## S3 Pharmacokinetic Analysis Details

Note. Some of the figures and tables refer to "OZ" or "OZ439" which are the same as artefenomel.

No formal population PK analysis of either artefenomel or ferroquine has been performed on the study data, contrary to what was specified in the protocol. Instead, population PK techniques were applied using historical population PK models to estimate only the individual patient PK parameters. The latter approach was pre-specified in an analysis plan.

All data processing, analysis, model setup and modelling result analysis were conducted within R (Microsoft Open R 3.5.1) combined with the IQR package (v1.1.1) developed by IntiQuan (IQR Tools, https://iqrtools.intiquan.com) to support the entire workflow of a PK/PD analysis from estimations to simulations. For all estimations, a nonlinear mixed effects (NLME) modelling approach was performed using the stochastic approximation expectation maximization (SAEM) method of Monolix (Monolix version 2019R1. Antony, France: Lixoft SAS, 2019) by automatically generating and running MONOLIX projects through IQR from R environment. The log-likelihood and the Fisher information matrix were approximated by linearization. The individual parameters were determined as conditional modes.

### Pharmacokinetic Samples

Per protocol, samples for pharmacokinetic analysis of artefenomel in plasma and ferroquine (FQ)/SSR97213 in blood (dried blood spot) were collected at a total of 16 time points for each patient in patients >14 years and body weight ≥35 kg (11 for artefenomel and 13 for FQ/SSR97213). In the younger patients the number of samples collected was either 5 for artefenomel or 7 for FQ/SSR97231 for patients >5 to ≤14 years or 4/5 for artefenomel and 5 for FQ/SSR97213 for patients >6 months to ≤5 years.

The samples were analysed for artefenomel, ferroquine and SSR97213 by LC MS/MS. The limit of quantification was 5 ng/mL for FQ/SSR97213 and 1 ng/mL for artefenomel. Using human blood, an LC-MS /MS assay method for quantification of FQ and its metabolite SSR97213 in dried blood spot (DBS) over a range of 5-500 ng/mL was developed and validated. Method was specific and selective relative to endogenous compounds, with process efficiency, 60%, and no matrix effect. Accuracy and precision for intraday and interday analyzes were <15% at all concentrations tested. FQ and its metabolite SSR97213 were stable at room temperature for a duration to cover study samples, and for at least 24 hours at 37°C with and without 95% relative humidity, to cover sampling, drying, and shipment conditions in the field.

Observations below the quantification limit (BQL) were included in the data set. Monolix handles these (left-censored data) by including the simulation of the censored data with a truncated Gaussian distribution in the Markov Chain Monte Carlo (MCMC) procedure.

**Pharmacokinetic Analysis**

The analysis used a non-linear mixed effect modelling approach as implemented in Monolix. The individual Empirical Bayes Estimates of the PK parameters for each individual patient and each analyte (artefenomel, FQ and SSR97213) were estimated applying the historical population PK models developed previously (described below). The historical structural population PK model was fitted to the observed data and dosing history of the study, providing the individual PK parameters for each subject as post-hoc estimates. From these, the individual exposures were estimated through simulation and calculation: $C_{max}$, $t_{max}$, $C_{day7}$, $C_{day14}$, $C_{day21}$, $C_{day28}$, $AUC_{(0-\infty)}$ as well as $AUC_{(0-day28)}$ (for FQ and SSR97213 only).

All patients who vomited after either ferroquine (which was administered first) or artefenomel were considered vomiters for the analyses and summaries, unless they were successfully re-dosed. If patients vomited after ferroquine, they were not to be re-dosed with ferroquine but received rescue medication. If patients vomited within 5 minutes after artefenomel administration, they were to be re-dosed with artefenomel only. These patients were not considered vomiters for the artefenomel analysis, but they were considered vomiters for the ferroquine summaries (this concerned 4 patients in the PK Set for ferroquine).

**Historical Population PK models**

A single population PK model including both ferroquine and its active metabolite SSR97213 was previously developed using data of 541 subjects from eight phase I and II studies conducted in healthy volunteers (HV), asymptomatic adult subjects and symptomatic adult and pediatric patients (>2 years old) [Boulu 2016]. It included a three- and two-compartment PK model for FQ and SSR97213 respectively. The absorption of FQ was described with a first-order absorption process, lag-time and relative bio-availability. Allometric scaling was implemented and disease status (*i.e* HV and asymptomatic subject *versus* symptomatic patients) was identified as a covariate. Some data (African adults >35 kg) from study DRI12805, where FQ was co-administered with artefenomel, were included in the model development. No effect of artefenomel on the pharmacokinetics of FQ or its metabolite was identified (Table 1).

**Table 1 Parameter estimates ferroquine historical population PK model in Patients [Boulu 2016]**

| Parameter | | Estimate[a] | BSV[b] (%) |
|---|---|---|---|
| | **ferroquine** | | |
| F | Relative Oral Bioavailability | 1 | - |
| tlag (hr) | Absorption lag time | 0.45 (1) | - |
| ka (1/hr) | Absorption rate constant | 0.71 (8) | 110 (12) |
| Cl/F (L/hr) | Apparent Clearance | $13.5(6) * \left(\frac{BW}{65}\right)^{0.75}$ | 46 (10) |
| V1/F (L) | Apparent central volume of distribution | $2590(4) * \left(\frac{BW}{65}\right)^{1}$ | 56 (10) |
| Q/F (L/hr) | Apparent inter compartmental Clearance 1 | $141(7) * \left(\frac{BW}{65}\right)^{0.75}$ | 90 (13) |
| V2/F (L) | Apparent peripheral volume of distribution 1 | $3540(4) * \left(\frac{BW}{65}\right)^{1}$ | 37 (16) |
| Q2/F (L/hr) | Apparent inter compartmental Clearance 2 | $19.5(8) * \left(\frac{BW}{65}\right)^{0.75}$ | 98 (11) |
| V3/F (L) | Apparent peripheral volume of distribution 2 | 12400 (5) | - |
| | **SSR97213** | | |
| Clpm (L/hr) | Transformation FQ to SSR | 0.25 (4) | 19 (18) |
| CL/F (L/hr) | Apparent Clearance | 0.20 (4) | 16 (26) |
| V1/F (L) | Apparent central volume of distribution | 1 | - |
| Q/F (L/hr) | Apparent inter compartmental Clearance 1 | 0.72 (6) | 42 (12) |
| V2/F (L) | Apparent peripheral volume of distribution 1 | 43 (5) | 47 (18) |
| residual | Proportional ferroquine | 0.22 (2) | |
| residual | Proportional SSR97213 | 0.26 (2) | - |

[a]Estimate, with between brackets the RSE (Relative Standard Error %)
[b]Between Subject Variability
BW= body weight (kg)

For artefenomel a population PK model was previously developed based on three phase II studies: two mono therapy studies (MMV_OZ439_10_002 and MMV_OZ439_12_006) and one study in combination with piperaquine which included African and Asian men and women; age 6 months to 60 years; body weight range 5.6 - 89 kg; single doses 100 - 1200 mg; 800 mg when dosed with piperaquine (MMV_OZ439_13_003) [Macintyre 2017]. It included a three-compartment disposition model with first-order absorption and a lag-time. Body weight was included allometrically using fixed exponents for of 0.75 for clearances and 1 for volumes. Vomiting, age, actual artefenomel dose and adult equivalent artefenomel dose were all identified as covariates. In none of the studies, artefenomel was co-administered with FQ (Table 2).

