INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

IPM's Next Generation Products

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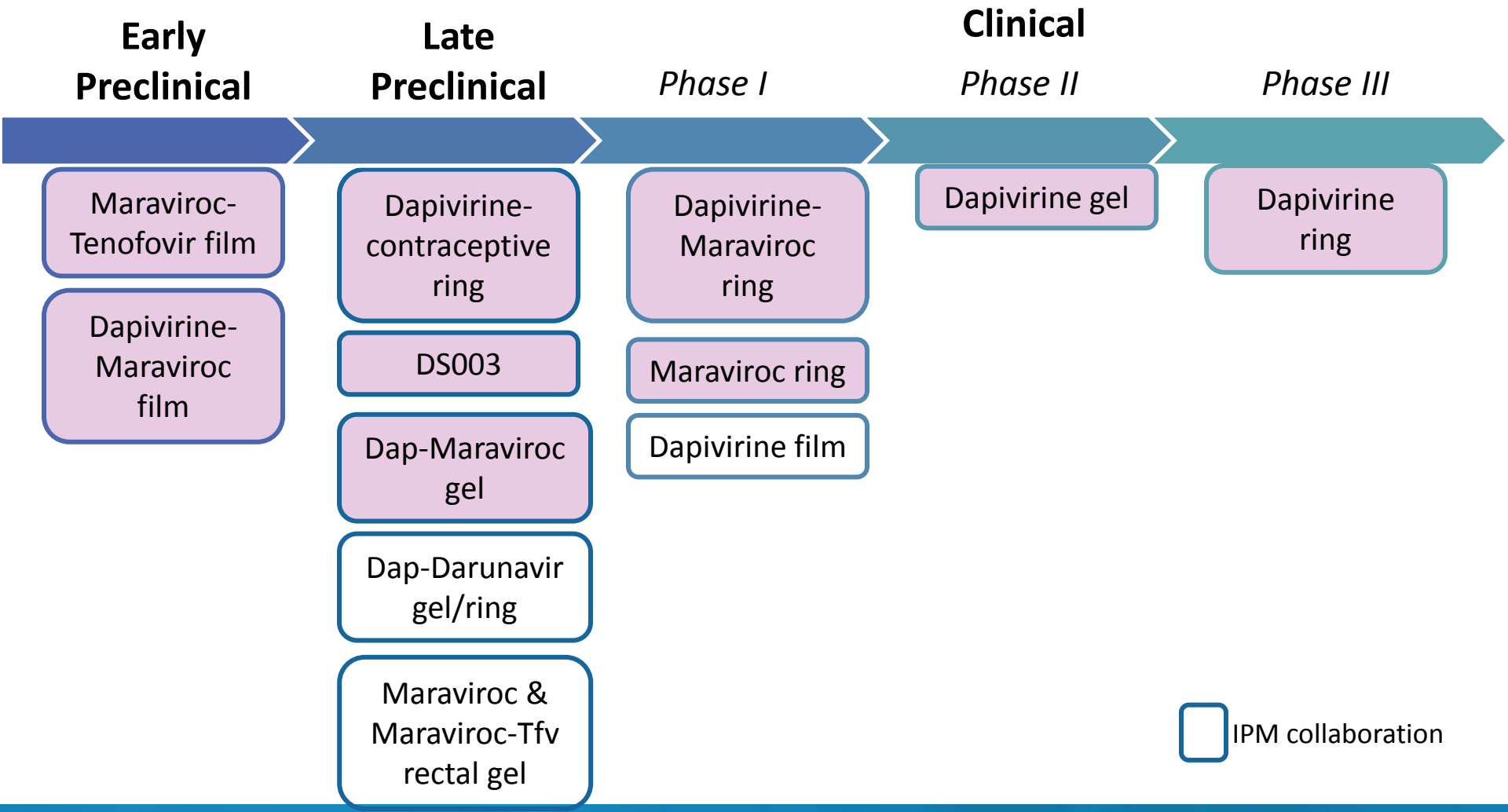
Developing HIV Prevention Products for Women worldwide

Summary of IPM Pipeline by Stages



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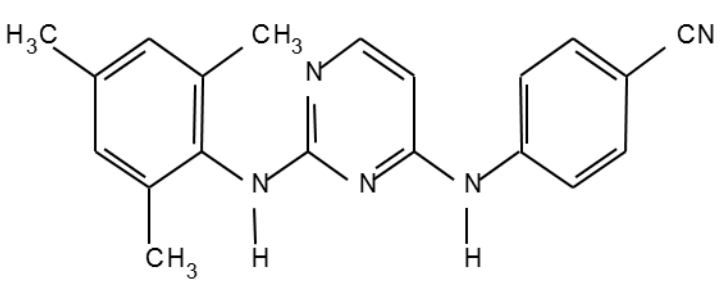
Dapivirine (TMC120)

- Highly potent ARV: non-nucleoside reverse transcriptase inhibitor (NNRTI)
- Developed by Janssen R&D Ireland
  - Originally tested as oral therapeutic in 11 clinical studies



- Licensed to IPM in 2004
  - Development as topical microbicide for HIV prevention in developing countries
- 15 Phase I/II safety studies (dapivirine ring or gel)
  - Good safety profile in all studies to date
  - Data on more than 700 study participants before efficacy studies
- Dapivirine Ring Licensure Program started in 2012

