A Scintigraphic Study to Evaluate the Localization and Delivery Function of a Drug Delivery System (DDS) Device in Patients with Active Ulcerative Colitis (UC) in Fasted State

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INTRODUCTION

Clinical remission in moderate to severe ulcerative colitis (UC) and Crohn's disease (CD) has plateaued at ~15-20% even with the approval of multiple biologic drugs. The ATLAS study demonstrated that the lack of an adequate amount of drug at the disease site is responsible for limited clinical benefit.[1]

The Drug Delivery System (DDS) is an ingestible electronic targeted delivery device containing a localization system designed to identify colon entry based on gastrointestinal (GI) anatomy independent of the variable GI physiological conditions and deliver a bolus of a therapeutic compound to the colon mucosa. The DDS device has the potential to improve efficacy and reduce systemic toxicity and associated risks with the currently approved products for moderate to severe UC. The DDS was well-tolerated and functioned as intended in identifying and releasing radiotracer in the colon of normal healthy volunteers **(see poster #B0402)**.

This was an open-label, single-center study that evaluated the safety, tolerability, and functionality of a single dose of the DDS device containing radiolabeled tracer using gamma scintigraphy imaging in active UC patients 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 a gas cell that displaces the drug reservoir from the device, thereby releasing drug 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 call), the device initiates the gas cell actuator for drug release **(Figure 1B)**.

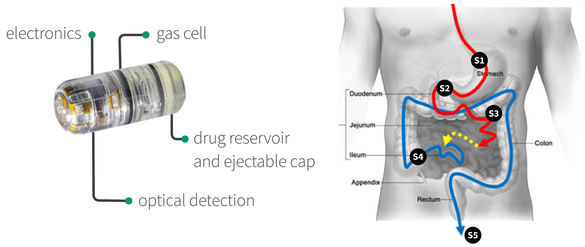

FIGURE 1. DDS with autonomous localization technology enables targeted delivery of therapeutics. A) Photograph of DDS device; B) The internal algorithm can detect five major anatomical locations: (S1) esophagus, (S2) pylorus (gastric emptying), (S3) small intestine, (S4) colon, and (S5) exit from body.

OBJECTIVE

- To assess the safety and tolerability of DDS devices in active UC patients in a fasted state by measuring the number, severity, expectedness, and type of device-related adverse events.
- To evaluate the localization and delivery function of DDS devices using gamma scintigraphy in 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 (^{99m}Tc-DTPA) was co-administered with the device to help delineate GI landmarks by gamma scintigraphy **(Figure 2)**.
- The GI transit of the device and its delivery location was confirmed by serial scintigraphic imaging and compared with the localization data in the recovered device.

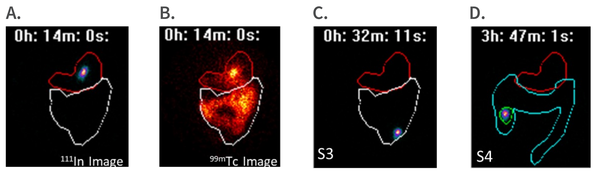

FIGURE 2. Gamma scintigraphy images of ^{111}In-DTPA in the DDS device and regions of interest in different GI segments with water containing ^{99m}Tc-DTPA co-administered with the devices. A. DDS device in the stomach; B. ^{99m}Tc-DTPA water delineated in regions of interest, including stomach (red) and proximal small intestine (white); C. DDS device (^{111}In-DTPA) at S3 detection in the proximal small intestine; D. DDS capsule (^{111}In-DTPA) at S4 detection in the colon (blue).

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 capsules.
- 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.

RESULTS

Safety and Tolerability of DDS

- Seven active UC patients (ages between 20-66 years; BMI 22.1-41.3 kg/m^2) with variable active UC status were enrolled, treated, and completed the study **(Table 1)**.
- The DDS device was well-tolerated by all the subjects.
- One subject experienced mild intermittent abdominal cramping that was assessed by the investigator as possibly related to the device administration and resolved on the same day. No other device-related adverse effects were observed.

