Where Are We With Long-Acting Treatment?

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ViiV Healthcare
Is a Long-Acting Solution Needed for HIV Treatment

• Patients report a strong desire for options
  – 82% of US respondents would definitely or probably try a monthly injection\(^1\)
    • Concerns about side effects were commonly stated but did not temper interest

• What is driving that desire
  – Current therapies are highly effective, well tolerated, and with smaller pill size
    • Stigma
    • Disclosure and Privacy
    • Travel
    • Emotional toll – daily reminder of HIV
      • Sense of freedom can emerge

• Current therapies continue to have adherence gaps in sub-groups
  – Adolescent and young adults, socially unstable, financially unstable,

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\(^1\) Williams et al, Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients, Nanomedicine, 2013
Population Mix

- Long-term stably suppressed
  - High end of HIV treatment cascade

- Multiple adherence risk factors – vary over time
  - Chaotic lifestyle, youth, toxicities, insurance

- Chronic intractable adherence issues
  - Homelessness, PWID, Mental Illness
## Drugs in LA development

<table>
<thead>
<tr>
<th>Drug/Combo</th>
<th>LA Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB + RPV</td>
<td>3</td>
</tr>
<tr>
<td>NRTTI (MK-8591)</td>
<td>1</td>
</tr>
<tr>
<td>Capsid Inhibitor (GS-CA1)</td>
<td>0/1</td>
</tr>
<tr>
<td>Pro 140</td>
<td>2/3</td>
</tr>
<tr>
<td>Ibiflumab</td>
<td>Approved</td>
</tr>
<tr>
<td>bNAbs</td>
<td>1/2</td>
</tr>
</tbody>
</table>
Update on CAB + RPV Development Program
Cabotegravir (CAB) LA Suspension

- CAB is an investigational HIV INSTI and chemical analogue of dolutegravir
- Low solubility crystalline drug suspended in aqueous vehicle
- Nanomilled to increase surface area and drug dissolution rate
  - Wet bead milling with terminal sterilisation by gamma irradiation
- Higher drug loading versus matrix approaches for lower injection volume
- Storage: 3-year shelf life at room temp; excursions permitted 2-30°C

<table>
<thead>
<tr>
<th>CAB LA 200 mg/mL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Component</strong></td>
<td><strong>Function</strong></td>
</tr>
<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 agent/stabiliser</td>
</tr>
<tr>
<td>Water for injection</td>
<td>Solvent</td>
</tr>
</tbody>
</table>

## Cabotegravir Clinical Pharmacology Attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Oral</th>
<th>Cabotegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>30mg</td>
<td>600mg Q8 week 400mg Q4 week</td>
</tr>
<tr>
<td><strong>Dosing frequency</strong></td>
<td>Once daily</td>
<td>Once monthly or once every two months</td>
</tr>
<tr>
<td><strong>Absorption rate constant</strong></td>
<td>$9 \times 10^{-1} \text{ h}^{-1}$</td>
<td>$9 \times 10^{-4} \text{ h}^{-1}$</td>
</tr>
<tr>
<td><strong>Elimination half-life</strong></td>
<td>~40 hours</td>
<td>~40 days (18-50 days) (Flip-flop kinetics)</td>
</tr>
<tr>
<td><strong>Systemic Clearance</strong></td>
<td></td>
<td>Very low (~0.2 L/hr)</td>
</tr>
<tr>
<td><strong>Impact of Food</strong></td>
<td>None</td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Inter-subject PK variability</strong></td>
<td>Low (%)</td>
<td>Moderate to High (%) consistent with IM dosing</td>
</tr>
<tr>
<td><strong>Impact of covariates on PK</strong></td>
<td>No age, race, or gender impact</td>
<td>Slower absorption rate in females and subjects with high BMI</td>
</tr>
<tr>
<td><strong>Drug Interaction Liability</strong></td>
<td></td>
<td>Primarily metabolized via UGT1A1 with minor UGT1A9 component</td>
</tr>
<tr>
<td><strong>Impact on QTc interval</strong></td>
<td></td>
<td>Low potential to cause or be a victim of drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No effect on cardiac repolarization at a supratherapeutic oral dose of 150mg</td>
</tr>
</tbody>
</table>
CAB LA Potential Indications

