Cabotegravir as Pre-Exposure Prophylaxis for HIV Prevention

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CABOTEGRAVIR

The artist formerly known as GSK1265744 or “744”
Favorable attributes for PrEP:
- High genetic barrier to resistance
- PK profile – half life of 21-50 days -- allows once-daily oral or 1-3 month injectable dosing using nanosuspension formulation

Muller et al, European Journal of Pharmaceutics and Biopharmaceutics, 2011
Spreen, 7th IAS, 2013; Min, ICAAC, 2009
Taoda, International Congress on Drug Therapy in HIV Infection, 2012
Cabotegravir (GSK 1265744) development

Early Phase
- NHP Models
- First-in-human/Phase 1
- Cardiac Safety, DDI

Indication
- Treatment
- Prevention cis women
- Prevention MSM/TGW

Phase 2a
- LATTE-1
- HPTN 077*
- ECLAIR

Phase 2b ± 3
- LATTE-2 Pivotal Phase 3
- HPTN 084
- HPTN 083

*INCLUDES BOTH MEN AND WOMEN
HPTN 077

• A phase 2 safety study designed to answer:
  – Could injectable cabotegravir, a non-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in women (and men) globally?
### Long Acting Cabotegravir

**HPTN 077 – Phase 2a**

A Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotegravir, in HIV-uninfected Men and Women

200 🌟🌟 HIV-uninfected, Ages 18-65

<table>
<thead>
<tr>
<th>WEEKS</th>
<th>4</th>
<th>41</th>
<th>81</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>ARM 1</td>
<td>N = 79</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 800 mg every 12 weeks at three time points</td>
</tr>
<tr>
<td>ARM 2</td>
<td>N = 27</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 12 weeks at three time points</td>
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<th>WEEKS</th>
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<tbody>
<tr>
<td><strong>Cohort 2</strong></td>
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<tr>
<td>ARM 1</td>
<td>N = 66</td>
<td>Daily Oral 744 30mg</td>
<td>Injections of 744LA 600 mg every 8 weeks after monthly load at five time points</td>
</tr>
<tr>
<td>ARM 2</td>
<td>N = 22</td>
<td>Daily Oral Placebo</td>
<td>Injections of 744LA placebo every 8 weeks after monthly load at five time points</td>
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**HPTN 077 – Phase 2a**

**US Sites**
- Los Angeles, California
- San Francisco, California
- Washington, DC
- Chapel Hill, North Carolina

**International Sites**
- Soweto, South Africa
- Vulindlela, South Africa
- Lilongwe, Malawi
- Rio de Janeiro, Brazil

Fully Enrolled as of May 27, 2016

67% Women

Primary Endpoint - March, 2017

Last Study Visit - January, 2018
ECLAIR

• A ViiV-sponsored phase 2 safety study designed to answer:
  – Could injectable cabotegravir, a NON-FDA-approved integrase inhibitor (currently being developed for HIV treatment in parallel) be a useful sustained-release PrEP agent in US-based men?
ÉCLAIR: Cabotegravir LA for PrEP in Low-Risk, HIV-Uninfected Men

### Phase 2a

- **Double-blind**
- Men 18 to 65 years of age
- Low-risk of acquiring HIV
- No PEP or ART
- No liver disease
- 5:1 randomization

<table>
<thead>
<tr>
<th>Oral Phase</th>
<th>Injection Phase</th>
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<tbody>
<tr>
<td><strong>Cabotegravir</strong></td>
<td></td>
</tr>
<tr>
<td>30 mg qd</td>
<td></td>
</tr>
<tr>
<td>(n=105)</td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
</tr>
<tr>
<td><strong>Cabotegravir LA</strong></td>
<td></td>
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<tr>
<td>800 mg IM every 12 weeks</td>
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<tr>
<td>(n=94)</td>
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<tr>
<td><strong>Saline Placebo</strong></td>
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<tr>
<td>IM every 12 weeks</td>
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<td>(n=21)</td>
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**Week** | 0 | 4 | 5 | 41

Baseline characteristics (cabotegravir oral phase):
- Median age: 31 years.
- White/black race/ethnicity: 56%/31%.
- Hispanic/Latino race/ethnicity: 15%.
- Median height: 176 cm.
- Median BMI: 26 kg/m².
- Risk for HIV acquisition:
  - Homosexual contact: 85%.
  - Heterosexual contact: 21%
  - Occupational exposure: 2%.

