Development of a novel drug delivery system to drugs locally to the colonic mucosa to improve efficacy and reduce systemic exposure, for the treatment of ulcerative colitis.

Supplemental information- localization

Localization performance

The DDS2 is an autonomous electronic drug delivery capsule. A key element of the device is a proprietary localization technology. The localization sub-system probes the gut environment with colored visible light and measures the return of reflected and scattered light. The DDS2 optical system consists of an array of three-color LEDs along with an interleaved array of photodetectors. The LEDs periodically illuminate the environment, and the returned signal is measured by the photodetectors. Variations in the returned colored signals are used to identify anatomical locations. During transit, there is a characteristic change in relative color signals as the capsule moves from the stomach into the small bowel, and again as the capsule moves from the small bowel into the colon. The on-board microprocessor analyzes the measured signals and generates a trigger signal when transitions are determined. With the DDS2 capsule trigger signal for colon entry starts an actuator that results in drug delivery from the reservoir.

The localization technology was developed and verified with the input from a series of three clinical studies with a localization specific test device. The test device was named Telemetric Localization Capsule (TLC) and included the optical system, a microprocessor, and a wireless communication chip. The TLC capsule device passed through the gastrointestinal (GI) tract while taking optical data measurements and running the detection algorithm on the microprocessor. Data capture and event status was reported wirelessly to a receiver and recorded for later analysis. The algorithm and control ran through a state progression from ingestion to end of capsule life. In the state progression, gastric emptying of the capsule is denoted S2, entry of the capsule into the jejunum region is denoted S3 and entry into the ascending colon region is denoted S4.

The first clinical study, TLC1, was performed with N = 20 normal healthy volunteers. TLC capsule device was ingested after an overnight fast. Capsule took measurements at a fixed interval of every 15 seconds. On-board transition detection of S2, S3 and S4 events along with light measurement data were reported by wireless communication to a wearable receiver. After notification of detection events at the wearable receiver, subject proceeded to a focal CT machine for abdominal image. Later analysis of the CT image was used to determine GI compartment location. In this method the location of the capsule shortly after landmark detection could be determined. This provided a check against accuracy of the algorithm state calls.

The second clinical study, TLC2, was performed with N = 30 volunteers with symptoms suggestive of SIBO (Small Intestinal Bacterial Overgrowth). Execution proceeded in a similar fashion to the TLC1 study with fasted subjects ingesting a capsule device and having focal CT image taken upon notification of detection events. The TLC capsule and operation were updated to improve mechanical construction and

execution of the data capture. The capsule was additionally programmed with an adaptive data measurement rate according to progression in the GI tract. Increased overall measurement frequency allowed more detailed characterization of the transition events of interest, particularly from ingestion through gastric emptying and small bowel transit.

The third clinical study, TLC3, was performed with N = 8 normal healthy volunteers. Each TLC capsule included the radioactive marker indium-111 chloride ($^{111}InCl_3$) to monitor capsule GI transit by gamma scintigraphy. Capsule was ingested after an overnight fast. Serial gamma scintigraphy images were recorded as a continuous series of 1-minute images for up to 30 minutes at a time. As much as possible periods of continuous images were scheduled to coincide with the time between notification of the S2 and S3 events at the wearable receiver. In addition, images were taken shortly after all notification events at the wearable receiver if not already captured. Later analysis of images was used to determine the time points of gastric emptying, arrival at the jejunum, and arrival time at the colon. With these time determinations the accuracy of the algorithm could be further determined.

In addition to analysis within each study, results of each were taken together to assess the performance of the localization system. For the CT image studies, TLC1 and TLC2, the light measurement data traces were examined. From each trace the time of small bowel entry and colon entry were determined by subjective examination for times of change in color levels indicative of a transition point. The subjective determinations were further anchored and adjusted if necessary, by position determined in the CT images. For the scintigraphy study, TLC3, times of small bowel entry and colon entry were determined from the image set by an experienced reader.

The localization algorithm was then evaluated retrospectively for accuracy of calls. Light data measurements were processed on computer through the algorithm to generate the call times. In the TLC1 study, one subject had capsule remain in stomach for and extended time and data was not measured beyond that. This subject was excluded from the analysis. In the TLC2 study one subject had a limited data set recorded likely due to a technical failure of the capsule or wearable receiver. This subject was excluded. Due to the increased measurement frequency with the TLC2 capsule, light measurement data was incomplete with several more subjects. There was one subject where data covered only stomach residence and was excluded from analysis of the S3 transition. This subject plus 8 others had data traces that stopped before entry into the colon and were excluded from analysis of the S4 transition. In the TLC3 study all subjects had data recorded up to colon entry.

Location of capsule at the call time returned by the algorithm was then compared to that determined from the image data. Call times of S3 entry into the jejunum, and S4 entry into the colon, were evaluated. Results are summarized in Table S1. Algorithm performance across the three clinical studies for S3 detection, entry into the jejunum, was correct in 54/55 cases (98.2%). Algorithm performance across the three clinical studies for S4 detection, entry into the ascending colon, was correct in 40/47 cases (85.1%). In the DDS2 application, start of drug actuation anywhere in the colon or in the terminal ileum is expected to result in sufficient colonic drug distribution for several envisaged applications. Taking this wider area determination as a success, algorithm performance across the three clinical studies for detection of entry into the region of terminal ileum or colon, was correct in 45/47 cases (95.7%).

Table S1: Location of capsule at the time of transition calls S3, entry into the jejunum, and S4, entry into the ascending colon, determined by the localization algorithm. Algorithm calls were made from light measurement data collected during clinical studies TLC1, TLC2 and TLC3. Position of capsule at algorithm call time was determined by analysis of image data; CT images in TLC1 and TLC2, and scintigraphic images in TLC3.

	TLC1	TLC2	TLC3
S3 at Jejunum	19/19	28/28	7/8
S3 Other	0/19	0/28	1/8
S4 at Terminal Ileum	1/19	1/20	1/8
S4 at Ascending Colon	17/19	16/20	7/8
S4 at Transverse or Descending Colon	1/19	1/20	0/8
S4 Other	0/19	2/20	0/8