Tolerability and Acceptability of Cabotegravir LA Injection: Results From the ECLAIR Study

Miranda Murray,1 Martin Markovitz,1 Ian Frank,1 Robert M. Grant,1 Kenneth H. Mayer,1 David A. Margolis,1 Krishan H. Hudson,5 Britt S. Stanoj,1 Susan L. Ford,1 Alex R. Rinehart,1 William R. Sprenkle1

1VIIV Healthcare, London, UK; 2The Aaron Diamond AIDS Research Center, an affiliate of the Rockefeller University, New York, NY; 3Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 4Institute of Virology & Immunology, Gladstone Institutes, San Francisco, CA; 5Department of Medicine, University of California, San Francisco, CA; 6The Fenway Institute, Fenway Health, Boston, MA; 7Beth Israel Deaconess Medical Center, Boston, MA; 8Harvard Medical School, Boston, MA; 9VIIV Healthcare, Research Triangle Park, NC; PALEXEL International (formerly employed by GileadSciences), Research Triangle, NC

Introduction
Multiple prevention strategies currently exist for both men and women, including agents for pre-exposure prophylaxis (PrEP). Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was approved by the FDA in 2012 for PrEP, and the Centers for Disease Control and Prevention and World Health Organization have offered interim guidance about TDF/FTC as a PrEP treatment. Long-acting injectables (LA) offer an alternative to daily pill-taking as adherence is a significant issue with oral TDF/FTC and may lead to PrEP failure in regions that rely on daily pill-taking. Therefore, development of alternative agents for PrEP, including LA, is a priority.

Cabotegravir (CAB, GSK1265744) is an LA in phase IIb development for the prevention of HIV (ECLAIR). The primary objectives of ECLAIR include evaluating the safety of CAB LA for HIV PrEP dosing by assessing the pharmacokinetics, tolerability, satisfaction, and acceptability of CAB LA.

Methods
ECLAIR was a phase IIa, randomized, multi-site, 2-arm, double-blind study, in the US, in men not at high risk of acquiring HIV. Participants were randomized (ratio 1:1) to receive oral CAB 30 mg or placebo (PBO) once daily for 4 weeks, after which they received intramuscular (IM) injections of CAB LA 800 mg (2 × 400 mg) injections) or PBO (saline) every 12 weeks × 3 cycles. Satisfaction, tolerability, and acceptability were self-assessed 1 week after injection with the Study Medication Satisfaction Questionnaire (SMSQ) and Study Medication Acceptability Questionnaire (SAQ) on Weeks 6, 18, and 30 (SAQ). The SMSQ has 11 items and was adapted from the HIV Treatment Satisfaction Questionnaire (VTSQ). The two versions used were the SMSQ Patient (P) and CAB version. The SMSQ is a 7-point Likert scale ranging from 1 ‘very dissatisfied’ to 7 ‘very satisfied’. The options were re-coded with 0 to 2 ‘dissatisfied’, 3 ‘neutral’, and 4 to 6 ‘satisfied’.

Figure 1. ECLAIR Study Design

Results
Study Disposition
- A total of 127 subjects were randomly assigned to receive treatment.
- All subjects were male, and the median age was 31 years. Subjects were randomized 86:41 for CAB or placebo.
- Eighteen subjects withdrew from CAB during the study: 5 withdrew during oral dosing, 6 after oral dosing but prior to injections, and 7 during the injection phase.
- During the injection phase, injection intolerability led to withdrawal in 4 of 94 subjects (4%) who received CAB LA.

Injection-Site Reactions in the Injection Phase
- In the PBO group, 57% of subjects experienced injection-site reactions (ISRs), whereas 93% of those in the CAB group experienced ISRs. Most of these events were Grade 1 or 2 severity. The symptoms associated with ISRs in the CAB and PBO groups were similar, with the exception of Grade 3 ISRs in the CAB group (Table 1).

Table 1. SMSQ in the Injection Phase

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PBO (N=41)</th>
<th>CAB (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISRs by maximum toxicity, n (%)</td>
<td>35 (85)</td>
<td>72 (84)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>17 (20)</td>
<td>35 (41)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10 (15)</td>
<td>37 (43)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (12)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Subjects’ Views of Pain, Discomfort, and Side Effects
- All PBO subjects (100%) reported pain during injections. With the exception of Grade 3 pain, all ISRs listed were Grade 1 or 2 in severity.
- Overall, no patients discontinued due to adverse events during the injection phase. With the exception of Grade 3 pain, all ISRs listed were Grade 1 or 2 in severity.

Discussion
- In the ECLAIR study, tolerability, acceptability, adverse events, and pain associated with CAB LA were assessed using subjects’ diaries as well as participant-reported outcome measures (SMSQ, SAQ). Results demonstrate that, while participants experienced pain with injections, they were largely satisfied with the treatment and were willing to continue in the study.
- Overall, ECLAIR subjects reported a high degree of satisfaction with their study medication; most subjects in the CAB group (79%) were willing to continue at Week 30. Likewise, when comparing subjects’ views in the LA group, subjects were more satisfied with LA than with oral CAB, especially on items related to convenience, flexibility, and lifestyle.

Conclusions
- Secondary endpoints including acceptability and tolerability, from ECLAIR, help the interpretation of the safety data and provide a robust subject-centered perspective.
- While Grade 1 to 2 injection-site pain associated with CAB LA was common, subjects experienced a high level of overall satisfaction and preference for LA on dimensions such as convenience, acceptability, and ease of use.

Acknowledgments
- The clinical trial was conducted in the success of the study, including all study participants, the ECLAIR clinical research team, all clinical investigators and their staff, the GSK and ViiV Healthcare study team, PPD, Quest, Covance, and Monogram Biosciences. This study was sponsored by ViiV Healthcare.

References
2. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Institute of Virology & Immunology, Gladstone Institutes, San Francisco, CA; Department of Medicine, University of California, San Francisco, CA; The Fenway Institute, Fenway Health, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Harvard Medical School, Boston, MA; ViiV Healthcare, Research Triangle Park, NC; PALEXEL International (formerly employed by GileadSciences), Research Triangle, NC.

23rd Conference on Retroviruses and Opportunistic Infections; February 22-25, 2016, Boston, MA