

# Hyper-osmolar (Fleet) Enema Damages Colorectal Lining Compared to Iso-osmolar (Normosol-R) Enema in Randomized, Blinded, Cross-over Comparison of Toxicity, Distribution, and Acceptability Study of Three Rectal Douches (Enemas) Identifying a Safe, Preferred Delivery Vehicle for Rectal Microbicides

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### Objectives

- Determine a relatively safe enema for use in future rectal microbicide development
- Explore the feasibility of an enema as rectal microbicide delivery vehicle

### Background

- Rectal douching (enema) prior to receptive anal intercourse (RAI) common among men who practice unprotected RAI (Carballo-Diequez 2007)
- Rectal douching associated with increased risk for HIV transmission (Coates 1988, Moss 1988)
- Tap water (hypo-osmolar) and Fleet (hyper-osmolar) enema most commonly used (Hylton 2007)
- Tap water & hyper-osmolar enemas show colonic epithelium damage (Meisel 1977, Schmelzer 2004)
- Rectal hyper-osmolar gels induce greater epithelial loss than iso-osmolar gels (Fuchs 2007)

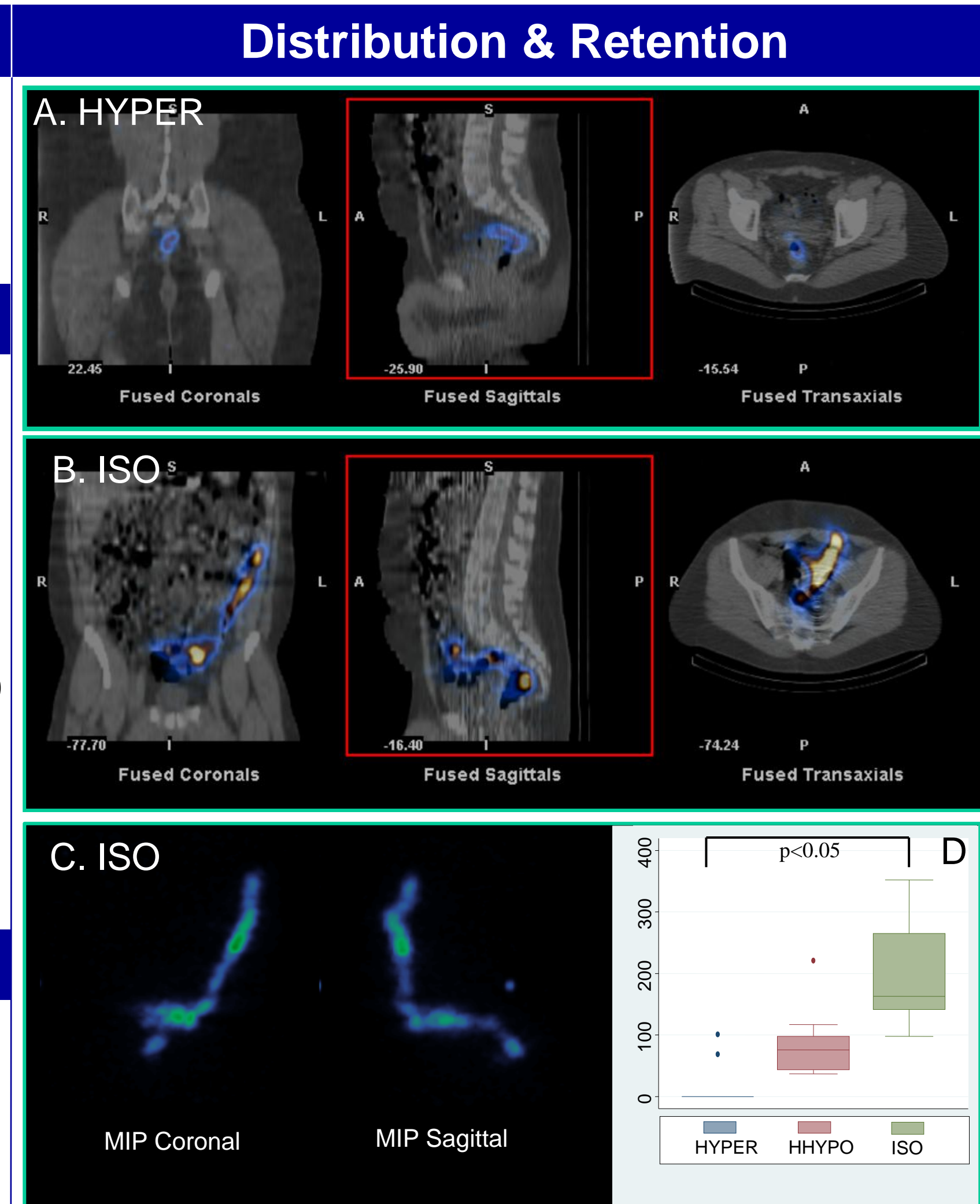
### Methods

- Randomized, blinded, comparative study.
- Population: 9 HIV negative MSM
- Administration of 125 mL enema of varying osmolality: Fleet (HYPER), tap water (HYPO), Normosol-R™ balanced salt solution (ISO)
- Doses: 1 inpatient radiolabeled dose and 3 outpatient doses (used in the context of RAI) for each of the 3 products

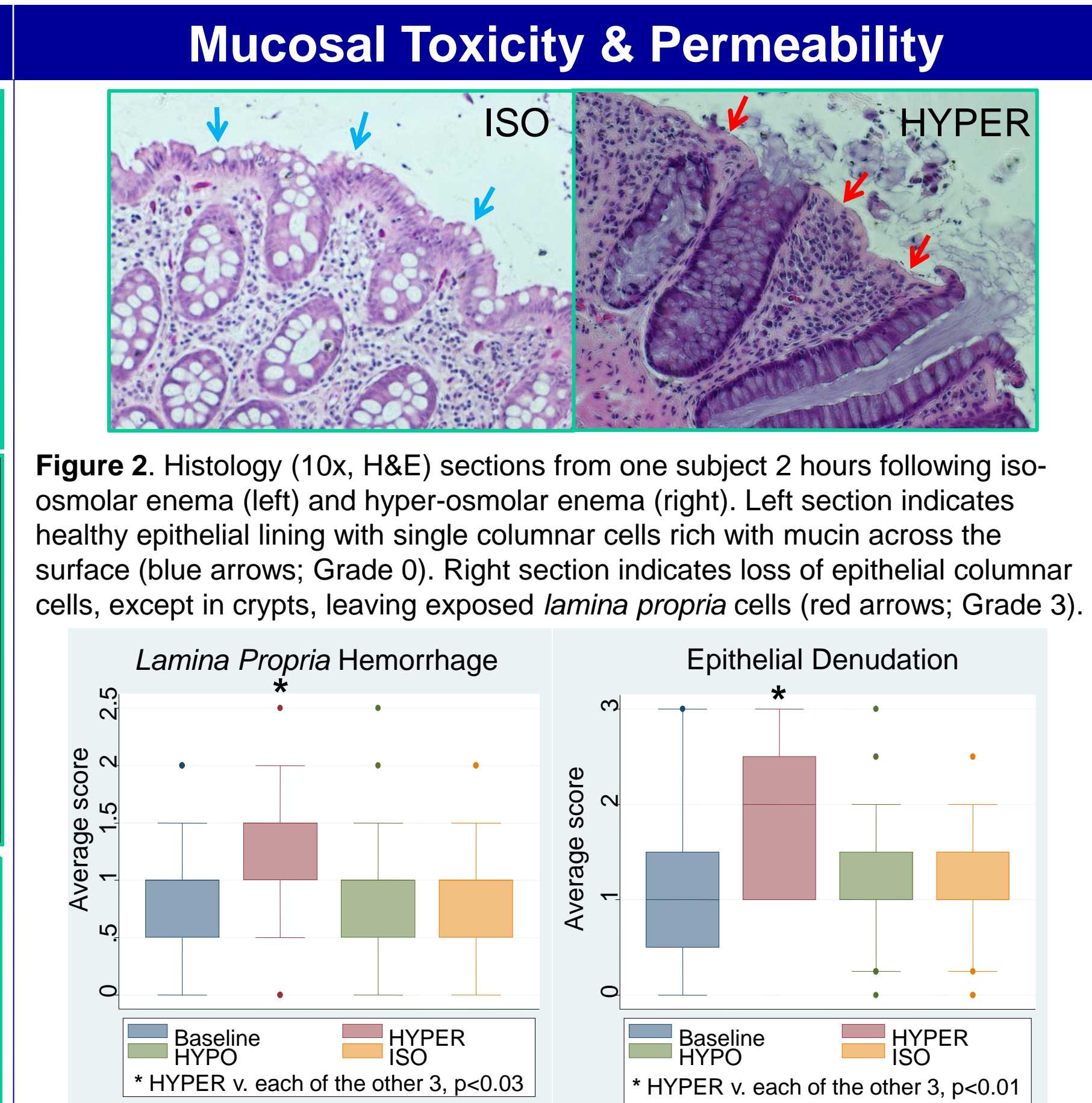
Stage 1: Enema A <6wk Stage 2: Enema B <6wk Stage 3: Enema C Study Exit

