



INTERNATIONAL  
PARTNERSHIP FOR  
MICROBICIDES

# Microbicide-Contraceptive MPT Ring

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*MTN Annual Meeting, March 17<sup>th</sup>, 2015  
Bethesda MA*

*Developing HIV Prevention Products  
for Women worldwide*

# Target Product

A 90-day vaginal ring providing hormonal contraception and prevention of HIV infection



# Development Strategy

Streamlined pathway to approval by leveraging existing products



MICROBICIDE



25 mg Dapivirine Vaginal Ring (28 days)

CONTRACEPTION

Levonorgestrel



# Approval Strategy Disclaimer

All approval strategies or pathways proposed herein are potential approaches proposed by the IPM development team and are not intended to reflect any FDA-approved approach.

Prior to initiation, and during clinical development of this product detailed consultation with the FDA will be required.



# Levonorgestrel

## Approval Strategy:

We anticipate that a contraceptive efficacy study will be required for product approval.

## Mechanistic Goal:

High potency contraception based on systemic effects on ovarian cycling similar to currently marketed products.



# Dapivirine

## Approval Strategy:

To demonstrate that the 90-day ring delivers more dapivirine on any single day of use than the lowest daily dose delivered by the 28-day ring.



# Key Product Characteristics

- Matrix ring of the same dimensions as the Dapivirine Vaginal Ring
- Silicone Polymer: Pt-catalysed (addition-cured)
- Developed for 90-days of use
- Stable for at least 36 months for SSA environment

