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

471

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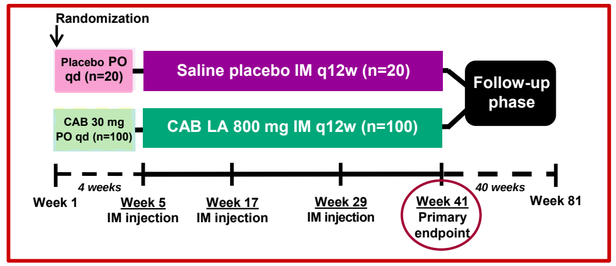
Introduction

- 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 injectable (LA) offers an alternative to daily pill-taking as adherence is a significant issue with oral TDF/FTC and may lead to PrEP failure in regimens 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 II development for treatment and prevention of HIV-1 infection
  - Primary objectives of ECLAIR include evaluating the safety of CAB LA for HIV PrEP; secondary objectives were to assess 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 of 5:1) 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 × 2-mL 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 questionnaire (SMQ) at Weeks 6, 18, and 30
  - The SMSQ has 11 items and was adapted from the HIV Treatment Satisfaction Questionnaire (HIVTSQ). The 2 versions used were the SMSQ status (SMSQ-s) and the SMSQ change (SMSQ-c) versions. The SMSQ-c was only administered at Week 18 as the intent was to compare LA with the oral phase
  - The SMSQ has 7 response options, scored on a Likert scale, ranging from 0 "very dissatisfied" to 6 "very satisfied." The options were re-coded with 0 to 2 as "dissatisfied," 3 as "neutral," and 4 to 6 as "satisfied"

Figure 1. ECLAIR Study Design



CAB, cabotegravir; IM, intramuscular; LA, long-acting; PO, orally; q12w, every 12 weeks; qd, once daily.

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 83% MSM, 31% African American, and 15% Hispanic
- 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 in severity
  - The majority of ISRs in each treatment group were attributed to injection-site pain (PBO, 27%; CAB, 92%), and the mean duration was 2 days in the PBO group and 5.4 days in the CAB group
  - No patients discontinued due to adverse events during the injection phase

Table 1. ISR Symptoms in the Injection Phase[a]

	PBO (N=21)	CAB (N=94)
Subjects with any ISR event, n (%)	12 (57)	87 (93)
Total number of injections, n	62	272
ISR events by maximum toxicity, n/N (%)[b]		
Pain	17/62 (27)	250/272 (92)
Grade 1	16 (26)	122 (45)
Grade 2	1 (2)[c]	101 (37)
Grade 3	0	27 (10)
Pruritus	4 (6)	26 (10)
Swelling	0	22 (8)
Nodule/Bump	0	21 (8)
Warm to touch	0	19 (7)
Bruising	1 (2)	16 (6)
Induration	0	15 (6)

[a]Only ISRs with ≥10 events reported are presented. [b]Percentages are out of the total number of injections. With the exception of Grade 3 pain, all ISRs listed were Grade 1-2. [c]Subject was misdosed with CAB on the third injection.

Subjects' Views of Pain, Discomfort, and Side Effects

- At Week 30, subjects rated their pain/discomfort (P/D) on a scale of 0 to 6; 60% of those in the PBO group and 12% in the CAB group reported no P/D. In addition, only 6% in the CAB group reported P/D "all of the time"
- All PBO subjects (100%) and two-thirds (66%) of CAB subjects reported being satisfied with side effects related to the study medication

Figure 2A. SMQ at Week 30: How Much P/D Have You Experienced With This Medication?

Figure 2B. SMSQ-s at Week 30: Satisfaction With Side Effects of Study Medication

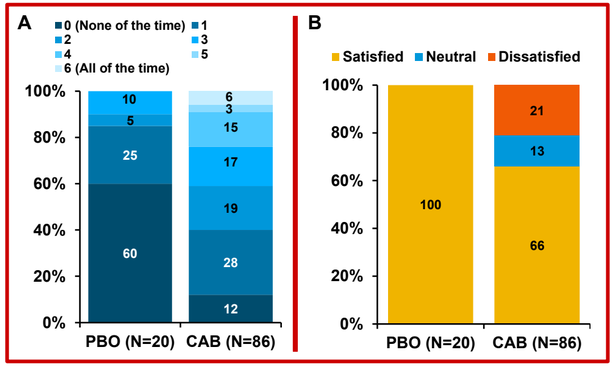


Figure 3. SMSQ-s: How Satisfied Would You Be to Continue With Your Present Form of Study Medication?

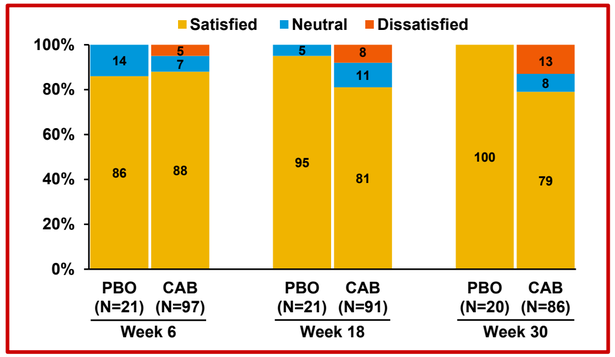
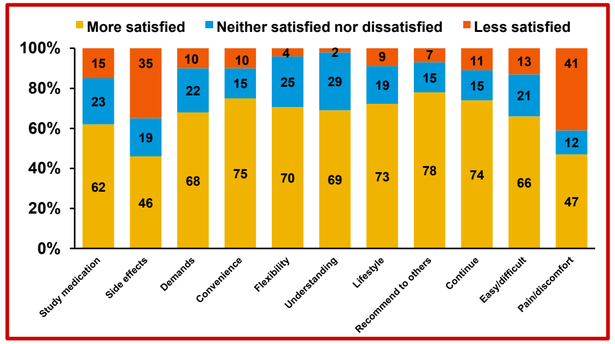


Figure 4. Overall Satisfaction With CAB LA Compared With Oral CAB at Week 18 SMSQ-c (N=91)



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 (SMQ; SMSQ). Results demonstrate that, while participants experienced pain with injectables, 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 an LA on dimensions such as convenience, flexibility, and ease of use

Acknowledgments

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Reference

1. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States–2014. A clinical practice guideline. http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf. Accessed February 16, 2016.