Inpt 000 Inpt 000 Inpt 000 Phone Interview

- Distribution/retention: Single photon emission computed tomography /computed tomography (SPECT/CT) imaging of radiolabeled enema @ 2 and 24 hours of inpatient dose
- Toxicity: Colonic biopsy with histology after 2 hour imaging; permeability to radiolabel for 24 hours after dose
- Acceptability: questionnaires after each dose, each product phase, and end of study; structured interviews at end

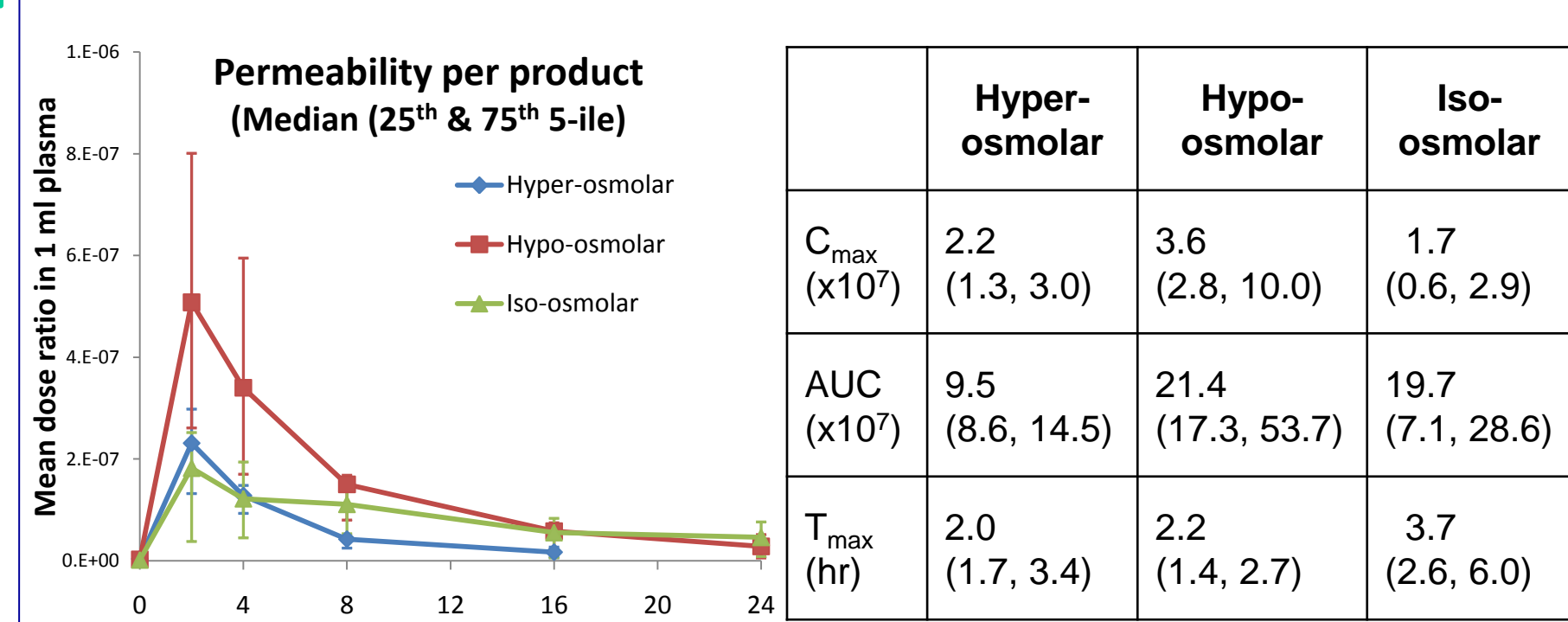


**Figure 1.** SPECT/CT Distribution 2 hours post-dose (Subject 5102). **Panel A** (top, HYPER) and **B** (middle, ISO) radiolabeled products appear in color scale SPECT image against grayscale CT image in coronal (right), sagittal (middle), and axial (left) views. HYPER distributes into rectosigmoid (further in this subject than in any other, most of which lost all signal or were restricted to rectum) while ISO distributes throughout the distal colon up to the splenic flexure (seen with ISO product in most subjects). **Panel C** (bottom left) is maximal intensity projection (MIP) which shows highest signal intensity across full thickness of SPECT scan unlike single slice in Panel A and B above. Same subject as Panel B. Signal begins in rectum, moves superior and anterior into sigmoid colon then to left and superior throughout the descending colon up to the splenic flexure. **Panel D** (lower right) boxplots of enema volume assessed 2 hours after dosing, indicating significantly greater retained volume of ISO compared to HYPER. Quantitative assessments for proximal distribution, volume retained, and residual concentration were all significantly greater for ISO compared to HYPER with HYPO intermediate (data not shown).



**Figure 2.** Histology (10x, H&E) sections from one subject 2 hours following iso-osmolar enema (left) and hyper-osmolar enema (right). Left section indicates healthy epithelial lining with single columnar cells rich with mucin across the surface (blue arrows; Grade 0). Right section indicates loss of epithelial columnar cells, except in crypts, leaving exposed lamina propria cells (red arrows; Grade 3).

**Figure 3.