and assess the magnitude of inter-subject and residual variability on the pharmacokinetics of atovaquone and proguanil.

Population pharmacokinetic analysis was performed using atovaquone and proguanil concentration - time data from 783 and 673 subjects, respectively. A one compartment model, supported by the previous data, was selected for both atovaquone and proguanil.

The pertinent findings obtained from the analysis are as follows:

**Atovaquone:**

- The CL/F for atovaquone was affected by body weight, race, gender and co-administration with tetracycline:
    - A power relationship between CL/F and body weight was found:
      Africans: CL (L/hr) = 0.135·WT0.783
      Oriental/Malaysians: CL/F (L/hr) = 0.350·WT0.783
    - CL/F in African patients was significantly lower as compared to Oriental/Malaysian patients (i.e., reduction of approximately 60%; p <0.005). For patients with the same body weight, the CL/F in Oriental/Malaysians is 2.6 CL/F in Africans
    - CL/F in females was 12.9% lower as compared to males.
    - CL/F in patients receiving atovaquone concomitantly with tetracycline was 52.9% higher as compared with patients who did not receive tetracycline.
- The apparent volume of distribution for atovaquone (V/F) increased linearly as a function of body weight: V/F=(8.83 L/kg • WT)
- The changes in CL/F and V/F for these patients resulted in an overall incremental increase in the half-life (T1/2) of atovaquone with the increase in body weight from 5 to 80 kg. The T1/2 estimates in the Oriental/Malaysian patients ranged from approximately 25 to 45 hr (~1 to 2 days). However, the T1/2 estimates in the African patients were substantially prolonged as compared to the Oriental/Malaysian patients and ranged from approximately 63 to 116 hr (~3 to 5 days).
- Based on these differences in CL/F and T1/2 estimates between the African and Oriental/Malaysian patients in this PPK analysis, although the sponsor did not determine post-hoc estimates of systemic exposure (i.e., AUC), it is expected that the systemic exposure to atovaquone would be higher in African patients given the same body weight based dose.

**Proguanil:**

- The CL/F for proguanil was affected by body weight and race.
    - A power relationship between CL/F and body weight was found (CL (L/h in African)=3.43·WT0.743).
    - Compared to African patients, the CL/F values were 19.5% higher and 23.2% lower in Orientals and Malaysians, respectively.

