Elucidation of the Relative Bioavailability of a Drug Candidate from Different Regions of the Human Gastrointestinal Tract

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Summary

This poster describes a pharmacokinetic study to investigate the relative absorption of an NCE from different regions of the human gastrointestinal tract, to support potential development of a sustained-release formulation. The drug was administered orally, either as an immediate release formulation, or via Enterion™ capsules, which were activated to release the drug at pre-determined locations in the gastrointestinal tract.

The study revealed that the drug was poorly absorbed from the colon, indicating that development of a sustained-release formulation was likely to be challenging. This case demonstrates the business value of conducting such a study early in development, when confronted with a drug candidate with a short half-life.

Objectives

The objective of this study was to determine the relative bioavailability of a drug candidate when delivered to the proximal small intestine, distal small intestine and ascending colon, in comparison to the oral administration of a conventional immediate-release (IR) formulation. This information would be used to assess the probability-of-success of developing a sustained-release formulation of this drug.

Background

The drug candidate was a weak base with a molecular weight of ~300. It was a BCS Class III drug (i.e., low permeability, high solubility) at the anticipated clinical dose. It had an effective half-life of 2-4 hours following oral administration, whereas a once- or twice-daily product was desired.

Experimental

Study Design

This was a partially-fixed sequence, crossover, open-label study conducted in 12 healthy adult subjects. The drug was administered either as an oral immediate release (IR) form (treatment A), or orally via Enterion™ capsules (treatments B-E), which were activated to release the drug when observed, by scintigraphy, to have reached the intended locations in the gastrointestinal tract. Treatments were single doses of 100mg administered following an overnight fast, and subjects continued to fast for 5 hours post-dose. Blood samples were taken at appropriate intervals for pharmacokinetic analysis.

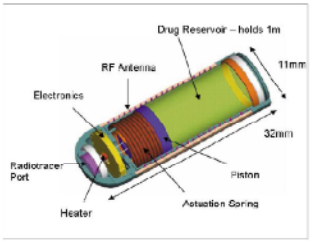
Experimental

Table 1: Study design

Treatment	API form	Formulation	Site of delivery
A	Solid	API in hard gelatin capsules	Stomach (oral administration)
B	Solid	API in Enterion™ capsule	Proximal small intestine
C	Solid	API in Enterion™ capsule	Distal small intestine
D	Solid	API in Enterion™ capsule	Ascending colon
E	Solution	Solution in Enterion™ capsule	Ascending colon

Enterion™ Capsule

The Enterion™ capsule was developed by Quotient Bioresearch – Clinical Sciences to provide a non-invasive means to evaluate human regional drug absorption of orally-administered pharmaceuticals. The location of the capsule in the gastrointestinal tract was determined using gamma scintigraphy using an ^{111}In label, which was sealed within a dedicated radioactive tracer port. A non-absorbable radioactive marker, ^{99m}Tc diethylene triaminepentaacetic acid, was mixed with the water that was taken with the capsule to provide visual (scintigraphic) confirmation of the subject's gastrointestinal anatomy. An external anatomical marker (^{111}In) was also used to assist in alignment of consecutive scintigraphic images. Capsule activation was initiated, thus releasing the dose, when the capsule reached the target location.



Results

The mean or median pharmacokinetic parameters of the drug following a single dose of 100 mg delivered as an oral IR capsule or Enterion™ capsules to the proximal small intestine (PSI), distal small intestine (DSI), and ascending colon (AC) are shown in Table 2.

Table 2: Mean (CV %) Pharmacokinetic Results from Regional Absorption Study

Treatment	Location	Cmax (ng/mL)	Tmax (hr) [a]	AUC(tf) (hr·ng/mL)	Relative bioavailability (%)
A (n=12)	Oral	292 (46)	0.88	546 (32)	-
B (n=12)	Proximal small intestine	309 (48)	0.26	568 (28)	107 (16)
C (n=12)	Distal small intestine	215 (38)	1.25	519 (37)	93.9 (22)
D (n=12)	Ascending colon (solid)	11.9 (101)	6	116 (73)	21.5 (80)
E2 (n=11)	Ascending colon (solution)	53.1 (33)	1	299 (31)	58.2(20)

a: Median

The mean plasma concentration-time profiles are presented in Figure 1, and individual and mean relative bioavailability, Cmax, and AUC(tf) values are presented in Figures 2-4, respectively.

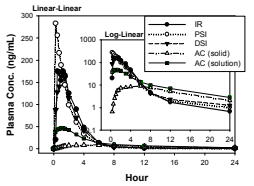


Figure 1: Plasma concentration-time profiles

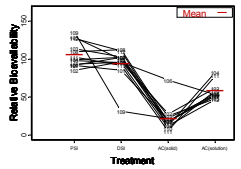


Figure 2: Relative bioavailabilities

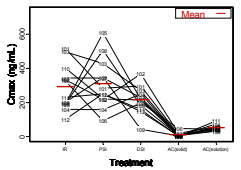


Figure 3: Individual and mean Cmax values

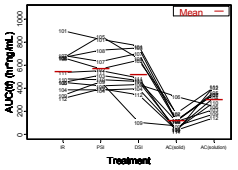


Figure 4: Individual and mean AUC(tf) values

Results

Delivery as immediate-release formulation

The drug was rapidly absorbed following oral administration as an IR formulation (**Treatment A**), with mean Cmax and AUC(tf) values of 292 ng/mL and 546 hr*ng/mL, respectively, and a median Tmax value of 0.88 hr.

Delivery to small intestine

When delivered to the PSI via Enterion™ capsules (**Treatment B**), the mean Cmax and AUC(tf) were comparable to Treatment A, the IR formulation. The mean relative bioavailability was 107%. No delay in absorption was observed.

When delivered to the DSI via Enterion™ capsules (**Treatment C**), the mean AUC(tf) was similar to Treatment A, the IR formulation. The mean relative bioavailability was 93.9%. The median Tmax value of 1.25 hr again suggested that the drug was rapidly absorbed.

These data suggested that the drug was rapidly and extensively absorbed from the proximal and distal small intestine.

Solid delivery to colon

When delivered to the AC as dry powder via Enterion™ capsules (**Treatment D**), both Cmax and AUC(tf) were reduced as compared to Treatment A, the IR formulation. The mean relative bioavailability was 21.5%. There was a delay in absorption, as seen from the Tmax (6 hr).

Solution delivery to colon

When delivered to the AC as a solution via Enterion™ capsules (**Treatment E**), both Cmax and AUC(tf) were increased as compared to Treatment D, solid delivery to the colon. The mean relative bioavailability was increased to 58.2%. No delay in absorption was observed.

Conclusions

The main conclusions of this study were the following:

- The drug was well absorbed following IR administration and administration to the proximal and distal small intestine;
- Exposure was lower when the drug was delivered to the ascending colon (bioavailability relative to IR of 21.5% for the solid, 58.3% for the solution);
- The difference in colonic absorption between the solid and solution treatments suggested that colonic absorption was to some extent dissolution-rate-limited;
- The incomplete colonic absorption, even following solution administration, suggested some degree of permeability-rate-limitation also;
- Development of a sustained-release formulation of this compound was predicted to be challenging;
- This case demonstrated the business value of conducting such a study early in development when confronted with a drug candidate with a short half-life, to assess the probability-of-success of a sustained-release formulation.