** Boxplots indicate median (interquartile range) of histology scores. HYPER enema was significantly greater in both scores compared to baseline, HYPO, ISO. Histologic scoring graded percent of epithelial denudation from 0% (Gr. 0) to >67% (Gr.3) and degree of lamina propria hemorrhage.



**Figure 4.** Permeability is quantified by fraction of radiolabeled dose absorbed into blood over time (right). Table shows median (25<sup>th</sup>, 75<sup>th</sup> %ile) indicating significant increase in peak and area under the curve (AUC) for HYPO product compared to HYPER (p<0.02); all other paired comparisons are not significant (p>0.05).

### Acceptability

**Table 2. Brief Acceptability Questionnaire**

Sexual satisfaction (% of occasions)	Hyper-osmolar M (SD) Range	Hypo-osmolar M (SD) Range	Iso-osmolar M (SD) Range
decreased	11.1	11.1	0
no effect	37.0	29.6	37.5
increased	51.9	59.3	62.5
Acceptability rating	3.33 (.68) 2-4	3.26 (.94) 1-4	3.33 (1.01) 1-4

**Table 3. Product Acceptability Questionnaire**

	Hyper-osmolar M (SD) range	Hypo-osmolar M (SD) range	Iso-osmolar M (SD) range
Liked douche overall	7.75(2.44) 2-10	7.67(2.83) 2-10	7.56(2.60) 2-10
Sexual enjoyment after product use	7.67(2.35) 3-10	8.22(1.79) 5-10	8.78(1.30)* 6-10
Reports of RAI being worse after douching (n)	1	2	0
Liked application process	6.89(2.47) 3-10	7.78(2.95) 1-10	8.33(1.58)* 5-10
Likelihood of future use	8.56(1.24) 7-10	8.78(1.48) 6-10	9.33(1.00) 7-10
Likelihood of use without condoms	9.86 (.38) 9-10	9.75 (.46) 9-10	9.57 (.53) 9-10
Likelihood of use if a 30-minute wait is required	8.11(1.76) 4-10	8.00(2.96) 1-10	8.44(2.83) 1-10

- Trends indicate that iso-osmolar enema has good acceptability, somewhat better than the hyper-osmolar enema.
- Subjects more neutral with respect to the hypo-osmolar enema

### Conclusions: Questions

- HYPER - greatest epithelial loss and hemorrhage; concern for transmission risk?
- HYPO - greatest permeability; enhance active drug ingredient tissue penetration?
- ISO - greatest distribution/retention/concentration, least toxicity, trend to more favorable acceptability; candidate for microbicide delivery vehicle?

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