**Table 2 Parameter estimates artefenomel historical population PK model in Patients [Macintyre 2017]**

| Parameter | | Estimate[a] | BSV[b] (%) |
|---|---|---|---|
| F | Relative Oral Bioavailability | $1 * \left(\frac{\text{AGE}}{20}\right)^{0.19(12)}$ | 62 (4) |
| Fvom | Relative Oral Bioavailability in Vomiters | $0.51(9) * \left(\frac{\text{AGE}}{20}\right)^{0.19(12)}$ | 86 (8) |
| tlag (hr) | Absorption lag time | 0.41 (1) | 14 (8) |
| ka (1/hr) | Absorption rate constant | $0.17(2) * \left(\frac{\text{ODOS}}{800}\right)^{-0.34(8)}$ | 22 (8) |
| Cl/F (L/hr) | Apparent Clearance | $49.2(2) * \left(\frac{\text{BW}}{50}\right)^{0.75} \left(\frac{\text{ODGP}}{800}\right)^{-0.37(11)}$ | 33 (5) |
| V1/F (L) | Apparent central volume of distribution | $135(5) * \left(\frac{\text{BW}}{50}\right)^{1}$ | 73 (6) |
| Q/F (L/hr) | Apparent inter compartmental Clearance 1 | $9.7(4) * \left(\frac{\text{BW}}{50}\right)^{0.75}$ | 36 (8) |
| V2/F (L) | Apparent peripheral volume of distribution 1 | $269(5) * \left(\frac{\text{BW}}{50}\right)^{1}$ | - |
| Q2/F (L/hr) | Apparent inter compartmental Clearance 2 | $7.0(3) * \left(\frac{\text{BW}}{50}\right)^{0.75}$ | - |
| V3/F (L) | Apparent peripheral volume of distribution 2 | $1130(4) * \left(\frac{\text{BW}}{50}\right)^{1}$ | 51 (2) |
| residual | proportional | 0.26 (2) | - |

[a]Estimate, with between brackets the RSE (Relative Standard Error %)
[b]Between Subject Variability
AGE=age (years); ODOS=actual administered dose (mg);ODGP=adult equivalent dose (mg); BW= body weight (kg)

## RESULTS

### Data

The analysis population (PK set) for artefenomel consisted of 364 patients out of 366 patients who were dosed with artefenomel. The PK Population for ferroquine consisted of 367 patients out of 373 patients who were dosed with ferroquine. The data sets included a total of 2220 samples for artefenomel and 2345/2348 samples for ferroquine/SSR97213.

There were no missing covariates or sample date-times for any of the three analytes. For the artefenomel analysis 1 sample was removed from the analysis because of a positive pre-dose artefenomel concentration. For the ferroquine/SSR97213 analysis 1 patient was removed since all samples were BLQ. This patient had vomited after FQ administration, and had received rescue medication as per protocol.

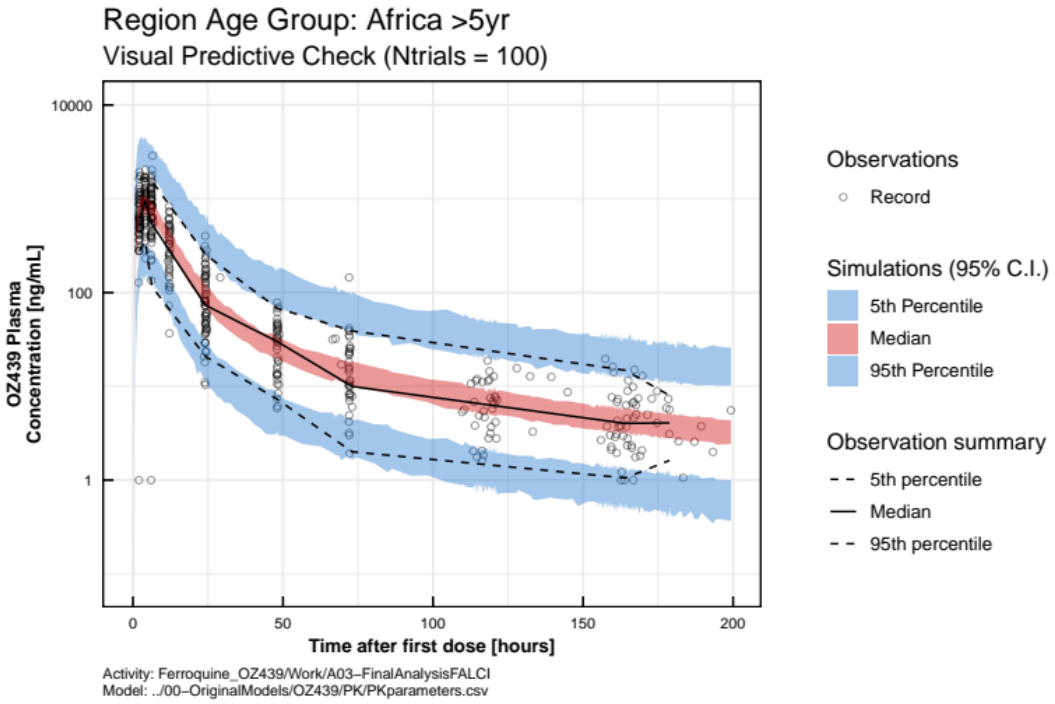
**Estimation of PK parameters**

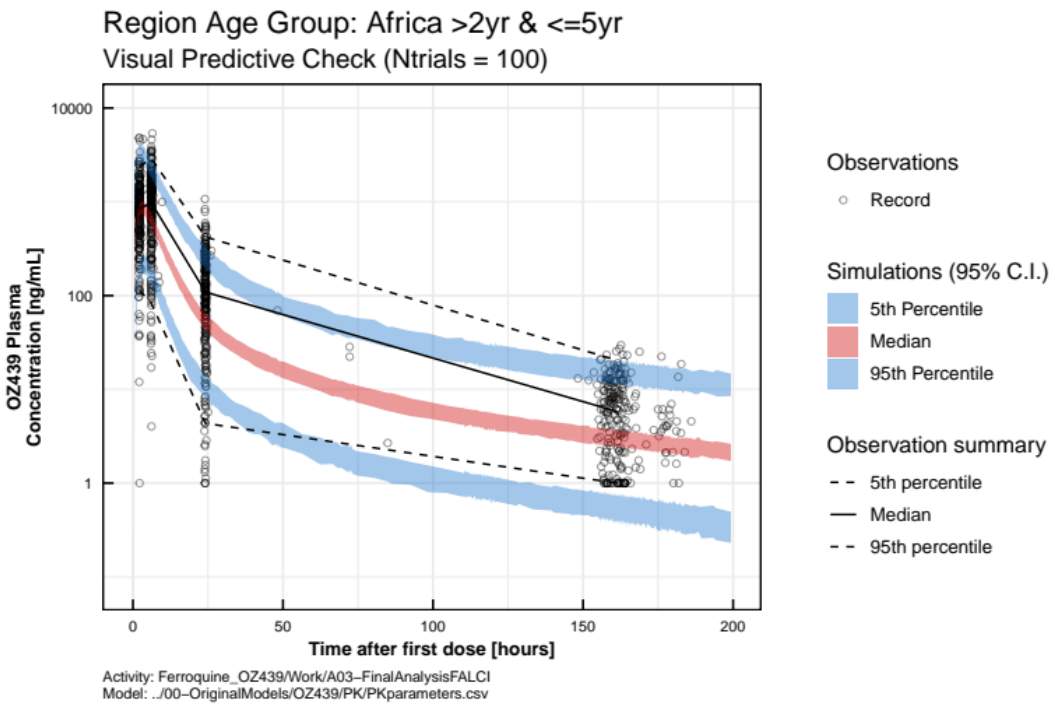
The comparison of observed artefenomel and ferroquine concentrations with the historical PK model predictions for this study population over the first 200 or 400 hours post-dose are shown in figures 1 and 2 respectively.

