Supplemental Material

Base model selection

During model building, incorporation of a second DHA compartment not only introduced model convergence issues, but also yielded implausibly long estimates of DHA half-life. Introduction of more complex absorption models was similarly unsuccessfully. Models including parallel first order absorption failed to converge; models with transit compartment absorption yielded unreasonable estimates of artesunate apparent volume of distribution (V2/F <100 L). Although a model with a mixed zero-order, lagged first-order absorption process did converge, there was a lack of improvement in DHA goodness-of-fit when compared to a simple first-order absorption model. Therefore, the increase in model complexity was deemed to be unjustified. Finally, a model was constructed with bioavailability (F1) set to 1 for the first day of treatment and estimated for the second and third days. This introduced substantial imprecision on parameter estimates (%RSE for CLM/F = 84%, V3/F = 220%), precluding utilization of the model. Interestingly, however, for that model, the estimated F1 values for days 2 and 3 were 0.711 (RSE: 48%) and 0.723 (RSE: 60%), respectively.

Incorporating IIV on artesunate bioavailability (F1) not only introduced substantial imprecision to the parameter estimates, but also markedly skewed the values of the estimates themselves. The alternative method of describing such variability, namely incorporating an η on F1, not only introduced substantial parameter estimate imprecision, but also markedly skewed the values of multiple parameters. Accounting for concentrations below the lower limit of quantification using either the M2 or M3 method proved unsuccessful, as the models estimated with the requisite Laplacian estimation method failed to converge.

All of the models implemented during model building were associated with substantial residual variability. Inspection of the data indicated that patients displayed marked interoccasion variability (IOV). Although systematic disease effects could be contributing to the variability, much of it appeared random. However, formally modeling IOV was not possible, since, for patients with more than one occasion, only a single sample of each analyte was available per occasion. To assess the extent to which IOV was contributing to residual variability, the final base model was implemented with data from each occasion being considered as representing a distinct individual. This yielded marked declines in residual variability estimates, suggesting that IOV was a substantial contributor to the observed residual variability, albeit one that could not be well accounted in the present analysis.

Effects of adolescent/adult data inclusion

The lack of bias associated with inclusion of adolescent and adult data was somewhat dependent on the results of the body size model selection process. Indeed, concordance between population predicted parameter estimates for models derived from the pediatric and the full dataset was a criterion used in evaluating various body size models. Inclusion of this consideration was not intended as a claim that a body size model which does not display this characteristic is intrinsically flawed. Indeed, had one of the body size models been associated with markedly superior goodness of fit for the pediatric data, but also displayed discrepant estimates as compared to the full dataset, that model would likely, on balance, have been the most justifiable selection for further modeling. Under such circumstances, were the full dataset to be utilized in further analyses, the effect of age on body size-parameter relationships would need to be defined. This would necessitate estimation of additional parameters, which could

destabilize the model or reduce estimate precision. Thus, giving a measure of preference to body size models yielding similar predictions for the two datasets essentially represented a means of avoiding unnecessary complications in modeling and potentially increasing the likelihood of developing a more parsimonious model.

Granule formulation effect

To explore the issue of the apparent formulation effect, plots of observed artesunate and DHA concentrations vs. time (stratified by dose received) were examined. These plots revealed a relative lack of data describing the absorption phase for the granules due both to the sparse sampling nature of a majority of the granule data, as well as the apparent quite rapid absorption of this formulation. These patterns were maintained even when comparing data for patients of similar ages, suggesting that a formulation effect rather than an age effect was operating. Once the distinct characteristics of this formulation were identified, attempts were also made to model a separate value for granule bioavailability relative to that of the tablet. However, these attempts failed to yield plausible estimates. Ultimately, the absorption rate constant for the granule formulation had to be set to a fixed value as it could not be accurately estimated**.**

TABLES

Table S1. NONMEM estimates and relative standard errors (%RSE) for DHA apparent clearance (CLM/F) in models incorporating body size descriptors.

