23.99	1 (n=6); 2 (n=4); 3 (n=1)

*Excluded one subject due to anomalous transit of the DDS device from the stomach to the duodenum and back into the stomach.

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Contact Info
Shaoying Nikki Lee, PhD
Associate Director, Clinical and Translational Science
nikki.lee@bioratherapeutics.com
bioratherapeutics.com

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