Cabotegravir Long-Acting (LA) Injectable Nanosuspension

Bill Sreen, for ViiV Healthcare & GSK Development Team

17th HIV-HEPPK – June 2016
Cabotegravir Long-Acting Nanosuspension

• CAB is an investigational HIV INSTI and analogue of dolutegravir
• Low solubility crystalline drug suspended in aqueous vehicle
• Wet bead nanomilled; terminal sterilization by gamma irradiation
• Storage: 3-year shelf life at room temp; excursions permitted 2-30°C

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabotegravir free acid (d50 ~200 nm)</td>
<td>Active drug</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Tonicity agent</td>
</tr>
<tr>
<td>Surfactant System</td>
<td>Wetting/Stabilizer</td>
</tr>
<tr>
<td>Water for Injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

Potential Indications

• HIV Treatment
  – CAB LA + RPV LA every 4 or 8 week IM injection as a two-drug maintenance regimen for HIV-infected patients
  – CAB + RPV attributes support LA approach
    - Different MOA, resistance profiles, metabolic pathways
    - Lack of drug interaction between CAB and RPV¹
    - Initial LA trials support q4-8 week synchronous dosing schedule
    - Oral formulations to facilitate treatment initiation, oral-bridging and discontinuation strategies
    - Well-established and favorable RPV safety profile

• HIV PrEP
  – CAB LA monotherapy, dosed IM once every 2-3 months, to reduce risk of sexually acquired HIV-1 (combined with safer sex practices)

¹ Ford S, AAC 2013:57, 5472-7
Progress Report: HIV Treatment
**LATTE-2 Study Design (1)**

**Inclusion criteria**
- >18 years old
- Naive to antiretroviral therapy
- CD4+ >200 cells/mm³

**Exclusion criteria**
- Positive for hepatitis B
- ALT ≥5 × ULN
- Creatinine clearance <50 mL/min

**Qualification for maintenance**
- HIV-1 RNA <50 c/mL between Week -4 and Day 1
Induction period

Maintenance period

CAB 400 mg IM + RPV 600 mg IM Q4W (n=115)
- CAB loading dose at Day 1
- CAB loading doses at Day 1 and Week 4

CAB 600 mg IM + RPV 900 mg IM Q8W (n=115)

CAB 30 mg + ABC/3TC PO QD (n=56)

Day 1
Randomization 2:2:1

Add RPV
4 weeks

Week 32
Primary analysis
Dosing regimen selection

Week 48
Analysis
Dosing regimen confirmation

Week 96

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

a Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period.
b Subjects can elect to enter LA Extension Phase beyond Week 96.
**LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)**

**Virologic outcomes**

- **95** * Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

**Treatment differences (95% CI)**

- **Q8W**
  - Oral: -4.8
  - IM: 3.7
  - CI: -12 to 12

- **Q4W**
  - Oral: -5.8
  - IM: 2.8
  - CI: -12 to 12

*Both Q8W and Q4W comparable to oral CAB at Week 32*

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)
2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)

--

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
LATTE-2: CAB and RPV Plasma Concentrations

Mean plasma CAB ± SD, µg/mL

Mean plasma RPV ± SD, ng/mL

Ct, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
LATTE-2: Patient-Reported Outcomes at Wk 32
Maintenance Treatment Compared With Oral Induction Treatment

How satisfied are you with your current treatment?

- Q8W (n=106): 97% More, 3% Neutral, 1% Less
- Q4W (n=100): 96% More, 1% Neutral, 3% Less
- Oral CAB (n=49): 29% More, 1% Neutral, 71% Less

How satisfied would you be to continue with your present form of treatment?

- Q8W (n=106): 98% More, 1% Neutral, 2% Less
- Q4W (n=100): 98% More, 1% Neutral, 1% Less
- Oral CAB (n=49): 29% More, 1% Neutral, 71% Less

Note: based on observed case dataset of subjects who completed Week 32 questionnaires.