HIV Treatment (with rilpivirine LA)

– 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 RPV [1]
  • 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 oral RPV safety profile

HIV PrEP (CAB monotherapy)

– CAB LA IM once every 2 months, to reduce risk of sexually acquired HIV-1 infection (combined with safer sex practices)
– Potential to deliver with LA contraception in family planning setting

CAB LA Development Program

Simultaneous Global Registration Programs for Treatment and Prevention

Indication Phase 2 Phase 3 Phase 3b

Treatment (adults)
LATTE (n=243)
LATTE-2 (n=309)
FLAIR (n=631)
ATLAS (n=618)
Q4W dosing
ATLAS 2M (n=1049)
Q8W dosing

Treatment (<18 yrs.)
MOCHA (n~155)

Prevention MSM/TGW
ECLAIR (n=127)

Prevention women
HPTN 077 (n=199)
HPTN 084 (n~3200)

Early Phase

MOCHA (IMPAACT 2017) Phase 1/2 study will provide supportive information for HIV prevention in adolescents
## Cumulative CAB Exposure Estimates (Phase 1 - 3 / Dec 2017)

<table>
<thead>
<tr>
<th>Treatment Population Dose</th>
<th>Duration</th>
<th>Completed</th>
<th>Ongoing/Concluded</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy Volunteers/HIV Uninfected</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 150 mg oral</td>
<td>Single dose</td>
<td>223</td>
<td>0</td>
<td>223</td>
</tr>
<tr>
<td>10 to 30 mg QD po</td>
<td>10 to 28 days</td>
<td>263</td>
<td>647</td>
<td>910</td>
</tr>
<tr>
<td>150 mg q12hr po</td>
<td>3 doses</td>
<td>40</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>100 – 800 mg IM/SC LA</td>
<td>Max 456 days</td>
<td>230</td>
<td>504</td>
<td>734</td>
</tr>
<tr>
<td>Any dose</td>
<td></td>
<td>584</td>
<td>647</td>
<td>1231</td>
</tr>
<tr>
<td><strong>HIV infected patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 30 mg QD po (Ph 2a)</td>
<td>10 days</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>10 to 60 mg QD po (Ph 2b)</td>
<td>Max 1946 days</td>
<td>0</td>
<td>181</td>
<td>181</td>
</tr>
<tr>
<td>30 mg QD po (Ph 2b/3/other)</td>
<td>Max 1313 days</td>
<td>0</td>
<td>944</td>
<td>944</td>
</tr>
<tr>
<td>Up to 800 mg IM LA</td>
<td>Max 1176 days</td>
<td>0</td>
<td>880f</td>
<td>880f</td>
</tr>
<tr>
<td>Any dose</td>
<td></td>
<td>15</td>
<td>1130</td>
<td>1145</td>
</tr>
<tr>
<td><strong>ALL Participants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose oral (5 to 150 mg)</td>
<td></td>
<td>223</td>
<td>0</td>
<td>223</td>
</tr>
<tr>
<td>Repeat dose QD po (5-60 mg)</td>
<td></td>
<td>278</td>
<td>1772</td>
<td>2050</td>
</tr>
<tr>
<td>150 mg oral every 12 hours x 3</td>
<td></td>
<td>40</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Single or repeat dose LA injection (100 to 800 mg)</td>
<td></td>
<td>230</td>
<td>1384</td>
<td>1614</td>
</tr>
<tr>
<td>Any dose</td>
<td></td>
<td>599</td>
<td>1777</td>
<td>2376</td>
</tr>
</tbody>
</table>

>26,000 CAB IM shots given (Oct '18)
Cabotegravir + Rilpivirine
Clinical Data
Safety and Efficacy of Long-Acting CAB and RPV as Two Drug IM Maintenance Therapy: LATTE-2 Week 96 Results