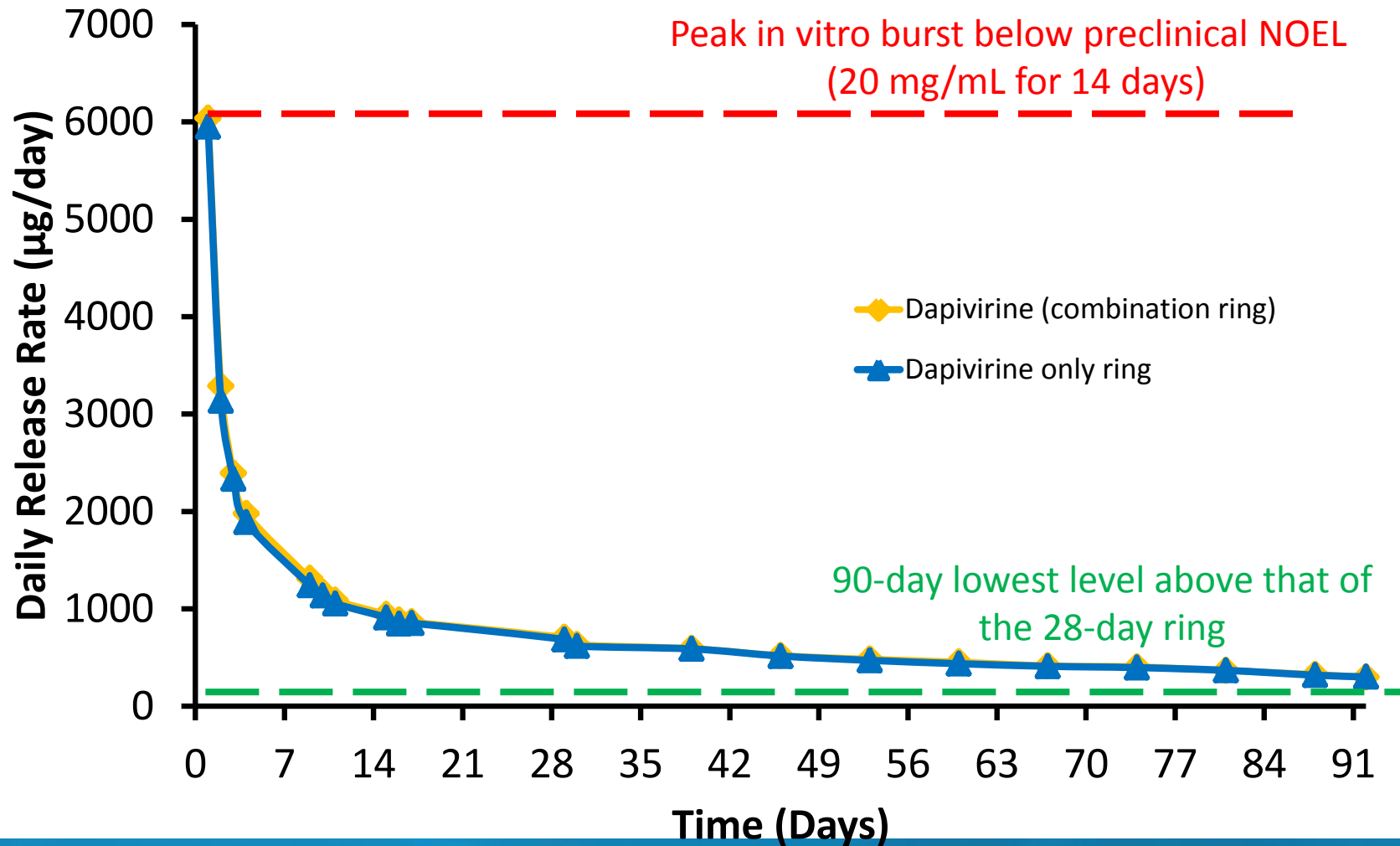


# Selection of Target Dose Levels





# Dapivirine release in IPA:water



# Levonorgestrel Exposure

- Pharmacokinetic targets derived from literature
  - Low dose: > 250 pg/mL in plasma
  - High dose: > 350 pg/mL in plasma