*aHIV Treatment Satisfaction Questionnaire change version (HIVTSQc).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

17th HIV-HEPPK
LATTE-2 : Week 32 Analysis Conclusions

• LATTE-2 results successfully demonstrate the potential to maintain HIV-1 viral load <50 c/mL with LA IM CAB + RPV, dosed once Q4W or Q8W

• Two subjects met PDVF criteria
  – Q8W (n=1), oral CAB (n=1); both without evidence of resistance at failure

• Injection tolerability
  – Majority of ISRs were Grade 1 to 2 pain, with a median duration of 3 days
  – Few subjects had an ISR that led to discontinuation, with high overall reported satisfaction

• Regimen selection criteria
  – Neither Q4W IM or Q8W IM dosing was ruled out on the basis of pre-specified criteria
  – Upcoming Week 48 analysis will contribute to final dose selection for phase 3 studies
CAB LA + RPV LA Treatment Phase 3 Program

• January 2016: ViiV and Janssen sign collaboration agreement for CAB LA + RPV LA Phase 3 program
  – Phase 3 preparation underway; 3Q 2016 start
• Primary intent: develop CAB LA + RPV LA as maintenance regimen in virologically-suppressed patients
  – Q4W dose strategy selected for Phase 3
  – Q8W dosing to be evaluated in future studies
• CAB oral tablets to be available for short-term use as oral lead-in agent or for injection-free (“oral bridging”) periods
CAB LA Phase 3 HIV Treatment Regimen:
600mg Loading Dose, then 400mg Q4W

- 8x PA
- 4x PA

2 week dose delay

- 1.35ug/ml
- 0.664ug/ml
- 0.166ug/ml

Simulated Median

90% Prediction Interval

17th HIV-HEPPK
Phase 3 ‘Integrase Switch’ Study (“FLAIR”)

**Randomized, open-label, multicenter, parallel-group, non-inferiority study**

- **Objective:** To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA compared to continuation of ABC/DTG/3TC over 48 weeks in HIV-1 antiretroviral naïve subjects.
- **Primary endpoint:** Proportion of subjects with a ‘virologic failure’ endpoint as per FDA Snapshot algorithm at Week 48.

---

**Screening Phase**
- ARV-naïve, HIV-1 RNA>1000 Any CD4 n≈620

**Induction Phase**
- ABC/DTG/3TC Single Tablet Regimen
- Oral CAB + RPV

**Maintenance Phase**
- CAB LA + RPV LA

**Extension Phase**
- Oral CAB + RPV
- Extension Phase

---

**First Long-Acting Injectable Regimen – FLAIR**

- Confirm HIV-1 RNA <50 c/mL
- 1º Endpoint
- 2º Endpoint

†Optional switch to CAB LA + RPV LA at Wk 104 for subjects randomized to ABC/DTG/3TC.

‡Subjects who withdraw from IM CAB LA + RPV LA treatment must enter the 52 week long term follow up phase.
Phase 3 ‘Stable Switch’ Study ("ATLAS")

Randomized, open-label, multicenter, parallel-group, non-inferiority study
• Objective: To demonstrate the non-inferior antiviral activity of switching to intramuscular CAB LA + RPV LA compared to continuation of current first line antiretroviral regimen over 48 weeks in HIV-1 infected antiretroviral therapy (ART)-experienced subjects
• Primary endpoint: Proportion of subjects with ‘virologic failure’ endpoint per FDA Snapshot at Week 48

Antiretroviral Therapy as Long Acting Suppression-ATLAS
Progress Report: HIV Prevention/PrEP
CAB LA PrEP Phase 2 Safety and PK Studies

<table>
<thead>
<tr>
<th>D1</th>
<th>W3</th>
<th>W4</th>
<th>W5</th>
<th>W9</th>
<th>W17</th>
<th>W25</th>
<th>W29</th>
<th>W33</th>
<th>W41</th>
<th>W53</th>
<th>W65</th>
<th>W77</th>
<th>W81</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB 30 mg PO qd</td>
<td>CAB LA 200mg/mL gluteal IM</td>
<td>Placebo (0.9% saline) gluteal IM</td>
<td>Follow-Up Phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo PO qd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ÉCLAIR - all subjects</th>
<th>HPTN 077 - Cohort 1</th>
<th>HPTN 077 - Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>IM</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>IM</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>IM</td>
<td>IM</td>
<td>IM</td>
</tr>
</tbody>
</table>