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 the normal healthy volunteers who were observed in a previous study (see poster #B0402) **(Table 1)**.
- All seven devices (100%: Wilson score 95% confidence interval [CI], 65% to 100%) correctly made S4 calls in the terminal ileum to colon region regardless of variable GI transit time, the level of inflammation, or the presence of blood in the stool **(Table 1)**.
- All seven devices (100%: Wilson score 95% CI, 65% to 100%) released the radioactive payload ^{111}In-DTPA into the colon.
- The dispersion of the ^{111}In-DTPA payload completely covered the colon over time and spread to match the ^{99m}Tc-DTPA water coverage area from the site of the release throughout the remainder of the colon **(Figure 3)**.

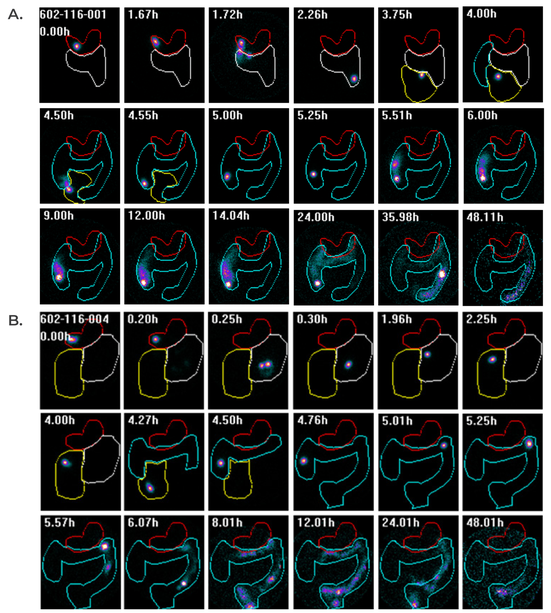

FIGURE 3: Cumulative distribution of radiotracer ^{111}In-DTPA release from device post-dose in subjects with various disease status. A. Subject 602-116-001, who has a Mayo score of 6 and frequent bowel movements with visible blood in the stool. B. Subject 602-116-004, who has a Mayo score of 2 and fast GI motility (gastric emptying in 14 min).

TABLE 1: Comparison of the GI transit and motility, location of device at time of S4 call, and release of payload between UC patients and normal healthy volunteers (NHV).

Subject ID	Device #	Mayo score	Gastric Emptying Time (min)	Small intestine residence time (min)	Arrival time at cecum (min)	Device location at time of S4 call	Release of ^{111}In-DTPA (min)	Device location at time of release	Device recovery time (hrs)	Visible blood in stool	Bowel movements to recover device
602-116-001	7357	6	104	169	273	Cecum	323	Cecum	47.67	Yes	3
602-116-002	7358	3	23	115	138	Cecum	188	Cecum	26.50	No	3
602-116-003	7359	8	38	285	323	Cecum	353	Cecum	32.83	Yes	5
602-116-004	7360	2	14	249	263	AscendingColon/ Splenic Flexure	308	Splenic Flexure	24.25	No	1
602-116-005	7361	6	9	149	158	Cecum	188	Cecum	6.83	Yes	3
602-116-006	7362	2	87	498	585	Cecum	616	Cecum/Ascending Colon	48.67	No	9
602-116-007	7407	3	465	105	570	Cecum/ Ascending Colon	638	Cecum/Ascending Colon	23.75	No	2
NHV (N=11)* Median			29	228	270		368	Cecum/ Ascending Colon/ Splendic Flexure	23.99	No	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.

SUMMARY

- This study demonstrated that the DDS device was well-tolerated in the active UC patient population.
- 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 provides precise dosing with a liquid formulation to deliver therapeutics directly to the disease site in the colon.

References

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2. Ibekwe VC, Fadda HM, McConnell EL, Khela MK, Evans DF, Basit AW. Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH responsive ileo-colonic release systems. *Pharm Res*. 2008;25(8):1828-1835.

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