Levonorgestrel/Tenofovir
Intravaginal Ring
MTN Annual Clinical Meeting 2016

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Phase I One-Month Safety, PK, PD, and Acceptability Study of Intravaginal Rings Releasing Tenofovir and Levonorgestrel or Tenofovir Alone (Protocol A13-128)

- First multipurpose ring in clinical trials (first patient screened OCT 2015)
- 86 women consented to complete 50 across 2 sites:
  - EVMS, Norfolk, VA: Annie Thurman, PI
  - Profamilia, Santo Domingo, DR: Vivian Brache, PI
- 3 treatment groups, randomized 2:2:1
  - TFV-only ring (8 – 10 mg/day) (n=20)
  - TFV (8 – 10 mg/day)/LNG (20 ug/day) ring (n=20)
  - Placebo ring (n=10)
- About 1 month of use, total 3 months participation
- 8 or 9 visits and 1 follow-up contact
Objectives

• Primary:
  – Genital and systemic safety
• Secondary:
  – Pharmacokinetics (PK) of LNG and TFV
• Tertiary:
  – Pharmacodynamics (PD) of LNG
  – Acceptability
• Exploratory:
  – PD Surrogates of TFV and LNG
  – Other markers of genital safety
  – Correlation of less/more invasive TFV PK eval
  – Objective biomarkers of IVR Adherence
## Study Design and Relation to Cycle Days

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Screening/Enrollment</th>
<th>Pre-treatment cycle to document ovulation</th>
<th>Ring in place</th>
<th>After ring removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>Visit 1</td>
<td>Visit 2, Visit 3</td>
<td>Visit 4</td>
<td>Visit 8 (24 hrs after Visit 7)</td>
</tr>
<tr>
<td>Visit 2</td>
<td></td>
<td></td>
<td>Visit 5</td>
<td>Visit 8 (24 hrs after Visit 7)</td>
</tr>
<tr>
<td>Visit 3</td>
<td></td>
<td></td>
<td>Visit 6</td>
<td>Visit 8 (24 hrs after Visit 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visit 7</td>
<td>Visit 9 (72 hrs after Visit 7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ring Day</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle Day</td>
<td>Any day</td>
<td>21</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

- As determined by ovulation predictor kit.
- Expect to see greatest effects of LNG at Visit 6:
  - Less favorable cervical mucus and poorer sperm migration
Primary Endpoints: Genital and Systemic Safety

- Treatment-emergent adverse events
- Changes in serum chemistries, lipids, and complete blood count (CBC)
- Development of cervicovaginal ulcerations, abrasions, edema, and other findings as assessed by naked eye and colposcopic visualization of the cervicovaginal epithelium
Primary Endpoints: Genital and Systemic Safety

- $\Delta$ in soluble markers of innate mucosal immunity and inflammatory response in the CVL (Baseline versus s/p TX)
- $\Delta$ in HIV-1 target cells, phenotype
- $\Delta$ in semi-quantitative vaginal culture and/or unculturable 16S RNA bacteria by quantitative PCR
- $\Delta$ in Nugent Score
Secondary Endpoints: PK of TFV and LNG

- [TFV] in plasma, CV fluid (aspirate and swab), and genital tissues
- [TFV-DP] concentrations in PBMCs and genital tissue
- [LNG] in blood, vaginal secretions (swabs) and cervical mucus
- SHBG in blood
- Weight of returned IVRs
- Amount of drug in returned IVRs
Tertiary Endpoints: PD of LNG

Surrogates of contraceptive efficacy:

- Cervical mucus assessment
  - Cervical mucus quality (Insler Score of $\geq 10$)
  - Sperm migration on the Simplified Slide test
- Ovulation by serum progesterone (P4)
- Effect on follicular development by serum estradiol concentration
Tertiary Endpoints: Acceptability

- Discontinuations
- Expulsions
- Removals
- Visible changes documented on photographs of returned IVRs
- Responses to key questions on acceptability questionnaire
Surrogates of Contraceptive Efficacy

- Cervical Mucus Sample at LH Surge (3 aliquots)
  - Cervical Mucus Quality (Insler Score)
  - In Vitro Sperm Penetration Assay (Simplified Slide Test)
  - Cervical Mucus LNG Concentration (USC Lab, Natavio et al)
- Blood
  - Serum LNG Concentration
  - Serum Progesterone Levels – Ovulation (no TVUS)
- Endometrial Characteristics
Cervical Mucus Quality

- Cervical Mucus Quality (Insler Score) normally a marker of fertility
  - Is poor cervical mucus (9 or less) a contraceptive PD marker?
- LNG = thick mucus in prior/current contraceptives, even in ovulatory cycles
  - Cervical mucus becomes poor in 7 out of 10 one day after Mirena IUS insertion, in 10 out of 10 by third day
    - Natavio 2012 Contraception 87(4):426-31
  - Skyla IUS users with poor cervical mucus
Sperm Penetration Assay in Prior Contraceptive Studies