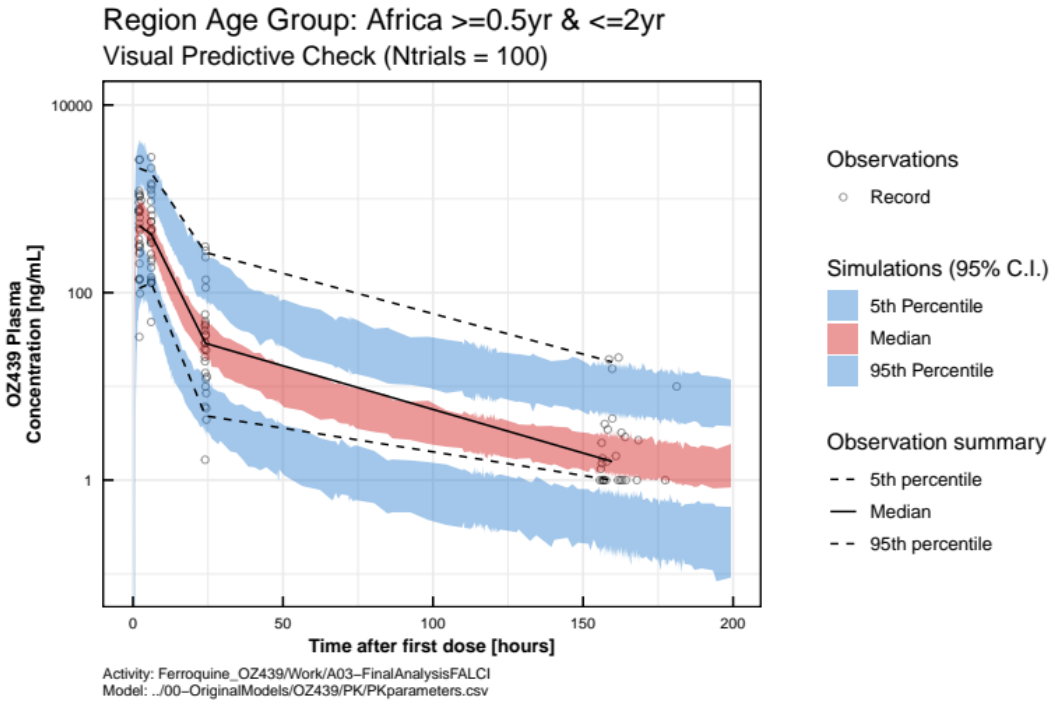
The historical population PK models were used to estimate the individual patient PK parameters, with all model parameter values fixed except for the residual proportional error. The estimated residual proportional errors were similar to the historical model values (0.27 and 0.26, respectively for artefenomel and 0.30/0.31 and 0.22/0.26 respectively for FQ/SSR97213).

The individual patient PK profiles were well described by the estimated individual PK parameters and considered adequate. Examples are shown below in Figures 3 and 5. More specifically, the observed concentrations around day 7, when available, were well described (Figures 4 and 6).

**Figure 1 Comparison of Observed Artefenomel Concentrations with the Historical Population PK Model Predictions by Region-Age Group**




Region Age Group: Africa >2yr & <=5yr
Visual Predictive Check (Ntrials = 100)
OZ439 Plasma Concentration [ng/mL]
10000
100
1
0
50
100
150
200
Time after first dose [hours]
Observations
Record
Simulations (95% C.I.)
5th Percentile
Median
95th Percentile
Observation summary
5th percentile
Median
95th percentile
Activity: Ferroquine_OZ439/Work/A03–FinalAnalysisFALCI
Model: ../00–OriginalModels/OZ439/PK/PKparameters.csv


Region Age Group: Africa >=0.5yr & <=2yr
Visual Predictive Check (Ntrials = 100)
OZ439 Plasma Concentration [ng/mL]
10000
100
1
0
50
100
150
200
Time after first dose [hours]
Observations
Record
Simulations (95% C.I.)
5th Percentile
Median
95th Percentile
Observation summary
5th percentile
Median
95th percentile
Activity: Ferroquine_OZ439/Work/A03–FinalAnalysisFALCI
Model: ../00–OriginalModels/OZ439/PK/PKparameters.csv

