Safety & Pharmacokinetics of Monoclonal Antibody VRC01LS in HIV-Exposed Newborns

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International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Mother-to-child transmission of HIV

- Maternal and infant ART has resulted in considerable progress to reduce transmission.
- However, an estimated 180,000 children were newly infected in 2017; 90% in Africa[1].
- Continued transmission is due to:
  - Women not diagnosed during pregnancy
  - Incomplete ART adherence during pregnancy or while breastfeeding
  - Women acquiring HIV while breastfeeding
  - Drug resistant virus
- To eliminate transmission to infants, additional strategies are needed.

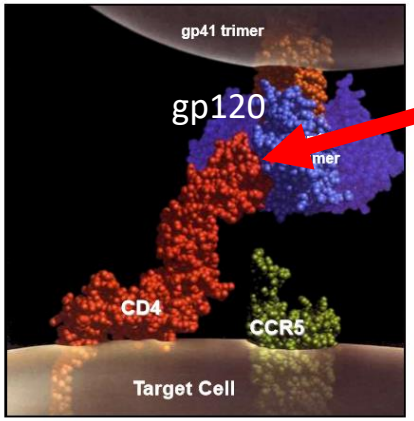
1. http://www.unaids.org/en/resources/documents/2018/core-epidemiology-slides

Passive immunization is a potential strategy to interrupt transmission

- Hepatitis B mother-to-infant transmission prevented with HBIG.
- HIV-1 specific broadly neutralizing monoclonal antibody protection in non-human primates (NHP).
  - Prevention from SHIV transmission via rectal challenge in adults and juvenile NHP [1]
  - Prevention from SHIV transmission via oral challenge in neonatal NHP [2]
- AMP study (HVTN/HPTN) enrolled and in follow-up
  - Phase 2b study of VRC01 for HIV prevention adults.

1. Pegu A et al. Sci Transl Med 2014: 6; 243ra288
2. Hessell AJ et al. Nat Med 2016: 22;362-368

Broadly neutralizing anti-CD4 binding site monoclonal antibody: VRC01



CD4 binding site on gp120 is functionally conserved: All viruses must bind CD4

Clade B (n=25)

	VRC01	b12
JRFL	0.029	0.022
YU2	0.081	2.18
89.6	0.178	0.14
6101.10	0.025	>50
7165.18	16.3	>50
6535.3	0.173	0.429
QH0692.42	0.284	0.97
SC422661.8	0.035	0.44
PVO.4	0.252	>50
TRO.11	0.071	>50
AC10.0.29	0.845	1.8
RHPA4259.7	0.014	0.12
THRO4156.18	1.78	1.21
REJO4541.67	0.014	5.92
TRJO4551.58	0.054	>50
WITO4160.33	0.028	8.54
CAAN5342.A2	0.635	>50
BL01.DG(5)	>50	1.650
BR07.DG	0.342	0.096
HT593.1	0.213	0.117
R2	0.235	1.170
BG1168.01	0.276	>50
QH0515.01	0.294	0.300
5768.04	0.033	0.249
3988	0.134	0.378

Clade A (n=24)

	VRC01	b12
RW020.2	0.182	10.1
UG037.8	0.081	>50
DJ263.8	0.143	0.812
KER2018.11	0.436	>50
Q259.w6	0.274	>50
Q769.h5	0.027	>50
Q168.a2	0.086	>50
Q23.17	0.038	>50
Q259.17	0.031	>50
Q461.e2	0.165	>50
Q842.d12	0.017	>50
BB201.B42	0.118	0.358
MB201.A1	0.062	>50
MB201.B10	0.093	>50
BB539.2B13	0.049	0.624
MB539.2D1	0.021	0.476
MB539.2B7	0.333	11.6
BI369.9A	0.062	28.9
MI369.A5	*0.400*	4.05
BS208.B1	0.017	0.042
MS208.A1	0.071	0.201
MS208.A3	0.029	0.505
KER2008.12	0.457	>50
KNH1209.18	0.059	0.227

Clade C (n=32)

