Rectal Microbicides

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Overview

- Rationale for rectal microbicide development
- Non-clinical evaluation of rectal microbicide candidates
- Design of Phase 1 rectal safety studies
- Rectal microbicide advocacy
- Implications for vaginal microbicide development
Rationale for Rectal Microbicide Development
Rectosigmoid Anatomy
Heterosexual Anal Intercourse in the US

- Gross M et al. 2000
- Civic D et al. 2000
- Mosher WD et al. 2005
- Erickson PI et al. 1995

(%) Lifetime experience of AI

(%) Lifetime experience of AI
EX-US Prevalence of Female RAI

US HIV Incidence in MSM

Sifakis F et al. JAIDS 2007
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
Non-Clinical Evaluation of Rectal Microbicide Candidates
MTN Algorithm

Products

Formulation Testing
- Osmolarity, pH, viscosity, in vitro release

In vitro Testing
- Dose Range
  - Cell lines
  - Lactobacillus
- HIV efficacy

Ex vivo Testing
- Cervical/colorectal tissue
- Absorption, permeability, and safety
- HIV efficacy

Human Studies
## Product Safety

### TFV 1% vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Active Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolarity</td>
<td>3347 nmol/kg</td>
<td>3189 nmol/kg</td>
</tr>
<tr>
<td>pH</td>
<td>4.45</td>
<td>4.39</td>
</tr>
</tbody>
</table>

Iso-osmolar is 290 nmol/kg

### SPL7013 vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Active Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolarity</td>
<td>683 nmol/kg</td>
<td>803 nmol/kg</td>
</tr>
<tr>
<td>pH</td>
<td>5.25</td>
<td>4.86</td>
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</table>
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

*Microbicides 2008 Poster #TA-057
Design of Phase 1 Rectal Safety Studies
UC-781 Trial Design

Screening  Enrollment  Baseline Endoscopy  Randomization

0.1%  0.25%  Placebo

Single dose  2nd Endoscopy  7 single Doses  3rd Endoscopy
UC-781 Phase 1 Rectal Safety Study

- **Secondary Objective:**
  - To determine whether use of study product is associated with rectal mucosal damage

- **Endpoints:**
  - Epithelial sloughing
  - Histopathology
  - Mucosal mononuclear cell phenotype
  - Mucosal cytokine mRNA
  - Mucosal immunoglobulins
  - Fecal calprotectin
  - Explants- Mucosal cytokine mRNA and susceptibility to HIV infection
Interim Results

• Appears safe and well-tolerated
• Subjects highly compliant
• Procedures well tolerated
• No drop outs/withdrawals
• No Grade 3 or 4 AE
• No procedure related AE
• 7 Grade 2 AE reported in 4 of 19 individuals completing
Explant Infection Kinetics After Single Dose of UC-781

Cumulative P-24 of explants at V3
(Viral_inoculum=10000, Biopsy_location=10cm, Visit_code=V3)

Days Post Explant Infection
MMC Phenotypes

<table>
<thead>
<tr>
<th>Group</th>
<th>% CCR5+ on CD4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>U19 (All) (n=27)</td>
<td></td>
</tr>
<tr>
<td>U19 (Non-resp) (n=9)</td>
<td></td>
</tr>
<tr>
<td>U19 (Med) (n=9)</td>
<td></td>
</tr>
<tr>
<td>U19 (Responder) (n=9)</td>
<td></td>
</tr>
<tr>
<td>HPTN056 (n=8, v=24)</td>
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Group: V2 V3 V5
Rectal Specific Applicators

- Incorporates Fleet™ tip
- Can be operated with one hand
- Has grips for the fingers
- Can deliver a precise dose up to 10 ml
- Used across clinical trials, this MDD will reduce sources of acceptability and adherence variability
- Can be manufactured in gray color
SPECT Linearization
Rectal Lymphocyte Distribution

\(^{99m}\text{Tc}-\text{Sulfur Colloid}\)
\(^{111}\text{In}-\text{Lymphocytes}\)

Cell-free HIV Surrogate
Cell-Associated HIV Surrogate
Normal Anal Canal

Epithelial Abrasion
Target Cells in Anal & Rectal Tissue

Rectal

Anal
# 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>Ongoing</td>
<td></td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>Polyanion</td>
<td>Planned</td>
<td>Q3 2008</td>
<td>NIAID/DMID</td>
</tr>
<tr>
<td>PRO-2000</td>
<td>Planned</td>
<td>Q2 2008</td>
<td>MDP MRC-UK</td>
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<tr>
<td>MTN-007</td>
<td>Planned</td>
<td>Q3 2008</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>MTN-006</td>
<td>Planned</td>
<td>Q3 2008</td>
<td>NIAID/DAIDS</td>
</tr>
<tr>
<td>UC-781 (RF)</td>
<td>Possible</td>
<td>Q4 2010</td>
<td>TBD</td>
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Rectal Microbicide Advocacy
A Global Force in Rectal Microbicide Advocacy

500+ members
40 countries
6 continents
Implications for Vaginal Microbicide Development
Impact of Rectal Sex on Power

Transmission Probability: 1X, 10X, 20X
Behavior at Enrollment by Arm in HPTN-059

<table>
<thead>
<tr>
<th></th>
<th>Coitally Dependent</th>
<th>Daily Use</th>
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<tbody>
<tr>
<td></td>
<td>Tenofovir</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=50</td>
<td>N=51</td>
</tr>
<tr>
<td>Ever anal sex</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Anal sex,</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>(past 7 days)</td>
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Summary

- Increasing evidence of RAI in heterosexuals and MSM
- Phase 1RM safety design evolving
- New animal models
  - NHP repeated low dose
  - Humanized mouse
- Research focus needs to shift from safety to efficacy
Acknowledgements

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