	Full dataset		Pediatric dataset	
CLM/F	**θ_1 (%RSE)**	**θ_2 (%RSE)**	**θ_1 (%RSE)**	**θ_2 (%RSE)**
Linear Weight	70.1 (4.0%)		79.4 (5.6%)	
Allometric Scaling	67.0 (4.1%)		67.2 (4.4%)	
Estimated Weight	67.6 (5.2%)	0.820 (9.3%)	88.9 (13.7%)	1.18 (15.8%)
Linear BSA	65.5 (8.8%)		64.1 (5.6%)	
Estimated BSA	67.0 (4.5%)	1.19 (9.7%)	84.8 (42.9%)	1.62 (48.4%)
Linear LBM1	64.7 (9.1%)		71.6 (9.4%)	
Estimated LBM1	63.6 (5.6%)	0.854 (14.3%)	91.0 (18%)	1.42 (19.9%)
Linear LBM2	67.3 (48%)		73.9 (5.9%)	
Estimated LBM2	66.0 (12.7%)	0.883 (29.4%)	82.2 (14.8%)	1.18 (20.4%)

Table S2. NONMEM estimates and relative standard errors (%RSE) for DHA apparent volume of distribution (V3/F) in models incorporating body size descriptors.

	Full dataset		Pediatric dataset	
Model: V3/F	**θ_3 (%RSE)**	**θ_4 (%RSE)**	**θ_3 (%RSE)**	**θ_4 (%RSE)**
Linear Weight	66.6 (8.8%)		75.5 (15.5%)	
Allometric Scaling	64.2 (4.1%)		74.6 (8.8%)	
Estimated Weight	64.8 (10.5%)	0.883 (19.6%)	99.3 (28%)	1.42 (33.7%)
Linear BSA	62.3 (5.1%)		61.0 (9.7%)	
Estimated BSA	64.1 (9.1%)	1.29 (11.8%)	95.7 (22.5%)	2.02 (15.7%)
Linear LBM1	61.6 (10.7%)		67.7 (5.2%)	
Estimated LBM1	60.7 (27.8%)	0.887 (34.2%)	106 (21.2%)	1.79 (20.6%)
Linear LBM2	64.2 (162%)		70.7 (8.2%)	
Estimated LBM2	63.5 (7.8%)	0.940 (48.3%)	89.7 (22.4%)	1.41 (29.6%)

Table S3. A summary of the results obtained from the Allometric Scaling model and linear BSA model as implemented with the full population dataset. RSE: Relative standard error.

	Allometric Scaling		Linear BSA	
Parameter[a]	**Model estimate (Bootstrap %RSE)**	**Bootstrap 95% CI**	**Model estimate (Bootstrap %RSE)**	**Bootstrap 95% CI**
CL/F (L/h)	900 (7.11%)	765, 1003	905 (7.71%)	762, 1030
V2/F (L)	1030 (13.1%)	797, 1314	906 (13.3%)	662, 1170
CLM/F (L/h)	63.5 (6.05%)	56.8, 71.3	62.6 (6.47%)	55.5, 71.4
V3F (L/hr)	72.9 (10.4%)	58.3, 87.7	66.9 (9.75%)	54.3, 79.5
Ka (hr^{-1})	3.88 (24.1%)	2.85, 6.51	2.99 (22.0%)	2.39, 5.12
Gender on CL/F	1.09 (7.96%)	0.933, 1.29	1.09 (88.0%)	0.921, 1.29
Gender on V2/F	1.07 (13.8%)	0.808, 1.39	1.11 (15.3%)	0.85, 1.49
Gender on CLM/F	1.10 (7.43%)	0.962, 1.28	1.10 (7.66%)	0.954, 1.28
Gender on V3/F	0.828 (13.5%)	0.647, 1.08	0.925 (12.4%)	0.734, 1.18
IIV-CL/F	0.186 (23.3%)	0.120, 0.291	0.207 (21.5%)	0.135, 0.305
IIV-V2/F	0.568 (23.8%)	0.296, 0.845	0.544 (25.4%)	0.284, 0.822
IIV - CLM/F	0.255 (22.8%)	0.149, 0.382	0.277 (22.1%)	0.158, 0.398
IIV-V3/F	0.427 (26.0%)	0.217, 0.650	0.436 (24.1%)	0.227, 0.659
IIV- Ka	2.28 (40.5%)	1.07, 4.84	1.96 (43.9%)	1.03, 4.54
$Sigma^2$ AS	0.623 (28.9%)	0.566, 1.32	0.623 (26.7%)	0.592, 1.25
$Sigma^2$ DHA	0.967 (10.9%)	0.768, 1.19	0.943 (12.0%)	0.736, 1.18

a. CL/F, V2/F, and Ka are artesunate apparent clearance, apparent volume of distribution, and absorption rate constant, respectively. CLM/F and V3/F are DHA apparent clearance and apparent volume of distribution, respectively

Table S4. Covariance estimates, with bootstrap relative standard errors and confidence intervals, for the Linear BSA and Allometric Scaling models as estimated with both the full population and pediatric only datasets. Presented values represent: Model estimate (Bootstrap Relative Error); [Bootstrap 95% confidence interval].