	VRC01	b12
Du123.6	10.1	1.82
Du151.2	6.55	3.79
Du156.12	0.037	0.656
Du172.17	>50	0.3
Du422.1	>50	0.464
ZM197M.PB7	0.105	>50
ZM214M.PL15	0.277	13.6
ZM233M.PB6	1.2	>50
ZM249M.PL1	0.035	3.81
ZM53M.PB12	0.604	32.6
ZM109F.PB4	0.073	>50
ZM135M.PL10a	0.422	>50
CAP45.2.00.G3	0.279	0.37
CAP210.2.00.E8	>50	27
CAP244.2.00.D3	0.326	>50
ZA012.29	0.087	>50
BR025.9	0.115	>50
ZM215.8	0.095	>50
ZM106.9	0.259	>50
ZM55.28a	0.340	>50
ZM53.21	0.390	9.54
ZM55.4a	0.450	32.6
ZM106.10	0.189	>50
ZM109.32	0.091	>50
ZM135.8a	0.374	>50
ZM146.7	0.333	18
ZM176.66	0.055	>50
ZM181.6	1.120	>50
SO18.18	0.069	13.9
286.36	0.188	0.701
288.38	0.992	>50
TZA125.17	>50	>50

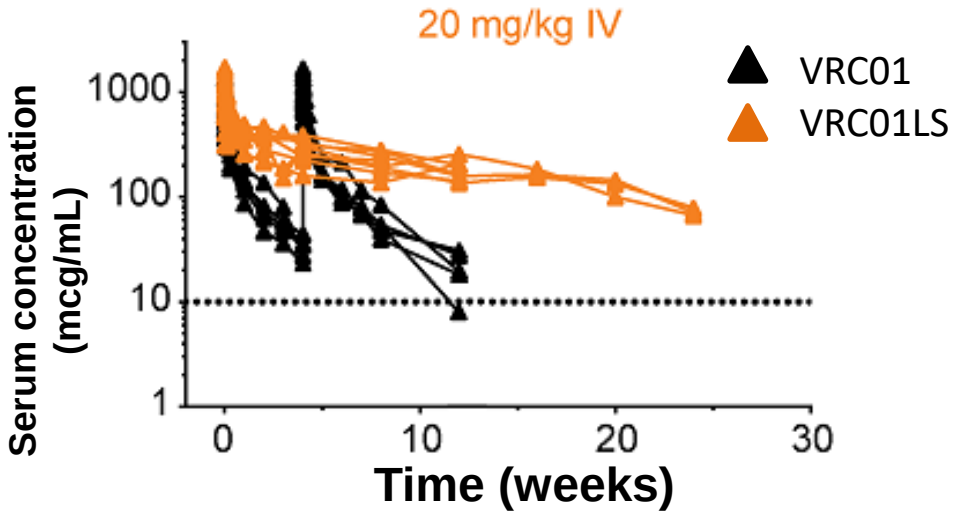
Red: < 1 µg/ml

Yellow: >/= 1 ug/ml and < 10 µg/ml

Green: >/= 10 µg/ml and < 50 ug/ml

VRC01LS: Increased affinity for neonatal Fc-receptor increases mAb half-life

- Two amino acid substitutions (M428L/N434S) result in increased affinity for the neonatal Fc-receptor at low pH and recirculation of functional IgG.
- These changes also result in increased antibody at mucosal surfaces.
- In adults, this results in a dramatic increase in half-life.



Ko et al, Nature, 514(7524) 2014
Guadinski et al, PLoS Med, 2018

IMPAACT P1112: *Study Overview*

Open label, dose-escalating, phase I study of safety and pharmacokinetics of single and multiple subcutaneous (SC) doses starting at birth

VRC01 (VRC-HIVMAB-060-00-AB)

- Dose group 1[1] (N=13 non-breastfed)
  - Birth dose 20mg/kg
- Dose group 2[1] (N=14, non-breastfed)
  - Birth dose 40mg/kg
- Dose group 3[2] (N=13, breastfed)
  - Birth dose 40mg/kg
  - Monthly dose 20mg/kg