- 800mg q12 wks (2 x 2mL)
- 800mg q12 wks (2 x 2mL)
- 600mg q8 wks (1 x 3mL)

HIV negative, at-risk adults (excluding high risk)
Drug PK sampling (blood plasma) in all study participants

**ViiV ÉCLAIR Study** (NCT02076178)
- n=126 (all injections complete)
- 800 mg IM
- 5:1 randomization
- Men including MSM
- US only (10 sites)

**HPTN 077 Study** (NCT02178800)
- n=200 (110 Cohort 1; 90 Cohort 2)
- Two Cohorts (800 and 600mg IM)
- 3:1 randomization
- 60% enrolment of women
- US, Brazil, SA, Malawi (8 sites)
ÉCLAIR: Predicted and Observed Mean (SD) CAB Concentration

C\textsubscript{T}, concentration at the end of the dosing interval; PA-IC\textsubscript{90}, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.
ECLAIR Study Conclusions

- Both CAB oral and LA were well tolerated, permitting continued development of CAB for PrEP
- The absorption rate following CAB LA injection was faster than predicted by early PK population models, leading to higher peak and lower trough exposures
- 15% to 31% of trough concentrations were <PA-IC$_{90}$, whereas 30% to 37% were ≥4 × PA-IC$_{90}$ across injection visits, below initial predictions
- Given observed trough levels, an 8-week dosing interval is currently under evaluation
- Participant satisfaction with IM CAB LA injections was high, including a preference for injections Q12W compared with oral CAB once-daily tablets

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.
CAB LA PK: what’s changed?

No change: CAB LA formulation
• Consistent manufacturing process
• Product critical quality attributes such as drug content, drug polymorphic form, impurities, particle size distribution, pH, and release testing results consistent over time

Changed: added phase 2 study populations at therapeutic doses
• PPK model update: same 2-compartment model with first-order input; added 323 subjects (now n=416) and ~3x PK data points
• Ka (CAB LA i.m.) increased ~2-fold from initial PPK (9.1 x10^-4 hr^-1)
• Clinical covariates: Ka LA
  – gender most significant (female ↓ ka vs. male)
  – BMI (inc. BMI inverse correlation with ka)
CAB LA Phase 2b/3 Studies for HIV Prevention

• HPTN 083 in MSM/TGW

<table>
<thead>
<tr>
<th>Title:</th>
<th>A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design:</td>
<td>Multi-site, double blind, two-arm, randomized (1:1), controlled non-inferiority trial of the efficacy of CAB LA compared to daily oral TDF/FTC for HIV prevention.</td>
</tr>
<tr>
<td>Population:</td>
<td>HIV-uninfected MSM and TGW at risk for acquiring HIV infection, ages 18 or older.</td>
</tr>
<tr>
<td>Study Size:</td>
<td>4500 total, 2250/arm at sites in Asia, S. Africa, N. and S. America</td>
</tr>
</tbody>
</table>

• HPTN 084 in at-risk women
  • Protocol under development
CAB LA HIV PrEP Regimen for HPTN 083: 600mg IM Day 1, W4, then Q8W
CONCLUSIONS - Cabotegravir LA Program

• Substantial progress over past year to characterize safety, PK and efficacy potential of CAB LA + RPV LA as two-drug regimen for HIV treatment
  – LATTE-2 study is first demonstration of once every 4-8 Week LA-ART and enables start of Phase 3 program

• CAB LA for HIV PrEP poised to start Phase 3
  – ÉCLAIR and HPTN 077 data informing PPK model and final plans
  – HPTN 083 (MSM/TGW) to use Q8W dose strategy
  – HPTN 084 (women) dose strategy to be confirmed 2H 2016 with ongoing HPTN 077 data
Acknowledgments

• All Clinical Study Participants and Investigative Staff
• ViiV Healthcare / GlaxoSmithKline R&D Cabotegravir Team
• Janssen R&D Rilpivirine Team
• Collaborators:
  • HIV Prevention Trials Network (HPTN)
  • Aaron Diamond AIDS Research Center
  • US CDC, Laboratory Branch, Division of HIV/AIDS Prevention
  • Preclinical Microbicide & Prevention Research Branch, DAIDS, NIAID, NIH