A Preview of New Rectal Microbicides Safety Studies

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So Who Is Having Anal Sex?

The Ultimate Guide to Anal Sex for Women, Tristan Taormino, Cleiss Press Inc. San Francisco 1998
Rectosigmoid Anatomy
N-9 Effect on Rectal Epithelium

Baseline
+ 15 minutes
+ 15 minutes
+ 2 hours
+ 2 hours
+ 8 hours

Phillips et al. Contraception 2004
Effect of Osmolality on Mucosal Integrity

Iso-osmolar

Hyperosmolar

Fuchs et al J Infect Dis 2007
# Lubricants Vary in Osmolality

<table>
<thead>
<tr>
<th>Product</th>
<th>Osmolality (Median mOsm/Kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap water</td>
<td>3</td>
</tr>
<tr>
<td>Femglide</td>
<td>42</td>
</tr>
<tr>
<td>Semen</td>
<td>340</td>
</tr>
<tr>
<td>Gynol II</td>
<td>1182</td>
</tr>
<tr>
<td>Fleet enema</td>
<td>2127</td>
</tr>
<tr>
<td>KY Jelly</td>
<td>2424</td>
</tr>
<tr>
<td>Astroglide</td>
<td>3126</td>
</tr>
<tr>
<td>Prepair</td>
<td>4026</td>
</tr>
</tbody>
</table>

Fuchs et al J Infect Dis 2007
Evaluation of Rectal Safety

- Preclinical
  - Cell lines
  - Animal models
  - Formal GLP animal toxicology

- Clinical
  - Phase 1
  - Phase 2
  - Phase 3

- Post licensure surveillance
Regulatory Issues

- No specific guidance for rectal microbicide development
- Ongoing Phase 1 studies linked to vaginal microbicide IND
- FDA seems to want Phase 1 rectal safety study for any vaginal microbicide
- Rectal specific microbicide will probably need its own IND
Rectal Safety Assessment

Vaginal Microbicide (Cellulose sulfate)

Rectal Microbicide (Product X)

Combination Microbicide (Tenofovir)

Animal Toxicology

Phase 1 Rectal Safety

• Preclinical Evaluation
  • Cell lines
  • Explant studies
  • Animal models
  • Animal toxicology

• Human studies
  • Phase 1
  • Phase 2
  • Phase 2B/3
Colorectal Intestinal Explants

Endoscopic biopsies + Absorbable gelatin sponge

Rectal Model Development

Macaca nemestrina
Rectal Lavage Assay

Lavage fluid

Day 4 Combo Animal
Day 4, T0 24 hrs post 3rd application
Day 4, T30 post 4th application

*TMicrobicides 2008 Poster #TA-057*
Design of Phase 1 Rectal Safety Studies
Previous Human Rectal Studies

- Tabet et al. 1999
  - Nonoxynol-9
- Phillips et al. 2004
  - Nonoxynol-9
- McGowan et al. 2007
  - HPTN-056
- Anton et al. 2008
  - UC-781 Phase 1 rectal safety study
Tabet et al.

- Open label frequency escalation safety study of 3.5% nonoxynol-9 gel versus replens
- Population – monogamous couples
  - 25 HIV negative MSM
  - 10 HIV positive MSM
- Gel BID + RAI 3 times per week for 6 weeks
- 68 (97%) participants completed study
- Minor anoscopic or histological findings common

Tabet et al. STD 1999
Phillips et al.

- Double blind study with four participants
- Products
  - 1% nonoxynol-9
  - 2% nonoxynol-9
  - Methyl cellulose
  - PC-515 (carrageenan)
- Endpoint
  - Saline lavage 15 minutes after exposure
  - Histology and EM

Phillips et al. Contraception 2000
Lavage Fluid

Phillips et al. Contraception 2000
Phillips et al.

- 2% Nonoxynol-9
- 18 participants - open label study
- Endpoint
  - Histology
- Sampling
  - Baseline
  - + 15 minutes
  - + 2 hours
  - + 8 hours

Phillips et al. Contraception 2004
HPTN 056 Study Design

Week -2 0 +2 +4

Screening
Consent
Physical
Anoscopy
Rectal GC/CH
HIV Ab
CD4 / Viral load

Baseline
Sigmoidoscopy
Intestinal biopsy at 10cm and 30cm
Cell isolation and flow cytometry
Tissue cytokines
Rectal immunoglobulins
Tissue / rectal secretion viral load