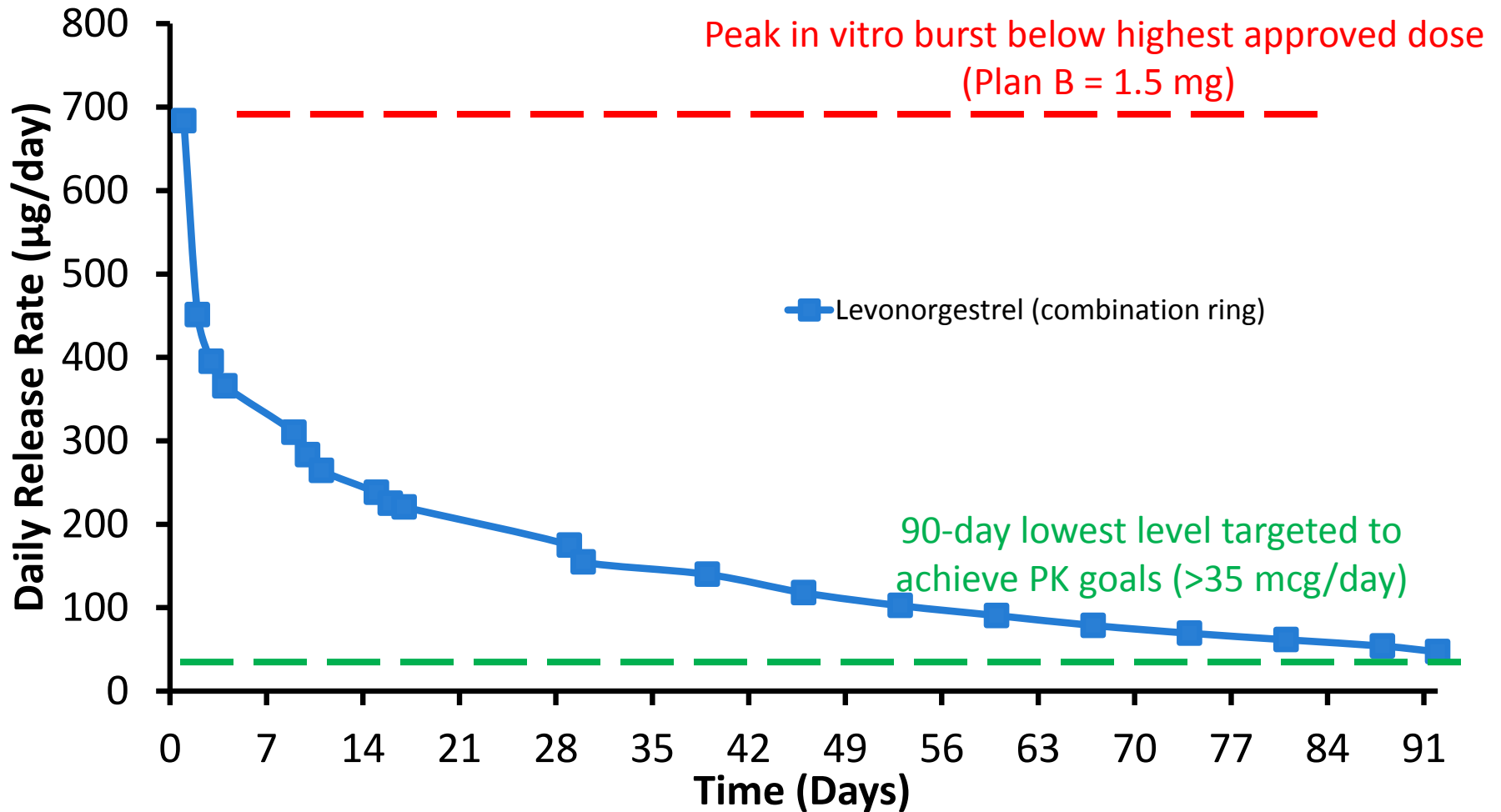


# Levonorgestrel Dose

- Multiple components incorporated
  - Extrapolation from literature on vaginal PK in women  
(Landgren '85, '86, '94; Brache '07, Sitruk-Ware '09,'09; Kives '05; Devoto '05)
  - In vitro release rates in high solvent (IPA:water) and “physiologic” (acetate buffer/solutol) conditions
  - In vivo release in sheep