VRC01LS (VRC-HIVMAB-080-00-AB)

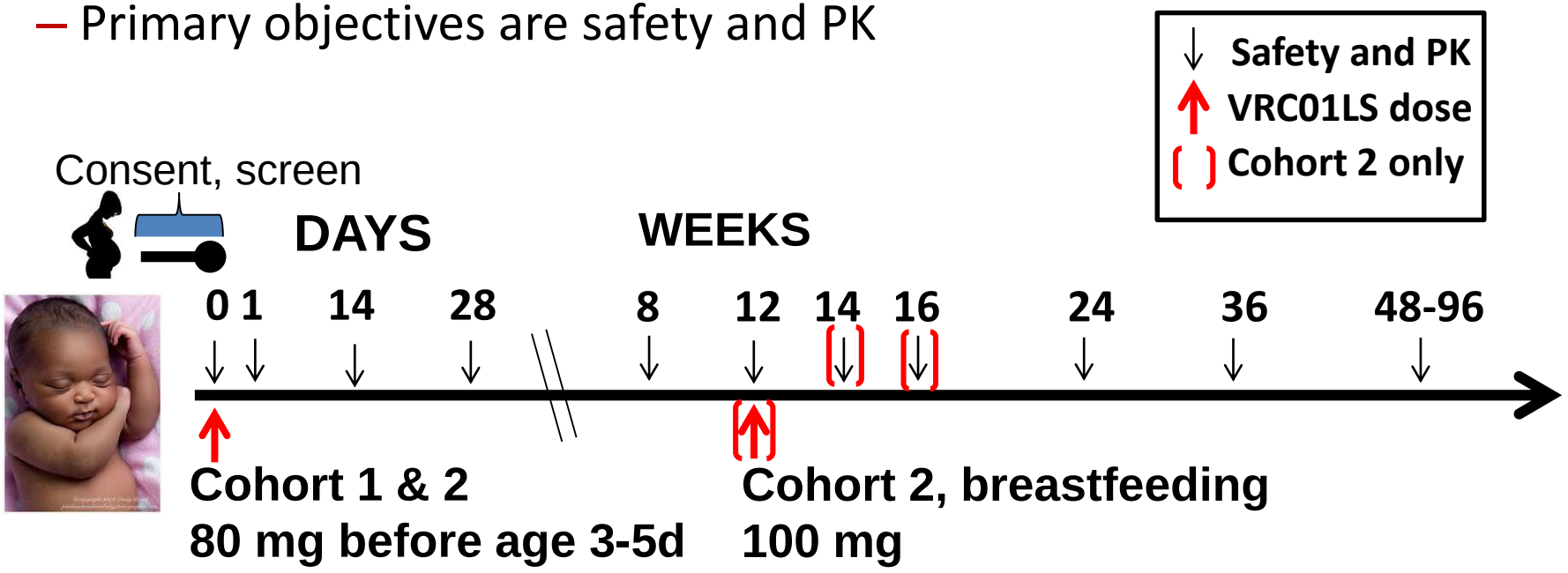
Dose group 4

- Cohort 1 (N=10, non-breastfed)
  - Birth dose weight bands
    - Wt <4.5 kg: 80mg
    - Wt ≥ 4.5 kg: 100mg
- Cohort 2 (N=11, breastfed)
  - Birth dose weight bands
    - Wt <4.5 kg: 80mg
    - Wt ≥ 4.5 kg: 100mg
  - 12 week dose 100mg

1. Cunningham et al. Abstract 760; CROI 2017, Seattle, WA
2. Cunningham et al. Abstract 0A08.05; HIV R4P 2018, Madrid, Spain

IMPAACT P1112 Dose Group 4:
study schedule

- HIV-exposed infants
  - ALL infants receive ART to prevent perinatal/breastmilk transmission
  - Followed on study 96 weeks
  - Primary objectives are safety and PK



