

## Distribution of Cabotegravir Following Intramuscular Injection into Plasma and Mucosal Tissues and Fluids

### Summary

- In most tissue and fluids tested the ratio of tissue/fluid to plasma cabotegravir concentrations following intramuscular injection was approximately 10-20%.<sup>1</sup>
- The relationship between tissue/fluid concentrations and efficacy (correlate of protection) is unknown.

Data regarding cervical, vaginal, and rectal tissue concentrations are available from a single-dose pharmacokinetic study in healthy adults where CAB LA was administered as a single 600-mg intramuscular (IM) injection following a 28-day oral lead-in period of cabotegravir 30 mg and a 14-42 day washout period.<sup>1</sup> Results can be found below in Tables 1, 2, 3, and 4.

**Table 1. Median (range) Tissue to Plasma Ratio by Tissue Type<sup>1</sup>**

| Tissue Type          | CAB LA 600 mg     | CAB oral 30 mg    |
|----------------------|-------------------|-------------------|
| Cervical (n=7)       | 0.14 <sup>a</sup> | 0.18 (0.11-0.25)  |
| Vaginal (n=7)        | 0.16 <sup>b</sup> | 0.14 (0.03-0.18)  |
| Cervicovaginal (n=7) | 0.08 (0.01-0.44)  | 0.13 (0.02-0.36)  |
| Rectal (n=13)        | 0.09 <sup>c</sup> | 0.10 (0.07-0.17)  |
| Rectal fluid (n=12)  | 0.32 <sup>d</sup> | 0.45 (0.15-10.40) |

<sup>a</sup><LLOQ-0.31

<sup>b</sup><LLOQ-0.34

<sup>c</sup><LLOQ-0.16

<sup>d</sup><LLOQ-11.38

CAB LA=long acting cabotegravir; LLOQ = lower limit of quantification

**Table 2. Pharmacokinetic Parameters After IM Injection of CAB LA 600 mg**

| Parameter <sup>a</sup>             | Plasma (n=15)  | Cervical Tissue (n=7) | Rectal Tissue (n=13) | Cervicovaginal Fluid (n=7) | Rectal Fluid (n=12) |
|------------------------------------|----------------|-----------------------|----------------------|----------------------------|---------------------|
| C <sub>max</sub> , µg/mL           | 5.04 (62)      | 0.81 (105)            | 0.5 (47)             | 0.55 (118)                 | 3.27 (172)          |
| T <sub>max</sub> , days            | 6.9 (3.9-52.2) | 7.0 (1.9-30.0)        | 7.0 (6.9-52.2)       | 7.0 (1.9-84.0)             | 7.0 (6.9-80.0)      |
| AUC <sub>0-Week 4</sub> , µg*h/mL  | 2141 (59)      | 277 (104)             | 206 (57)             | 203 (126)                  | 1170 (192)          |
| AUC <sub>0-Week 8</sub> , µg*h/mL  | 3214 (40)      | 365 (85)              | 287 (39)             | 282 (125)                  | 1576 (203)          |
| AUC <sub>0-Week 12</sub> , µg*h/mL | 3639 (36)      | 350 (79)              | 324 (55)             | 381 (108)                  | 1345 (138)          |
| t <sub>1/2</sub> , days            | 19.1 (81)      | 15.14 (NA)            | 23.65 (23)           | 14.83 (79)                 | 12.77 (4)           |

<sup>a</sup>all values are geometric mean (%CVb) except T<sub>max</sub> which is median (range)

CAB LA = long-acting cabotegravir; C<sub>max</sub> = maximum concentration; T<sub>max</sub> = time to maximum concentration; AUC = area under the concentration versus time curve; t<sub>1/2</sub> = half-life; NA = not available; %CVb = geometric coefficient of variation