  - Sheep PK (data pending)
  - CONRAD Phase I PK (data pending)



# Levonorgestrel release in IPA:water



# In vitro and In vivo release data



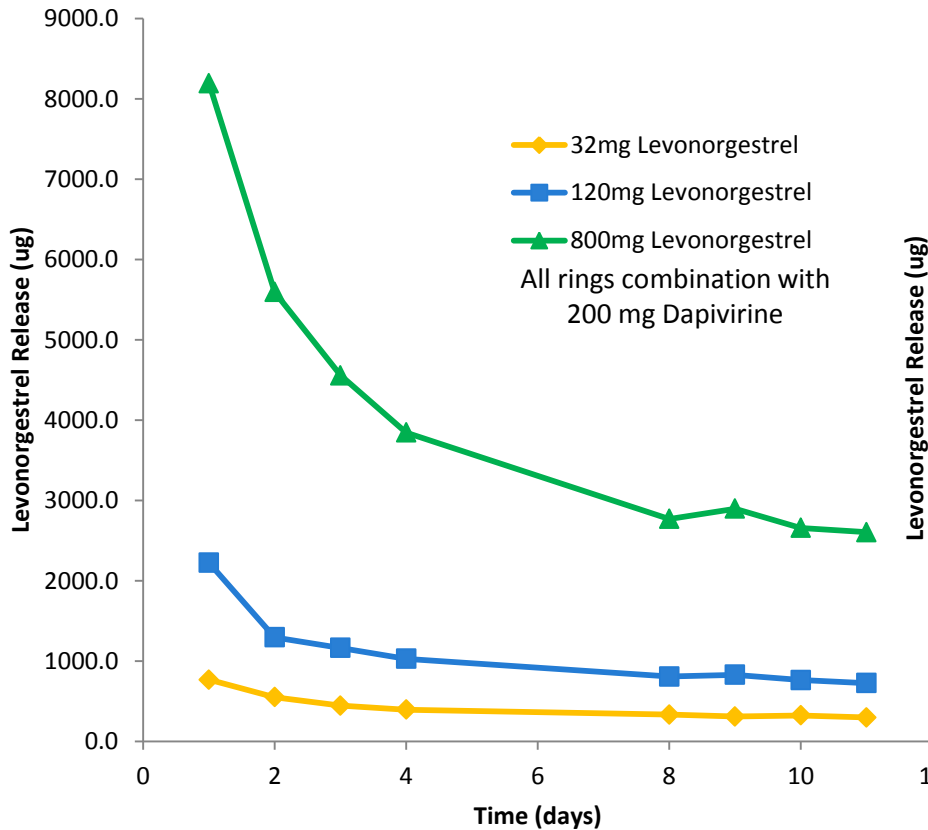
# Release Modelling in Sheep

- Female sheep with ring in place for 5, 10 or 15 days
- Dapivirine only: 75, 200 and 530 mg
- 200mg Dapivirine with 32, 120 and 800 mg Levonorgestrel
  
