Fasted State Quantification of Gastrointestinal Liquid following a 240 ml Dose of Water
L. Marciani 1, D. M. Mudie 2, K. Murray 1, S. E. Pritchard 1, C. L. Hoad 1, M. C. Garnett 1, G. L. Amidon 2, P. A. Gowland 1, R. C. Spiller 1, G. E. Amidon 2
1 University of Nottingham, 2 University of Michigan

Purpose
The rate and extent of drug dissolution and absorption from solid oral dosage forms is highly dependent on the volume of gastric and small intestinal liquid. However, little is known about the time courses of liquid volumes in vivo in an undisturbed gut. Previous imaging studies offered a snapshot of liquid distribution in fasted humans and showed that liquid in the small intestine is distributed in small pockets. This study aimed to quantify the volume and number of liquid pockets in the upper gut of fasted healthy humans following ingestion of 240ml of water (conditions recommended for Bioavailability/Bioequivalence (BA/BE) studies), using recently validated non invasive Magnetic Resonance Imaging (MRI) methods.

Methods
Twelve healthy volunteers underwent upper and lower abdominal MRI scans before drinking 240ml (8 fluid ounces) of water. After ingesting the water they were scanned at intervals for 2 hours. The drink volume, inclusion criteria and fasting conditions matched the international standards for BA/BE testing in healthy volunteers. The images were processed for gastric and intestinal total liquid volumes and for the number and volume of separate intestinal liquid pockets larger than 0.5ml.

Results
The fasted stomach contained 35±7ml (mean±SEM) of resting liquid. Upon drinking, the gastric fluid rose to 242±9ml. The gastric liquid volume declined rapidly after that with half emptying time (T50%) of 13±1 minutes. The mean gastric volume returned back to baseline values within 45 minutes after the drink. The fasting small bowel contained a total liquid volume of 43±14ml distributed in 8±1 pockets of 4±1ml on average each. At 45 minutes, when the stomach had emptied, the total intestinal liquid had risen to 77±15ml distributed into 16±3 pockets of 5±1ml volume each.

Conclusion
MRI provided unprecedented insights on the time course, number and volume of liquid pockets in the small intestine under conditions that represent standard BA/BE studies. These data add to our current understanding of gastrointestinal physiology and will help improve physiological relevance of in vitro testing methods and in silico transport analyses for prediction of bioperformance of oral solid dosage forms, particularly for low solubility, high permeability BCS 2 compounds.