**Figure 1. Population predicted vs observed atovaquone concentrations for final model**

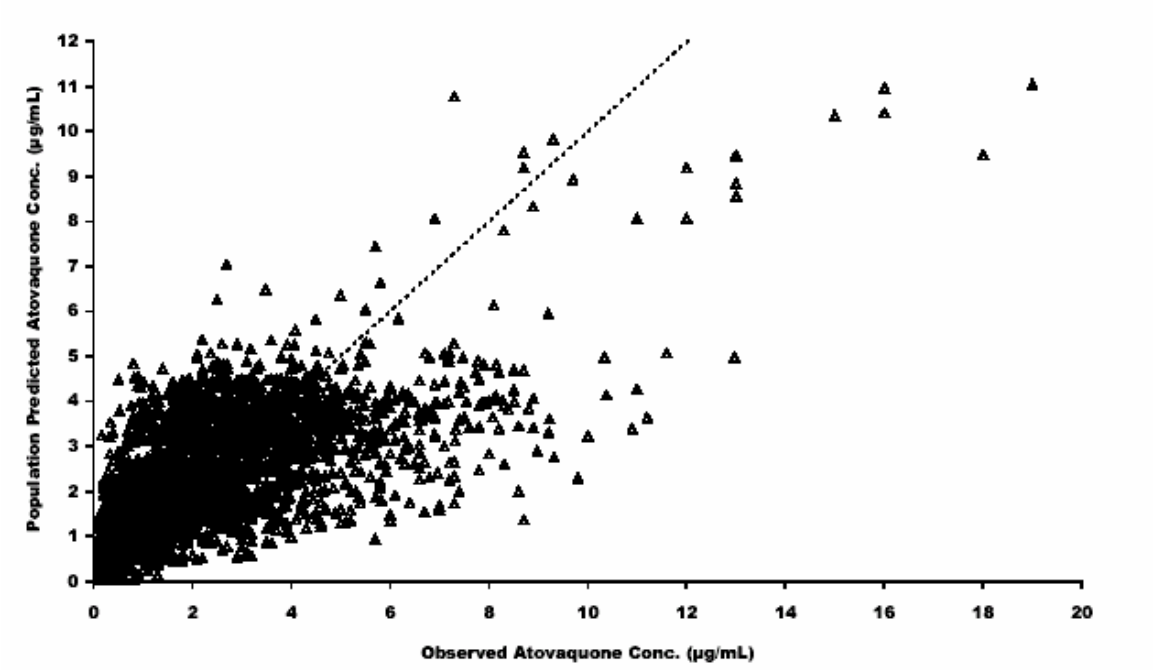



**Figure 2. Individual predicted vs observed atovaquone concentration for final model**

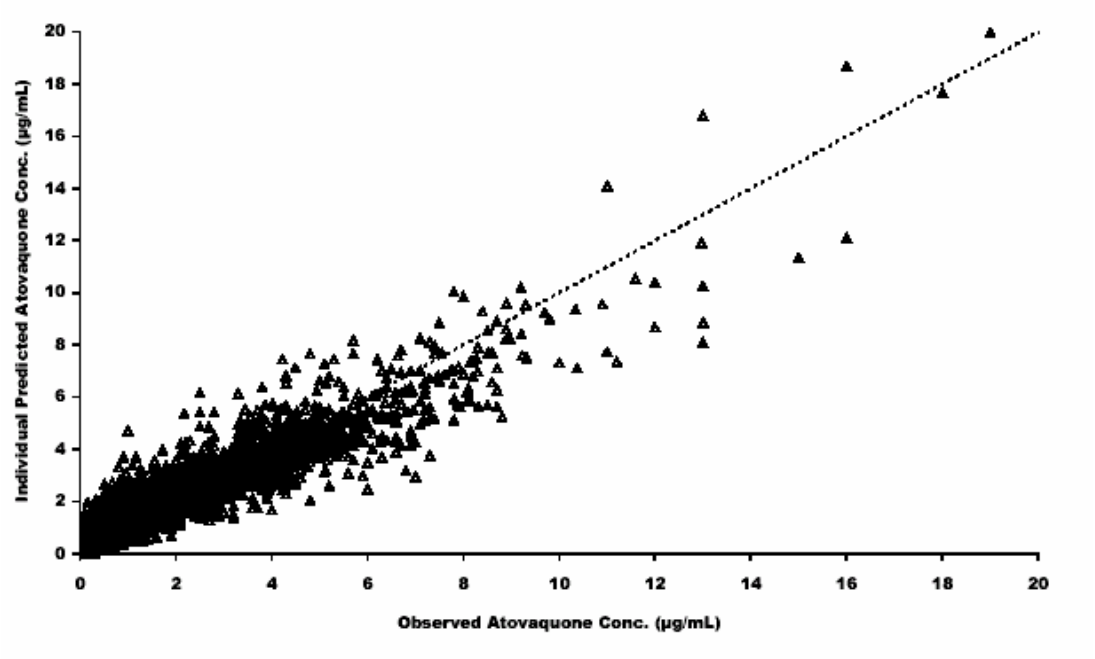

Individual Predicted Atovaquone Conc. (µg/mL)
Observed Atovaquone Conc. (µg/mL)
0
2
4
6
8
10
12
14
16
18
20

**Figure 3. Weighted residuals vs predicted atovaquone and residual vs predicted atovaquone concentration for the final model**

