Can "Equivalence" of a Generic Cabotegravir LA Be Inferred From a Shortened Pharmacokinetic Study?

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BACKGROUND

- Long acting injectable (LAI) antiretrovirals hold enormous potential for treatment and prevention of HIV in low- and middle-income countries (LMIC) but significant access challenges exist.
- One obstacle for generic LAIs is the assessment of "equivalence" with originator products.
- Accepted standards of bioequivalence for oral generic products may be sub-optimal because small differences may be accentuated over long dosing intervals, and the need for phase III studies would present major funding and timeline obstacles to access.
- Partial AUCs and/or truncated pharmacokinetic (PK) assessments have been postulated as possible approaches to accelerate approval of generic LAIs[1].
- The current study sought to assess potential feasibility of such an approach through re-analysis of published PK for cabotegravir (CAB) LAI.

METHODS

- A single 800 mg dose CAB LAI plasma PK profile (32 week duration) from the literature[2] was fitted with an empirical 1-compartment PK disposition model with a 2-fraction 1st order input depot release.
- Repeated fits successively truncating the last timepoint of the profile from the dataset were undertaken.
- PK model parameter estimates for truncated profiles were then compared to those from the full profile.

RESULTS

- Adequate fitting of the model was obtained with the dataset truncated up to the first 12 weeks.
- Parameter estimates up to this degree of truncation remained within 10% deviation from those obtained using the full profile (Figure 1, Table 1).
- Truncation to 10 weeks resulted in 14% and 16% deviation in estimates of CL/F and $AUC_{0\text{-inf}}$ relative to estimates from the full profile.

Truncation of a 32 week LA Cabotegravir PK profile to 10 weeks (or less) is unable to provide equivalent PK parameter estimates to the full duration profile