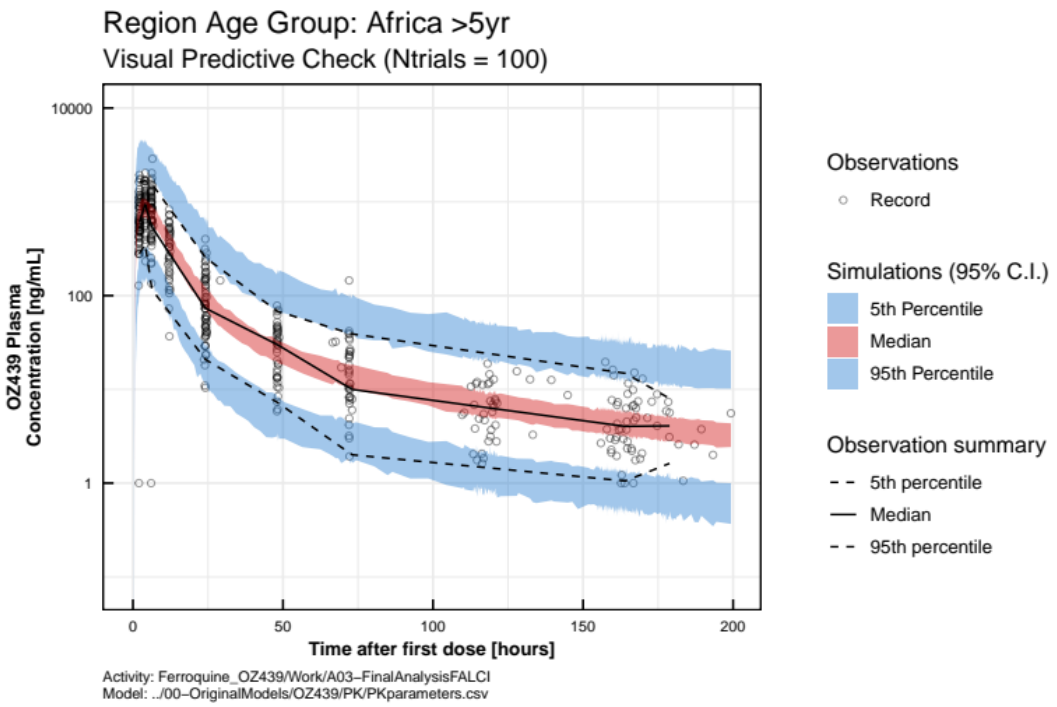
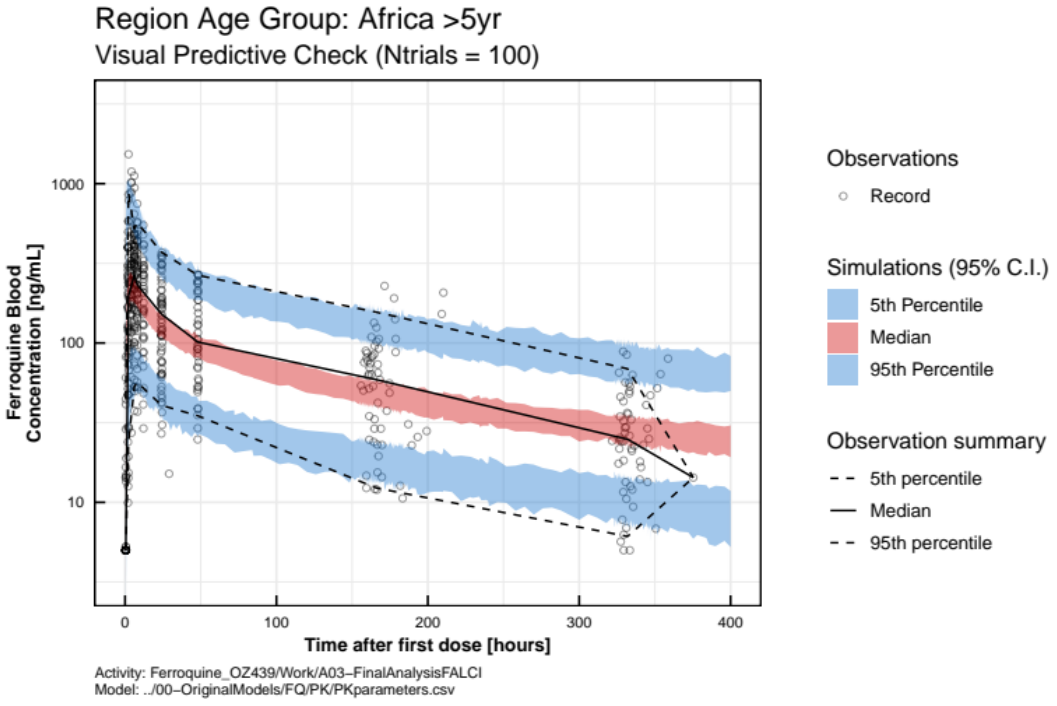
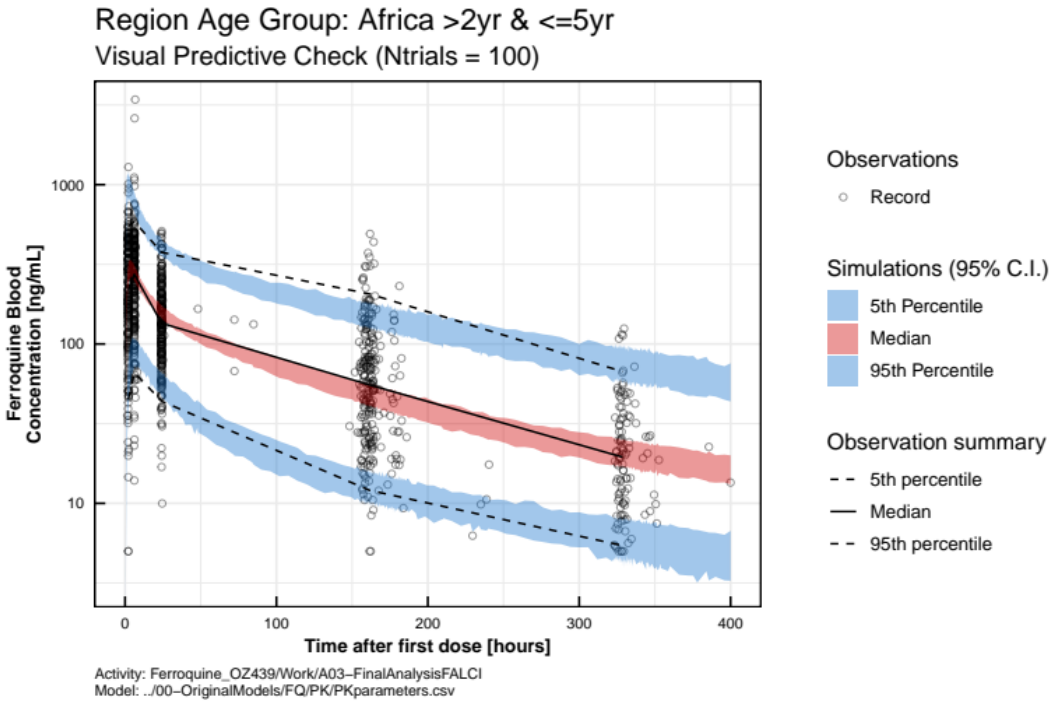
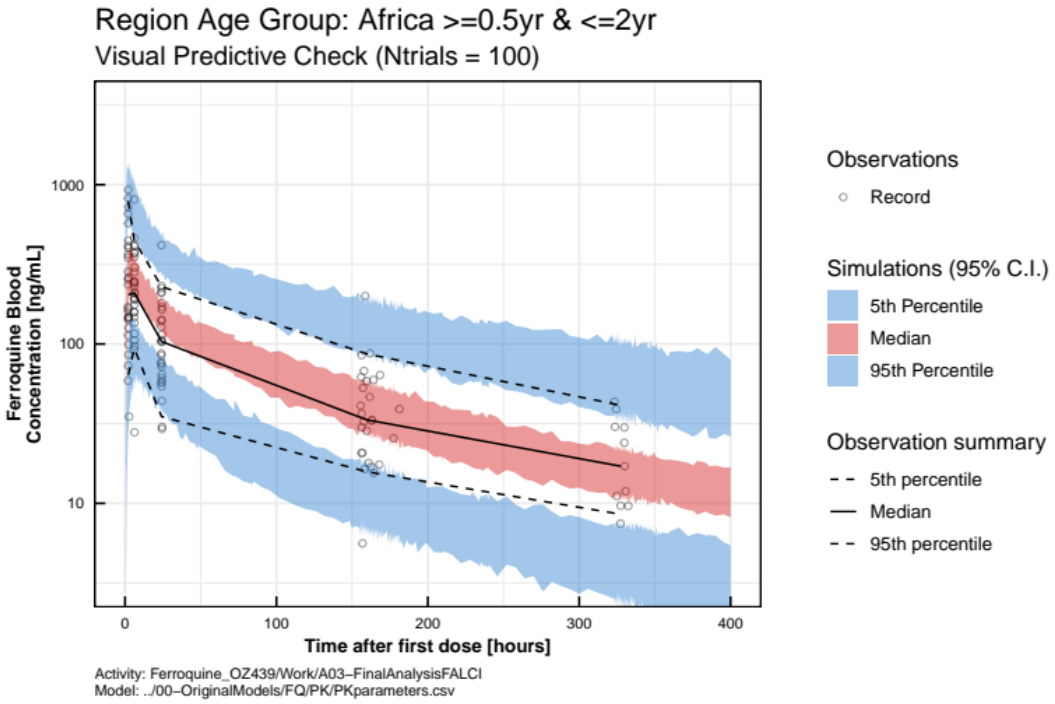



**Figure 2 Comparison of Observed Ferroquine Concentrations with the Historical Population PK Model Predictions by Region-Age Group**




Region Age Group: Africa >2yr & <=5yr
Visual Predictive Check (Ntrials = 100)
Ferroquine Blood Concentration [ng/mL]
1000
100
10
0
100
200
300
400
Time after first dose [hours]
Observations
Record
Simulations (95% C.I.)
5th Percentile
Median
95th Percentile
Observation summary
5th percentile
Median
95th percentile
Activity: Ferroquine_OZ439/Work/A03–FinalAnalysisFALCI
Model: ../00–OriginalModels/FQ/PK/PKparameters.csv


Region Age Group: Africa >=0.5yr & <=2yr
Visual Predictive Check (Ntrials = 100)
Ferroquine Blood Concentration [ng/mL]
1000
100
10
0
100
200
300
400
Time after first dose [hours]
Observations
Record
Simulations (95% C.I.)
5th Percentile
Median
95th Percentile
Observation summary
5th percentile
Median
95th percentile
Activity: Ferroquine_OZ439/Work/A03–FinalAnalysisFALCI
Model: ../00–OriginalModels/FQ/PK/PKparameters.csv

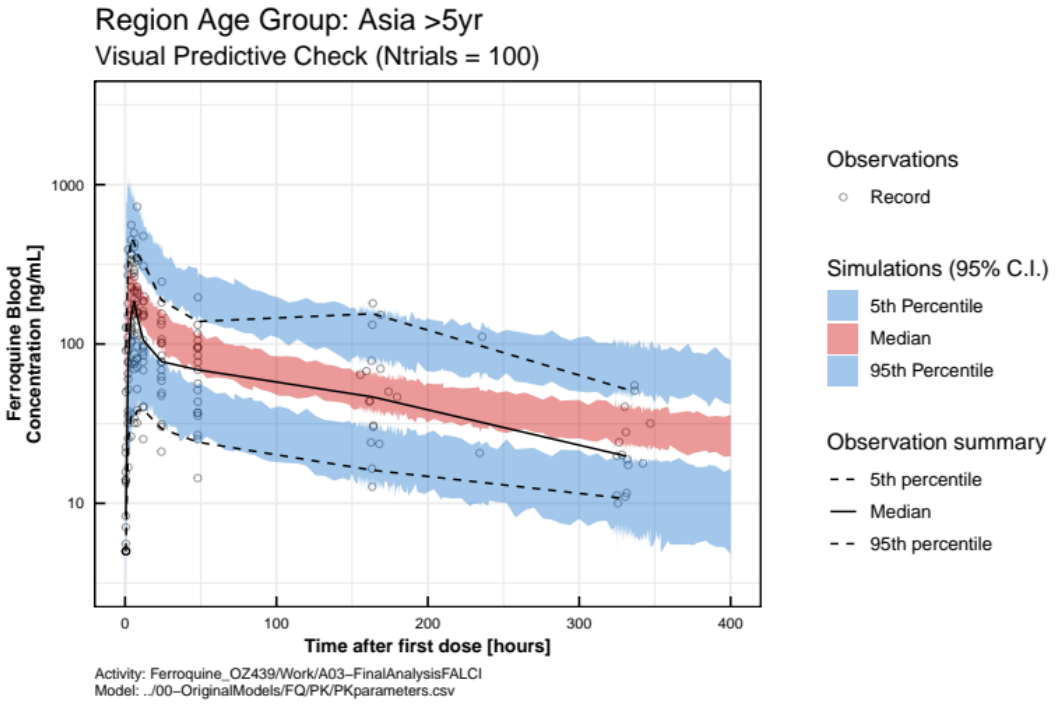



**Figure 3 Example: Comparison of Observed Artefenomel Concentrations with the Individual Model Fit by Individual Patient**

