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RESEARCH**

*APPLICATION NUMBER:*  
**75203**

**STATISTICAL REVIEW(S)**

## **Statistical Review of ANDA 75-203, Propafenone Hydrochloride, Tablets 225 mg**

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In this trial, thirty-six fasted healthy male volunteers were dosed in an open-label randomized single-application, two sequence, four period, two treatment crossover bioequivalence study to assess the bioequivalence of a test formulation (Watson Laboratories, Inc.), and an equivalent oral dose of the commercially available propafenone HCl (Rythmol<sup>®</sup>, Knoll Laboratories, A Division of Knoll Pharmaceutical Company). There was a seven-day washout interval between the single dose administrations.

### *Study Design:*

Open-label, randomized, single-application, crossover bioequivalence study.

### Experimental Treatment:

Test: A = Propafenone, 225 mg tablet (Watson Laboratories, Inc.)

Reference: B = Rythmol<sup>®</sup>, 225 mg tablet (Knoll Laboratories, A Division of Knoll Pharmaceutical Company)

Experimental Design: four periods, two sequences

Sequence 1: ABAB (17 subjects)

Sequence 2: BABA (17 subjects)

Thirty-six subjects were initially enrolled. Thirty-four subjects completed all phases of the study. Subject #14 dropped out prior to period II dosing, the last PK sample was obtained at the 72 hour point of phase I. Subject #28 dropped out prior to phase IV dosing, the last PK sample was obtained at the 72 hour point of phase III. Therefore the data of these two subjects are not included in the study. The study was conducted on propafenone as a parent drug, as well as on two metabolites: 5-hydroxypropafenone and N-depropylpropafenone.

***Statistical Analysis:***

The following primary pharmacokinetic parameters derived from the plasma concentration-time curves for the parent drug and the two metabolites were statistically analyzed to assess bioequivalence of the two products:

$$\begin{aligned} \text{lauct} &= \log(\text{AUCt}) \\ \text{laucinf} &= \log(\text{AUCinf}) \\ \text{lcmx} &= \log(\text{Cmax}) \end{aligned}$$

The pharmacokinetic parameters analyzed were area under the concentration time curve from time zero to the time of last quantifiable drug concentration (AUCt), area under the concentration time curve extrapolated to infinity (AUCinf), and maximum concentration (Cmax). The two one-sided tests procedure was performed to assess the bioequivalence between the two products. This test is conducted by constructing a 90% confidence interval for the ratio of the test mean to the reference mean. All of the confidence intervals need to be contained within the bounds of 80 to 125% for the products to be considered bioequivalent.

Our analysis used SAS Proc Mixed on the log transformed data of AUCt, AUCinf, and Cmax. The factors in the model included sequence, period, treatment and subject. The subject was treated as a random effect. Our model contained between-subject variability terms.

For a given endpoint, (e.g.  $\log(\text{AUCt})$ ), we used the following statistical model: let  $Y_{ijkl}$  be a measurement of this endpoint for subject  $j$  in sequence  $i$ , at period  $k$ , at which time this subject received treatment  $l$ , then

$$Y_{ijkl} = \mu + \alpha_i + \gamma_k + T_l + \tau_{ijl} + \varepsilon_{ijkl}$$

$\mu$  = mean response

$\alpha_i$  = sequence effect

$\gamma_k$  = period effect

$T_l$  = treatment effect

$\tau_{ijl}$  = random effect for subject by treatment

$\varepsilon_{ijkl}$  = random error

Where

$$\varepsilon_{ijk} \sim N(0, \sigma_W^2)$$

$$\tau_{ijl} \sim N(0, \sigma_{Bl}^2)$$

$$\text{COV}(\tau_{iT}, \tau_{iR}) = \rho \sigma_{BT} \sigma_{BR}$$

Here *B* denotes “between” and *W* denotes “within”.  $\rho$  denotes correlation coefficient. T refers to treatment (A) and R refers to reference (B).

**SAS code:**

```
Proc mixed;  
Class sequence subject treat period;  
Model y= sequence period treat/ddfm=satterth;  
Random treat / type=fa0(2) subject=subject g;  
Repeated / subject= subject group=treat;  
Estimate 'A vs. B' treat 1 -1/CL alpha=0.10;
```

These models and SAS statements allow for possible subject-by-treatment interaction and also allow the within subject variance of test and reference to differ. The analysis provides an estimated variance-covariance matrix for the subject-specific treatment means. All analyses were carried out on the log scale, and confidence limits were transformed back to the original scale of measurement.

**Results:**

Propafenone analysis:

The results for propafenone are listed in table 1. The confidence intervals for all three parameters are within the boundary of 80% to 125%.

**Table 1:**

Endpoint (Propafenone)	Ratio Test/Reference	90% CI Lower	90% CI Upper
AUCt	103.7	93.3	115.2
AUCinf	103.8	93.9	114.8
Cmax	100.7	89.2	113.6

5-Hydroxypropafenone Analysis:

The results for 5-hydroxypropafenone are listed in table 2. The intervals for all three parameters are within the boundary of 80 to 125%.

**Table 2:**

Endpoint 5-Hydroxypropafenone:	Ratio Test/Reference	90% CI Lower	90% CI Upper
AUC <sub>t</sub>	103.8	99.0	108.8
AUC <sub>inf</sub>	103.8	99.3	108.5
C <sub>max</sub>	101.0	93.5	109.2

N-Depropylpropafenone Analysis:

The results for N-depropylpropafenone are listed in table 3. The intervals for all three parameters are within the boundary of 80 to 125%.

**Table 3:**

Endpoint (N-Depropylpropafenone)	Ratio Test/Reference	90% CI Lower	90% CI Upper
AUC <sub>t</sub>	102.9	97.0	109.2
AUC <sub>inf</sub>	102.5	97.3	108.0
C <sub>max</sub>	102.1	95.0	109.8

*Comments on the Sponsor's results:*

The sponsor assessed bioequivalence by using a mixed linear model for parameters AUC<sub>t</sub>, AUC<sub>inf</sub>, K<sub>el</sub>, T<sub>1/2el</sub>, C<sub>max</sub> and T<sub>max</sub>. However, they did not specify the terms used in their model.

The sponsor's results are summarized in Table 4, Table 5 and Table 6. The intervals for all three parameters are within the boundary of 80% and 125%.

**Table 4. (Sponsor's results for Propafenone)**

Endpoint (Propafenone)	Ratio Test/Reference	90% CI lower	90% CI upper
AUCt	104	93.3	115
AUCinf	104	93.9	115
Cmax	101	89.3	114

**Table 5. (Sponsor's results for 5-Hydroxypropafenone)**

Endpoint (5-Hydroxypropafenone)	Ratio Test/Reference	90% CI lower	90% CI upper
AUCt	104	99.0	109
AUCinf	104	99.3	109
Cmax	101	93.6	109

**Table 6. (Sponsor's results for N-Depropylpropafenone)**

Endpoint (N-Depropylpropafenone)	Ratio Test/Reference	90% CI lower	90% CI upper
AUCt	103	97.0	109
AUCinf	103	97.3	108
Cmax	102	95.0	110

***Conclusion:***

The outcome of our analysis of bioequivalence is very close to that of the sponsor (see tables 1,2, 3, 4, 5 and 6).

Since all of the parameters of interest satisfy the 80% to 125% bioequivalence standard, we support approval of this ANDA.