- Norplant: 3d post insertion, sperm penetration becomes poor despite high estradiol levels
  - Dunson 1998 Fertil Steril 69: 258-66

- Mirena IUS: 1d post insertion, 9/10 with poor sperm penetration (SST), no sperm migration despite ovulation
  - Lewis 2010 Contraception 82(6):491-6

- LNG 20 µg ring: Inhibition of sperm migration in 92% of post-coital tests
  - WHO J Steroid Biochem 1979;11:461-7
LNG Concentrations in Cervical Mucus

- Exploratory endpoint (USC Laboratory)
- N = 10, urinary LH and CM Insler score
- LNG IUS inserted at LH surge/peak CM quality (day 10 – 16)
- Insler Score, Sperm Penetration, Serum LNG, Serum P4, CM LNG obtained 1, 3 and 5 days post IUS insertion

- Natavio et al Contraception 2012 87(4):425-31
# Plasma [LNG] Historic Data

## 20 ug/day IVR

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Plasma LNG</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.6 – 1.1 nmol/L</td>
<td>Mean 134 lbs. Plasma levels 72% of initial at 6 mos., 52% of initial at one year. LNG IVR for 1 year.</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>Mean 0.7 nmol/L, range 0.6 – 1.1 nmol/L</td>
<td>LNG IVR for 90 days</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>419 – 682 pg/mL</td>
<td>LNG IVR for 90 days. Plasma levels were 54% of initial at 3 months</td>
</tr>
</tbody>
</table>

Range is 187 – 682 pg/mL or 0.6 – 1.1 nmol/L

1 = Landgren et al. Contracept 1986;33:473-85  
3 = Xiao Bilian et al Contracept 1985;32;455-71.
### [LNG] Concentrations from Previous LNG Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Product</th>
<th>Plasma LNG Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 3</td>
<td>20 ug/day IVR</td>
<td>187 – 682 pg/mL or 0.6 – 1.1 nmol/L</td>
</tr>
<tr>
<td>4 – 6</td>
<td>20 ug/day IUS</td>
<td>147 – 428 pg/mL or 0.470 – 1.37 nmol/L</td>
</tr>
<tr>
<td>7</td>
<td>13.5 ug/day IUS</td>
<td>61 – 192 pg/mL</td>
</tr>
<tr>
<td>8</td>
<td>LNG Implant (Jadelle)</td>
<td>280 - 435 pg/mL (7 years 224 pg/mL)</td>
</tr>
<tr>
<td>9 – 11</td>
<td>LNG Implant (Norplant)</td>
<td>250 – 370 pg/mL</td>
</tr>
</tbody>
</table>

Serum P4 Concentrations and Ovulation

• Expect ovulation in 40 – 50% of participants

• Elected to not follow follicular development via TVUS
Interim Analysis Results

- **Purpose:**
  - To obtain early indication of ring performance so that reformulation work, if needed, can start as soon as possible.

- **Evaluated:**
  - TFV and LNG PK
  - LNG PD

- **19 participants**
  - 2 placebo
  - 9 TFV-only ring
  - 8 TFV/LNG ring

- **CONRAD blind to individual participants’ data**
TFV PK: Interim Analysis

• Achieved targeted TFV and TFV-DP in vaginal tissues within 24 hours of insertion
• Achieved targeted 8 – 10 mg/day TFV release from ring
LNG PK: Interim Analysis

- LNG in Cervical Mucus similar to 52 mg LNG IUS users (Natavio et al study)
- LNG in plasma higher than previous 20 ug LNG IVRs, with peak at 24 hours
LNG PD: Interim Analysis

- Ovulation in <50% of TFV/LNG IVR users (of those who ovulated, all protected by either poor cervical mucus or abnormal SPA)
  - Ovulation in TFV IVR + Placebo IVR 73%
- Cervical Mucus Quality score < 10 in 100% of TFV/LNG IVR users (mean = 4)
- Sperm Migration normal in few TFV/LNG IVR users
- Endometrium thinner (mean 8 mm) in TFV/LNG IVR users
Preliminary Conclusions from Interim Analysis

• TFV:
  • Low systemic exposure
  • Levels in aspirate and tissue high 24 hours after insertion and sustained
  • Distributed throughout vagina
  • Release rates in the target range

• LNG:
  • Systemic levels somewhat higher than older rings
  • Cervical mucus levels similar to LNG 52 mg IUS users
  • Effect evident systemically and locally
  • Insertion and comfort during use very good

Based on preliminary interim analysis results, no obvious need for reformulation
Current Status Study

- Participant follow up complete and sites closed out January 2016
- CRF Database locked February 2016
- As of February 2016, all samples shipped to respective central laboratories; endpoint analysis ongoing
Next Steps

• Proceed to 90 day PK/PD study
• Human Centered Design Data for MPT Ring highly favorable (Project EMOTION)
  – Contraceptive component reduce stigma
• High unmet need for effective contraception and microbicide product
• TFV HSV prevention indication