	Allometric: Full Pop.	**Linear BSA: Full pop.**	**Allometric: Pediatric only**	**Linear BSA: Pediatric only**	**Allometric: Pediatric only**
COV(CL, V2)	0.217 (27.5%); [0.110, 0.340]	0.233 (26.5%); [0.118, 0.370]	0.348 (25.1%); [0.193, 0.545]	0.346 (26.4%); [0.184, 0.560]	0.348 (25.1%); [0.193, 0.545]
COV(CLM, CL)	0.179 (23.3%); [0.108, 0.276]	0.189 (22.0%) [0.119, 0.284]	0.210 (23.2%); [0.123, 0.322]	0.214 (23.1%); [0.126, 0.325]	0.210 (23.2%); [0.123, 0.322]
COV(CLM, V2)	0.315 (25.2%); [0.161, 0.471]	0.328 (25.1%); [0.165, 0.499]	0.336 (24.8%); [0.190, 0.520]	0.346 (25.2%); [0.195, 0.540]	0.336 (24.8%); [0.190, 0.520]
COV(V3, CL)	0.242 (25.4%); [0.139, 0.379]	0.260 (23.0%); [0.151, 0.396]	0.259 (27.7%); [0.125, 0.397]	0.267 (27.5%); [0.126, 0.406]	0.259 (27.7%); [0.125, 0.397]
COV(V3, V2)	0.229 (36.6%); [0.0855, 0.414]	0.279 (29.9%); [0.117, 0.451]	0.178 (49.6%); [0.0121, 0.367]	0.208 (44.7%); [0.0317, 0.418]	0.178 (49.6%); [0.0121, 0.367]
COV(V3, CLM)	0.276 (26.9%); [0.146, 0.432]	0.304 (23.9%); [0.159, 0.456]	0.250 (32.3%); [0.117, 0.435]	0.268 (31.0%); [0.126, 0.448]	0.250 (32.3%); [0.117, 0.435]

Table S5. Results of stratified numerical predictive checks for DHA. Cells contain percentages of observations falling below the 5th percentile/above the 95th percentile for each model and dataset.

	≤ 5 years	**6 - 11 years**	**12 - 18 years**	**>18 years**
Allometric Scaling: Full dataset	4.1%/3.8%	5.4%/1.8%	6.3%/2.6%	8.0%/1.8%
Allometric Scaling: Pediatric	3.8%/4.4%	6.1%/3.4%		
Linear BSA: Full dataset	2.4%/3.2%	5.2%/2.9%	5.3%/2.1%	7.2%/1.8%
Linear BSA: Pediatric	3.8%/4.1%	5.9%/2.9%		