J Eron,1 D Margolis,2 J Gonzalez-Garcia,3 H-J Stellbrink,4 Y Yazdanpanah,5 D Podzamczer,6 T Lutz,7 JB Angel,8 GJ Richmond,9 B Clotet,10 F Gutierrez,11 L Sloan,12 KC Sutton,2 D Dorey,13 KY Smith,2 PE Williams,14 WR Spreen2

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LATTE-2 Objectives

• Establish proof of principle for the first ever long-acting (LA) injectable HIV treatment regimen

• **Primary Objectives**
  • Evaluate the safety and efficacy of CAB LA + RPV LA as maintenance therapy
  • Select a dosing schedule of CAB LA + RPV LA for progression into phase III studies

• **Key Secondary Objectives**
  • Characterize pharmacokinetics after depot injections
  • Evaluate the tolerability and acceptability of intramuscular dosing

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THBD02LB.
# LATTE-2 Study Design

## 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

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ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period. bSubjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LATTE-2 Study Design

Induction period

CAB 30 mg + ABC/3TC for 20 weeks

CAB loading dose at Day 1

CAB loading doses at Day 1 and Week 4

Maintenance period

CAB 400 mg IM + RPV 600 mg IM Q4W (n=115)

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

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

Add RPV PO QD 4 weeks

Day 1
Randomization 2:2:1

Week 32
Primary analysis Dosing regimen selection

Week 48
Analysis Dosing regimen confirmation

Week 96

ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. aSubjects who withdrew after at least 1 IM dose entered the long-term follow-up period. bSubjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LATTE-2: HIV-1 RNA <50 c/mL at Week 48

ITT-ME (Snapshot)

Virologic outcomes

Treatment differences (95% CI)

Both Q8W and Q4W comparable to Oral CAB at Week 48

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
LATTE-2 Week 96 Results
HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Oral CAB induction period (ITT-ME population) Maintenance period

Proportion of patients with virological suppression, %

Study visit, weeks

<table>
<thead>
<tr>
<th>Snapshot success</th>
<th>Day 1</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8W IM (n=115)</td>
<td>95%</td>
<td>92%</td>
<td>94%</td>
</tr>
<tr>
<td>Q4W IM (n=115)</td>
<td>99%</td>
<td>91%</td>
<td>87%</td>
</tr>
<tr>
<td>Oral (n=56)</td>
<td>98%</td>
<td>89%</td>
<td>84%</td>
</tr>
</tbody>
</table>

BL, baseline; CAB, cabotegravir; ITT-ME, intent-to-treat maintenance exposed; Q4W, every 4 weeks; Q8W, every 8 weeks.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.
Comparative Response Across Arms

Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt;50c/mL, %</th>
<th>Virologic success</th>
<th>Virologic nonresponse</th>
<th>No virologic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>CAB + RPV LA Q8W (n=115)</td>
<td>94%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>CAB + RPV LA Q4W (n=115)</td>
<td>87%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>CAB + NRTIs PO (n=56)</td>
<td>84%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Treatment differences (95% CI)

- Oral vs. IM
  - Q8W IM: 14.4% (10.0% 20.5%)
  - Q4W IM: 0.6% (-8.4% 3.0%)

- CAB, cabotegravir; CI, confidence interval; IM, intramuscular; ITT-ME, intent-to-treat maintenance exposed; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.
Protocol-Defined Virologic Failure (CVF)\textsuperscript{a}

ITT-ME

• Through 96 Weeks
  • 2 CVFs Q8W
    • 1 without treatment emergent resistance (Week 4)\textsuperscript{b}
    • 1 with INI + NNRTI mutations (Week 48)\textsuperscript{c}
      • NNRTI—K103N, E138G, and K238T (FC RPV=3.3; etravirine=1.9); INI—Q148R (FC CAB=5.1; dolutegravir=1.38).
  • No CVFs Q4W
  • 1 CVF Oral CAB + NRTIs (Week 8)
    • No treatment emergent resistance
  • No additional CVFs occurred after Week 48 in any arm

\textsuperscript{a}CVF: <1.0 log_{10} c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA \geq 200 c/mL after prior suppression to <200 c/mL, OR >0.5 log_{10} c/mL increase from nadir HIV-1 RNA value \geq 200 c/mL. \textsuperscript{b}No detectable RPV at Week 4 and Week 8, suggesting maladministration at Day 1. \textsuperscript{c}NNRTI—K103N, E138G, and K238T (FC RPV=3.3; etravirine=1.9); INI—Q148R (FC CAB=5.1; dolutegravir=1.38).

