

Population pharmacokinetics of etravirine in HIV-1-infected treatment experienced children and adolescents

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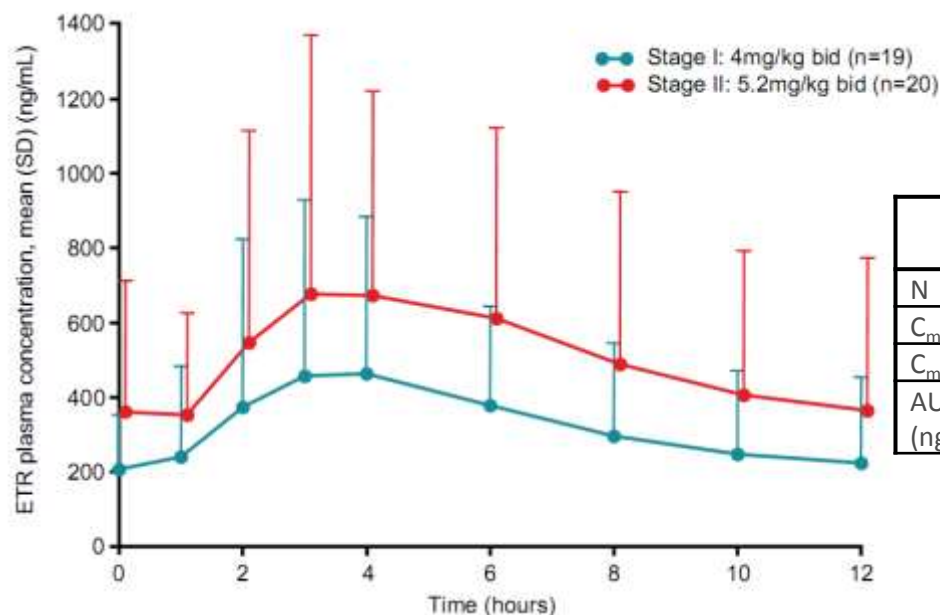
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Background

- Etravirine is an NNRTI approved in the treatment of HIV-infected treatment-experienced adults
 - 200 mg b.i.d.
- Phase I pediatric (ages 6 to <18 years) PK trial (TMC125-C126) showed comparable PK to adults when dosed 5.2 mg/kg b.i.d.



Mean (SD) PK parameters:

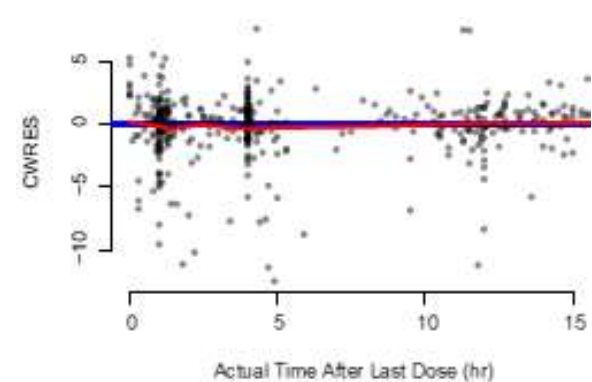
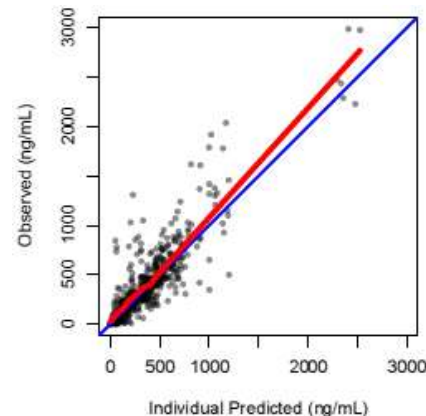
	4 mg/kg BID	5.2 mg/kg BID	200 mg BID
N	19	20	574
C_{max} (ng/mL)	495 (453)	757 (680)	-
C_{min} (ng/mL)	184 (151)	294 (278)	393 (391)
AUC_{12h} (ng·h/mL)	4050 (3602)	6141 (5586)	5506 (4710)

Developing a pediatric population PK model for etravirine

- Sequential zero- (D1) and first-order (KA) absorption with lag time (ALAG1) and 1-compartment disposition (adult model)
 - 1045 plasma concentration-time points from 141 adult and pediatric subjects
 - Rich sampling from TMC125-C126 and DUET
 - Sparse sampling from TMC125-C213 (PIANO) at week 12
 - total body weight as a covariate on apparent oral clearance (CL/F) and volume of distribution (Vd)
 - Parameter estimates (SEE, CV%)

	Adult model	Pediatric model
CL/F (L/h)	36.5 (10)	45.9 (11)
V/F (L)	559 (2.9)	573 (7.2)
KA (h ⁻¹)	1.83 (24)	0.89 (29)
D1 (h)	2.49 (2.5)	2.24 (17)
ALAG1 (h)	0.0353 (52)	0.328 (36)
Residual error (CV%)	29.4% (23%)	28.0% (2%)

SEE = standard error of the estimate



Pediatric trial with Intelence as an Active NRTI Option (TMC125-C213)

- Sparse PK sample
 - One sample at week 4, 8, 12, and 48
 - Two samples at week 12: trough and >1 hour post-dose
- 467 plasma concentration-time points from 101 pediatric subjects

Pharmacokinetics Parameter	Children ≥ 6 to < 12 years N = 41	Adolescents ≥ 12 to < 18 years N = 60	All subjects N = 101
AUC_{12h} (ng.h/mL)			
n	41	60	101
Mean (SD)	5764 (4044.36)	4874 (4486.63)	5235 (4314.21)
Median (Min; Max)	5289 (513; 24291)	3774.5 (62; 28865)	4499 (62; 28865)
C_{0h} (ng/mL)			
n	41	60	101
Mean (SD)	381 (320.56)	324 (357.20)	347 (342.34)
Median (Min; Max)	342 (33; 1879)	236 (2; 2276)	287 (2; 2276)

- PK in children is comparable to adults
- PK correlated with age, weight, race and adherence but not sex
- IAS late breaker on efficacy and safety (TULBPE027)