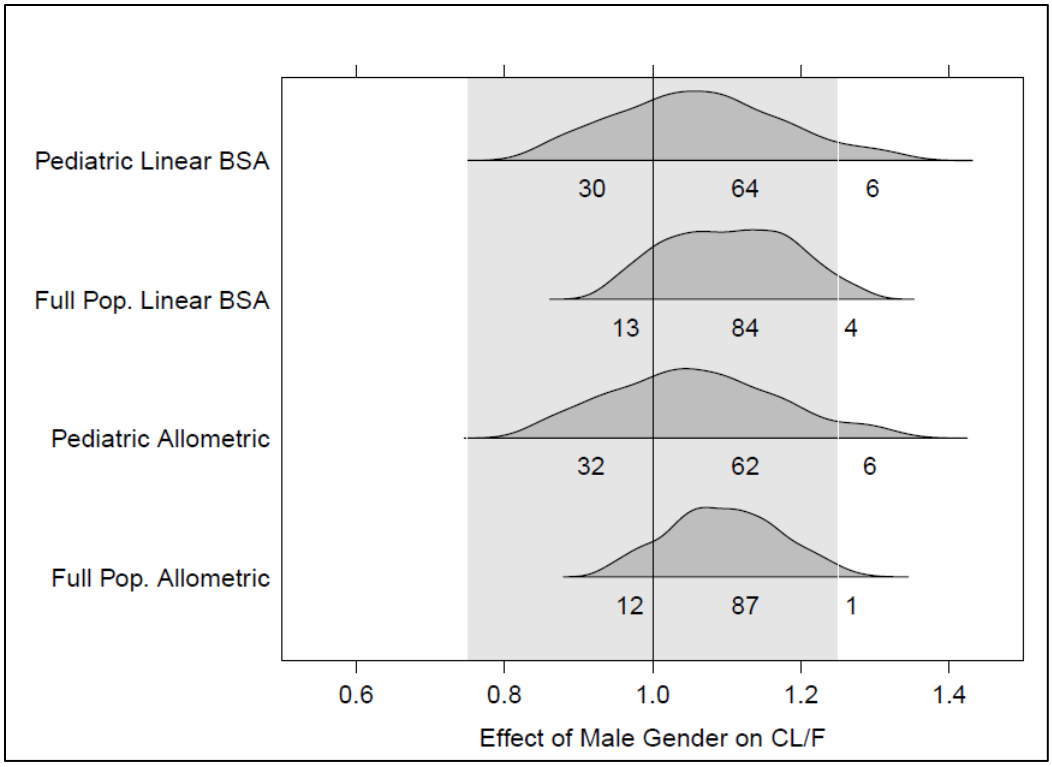

Figure S1. Covariate effect plots for CL/F. Distributions correspond to the 2.5th to 97.5th percentile for gender effects obtained from the bootstrap results from each model.

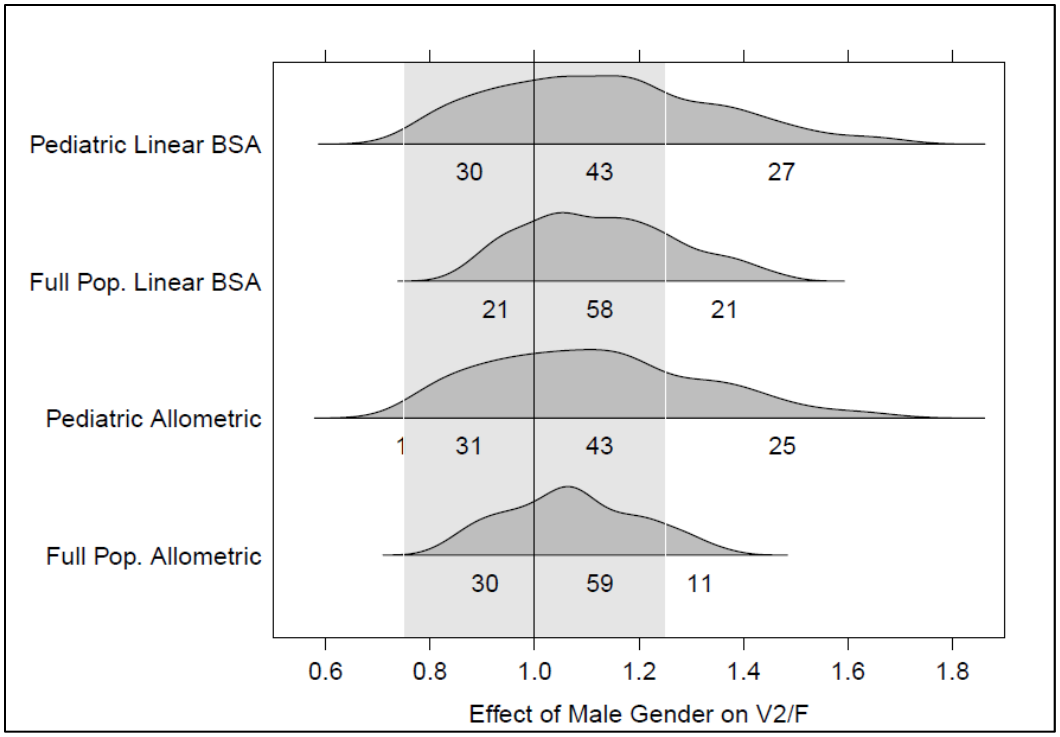

Figure S2. Covariate effect plots for V2/F. Distributions correspond to the 2.5th to 97.5th percentile for gender effects obtained from the bootstrap results from each model.