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.
99% of ISR events were mild (84%) or moderate (15%), and 89% resolved within 7 days.

Most common ISR events: pain (66%), nodules (8%), swelling (6%), and pruritus (6%).

2 of 230 subjects (<1%) had an ISR that led to discontinuation (Q8W) through Week 96.

AE, adverse event; CAB, cabotegravir; IM, intramuscular; ISR, injection-site reaction; LA, long acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.
Patient-Reported Outcomes at Week 96 Maintenance Treatment

- Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

- CAB, cabotegravir; IM, intramuscular; LA, long acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

- Based on observed case data set of subjects who completed HIV Treatment Satisfaction Questionnaire status version at Week 96.

**How satisfied are you with your current treatment?**

- CAB LA + RPV LA IM
  - Q8W (n=108): 85%
  - Q4W (n=100): 76%
  - Oral CAB (n=46): 76%

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

- CAB LA + RPV LA IM
  - Q8W (n=108): 89%
  - Q4W (n=100): 88%
  - Oral CAB (n=46): 43%
Pharmacokinetics

- Both Q4W and Q8W steady state exposures approximate once-daily oral dosing.

Ct, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.
PK Tail: Therapy Discontinuation and Drug Resistance Risk

- CAB and RPV LA concentrations wane over months – for unknown critical time period risk of INI and NNRTI resistance generation

  • Mitigation: adherence to injection dosing schedule (+/- 1 week flexibility)
  • Can cover planned gaps in LA dosing with ‘oral bridging’
  • Initiate oral ART to cover PK tail; good DDI profile of both CAB and RPV permit this strategy
CAB LA + RPV LA Treatment Phase 3 Program

- Primary intent: develop CAB LA + RPV LA as maintenance regimen in virologically-suppressed patients
  - Q4W dose selected for Phase 3 from LATTE-2 Week 48 results
  - LATTE-2 continued dosing comparison to 96 weeks
- Randomized, open-label, multicentre, non-inferiority designs
- Phase 3 studies began Oct 2016
- CAB oral tablets to be developed for short-term use as oral lead-in agent or for injection-free ("oral bridging") periods

**FLAIR (Integrase Switch)**

**ATLAS (Stable Switch)**
Phase 3 Study Status

- As of August 2018, all participants in ATLAS/FLAIR have completed the primary analysis endpoint – Week 48

- ATLAS headline data demonstrated non-inferior efficacy of CAB LA + RPV LA to continuation of once daily 3 drug ART (press release August 15\textsuperscript{th} 2018)

- FLAIR headline data expected 4Q18

- Both ATLAS/FLAIR will be submitted together for public presentation
Phase 3b Q8W Dosing Program

- Positive LATTE-2 W96 data enabled Q8W program
  - Week 96 demonstrated long term durability and safety/tolerability of both Q8W and Q4W dosing arms
  - No PDVF after W48 in any arm

- ATLAS-2M study was created to allow for a powered study comparison of Q4W and Q8W dosing

- Randomized, open-label, multicentre, non-inferiority design

- Primary goal to demonstrate non-inferiority between Q8W and Q4W dosing options and to extend dosing options for patients

N=1020, randomized 1:1 to each arm and stratified by prior CAB + RPV Exposure

†Optional Extension Phase to continue randomized CAB LA + RPV LA Q4W or Q8W at Wk 100
• Designed to address efficacy in patients with a history of failure and non-adherence
• Anticipated start Dec 2018/Jan 2019

Ongoing compassionate use program is available to patients with significant adherence issues
Evolution of research focus

Areas of interest
• Clinic site flow and logistics
• Patient flow and logistics
• Patient and site education and training
• Alternative Injection location options (pharmacy, minute clinics….)
Thank You