IPM’s Next Generation Products

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Summary of IPM Pipeline by Stages

**Early Preclinical**
- Maraviroc-Tenofovir film
- Dapivirine-Maraviroc film

**Late Preclinical**
- Dapivirine-contraceptive ring
- DS003
- Dap-Maraviroc gel
- Dap-Darunavir gel/ring
- Maraviroc & Maraviroc-Tfv rectal gel

**Clinical**

- Phase I
  - Dapivirine gel
  - Dapivirine-Maraviroc ring
  - Maraviroc ring
  - Dapivirine film

- Phase II
  - Dapivirine gel
  - Dapivirine ring

- Phase III

IPM collaboration
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

<table>
<thead>
<tr>
<th>Activity</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td><strong>Matrix Ring Program</strong></td>
<td></td>
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<tr>
<td>non-GMP ring production and 3M stability</td>
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<td></td>
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<td>GMP Manufacturing Transfer &amp; Setup</td>
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<td>GMP Analytical Transfer &amp; Setup</td>
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<td></td>
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<tr>
<td>GMP Scale-up &amp; batch manufacture</td>
<td></td>
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<td>Preclinical Study with final ring</td>
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<td>Initial GMP stability (3M &amp; 6M)</td>
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<tr>
<td>GMP Manufacture for Phase I</td>
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<td><strong>Stability</strong></td>
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<tr>
<td><strong>IND</strong></td>
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**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:
  o Maraviroc rings alone and in combination with dapivirine

• Preclinical development:
  o Maraviroc gel (rectal use)- Magee Women’s Research Institute
  o Maraviroc/tenofovir combination in early preclinical development
Dapivirine/Maravirooc Ring Trial

• **MTN-013 / IPM 026: Phase 1 PK & safety vaginal ring**
  o 3 US research centers: Fenway, Pittsburgh and UAB

• **Study design:**
  o 4 arms: dapivirine-maravirooc ring, dapivirine ring, maravirooc ring, placebo
  o N = 48 women
  o 28 days on product + 24 days f/u

*First clinical trial of a combination microbicide & first clinical trial of maravirooc for HIV prevention*
IPM 026/MTN 013 Conclusions

• All vaginal rings were safe, well-tolerated and acceptable

• Pharmacokinetics:
  o Dapivirine detectable in plasma, vaginal fluid & cervical tissue
  o 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

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