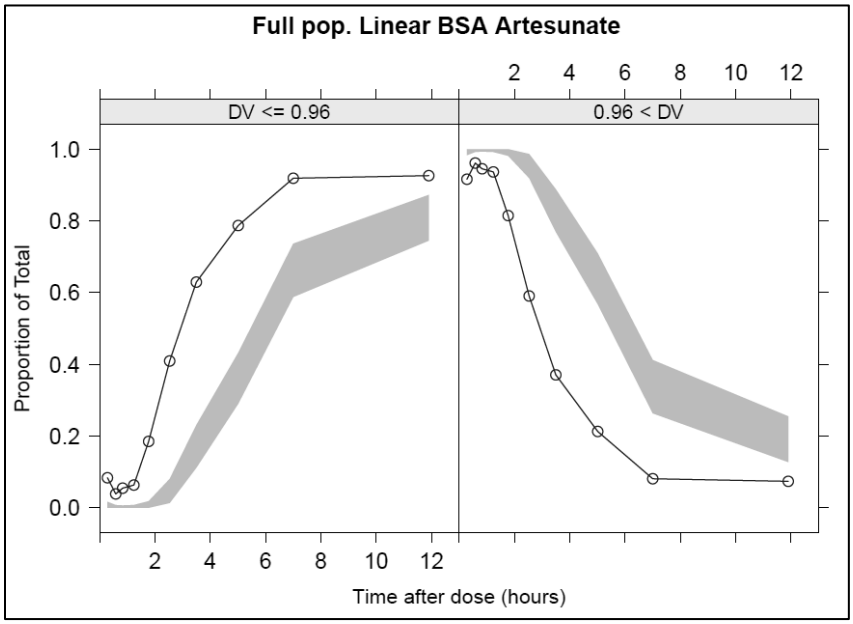

Figure S3. Categorical VPC for proportion of artesunate concentrations below and above the lower limit of quantification. The line represents the observed data; the shaded area represents the 95% confidence interval for the simulated data.

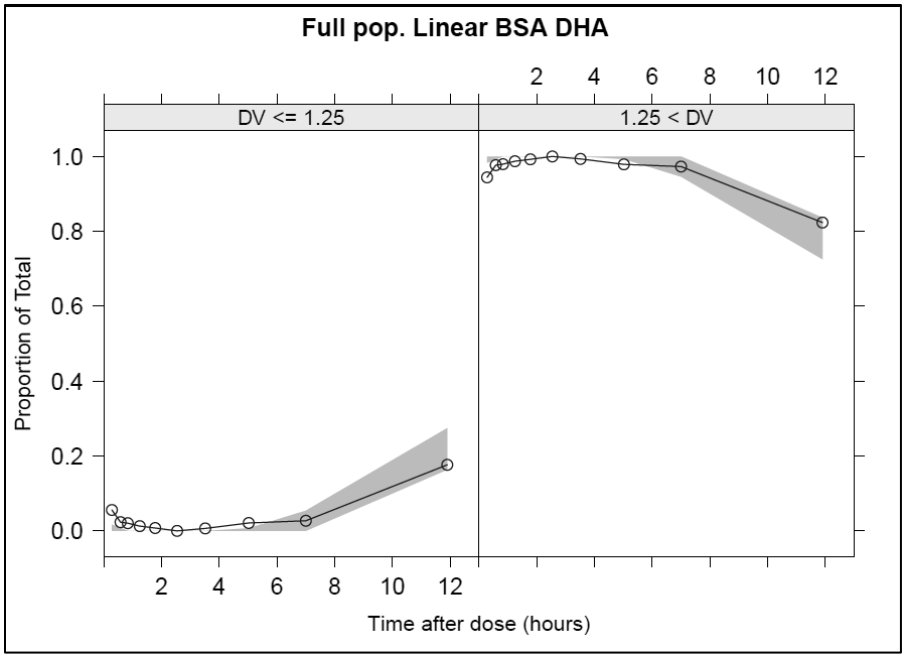

Figure S4. Categorical VPC for proportion of DHA concentrations below and above the lower limit of quantification. The line represents the observed data; the shaded area represents the 95% confidence interval for the simulated data.