- In vitro release (IPA:water and acetate/solutol)
- Residual drug levels after use
- Plasma and vaginal fluid PK

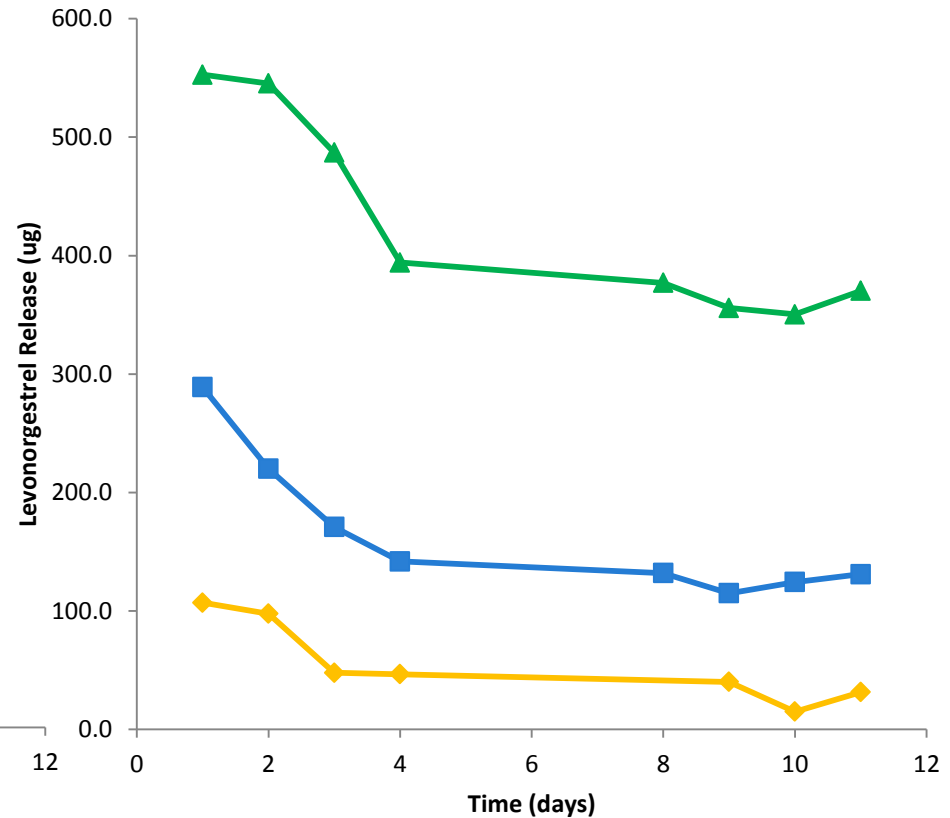


# Levonorgestrel In vitro release

## In vitro release (IPA:Water)

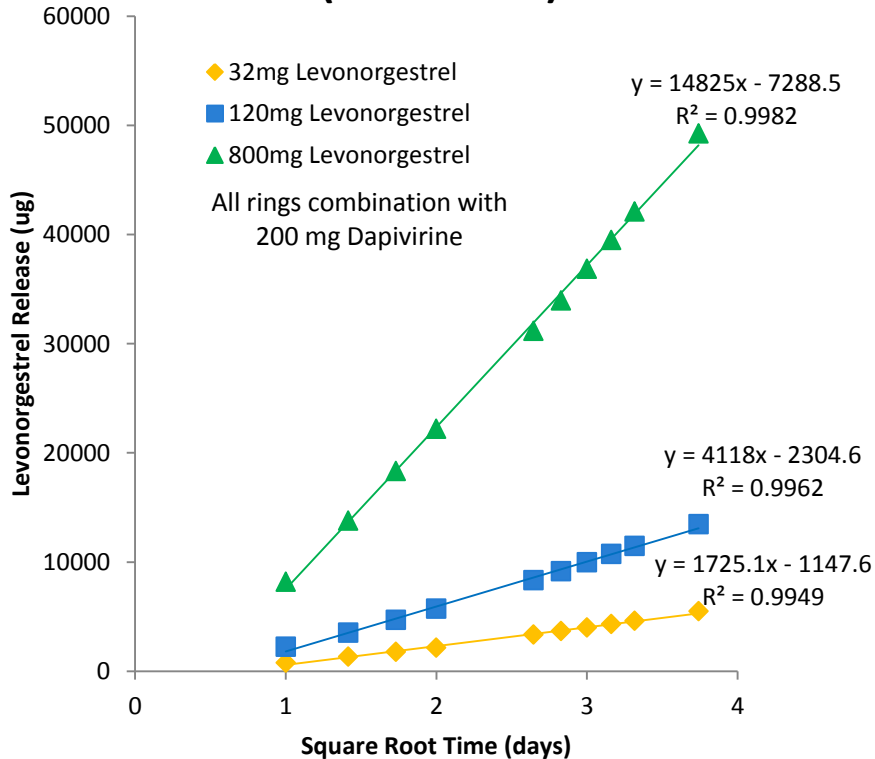