**Individual fits**

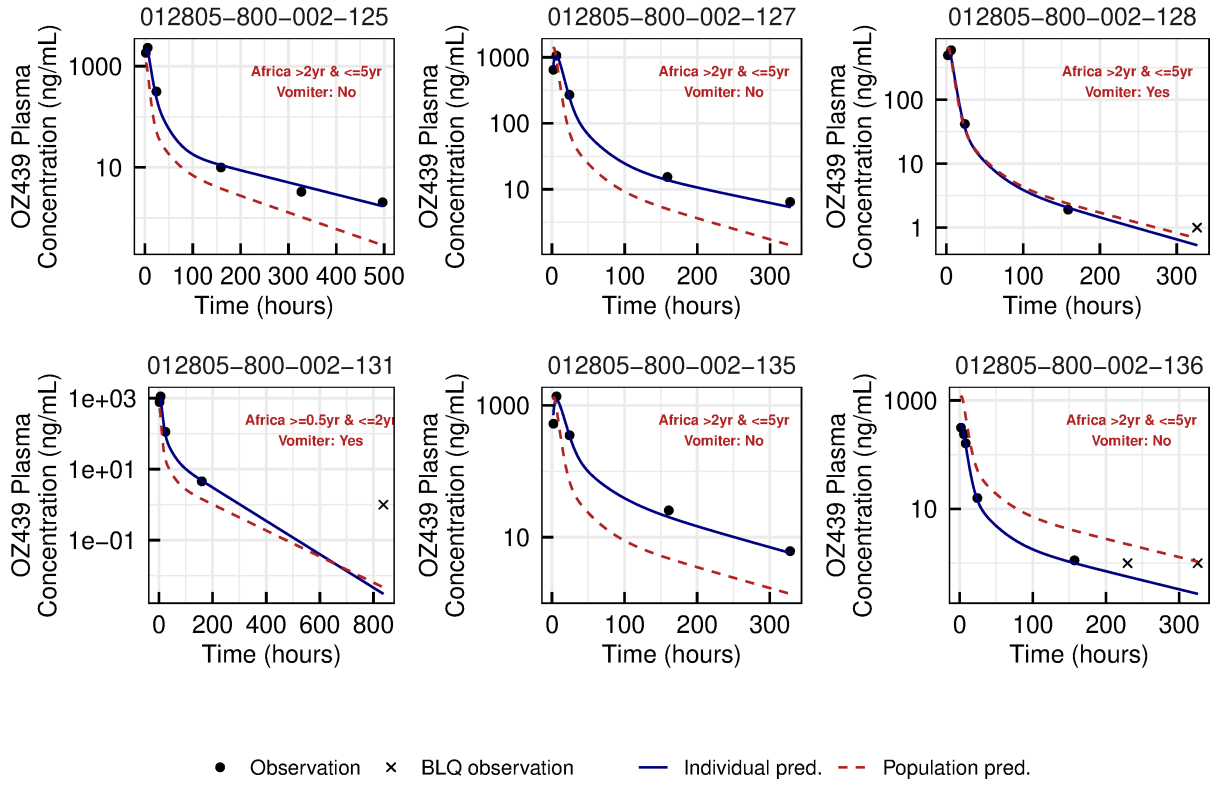


**Figure 4 Observed vs Predicted Artefenomel concentrations for PK Samples taken between days 6 and 8 post-dose**

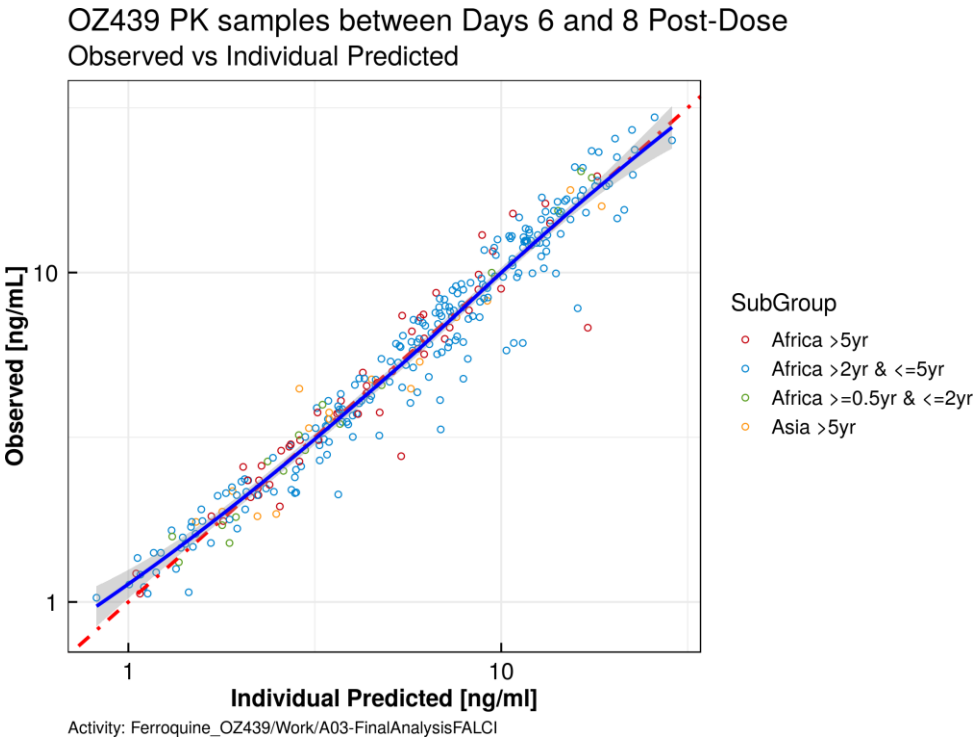



**Figure 5 Example: Comparison of Observed Ferroquine Concentrations with the Individual Model Fit by Individual Patient**