Mean (SD) Plasma CAB Conc-Time Profiles following 800mg IM Q12W in ÉCLAIR and Predicted in original Phase 2 Model
Numbers of Subjects in CAB Concentration Ranges by Injection Visit - ÉCLAIR

- Injection 1
- Injection 2
- Injection 3

- <1 × PA-IC<sub>90</sub>:
  - 24%
  - 15%

- <1 × to <4 × PA-IC<sub>90</sub>:
  - 31%
  - 32%

- >4 × PA-IC<sub>90</sub>:
  - 31%
  - 37%
  - 30%
Multi-Stakeholder Input to Dose-Finding

- HPTN 083 Team Leadership
- HPTN Network Leadership
- HPTN Laboratory Center Leadership
- NIH/DAIDS
- ViiV
Simulated Median (90% PI) Conc-Time profile following (CAB) LA 600mg IM at Day 1, Week 4 and Q8W thereafter in Males (Updated PopPK Model)
HPTN 083: Study Visit Schema

Blinded Injections & Safety Visits

Arm A:
- Week 2: CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter
- Week 4: Plus Daily Oral Placebo for TDF/FTC
- Week 5: CAB LA 600 mg IM at Weeks 5, 9, and Q8 Weeks thereafter
- Week 9: Plus Daily Oral Placebo for TDF/FTC
- Week 10: CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter
- Step 1: Oral Phase
- Step 2: Injection/Oral Phase
- Step 3: Open Label Follow Up

Arm B:
- Week 2: Daily Oral TDF/FTC Plus Placebo for CAB LA IM at Weeks 5, 9, and Q8 Weeks thereafter
- Step 1: Oral Phase
- Step 2: Injection/Oral Phase
- Step 3: Open Label Follow Up

Key:
- Cabotegravir placebo
- TDF/FTC oral
- TDF/FTC placebo
- Cabotegravir injection
- Cabotegravir oral
Protocol Objectives

• **Primary**
  – Efficacy of CAB vs. TDF/FTC
  – Safety of CAB vs. TDF/FTC

• **Secondary**
  – Efficacy in pre-specified subgroups of CAB vs. TDF/FTC
  – Kidney, liver, and bone safety in CAB vs. TDF/FTC
  – ART resistance in seroconverters on CAB vs. TDF/FTC
  – HIV incidence based on strata of study product adherence
  – Acceptability and preferences for oral vs. injectable PrEP

• **Tertiary**
  – Rates, patterns, correlates of adherence
  – Changes in sexual risk behavior (self-report and biomarkers, i.e., STIs)
  – Cost effectiveness considerations
Study Population

• Cis-MSM and TGW, 18 yo or older, at high-risk for HIV acquisition defined as:
  – In past 6 months: Any ncRAI; >5 partners; stimulant drug use; rectal or urethral STI

• Enrollment goals:
  – Minimum 50% of US enrollment BMSM (~ 950)
  – Overall minimum 10% TGW (~ 450)
  – Overall > 50% under age 30
HPTN 083 Sites – Phase 2b/3
42 Sites in 8 Countries

Anticipated Start – 3rd Q 2016 US Sites
Non-US TBD*
*Based on local regulatory approvals
HPTN 084: Efficacy of Injectable Cabotegravir for PrEP in HIV-uninfected Women

- In the early stages of protocol development
- Sites will be in sub-Saharan Africa
- Team currently discussing:
  - Superiority study
  - Open-label
  - 1:1 Randomization

Primary objective: HIV Incidence
HAMILTON
THE
REVOLUTION
LIN-MANUEL MIRANDA and JEREMY MCCARTER
Thank You