**Table 3. Tissue to Plasma Ratio by Tissue Type After IM injection of CAB LA 600 mg<sup>1</sup>**

| Parameter                                   | Cervical Tissue<br>(n=7) | Rectal Tissue<br>(n=13) | Cervicovaginal<br>Fluid<br>(n=7) | Rectal Fluid<br>(n=12) |
|---------------------------------------------|--------------------------|-------------------------|----------------------------------|------------------------|
| <b>C<sub>max</sub></b> , µg/mL              | 0.2 (0.16-0.25)          | 0.1 (0.08-0.11)         | 0.13 (0.07-0.26)                 | 0.62 (0.31-1.25)       |
| <b>AUC<sub>0-Week 4</sub></b> ,<br>µg*h/mL  | 0.16 (0.09-0.26)         | 0.1 (0.09-0.11)         | 0.1 (0.04-0.25)                  | 0.55 (0.23-1.28)       |
| <b>AUC<sub>0-Week 8</sub></b> ,<br>µg*h/mL  | 0.15 (0.07-0.33)         | 0.11 (0.09-0.13)        | 0.09 (0.04-0.23)                 | 0.49 (0.21-1.11)       |
| <b>AUC<sub>0-Week 12</sub></b> ,<br>µg*h/mL | 0.12 (0.04-0.38)         | 0.11 (0.09-0.14)        | 0.09 (0.02-0.33)                 | 0.39 (0.14-1.07)       |

CAB LA = long-acting cabotegravir; C<sub>max</sub> = maximum concentration; T<sub>max</sub> = time to maximum concentration; AUC = area under the concentration versus time curve; t<sub>1/2</sub> = half-life; NA = not available; %CVb = geometric coefficient of variation

Median cabotegravir concentrations in all tissues and cervicovaginal fluid were below PA-IC<sub>90</sub> at Week 8 after IM injection (Table 4.).

**Table 4. Proportion of Participants with Cabotegravir Concentrations >PA-IC<sub>90</sub> and ≥4x PA-IC<sub>90</sub> by Tissue Type after Repeat Oral Dosing and After IM injection of CAB LA 600 mg<sup>1</sup>**

| Visit                   | Plasma<br>(n=15) | Cervical<br>Tissue<br>(n=7) | Vaginal<br>Tissue<br>(n=7) | Cervicovaginal<br>Fluid<br>(n=7) | Rectal<br>Tissue<br>(n=13) | Rectal<br>Fluid<br>(n=12) |
|-------------------------|------------------|-----------------------------|----------------------------|----------------------------------|----------------------------|---------------------------|
| <b>Oral 30 mg</b>       |                  |                             |                            |                                  |                            |                           |
| <b>Day 28</b>           |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 100              | 100                         | 100                        | 86                               | 100                        | 100                       |
| ≥4x PA-IC <sub>90</sub> | 100              | 71                          | 29                         | 43                               | 23                         | 100                       |
| <b>IM 600 mg</b>        |                  |                             |                            |                                  |                            |                           |
| <b>Day 3</b>            |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 100              | 100                         | 71                         | 86                               | 69                         | 92                        |
| ≥4x PA-IC <sub>90</sub> | 100              | 43                          | 29                         | 29                               | 8                          | 50                        |
| <b>Day 8</b>            |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 100              | 86                          | –                          | 100                              | 92                         | 100                       |
| ≥4x PA-IC <sub>90</sub> | 100              | 43                          | –                          | 29                               | 39                         | 100                       |
| <b>Week 4</b>           |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 100              | 71                          | –                          | 43                               | 77                         | 83                        |
| ≥4x PA-IC <sub>90</sub> | 100              | 29                          | –                          | 14                               | 0                          | 50                        |
| <b>Week 8</b>           |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 100              | 43                          | 43                         | 14                               | 23                         | 67                        |
| ≥4x PA-IC <sub>90</sub> | 53               | 0                           | 0                          | 0                                | 0                          | 8                         |
| <b>Week 12</b>          |                  |                             |                            |                                  |                            |                           |
| >PA-IC <sub>90</sub>    | 60               | 14                          | –                          | 14                               | 8                          | 33                        |
| ≥4x PA-IC <sub>90</sub> | 20               | 0                           | –                          | 0                                | 0                          | 17                        |

CAB LA = long-acting cabotegravir; PA-IC<sub>90</sub> = in vitro protein-adjusted 90% maximal inhibitory concentration

This information is scientific and non-promotional in nature and is not intended for further distribution. Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

## REFERENCES

1. Shaik JS, Weld ED, Edick S, et al. Multicompartmental pharmacokinetic evaluation of long-acting cabotegravir in healthy adults for HIV preexposure prophylaxis. *Br J Clin Pharmacol*. 2021. doi:<http://dx.doi.org/10.1111/bcp.14980>.