**Individual fits**

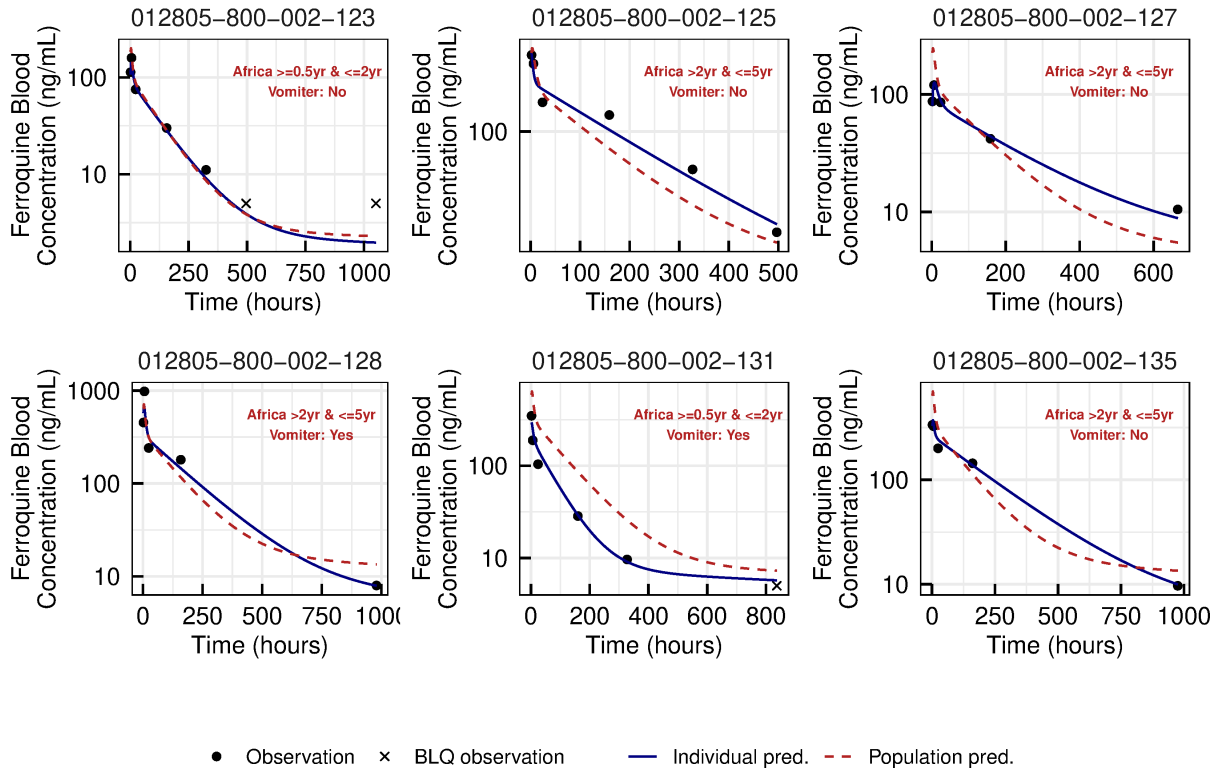
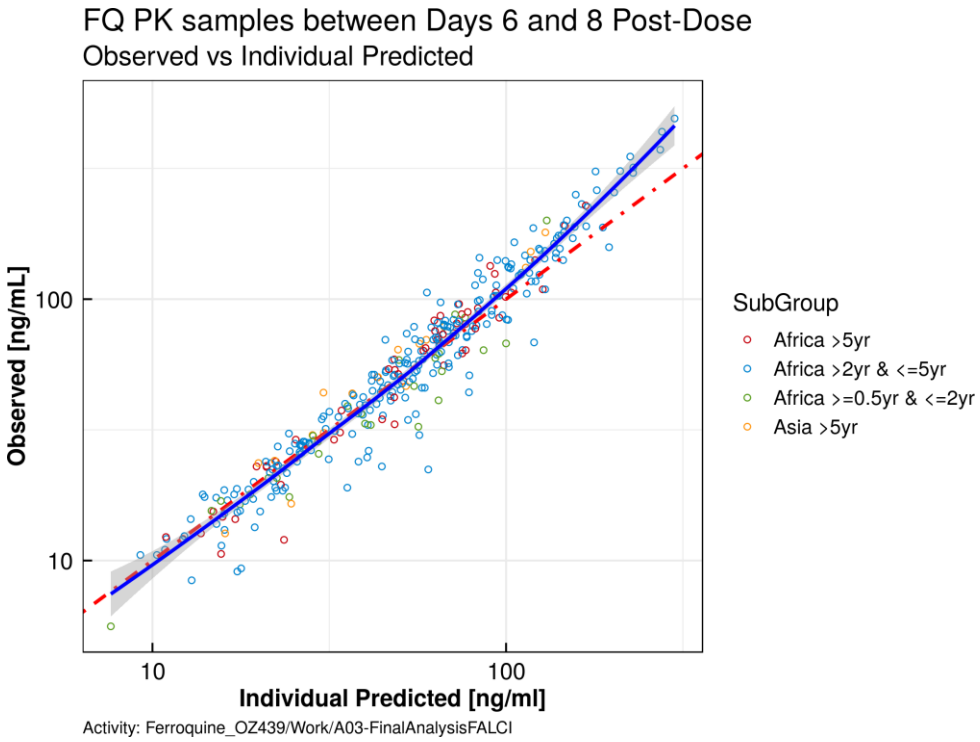


**Figure 6 Observed vs Predicted Ferroquine Concentrations for PK Samples taken between days 6 and 8 post-dose**




## Estimated Individual Exposures

Tables 3, 4 and 5 summarize the estimated individual exposures for artefenomel, ferroquine and SSR97213, respectively.

## Table 3 Selected Summary Statistics of the Individual Artefenomel Plasma Exposure Estimates by Treatment Arm for Various Sub-Populations (total n=364).

| Treatment Arm | Sub-Group | n[a] | $C_{max}$[b] [ng/mL] | $C_{day7}$[b] [ng/mL] | $AUC_{(0-\infty)}$[b] [ug*hr/mL] |
|---|---|---|---|---|---|
| 400mgFQ+800mgOZ | All patients | 88 | 1072 (95%) | 4.642 (170%) | 14.24 (124%) |
| 600mgFQ+800mgOZ | All patients | 93 | 936.7 (91%) | 4.212 (176%) | 12.41 (127%) |
| 900mgFQ+800mgOZ | All patients | 93 | 771.8 (92%) | 3.047 (172%) | 9.621 (130%) |
| 1200mgFQ+800mgOZ | All patients | 90 | 797.8 (119%) | 2.984 (196%) | 9.605 (147%) |
| **Vomiting Status** | | | | | |
| 400mgFQ+800mgOZ | Non-Vomiters | 70 | 1324 (60%) | 6.374 (102%) | 18.66 (73%) |
| | Vomiters | 18 | 471.1 (146%) | 1.352 (257%) | 4.978 (199%) |
| 600mgFQ+800mgOZ | Non-Vomiters | 70 | 1209 (47%) | 6.29 (92%) | 17.42 (63%) |
| | Vomiters | 23 | 431.2 (136%) | 1.243 (242%) | 4.421 (183%) |
| 900mgFQ+800mgOZ | Non-Vomiters | 71 | 972.7 (77%) | 4.323 (135%) | 13.17 (101%) |
| | Vomiters | 22 | 365.8 (68%) | 0.9859 (112%) | 3.492 (87%) |
| 1200mgFQ+800mgOZ | Non-Vomiters | 69 | 1034 (71%) | 4.155 (119%) | 13.05 (86%) |
| | Vomiters | 21 | 340 (193%) | 1.005 (312%) | 3.509 (234%) |
| **Body Weight Band** | | | | | |
| 400mgFQ+800mgOZ | 7-9.9kg | 6 | 818.2 (68%) | 1.985 (141%) | 8.277 (97%) |
| | 10-14.9kg | 46 | 1006 (112%) | 4.666 (201%) | 13.41 (149%) |
| | 15-23.9kg | 18 | 1536 (105%) | 6.429 (203%) | 20.11 (138%) |
| | 24-34.9kg | 2 | 941.5 (51%) | 3.25 (35%) | 10.38 (45%) |
| | over35kg | 16 | 964.2 (34%) | 4.558 (69%) | 14.63 (46%) |
| 600mgFQ+800mgOZ | 7-9.9kg | 7 | 521 (115%) | 1.248 (174%) | 4.812 (134%) |
| | 10-14.9kg | 41 | 1023 (99%) | 4.419 (198%) | 13.08 (138%) |
| | 15-23.9kg | 26 | 1024 (92%) | 5.374 (173%) | 14.56 (127%) |
| | 24-34.9kg | 4 | 1167 (26%) | 8.147 (34%) | 20.49 (30%) |
| | over35kg | 15 | 781.4 (54%) | 3.583 (94%) | 11.09 (77%) |
| 900mgFQ+800mgOZ | 7-9.9kg | 6 | 408.2 (103%) | 0.8649 (127%) | 3.576 (110%) |
| | 10-14.9kg | 48 | 762.5 (104%) | 2.913 (187%) | 9.147 (143%) |
| | 15-23.9kg | 19 | 947 (91%) | 4.8 (202%) | 13.65 (148%) |
| | 24-34.9kg | 3 | 713.7 (15%) | 3.051 (25%) | 10.31 (21%) |
| | over35kg | 17 | 806.6 (56%) | 3.248 (80%) | 10.52 (62%) |
| 1200mgFQ+800mgOZ | 7-9.9kg | 10 | 312.7 (162%) | 0.798 (222%) | 3.245 (187%) |
| | 10-14.9kg | 36 | 820.1 (93%) | 3.213 (151%) | 10.12 (119%) |
| | 15-23.9kg | 28 | 936.1 (154%) | 3.615 (251%) | 11.41 (185%) |
| | 24-34.9kg | 1 | 703.7 | 2.445 | 6.902 |
| | over35kg | 15 | 1043 (38%) | 4.263 (91%) | 12.94 (56%) |
| **Region / Age Band** | | | | | |
| 400mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 984.6 (85%) | 2.591 (179%) | 10.42 (112%) |
| | Africa >2yr & <=5yr | 62 | 1125 (113%) | 5.099 (204%) | 14.93 (150%) |
| | Africa >5yr | 15 | 907 (34%) | 4.425 (72%) | 13.32 (51%) |
| | Asia >5yr | 4 | 1095 (34%) | 3.592 (53%) | 15.21 (31%) |
| 600mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 8 | 531.2 (111%) | 1.782 (280%) | 5.943 (159%) |
| | Africa >2yr & <=5yr | 65 | 1018 (95%) | 4.57 (185%) | 13.29 (133%) |
| | Africa >5yr | 15 | 924.5 (54%) | 4.822 (104%) | 13.96 (77%) |
| | Asia >5yr | 5 | 817.7 (73%) | 3.859 (97%) | 11.67 (92%) |
| 900mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 6 | 471.2 (71%) | 1.159 (93%) | 4.526 (75%) |
| | Africa >2yr & <=5yr | 64 | 824.2 (105%) | 3.351 (203%) | 10.28 (153%) |
| | Africa >5yr | 17 | 637.8 (58%) | 2.861 (112%) | 8.689 (79%) |
| | Asia >5yr | 6 | 1076 (30%) | 3.479 (41%) | 13.5 (36%) |
| 1200mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 378.1 (146%) | 1.145 (162%) | 4.182 (149%) |
| | Africa >2yr & <=5yr | 63 | 802.1 (134%) | 3.023 (231%) | 9.748 (170%) |
| | Africa >5yr | 15 | 1007 (31%) | 3.96 (48%) | 12.24 (37%) |
| | Asia >5yr | 5 | 1053 (69%) | 4.133 (211%) | 12.34 (114%) |