## In vitro release (Acetate/solutol)

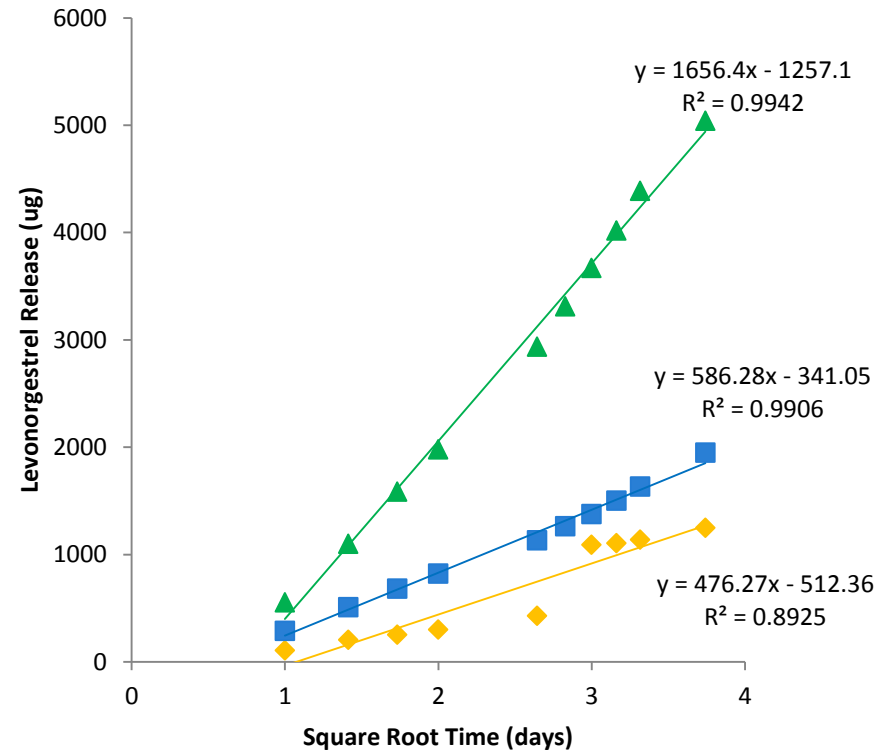


# Levonorgestrel Cumulative Release (In vitro)

## Cumulative Release (IPA: Water)



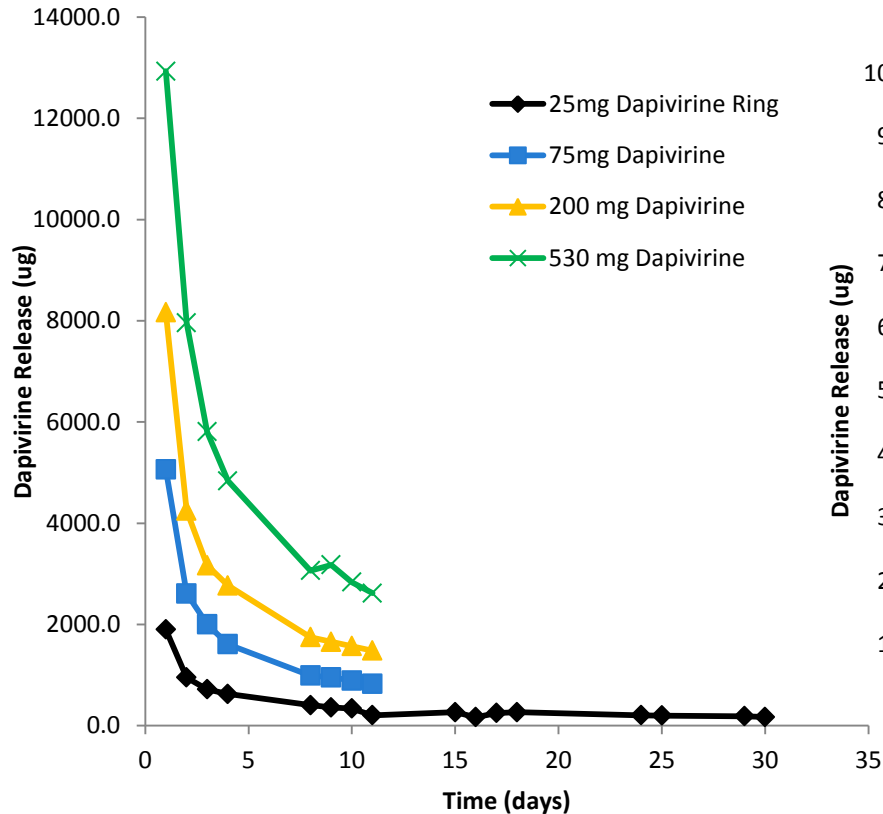
## Cumulative Release (Acetate/Solutol)