Dose Group 4: Baseline characteristics

	Cohort 1 (non-breastfed) N= 10	Cohort 2 (breastfed) N= 11	Total N= 21
Site			
African*	3 (30%)	11 (100%)	14 (67%)
United States	7 (70%)		7 (33%)
Age (days)	2 (± 0.9)	2.4 (± 0.8)	2.2 (± 0.9)
Weight (grams)	3123 (± 534)	2948 (± 381)	3031 (± 457)
Infant ARV			
One drug (NVP or ZDV)	7 (70%)	11 (100%)	18 (86%)
Combination	3 (30%)		3 (14%)
Received VRC01LS			
Dose 1	10 (100%)	11 (100%)	21 (100%)
Dose 2	NA	10 (91%)	10 (91%)

* South Africa and Zimbabwe

IMPAACT P1112 Dose Group 4: *Current status*

- Enrollment between Jan 2017-Feb 2018.
- All infants (N=21) received 1st dose; 10 infants received 2nd dose.
- No Grade 3 or 4 adverse events related to VRC01LS.
- No infants stopped study treatment due to adverse events.
- Ongoing follow-up (N=18) through Feb 2020.
  - Cohort 1 – two infants discontinued at 2 and 4 weeks[1]
  - Cohort 2 – one infant discontinued at 22 weeks[2]

[1] Withdrew consent, lost to follow-up

[2] Withdrew consent

Dose Group 4: Local Reactions

Local reactions were common, especially with the first dose; almost all mild and resolved within hours

	Cohort 1: dose 1 (n=10)	Cohort 2: dose 1 (n=11)	Cohort 2: dose 2 (n=10)
Volume per site, mean (min/max)	0.8 mL (0.8/0.8)	0.6 mL (0.4/0.8)*	0.6 mL (0.3/1.0)*
% of children with any reaction^	50%	82%	20%
Grade mean (min/max)&	1 (1/1)	1 (1/1)	2 (2/2)
Resolution by 1 hr	60%	89%	0%
Resolution by 24 hr	100%	100%	100%

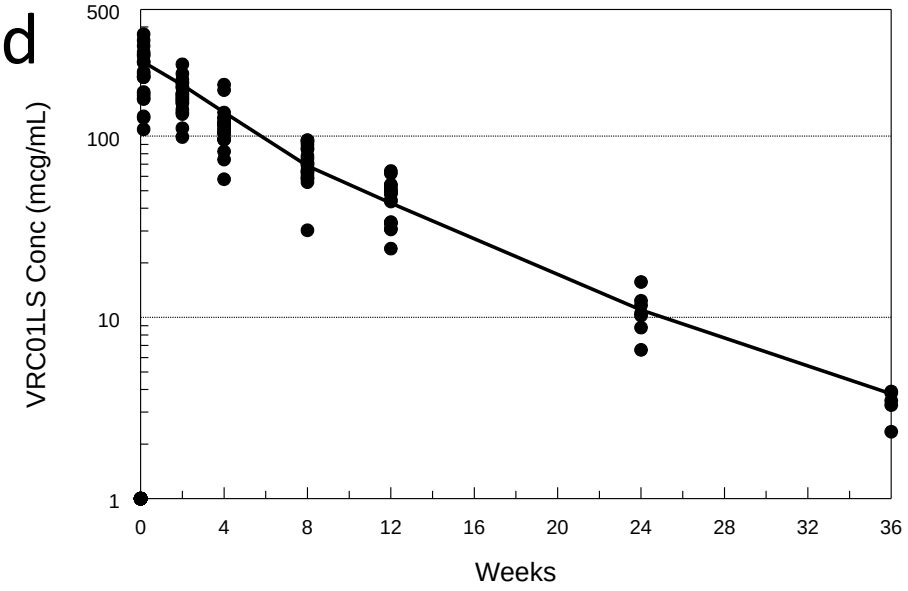
* Some infants received dose split across two injection sites