Week 2
Week 4

McGowan et al. JAIDS 2007
UC-781 Trial Design

- **Screening**
- **Enrollment**
- **Baseline Endoscopy**
- **Randomization**

Doses:
- 0.1%
- 0.25%
- Placebo

Procedures:
- Single dose
- 2nd Endoscopy
- 7 single Doses
- 3rd Endoscopy

Anton et al. CROI 2009
# Future Phase 1 Rectal Microbicide Safety Studies

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
<th>Timeline</th>
<th>Sponsor</th>
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</thead>
<tbody>
<tr>
<td>UC-781</td>
<td>Completed</td>
<td></td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>MTN-007</td>
<td>Planned</td>
<td>Q2 2009</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>MTN-006</td>
<td>Planned</td>
<td>Q2 2009</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>VivaGel</td>
<td>Planned</td>
<td>Q4 2009</td>
<td>NIAID/DMID</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q4 2009</td>
<td>MDP MRC-UK</td>
</tr>
<tr>
<td>UC-781 (RF)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
</tr>
</tbody>
</table>
MTN-007
MTN-007

- Phase 1 randomized, double-blinded, placebo-controlled rectal safety and acceptability study of tenofovir 1% gel
- Approximately 60 sexually (RAI) abstinent, HIV-negative adults men and women
- Four study arms:
  - 1% vaginal formulation of tenofovir
  - Hydroxyethyl cellulose (HEC) placebo gel
  - 2% nonoxynol-9 (Ortho-Gynol II)
  - No product arm
Primary Objective

- To evaluate the safety of tenofovir 1% gel when applied rectally
Primary Endpoint

- Grade 2 or higher AEs as defined by:
  - The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004
  - Addenda 1 and 3 (Female Genital and Rectal Grading Tables for Use in Microbicide Studies)
Secondary Objectives

- To evaluate the acceptability of tenofovir 1% gel when applied rectally
- To evaluate the safety of HEC gel when applied rectally
- To determine whether use of tenofovir 1% gel is associated with rectal mucosal damage
- To determine whether use of 2% Nonoxynol-9 gel (Gynol-II®) is associated with rectal mucosal damage
Secondary Endpoints (1)

- Acceptability:
  - The proportion of participants who at their Final Clinic Visit report via the acceptability questionnaire that they would be very likely to use the candidate microbicide during receptive anal intercourse.
Secondary Endpoints (2)

- Safety:
  - Grade 2 or higher adverse events in the HEC gel arm
  - Mucosal safety
Secondary Endpoints (3)

- Mucosal safety parameters:
  - Epithelial sloughing
  - Intestinal histopathology
  - Intestinal mucosal mononuclear cell phenotype
  - Intestinal mucosal cytokine Intestinal mucosal gene expression arrays
  - Cytokine profile in rectal secretions
  - Fecal calprotectin
  - Microflora
Exploratory Objective

- To determine whether regional heterogeneity exists between mucosal endpoints in samples collected at 9 cm and 15 cm for all parameters examined.
- To determine whether there is a correlation between histological abnormality and changes in mucosal biomarkers.
Exploratory Endpoints

- Epithelial sloughing
- Intestinal histopathology
- Intestinal mucosal mononuclear cell phenotype
- Intestinal mucosal cytokine mRNA
- Intestinal mucosal gene expression arrays
- Cytokine profile in rectal secretions
- Fecal calprotectin
- Microflora
MTN-007 Design

N=60

2% N-9 (N=15)

1% Tenofovir (N=15)

HEC (N=15)

No Treatment (N=15)

Baseline Evaluation

Single dose

7 day daily doses

7-14 day interval

Endoscopy Safety/behavioral assessment

Screening
MTN-007 Study Sites

- Pittsburgh, PA
  - IOR: Ross Cranston MD
- Birmingham, AL
  - IOR: Craig Hoesley MD
- Boston, MA
  - IOR: Ken Mayer MD
Why have an N-9 arm in MTN-007?

- Assessment of mucosal injury requires the use of esoteric and expensive assays
- Preliminary data from a UC-781 Phase 1 rectal safety study have not demonstrated changes in these mucosal safety parameters
- Rectal exposure to N-9 results in mild and transient epithelial disruption
  - Mice
  - Macaques
  - Humans
Safety Biomarkers

Anton et al. Microbicides 2008
Is inclusion of an N-9 arm safe?

- Histological recovery occurs within 1-8 hours
  - Mice
  - Humans
  - Macaques
- Tabet et al. demonstrated minimal histological inflammation after up to 6 weeks treatment with a 3.5% formulation of N-9
- All participants in MTN-007 will be sexually abstinent
Current Status of MTN-007

- Protocol completed
- Undergoing regulatory review
- Anticipated enrolment starts
  - July 2009
- Completion
  - June 2010
Acknowledgements

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Bargello Museum, Florence, Italy