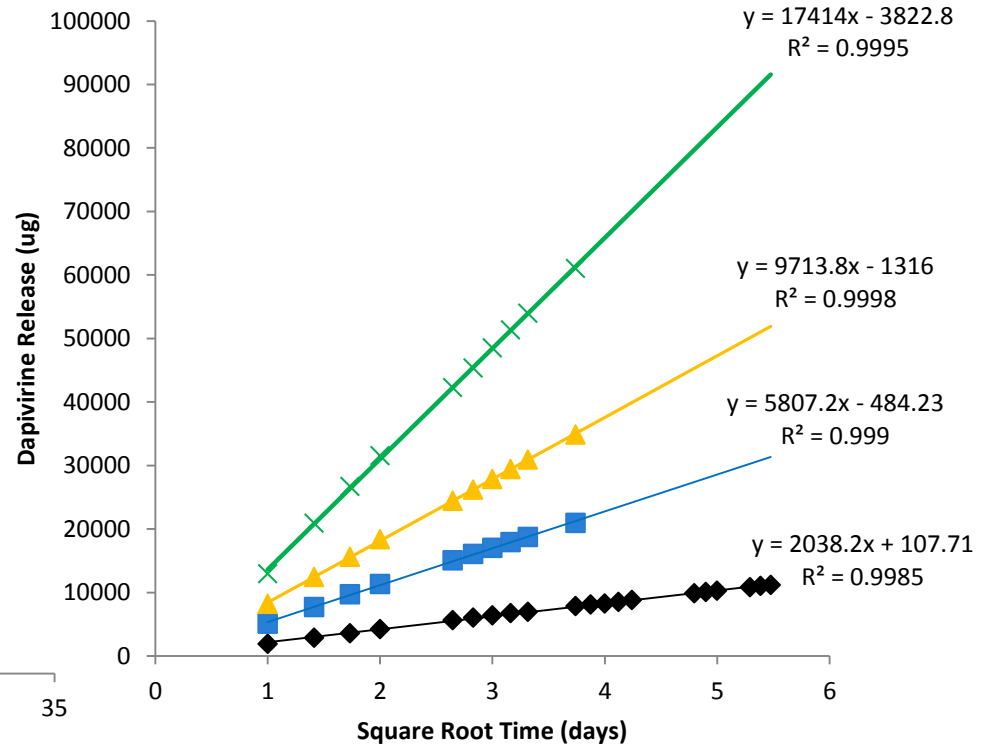


# Dapivirine In vitro Release

## In vitro release (IPA:Water)



## Cumulative Release



# Release Values ( $\mu\text{g}/\text{day}$ )

Levonorgestrel load		32 mg	120 mg	800mg
Day 1	IPA:Water	768	2224	8190
	Acetate/solutol	107	289	553
Day 90 (predicted)	IPA:Water	91	218	784
	Acetate/solutol	25	31	88

Dapivirine Load	25 mg	75 mg	200 mg	530 mg
Day 1	1901	5063	8164	12928
Day 28 actual	198	NA	NA	NA
Day 28 (predicted)	194	553	926	1660
Day 90 (predicted)	107	307	513	920

Dapivirine release testing in IPA:water



# Target Drug Loads

- Dapivirine: 200 mg load
- Levonorgestrel load estimates
  - 64 mg LNG and 200 mg DPV
  - 150 mg LNG and 200 mg DPV
- Pending confirmation with data from
  - Sheep pharmacokinetics
  - CONRAD Phase I PK



# Phase I Design Overview

*(IPM 041 / MTN-030)*



# Study Objectives

- First in Human Safety and Pharmacokinetic study:
  - Safety and tolerability (Primary objective)
  - Local and systemic PK (Primary objective)
  - Residual levels of DPV and LNG in rings
  - PD measures of contraceptive effects
  - Vaginal bleeding rates



# Draft Phase I Clinical Design

- Randomized, double-blind, placebo-controlled study in 32 healthy HIV-negative women, aged 18-45 years with demonstrated ovulation
- Randomized in 1:1:1:1 ratio, to use a vaginal ring for 90 days:
  - Placebo
  - Dapivirine (200mg) + 64mg levonorgestrel ring
  - Dapivirine (200mg) + 150mg levonorgestrel ring
  - Dapivirine 200mg only ring

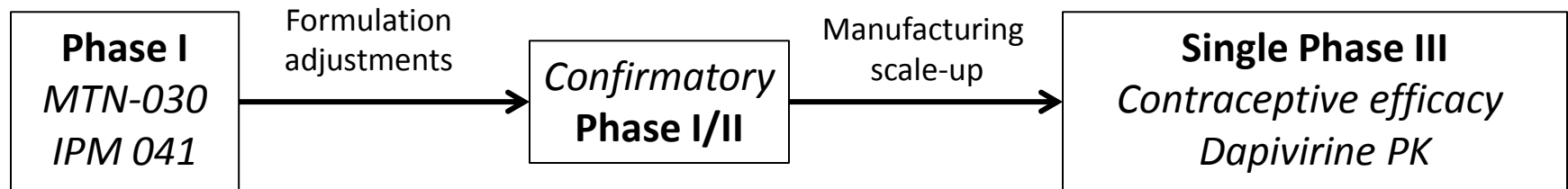


# Program Status

- Ring formulation defined
- Technology Transfer to GMP manufacturer underway
- Final LNG dose levels defined by sheep data in March/April 2015
- Clinical rings manufacture starting end Q3 2015
- IND filing Q4 2015



# Overall Development Plan



- Safety and PK
- Contraceptive PD
- Two LNG dose levels

- PK confirmation
- Refined contraceptive PD
- Possibly larger groups sizes
- Single active dose level



# Acknowledgements



**USAID**  
FROM THE AMERICAN PEOPLE



- QUB
  - Karl Malcolm
  - Clare McCoy
  - Diarmaid Murphy
  - Peter Boyd
  - Susan Featherstone
- IPM Product Team
  - Brid Devlin
  - Andrew Brimer
  - Wendy Blanda
  - Euan Seaton
  - Tiffany Derrick
  - Kathie Windle

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