^ Erythema 9-55%; edema 10-45%, induration 0-20%, bruising: 1 infant

& Reaction size: most 1-2 cm; maximum 3.5 cm

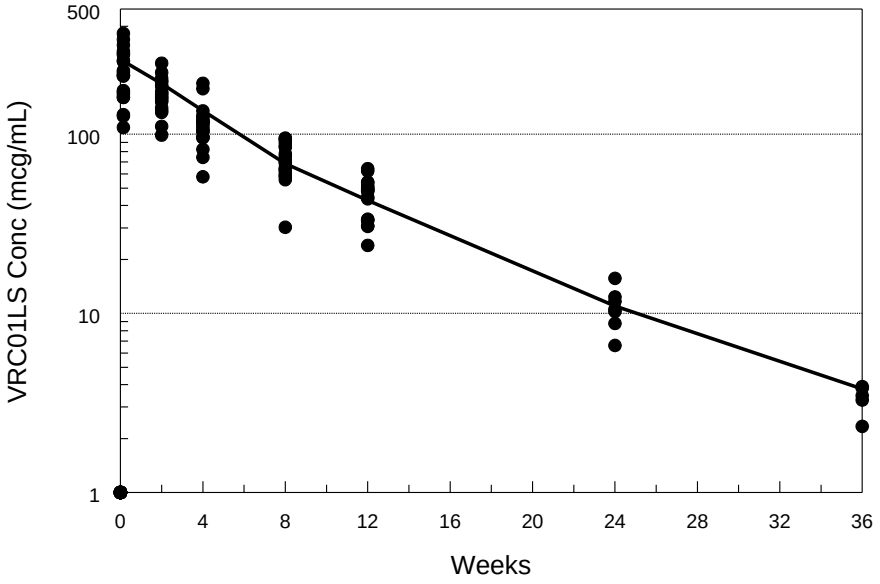
VRC01LS Infant PK parameters First Dose: 80mg SC (n=21)

- Preliminary PK Parameters (mean ± sd)
  - Vd/F: 0.121 ± 0.007 L/kg
  - CL/F: 1.45 ± 0.23 mL/kg/d
  - $T_{1/2}$: 59 ± 8 days



VRC01LS Infant PK Day 1 and Week 12

- Day 1
  - Mean (SD) 222 (± 72) mcg/mL
  - >100 mcg/mL 100%
- Week 12
  - Mean (SD) 44.72 (± 11.44) mcg/mL
  - > 50mcg/mL 33%
  - > 20mcg/mL 100%



VRC01LS PK parameters infants vs. healthy adults

Newborn (birth dose, SC)

- Preliminary PK (mean ± sd)