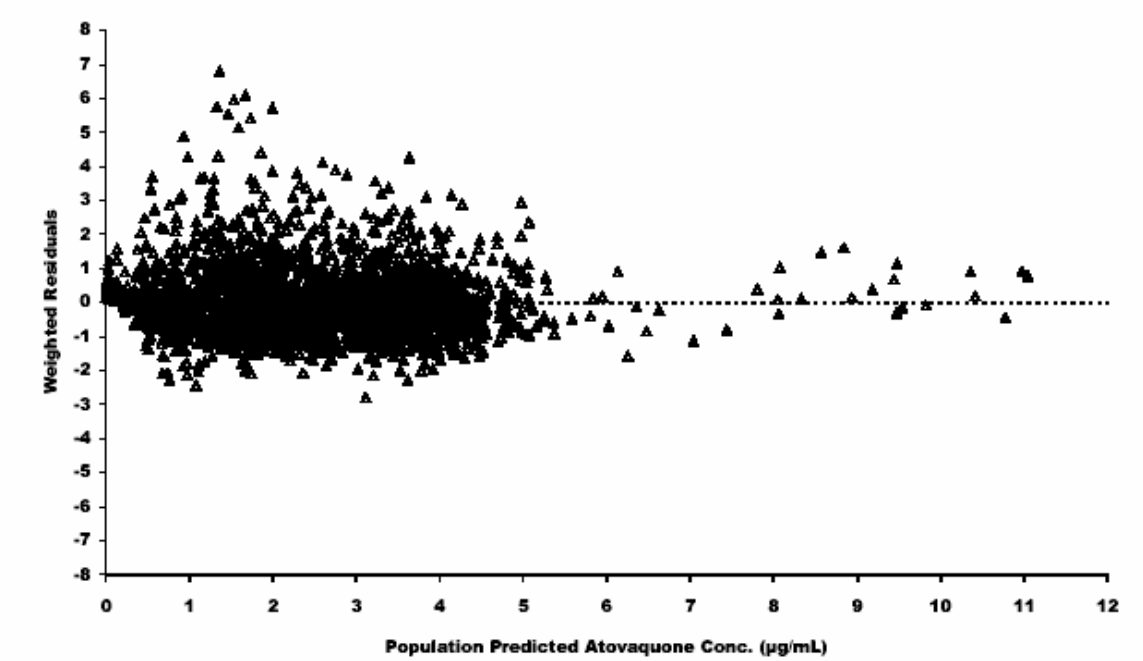



**Figure 4. Population predicted vs observed proguanil concentrations for final model**

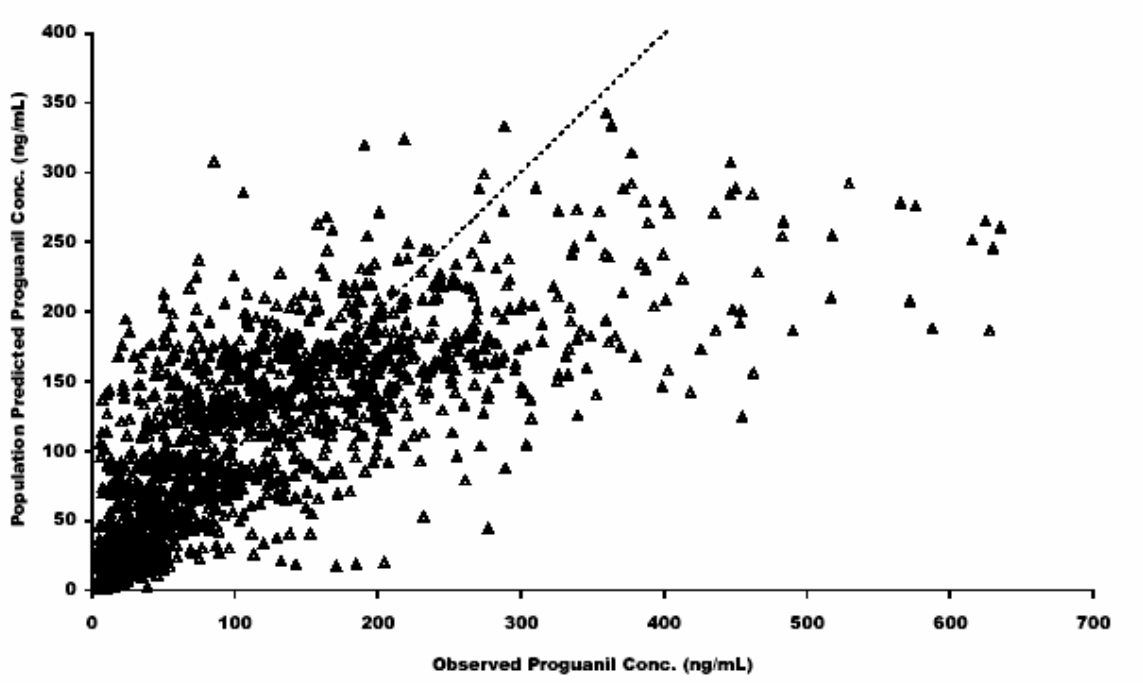


**Figure 5. Individual predicted vs observed proguanil concentrations