The reported concentrations are plasma concentrations.
No patients were recruited into the lowest body weight band (5-6.9kg) in this study.
[a] Number of patients with determinable metric;
[b] Geometric Mean (CV%).

## Table 4 Selected Summary Statistics of the Individual Ferroquine Blood Exposure Estimates by Treatment Arm for Various Sub-Populations (total n=367).

| Treatment Arm | Sub-Group | n[a] | $C_{max}$[b] [ng/mL] | $C_{day7}$[b] [ng/mL] | $AUC_{(0-day28)}$[b] [ug*hr/mL] |
|---|---|---|---|---|---|
| 400mgFQ+800mgOZ | All patients | 88 | 148.1 (52%) | 27.08 (51%) | 14.92 (40%) |
| 600mgFQ+800mgOZ | All patients | 93 | 222.8 (66%) | 40.94 (65%) | 22.56 (48%) |
| 900mgFQ+800mgOZ | All patients | 93 | 350 (55%) | 63.72 (61%) | 33.84 (48%) |
| 1200mgFQ+800mgOZ | All patients | 90 | 467.6 (80%) | 87.52 (70%) | 46.4 (52%) |
| **Vomiting Status** | | | | | |
| 400mgFQ+800mgOZ | Non-Vomiters | 69 | 157.2 (52%) | 28.95 (48%) | 15.67 (38%) |
| | Vomiters | 19 | 119.4 (48%) | 21.26 (54%) | 12.49 (42%) |
| 600mgFQ+800mgOZ | Non-Vomiters | 70 | 246.9 (53%) | 46.6 (54%) | 24.87 (42%) |
| | Vomiters | 23 | 163.2 (88%) | 27.61 (74%) | 16.76 (50%) |
| 900mgFQ+800mgOZ | Non-Vomiters | 69 | 398.5 (48%) | 72.82 (52%) | 37.99 (41%) |
| | Vomiters | 24 | 240.9 (53%) | 43.41 (64%) | 24.25 (48%) |
| 1200mgFQ+800mgOZ | Non-Vomiters | 68 | 509.3 (82%) | 95.72 (73%) | 50.63 (52%) |
| | Vomiters | 22 | 359.3 (66%) | 66.38 (51%) | 35.43 (40%) |
| **Body Weight Band** | | | | | |
| 400mgFQ+800mgOZ | 7-9.9kg | 6 | 129 (28%) | 21.67 (36%) | 11.76 (26%) |
| | 10-14.9kg | 46 | 163.1 (55%) | 27.92 (55%) | 15.5 (40%) |
| | 15-23.9kg | 18 | 177.1 (38%) | 30.74 (58%) | 17.17 (44%) |
| | 24-34.9kg | 2 | 107.6 (11%) | 19.24 (34%) | 10.54 (20%) |
| | over35kg | 16 | 100.5 (45%) | 24.41 (34%) | 13.05 (33%) |
| 600mgFQ+800mgOZ | 7-9.9kg | 7 | 256 (71%) | 27.12 (84%) | 16.69 (50%) |
| | 10-14.9kg | 41 | 227.8 (61%) | 45.07 (69%) | 24.47 (49%) |
| | 15-23.9kg | 26 | 267.2 (50%) | 42.25 (54%) | 23.23 (37%) |
| | 24-34.9kg | 4 | 203.1 (92%) | 37.47 (93%) | 21.23 (69%) |
| | over35kg | 15 | 147.1 (78%) | 36.99 (53%) | 20.08 (53%) |
| 900mgFQ+800mgOZ | 7-9.9kg | 6 | 311.5 (79%) | 36.42 (53%) | 23.63 (39%) |
| | 10-14.9kg | 48 | 339.8 (59%) | 61.25 (62%) | 32.27 (48%) |
| | 15-23.9kg | 19 | 388.9 (50%) | 78.73 (69%) | 40.12 (56%) |
| | 24-34.9kg | 3 | 354.6 (37%) | 58.86 (17%) | 30.77 (15%) |
| | over35kg | 17 | 351.4 (47%) | 69.51 (42%) | 36.9 (37%) |
| 1200mgFQ+800mgOZ | 7-9.9kg | 10 | 428 (94%) | 51.39 (85%) | 31.45 (42%) |
| | 10-14.9kg | 36 | 462.6 (62%) | 91.95 (71%) | 48.6 (50%) |
| | 15-23.9kg | 28 | 516.8 (87%) | 100.1 (63%) | 51.1 (54%) |
| | 24-34.9kg | 1 | 717.7 | 71.99 | 38.69 |
| | over35kg | 15 | 410.5 (111%) | 87.38 (59%) | 45.46 (53%) |
| **Region / Age Band** | | | | | |
| 400mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 141.6 (58%) | 23.6 (48%) | 13.09 (37%) |
| | Africa >2yr & <=5yr | 62 | 166.9 (49%) | 28.96 (54%) | 16 (41%) |
| | Africa >5yr | 15 | 104.5 (45%) | 23.06 (41%) | 12.59 (36%) |
| | Asia >5yr | 4 | 93.36 (26%) | 22.28 (21%) | 12.02 (21%) |
| 600mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 8 | 259 (63%) | 33.07 (107%) | 19.62 (69%) |
| | Africa >2yr & <=5yr | 65 | 242.1 (58%) | 43.26 (62%) | 23.7 (44%) |
| | Africa >5yr | 15 | 184.5 (68%) | 40.34 (60%) | 21.95 (54%) |
| | Asia >5yr | 5 | 105.2 (92%) | 29.38 (41%) | 16.14 (41%) |
| 900mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 6 | 296.2 (54%) | 44.77 (49%) | 25.67 (22%) |
| | Africa >2yr & <=5yr | 64 | 358.9 (59%) | 65.79 (65%) | 34.6 (51%) |
| | Africa >5yr | 17 | 326 (36%) | 64.95 (56%) | 34.7 (44%) |
| | Asia >5yr | 6 | 386.9 (63%) | 61.16 (36%) | 32.69 (34%) |
| 1200mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 352.3 (65%) | 67.05 (52%) | 35.37 (39%) |
| | Africa >2yr & <=5yr | 63 | 492.7 (78%) | 91.28 (78%) | 48.68 (55%) |
| | Africa >5yr | 15 | 533.6 (60%) | 91.42 (41%) | 47.28 (38%) |
| | Asia >5yr | 5 | 242.6 (162%) | 65.72 (73%) | 35 (64%) |