Dapivirine-Levonorgestrel Vaginal Ring

Multi-prevention vaginal ring that provides HIV-prevention and contraception for a minimum of 60 days

Key factors

1. Leverage Phase III data from Dapivirine Ring-004 program
2. Incorporate approved and widely used contraceptive

Current Status

- Levonorgestrel (LNG) selected as hormone component at two levels:
  - 35 µg and 70 µg
- Preclinical *in vitro* assessments of drug-drug interaction potential completed
- Analytical methods developed in support of Phase I program
- GMP LNG suppliers identified
- GMP manufacturers identified and audited

Current Status (cont)

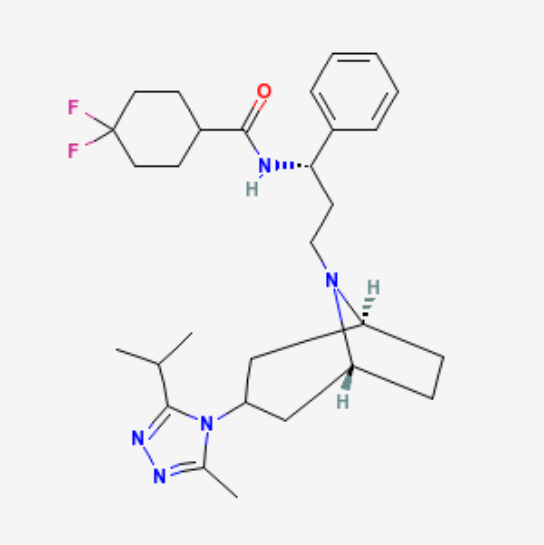
- Matrix ring prototypes selected at loading levels that would achieve target release rates for up to 90 days
  - 200 mg dapivirine with 16 and 32 mg LNG
- Increased release rate of levonorgestrel in the presence of dapivirine
- Currently working on defining particle size appropriate for levonorgestrel

Timeline for Phase I

	2014				2015			
Activity	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Matrix Ring Program								
non-GMP ring production and 3M stability								
GMP Manufacturing Transfer & Setup								
GMP Analytical Transfer & Setup								
GMP Scale-up & batch manufacture								
Preclinical Study with final ring								
Initial GMP stability (3M & 6M)								
GMP Manufacture for Phase I								
Stability								
IND								
Phase 1								

Maraviroc

- CCR5 blocker with established safety profile as marketed oral therapeutic (Selzentry™)
- Developed by Pfizer
- Licensed to IPM in 2008 for microbicide indication in developing world
- Clinical development:
  - Maraviroc rings alone and in combination with dapivirine
- Preclinical development:
  - Maraviroc gel (rectal use)- Magee Women's Research Institute
  - Maraviroc/tenofovir combination in early preclinical development



Dapivirine/Maraviroc Ring Trial

- **MTN-013 / IPM 026: Phase 1 PK & safety vaginal ring**
  - 3 US research centers: Fenway, Pittsburgh and UAB
- **Study design:**
  - 4 arms: dapivirine-maraviroc ring, dapivirine ring, maraviroc ring, placebo
  - N = 48 women
  - 28 days on product + 24 days f/u

First clinical trial of a combination microbicide & first clinical trial of maraviroc for HIV prevention

IPM 026/MTN 013 Conclusions

- All vaginal rings were safe, well-tolerated and acceptable
- Pharmacokinetics:
  - Dapivirine detectable in plasma, vaginal fluid & cervical tissue
  - Maraviroc detectable in vaginal fluid but not in plasma (below LLOQ of 0.5 ng/mL) and most cervical tissue samples
- *ex vivo* challenge showed linear correlation between tissue dapivirine levels and protection against HIV
- Residual drug levels in the rings (4-5 mg released for both drugs) consistent with ring use

Next Steps for Maraviroc

- Maraviroc plasma samples being retested at lower LLOQ to see if maraviroc present (early March)
- If maraviroc present at acceptable levels, pursue higher loading maraviroc ring
  - Stable EVA prototypes developed with up to 300 mg maraviroc loading
- Timing for availability of clinical trial material is approx. 9 months

DS003 (BMS 793)

- Potent gp120 binding entry inhibitor of HIV-1 infection
  - Licensed from Bristol-Myers Squibb in 2005
  - Targets the virus, not the host cell
  - Mechanism of action not currently in microbicide or treatment
  - Can be developed in combination with other ARVs

DS003: Ongoing & Planned Activities

- Pre-IND consultation with FDA
- Preparation for GMP manufacturing in 2014
- First in human Phase I clinical trial with DS003 in tablet dosage form
  - Tablet represents fastest route to initial clinical trial
  - Vaginal ring is ultimate target, either alone or in combination with another ARV
  - Early safety and PK data from trial will inform DS003 based ring development
  - Trial targeted early 2015

Dapivirine - Darunavir Gel and Ring

- Darunavir
  - Protease inhibitor
  - Marketed as Prezista® by Janssen Pharmaceuticals
- Collaborative development under CHAARM (European Consortium)
- Preclinical evaluations of ring PK ongoing in animal models
- Preclinical vaginal irritation studies for gel underway
- Phase I clinical trial for combo gel in 2014 (Univ. of York)

Acknowledgements

- IPM team
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