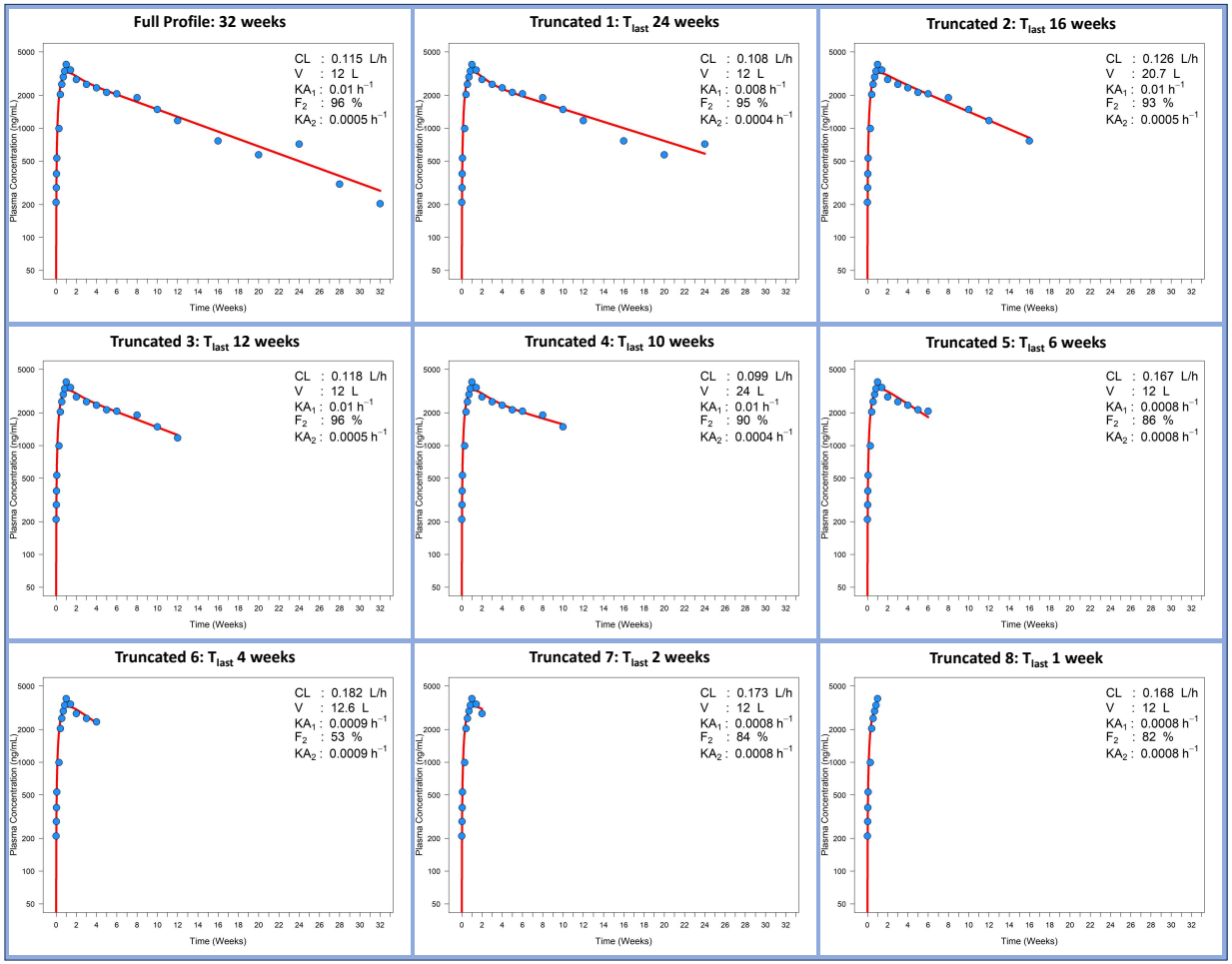


Figure 1: PK model fittings to a Cabotegravir LAI 800 mg IM Plasma PK profile (Spreen et al. 2014) with increasing truncation

RESULTS (contd.)

- Subsequent truncation resulted in significant deviation of estimates from those achieved with the full profile for all parameters (>26% deviation) with poorer precision of estimates reflected in higher relative standard errors.

Table 1: Model Fitting PK Parameter Estimates:

T_{last} (weeks)	CL/F (L/h) [%RSE]	V/F (L) [%RSE]	ka1 (h^{-1}) [%RSE]	ka2 (h^{-1}) [%RSE]	F2 (%) [%RSE]	AUC_{inf} (µg.h/mL)
32	0.115 6.6%	12.0 0.0%	0.010 32.2%	0.0005 9.2%	96% 0.3%	6945.6
24	0.108 7.9%	12.0 0.0%	0.008 52.5%	0.0004 15.9%	95% 2.8%	7410.6
16	0.126 9.2%	12.0 0.0%	0.011 86.9%	0.0005 18.1%	97% 2.7%	6330.1
12	0.118 18.3%	12.0 0.0%	0.010 69.7%	0.0005 33.1%	96% 3.4%	6765.8
10	0.099 60.2%	23.5 0.0%	0.013 29.4%	0.0004 97.5%	90% 4.2%	8041.0
6	0.166 27.7%	12.0 0.0%	0.001 7357.8%	0.0008 1285.3%	86% 0.0%	4812.7
4	0.182 35.5%	12.6 0.0%	0.001 1904.5%	0.0009 1293.4%	62% 0.0%	4395.6
2	0.173 23.4%	12.0 0.0%	0.001 20.6%	0.0008 21.0%	84% 0.0%	4629.8
1	0.168 12242.8%	12.0 2.1%	0.001 1229.0%	0.0008 7190.1%	82% 0.0%	4769.5

CONCLUSIONS

- Analysis was undertaken using a single dataset for CAB LAI, which represents a best-case scenario for a generic product by mimicking an identical product given to the same recipients.
- Despite this low bar, truncation of the profiles to below 10 weeks for 800mg fittings was unable to accurately predict parameters determined from the full profile.
- The analysis sheds light on the complexity of the challenge and may be useful to inform further development of strategies for accelerated "equivalence" evaluation for generic LAI.
- This may include the use of a Bayesian forecasting approach[1] from an incomplete dosing interval (i.e. partial AUC or profile) to assess the likelihood of bioequivalence based on incomplete interval PK data.

REFERENCES

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2. Spreen W, et al. Journal of acquired immune deficiency syndromes. 2014;67(5):481-6.

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