The reported concentrations are blood concentrations.
No patients were recruited into the lowest body weight band (5-6.9kg) in this study.
Patients who vomited after FQ dosing and never received artefenomel were not included in the summaries: 400mg FQ (N=2) or 1200mg (N=1).
[a] number of patients with determinable metric;
[b] Geometric Mean (CV%).

## Table 5 Selected Summary Statistics of the Individual SSR97213 Blood Exposure Estimates by Treatment Arm for Various Sub-Populations (total n=367).

| Treatment Arm | Sub-Group | n[a] | $C_{max}$[b] [ng/mL] | $C_{day7}$[b] [ng/mL] | $AUC_{(0-day28)}$[b] [ug*hr/mL] |
|---|---|---|---|---|---|
| 400mgFQ+800mgOZ | All patients | 88 | 34.62 (58%) | 26.4 (56%) | 13.57 (52%) |
| 600mgFQ+800mgOZ | All patients | 93 | 59.65 (78%) | 42.83 (76%) | 22.37 (66%) |
| 900mgFQ+800mgOZ | All patients | 93 | 94.04 (75%) | 68.15 (71%) | 35.06 (66%) |
| 1200mgFQ+800mgOZ | All patients | 90 | 140.9 (84%) | 98.91 (82%) | 50.96 (75%) |
| **Vomiting Status** | | | | | |
| 400mgFQ+800mgOZ | Non-Vomiters | 69 | 38.6 (53%) | 28.79 (54%) | 14.76 (50%) |
| | Vomiters | 19 | 23.33 (54%) | 19.3 (48%) | 10 (44%) |
| 600mgFQ+800mgOZ | Non-Vomiters | 70 | 69.75 (63%) | 49.62 (64%) | 25.55 (56%) |
| | Vomiters | 23 | 37.06 (92%) | 27.35 (88%) | 14.94 (74%) |
| 900mgFQ+800mgOZ | Non-Vomiters | 69 | 115.9 (57%) | 81.95 (55%) | 41.88 (51%) |
| | Vomiters | 24 | 51.52 (76%) | 40.11 (77%) | 21.03 (69%) |
| 1200mgFQ+800mgOZ | Non-Vomiters | 68 | 160.3 (80%) | 109.8 (83%) | 56.98 (76%) |
| | Vomiters | 22 | 94.64 (78%) | 71.68 (64%) | 36.11 (58%) |
| **Body Weight Band** | | | | | |
| 400mgFQ+800mgOZ | 7-9.9kg | 6 | 29.08 (28%) | 26.17 (31%) | 11.85 (30%) |
| | 10-14.9kg | 46 | 36.42 (64%) | 27.31 (60%) | 13.9 (54%) |
| | 15-23.9kg | 18 | 44.62 (36%) | 32.93 (51%) | 16.92 (50%) |
| | 24-34.9kg | 2 | 28.25 (8%) | 19.77 (21%) | 9.704 (20%) |
| | over35kg | 16 | 24.66 (58%) | 19.44 (43%) | 10.86 (43%) |
| 600mgFQ+800mgOZ | 7-9.9kg | 7 | 46.51 (74%) | 33.15 (91%) | 16.55 (79%) |
| | 10-14.9kg | 41 | 61.68 (80%) | 47.19 (81%) | 24.47 (69%) |
| | 15-23.9kg | 26 | 68.28 (66%) | 45.21 (64%) | 23.14 (53%) |
| | 24-34.9kg | 4 | 54.46 (131%) | 32.62 (109%) | 17.88 (108%) |
| | over35kg | 15 | 49.55 (84%) | 36.22 (72%) | 20.19 (67%) |
| 900mgFQ+800mgOZ | 7-9.9kg | 6 | 60.34 (116%) | 40.39 (60%) | 21.28 (60%) |
| | 10-14.9kg | 48 | 92.05 (79%) | 68.03 (77%) | 34.03 (68%) |
| | 15-23.9kg | 19 | 107.1 (78%) | 82.19 (77%) | 41.4 (76%) |
| | 24-34.9kg | 3 | 76.33 (61%) | 52.21 (24%) | 26.52 (34%) |
| | over35kg | 17 | 104.8 (47%) | 70 (47%) | 39.7 (43%) |
| 1200mgFQ+800mgOZ | 7-9.9kg | 10 | 114 (99%) | 60.09 (86%) | 31.99 (73%) |
| | 10-14.9kg | 36 | 133.8 (72%) | 105.5 (73%) | 52.46 (70%) |
| | 15-23.9kg | 28 | 158.5 (83%) | 114.3 (83%) | 58.48 (75%) |
| | 24-34.9kg | 1 | 180.6 | 77.89 | 42.52 |
| | over35kg | 15 | 145.3 (114%) | 91.55 (89%) | 50.8 (83%) |
| **Region / Age Band** | | | | | |
| 400mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 33.12 (53%) | 28.79 (40%) | 13.69 (43%) |
| | Africa >2yr & <=5yr | 62 | 38.58 (56%) | 28.91 (57%) | 14.69 (53%) |
| | Africa >5yr | 15 | 24.13 (58%) | 18.81 (46%) | 10.31 (46%) |
| | Asia >5yr | 4 | 27.11 (34%) | 19.85 (20%) | 11.02 (24%) |
| 600mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 8 | 49.76 (71%) | 37.72 (100%) | 18.95 (90%) |
| | Africa >2yr & <=5yr | 65 | 64.21 (75%) | 46.08 (74%) | 23.77 (62%) |
| | Africa >5yr | 15 | 56.48 (81%) | 38.29 (74%) | 21.13 (72%) |
| | Asia >5yr | 5 | 36.03 (98%) | 28.3 (75%) | 15.8 (67%) |
| 900mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 6 | 68.46 (63%) | 50.47 (43%) | 25.89 (39%) |
| | Africa >2yr & <=5yr | 64 | 96.43 (85%) | 71.46 (79%) | 35.92 (72%) |
| | Africa >5yr | 17 | 95.59 (57%) | 64.65 (58%) | 35.08 (58%) |
| | Asia >5yr | 6 | 94.37 (28%) | 64.42 (45%) | 36.67 (45%) |
| 1200mgFQ+800mgOZ | Africa >=0.5yr & <=2yr | 7 | 95.9 (79%) | 73.03 (68%) | 37.37 (62%) |
| | Africa >2yr & <=5yr | 63 | 145.3 (82%) | 104.7 (86%) | 53.28 (78%) |
| | Africa >5yr | 15 | 161.3 (71%) | 98.79 (53%) | 52.44 (55%) |
| | Asia >5yr | 5 | 110 (171%) | 73.94 (145%) | 41.24 (116%) |

The reported concentrations are blood concentrations.
No patients were recruited into the lowest body weight band (5-6.9kg) in this study.
Patients who vomited after FQ dosing and never received artefenomel were not included in the summaries: 400mg FQ (N=2) or 1200mg (N=1).
[a] number of patients with determinable metric;
[b] Geometric Mean (CV%).

## References

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