for final model**

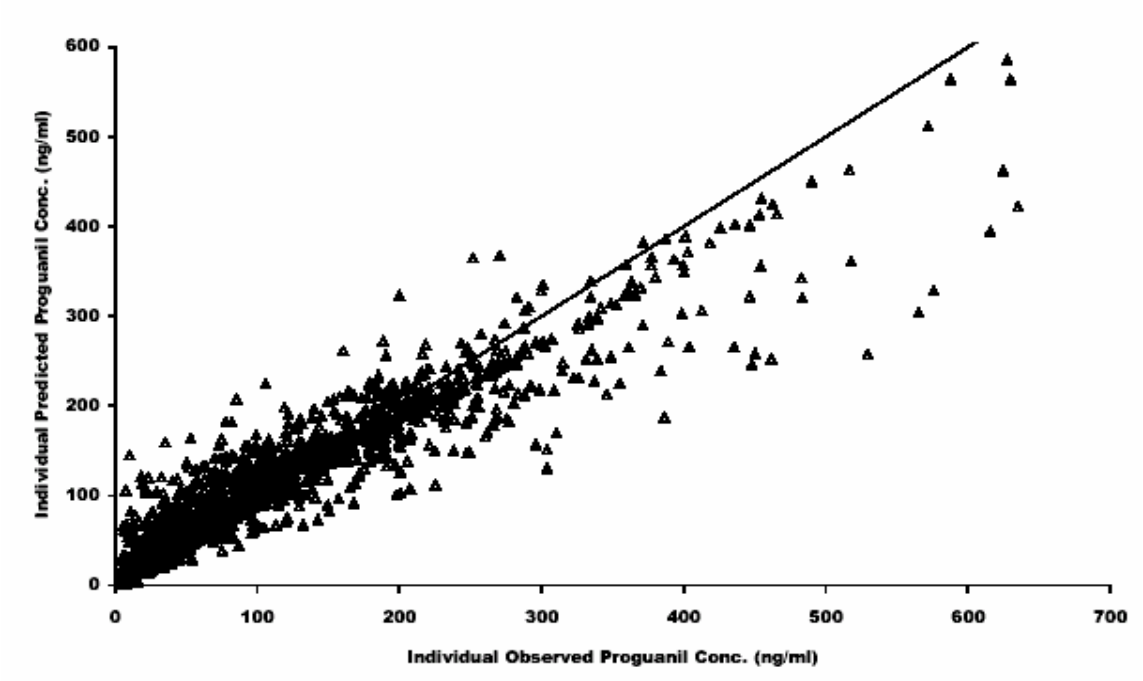
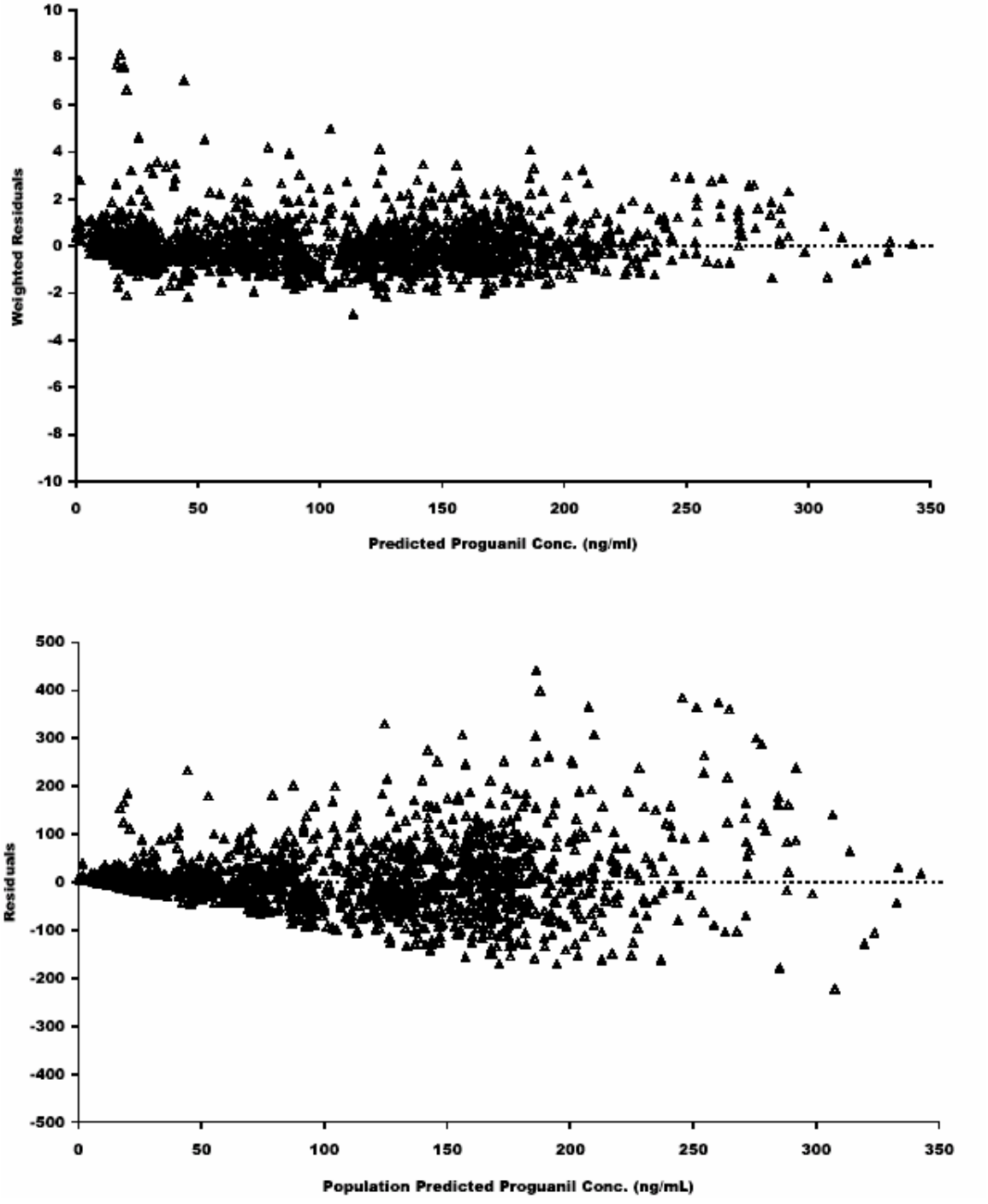


**Figure 6. Weighted residuals vs predicted concentrations and residuals vs predicted proguanil concentrations for final model**

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**APPENDIX 2:**

**Proposed Labeling for Malarone**
**With**
**Clinical Pharmacology / Biopharmaceutics Revisions**

**Version: 11/17/03**

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