  $T_{1/2}$: 59 ± 8 days

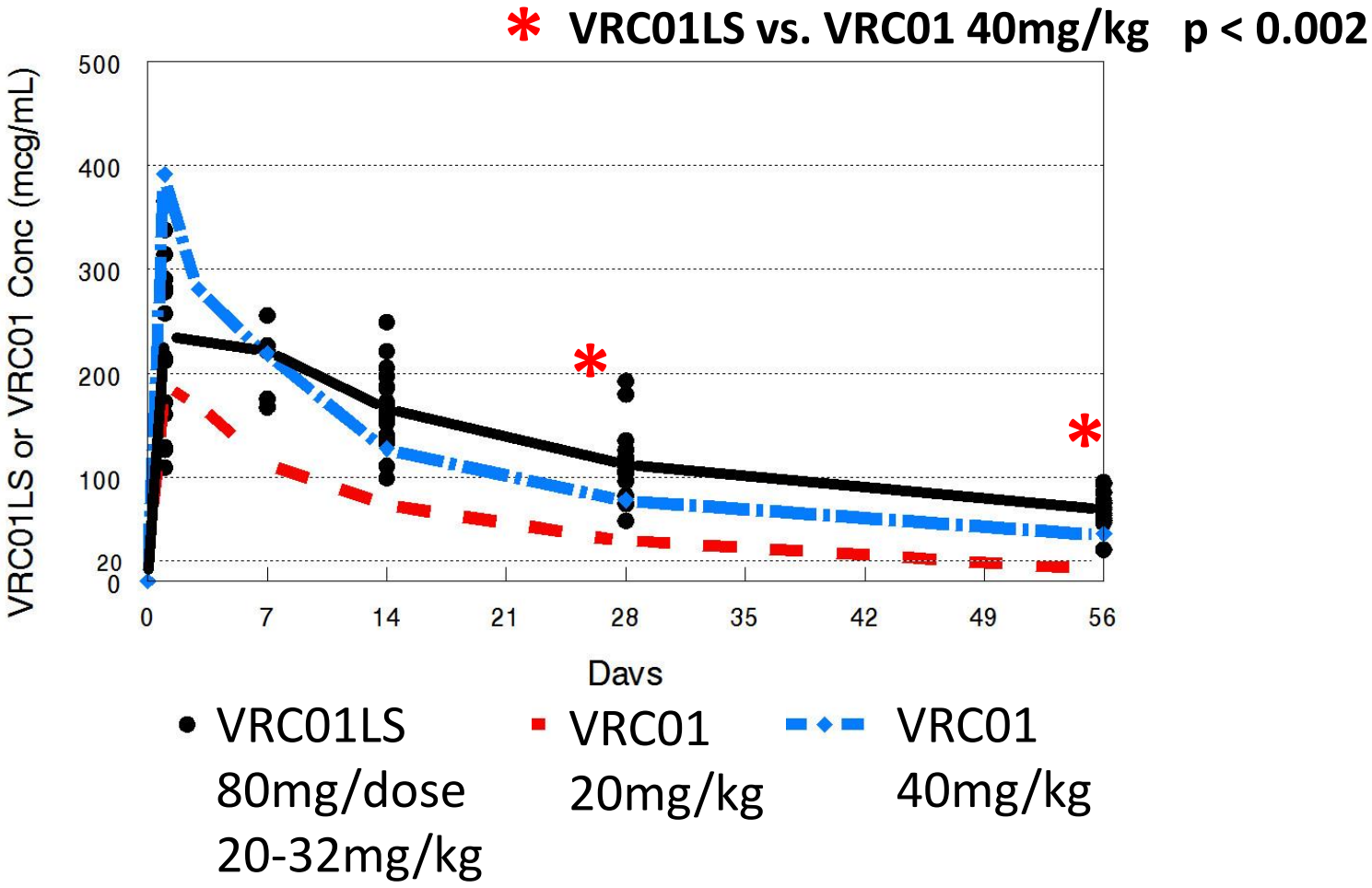
Healthy adults [1] (averaged for IV and SC)

- PK Parameters (mean ± sd)

  $T_{1/2}$: 71 ± 18 days

[1]*Gaudinski et al. Plos Med; 2018*

Infant PK parameters
VRC01LS vs. VRC01: 1st dose PK



VRC01 data from Cunningham et al. Abstract 760; CROI 2017, Seattle, WA

In conclusion

- VRC01LS is well tolerated.
- VRC01LS can be administered at birth and 1-2 times per year to achieve desired levels.
- Broadly neutralizing antibodies are feasible as an additional strategy to prevent mother-to-child transmission of HIV in infants at increased risk of HIV transmission.
- **Next steps:**
  - New agents
    VRC07-523LS - increased potency & breadth
    (*IMPAACT P1112)*
  - Studies of bNAb as adjunct to ART for neonatal HIV prevention and early treatment
    (IMPAACT 2008; IMPAACT P1115)

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Sites

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Extra slide: PK methods

The data were fit to one and two compartment population PK models using the computer program NONMEM (ver 7.3). Empiric Bayesian estimates of the individual participants PK parameters were generated using the POSTHOC subroutine. The mean +/-sd parameter values represent the summary statistics for these empiric Bayesian values. The mean of the individual Bayesian values and the typical population model values were nearly identical. The one compartment model was sufficient to describe the data, in other words the two compartment model did not improve the overall fit of the data (and generated a nearly identical t1/2 to the one-compartment model). The ability of a one compartment model to fit the data as well as a two compartment model in infants is likely due to the SC administration and limited early PK samples (Day 1 then Week 2).