
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

	Screening/ Enrollment	Pre-treatment cycle to document ovulation		Ring in place				After ring removal	
Visit #	Visit 1	Visit 2	Visit 3	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation*	Visit 7 Ring removal	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Ring Day	NA	~-14	~-10	1	2	~8	~16-18	~17-19	~19-21
Cycle Day	Any day	21	24	7	8	~14	~22-24	~23-25	~25-27

- 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

- Δ in soluble markers of innate mucosal immunity and inflammatory response in the CVL (Baseline versus s/p TX)
- Δ in HIV-1 target cells, phenotype
- Δ in semi-quantitative vaginal culture and/or unculturable 16S RNA bacteria by quantitative PCR
- Δ 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 ≥ 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
 - Apter 2014 Fertility and Sterility 2014;101(6):1656-62

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
 - » Natavio et al. Contraception 2012 87(4):426-31.
 - » 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

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

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

- 1 = Landgren et al. Contracept 1986;33:473-85
- 2 = Landgren et al. Contracept 1982;26:567-85.
- 3 = Xiao Bilian et al Contracept 1985;32;455-71.

[LNG] Concentrations from Previous LNG Studies

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

1 = Landgren et al. Contraception 1986;33:473-85, 2 = Landgren et al. Contraception 1982;26:567-85, 3 = Xiao Bilian et al Contraception 1985;32:455-71, 4 = Seeber et al. Contraception, 2012. 86(4): p. 345-9., 5 = Lockhat et al. Fertil Steril, 2005. 83(2): p. 398-404., 6 = Hidalgo et al. Contraception, 2009. 80(1): p. 84-9., 7. Bayer Health Care. Skyla Package Insert 8. Sivin et al 2001 Contraception 64:43-49 9. Olsson, S.E., et al., Contraception, 1987. **35**(3): p. 215-28. 10. Sivin, I., Drug Saf, 2003. **26**(5): p. 303-35. 11. Croxatto, H.B., et al., Contraception, 1981. **23**(2): p. 197-209.

Serum P4 Concentrations and Ovulation

- Expect ovulation in 40 – 50% of participants
 - Landgren BM et al. Contraception 1982;26:567-85.
 - WHO. Journal of Steroid Biochemistry. 1979;11:461-467.
- 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

Acknowledgements



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