A Scintigraphic Study to Evaluate the Safety, Tolerability, and Functionality of a Drug Delivery System (DDS) Device in Healthy Volunteers in Fasted State

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INTRODUCTION

Clinical remission in moderate to severe ulcerative colitis (UC) and Crohn's disease 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 to improve efficacy and reduce systemic toxicity and associated risks.

This was an open-label, single-center study to evaluate the safety, tolerability and functionality of a single dose of the DDS device containing radiolabeled tracer using gamma scintigraphy imaging in normal healthy volunteers (NHV) 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)**.

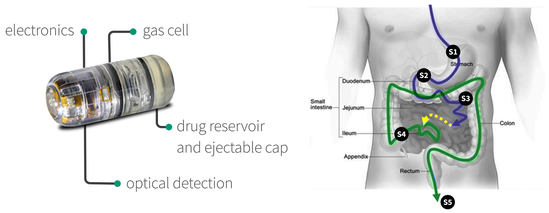

FIGURE 1. DDS with autonomous localization technology enables targeted delivery of therapeutics. A. Photograph of DDS device. B. The internal algorithm can detect five major anatomical locations: (S1) entry to stomach, (S2) pylorus (gastric emptying), (S3) small intestine, (S4) colon, and (S5) exit from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

OBJECTIVE

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

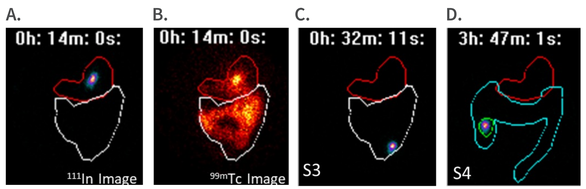

FIGURE 2. Gamma scintigraphy images of ^{111}In-DTPA in the DDS device and regions of interest in different GI segments with water containing ^{99m}Tc-DTPA co-administered with the devices. A. DDS device in the stomach; B. ^{99m}Tc-DTPA water delineated in regions of interest, including stomach (red)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

Main Inclusion and Exclusion Criteria

- Normal healthy male subjects between 18 and 65 years of age with body weight ≥ 50 kg and body mass index between 17.5 and 34.0 kg/m^2.
- Subjects were able to swallow size 000 capsules and had a history of regular bowel movements over the past 30 days.
- Subjects with current or recent (within 6 months) clinically significant GI disease, GI surgery, or a history of increased risk for bowel obstruction, including GI functional disorder, abnormal GI anatomy, or motility, diarrhea (> 3 episodes of loose stools), constipation (< 3 stools per week) were excluded.

RESULTS

Safety and Tolerability of DDS

- Twelve healthy male subjects (ages 24-51; BMI 22.4-32 kg/m^2) were enrolled, treated, and completed the study **(Table 1)**.
- No device-related adverse events were observed in any of the subjects.

Localization Validation and Delivery Performance

- GI transit times were comparable to those reported in the literature with similar-sized medical devices in NHV,[2] and the time stamps of internal algorithm calls at different locations were compared to the location of the capsule.
- No early release of drug payload before the colon entry event (S4 call) was observed.
- 10/12 (83%) devices correctly made S3 calls in the proximal small intestine **(Table 1)**.
- 10/12 (83%) devices correctly made S4 calls in the terminal ileum to colon region **(Table 1)**.
- 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 release throughout the remainder of the colon **(Figure 3)**.

TABLE 1: Location of DDS device at different internal algorithm calls.
S2 (gastric emptying), S3 (proximal small intestine), and S4 (colon entry)

Device #	Subject ID	S2	S3	S4
6398	601-01-008	PSI	PSI	Cecum / ASC
6413	601-01-005	Duodenum	PSI	TI
6419	601-01-010	PSI	PSI	Cecum / ASC
6420	601-01-003	Duodenum	PSI	Cecum / ASC
6471	601-01-015	PSI	PSI	TRC
6484	601-01-011	Duodenum	Duodenum	Cecum / ASC
6486	601-01-001	Duodenum	PSI	Cecum / ASC
6491	601-01-006	–	–	Out of body
6500	601-01-007	PSI	PSI	Cecum / ASC
6507	601-01-009	Duodenum	PSI	TRC
6516	601-01-004	Stomach	Stomach	TRC
6517	601-01-013	Duodenum	Duodenum	Duodenum

Note: PSI: Proximal Small intestine; ASC: Ascending Colon; TI: terminal ileum; TRC: transverse colon

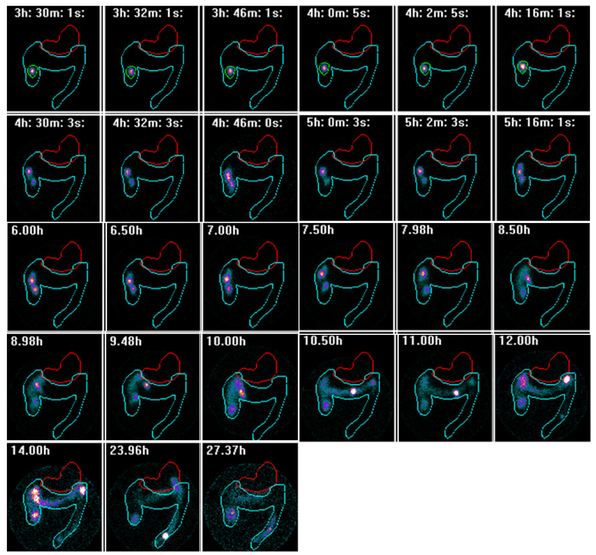

FIGURE 3: Cumulative distribution of radiotracer ^{111}In-DTPA release from DDS post dose over time in the colon. Region of interest: stomach (red line); colon (blue)

SUMMARY

- This study demonstrated that the DDS device was well-tolerated, no device-related adverse events were observed, and the device functioned as intended in identifying colon entry and releasing payload in the colon.
- 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.
- A similar device function study was also performed in patients with active ulcerative colitis which demonstrated precise delivery to the colon; see poster #E0341.

References

1. Yarur AJ, Jain A, Sussman DA, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut*. 2016;65(2):249-255.
2. O'Grady J, Murphy CL, Barry L, Shanahan F, Buckley M. Defining gastrointestinal transit time using video capsule endoscopy: a study of healthy subjects. *Endosc Int Open*. 2020;8(3):E396-E400.

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