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APPLICATION NUMBER:

20-402/SCM-001/S-002/S-003/S-004/S-005

STATISTICAL REVIEW(S)

Statistical Consultation

NDA 20-402 [redacted] SN002
 Name of Drug: Provel (ibuprofen 200 mg liquigel)
 Sponsor: Whitehall Robins
 Study Protocol: PV-96-04 (OTC Phase IV Safety Study)
 Documents Reviewed: One un-numbered volume of NDA 20-402 dated
 6/12/96 and volumes 2.1 and 2.2 of [redacted]
 [redacted] SN002 dated 8/2/96 by CDER
 Reviewer: Hoi M. Leung, Ph.D.
 Date of Consultation: 8/13/96

The proposed randomized, parallel, placebo controlled study is to compare the gastrointestinal (GI) adverse event profile of Advil liquigel 200 mg capsules to the film-coated ibuprofen 200 mg tablets at the maximum labeled OTC dose (1200 mg/day) for 10 days. The description of the study protocol can be found in the medical reviews (L. Hu, HFD-560 and K. Johnson, HFD-550). The following are comments on statistical issues regarding the GI adverse event rate and the sample size impacts of the study.

1. Historical GI adverse event rate

The sponsor's estimated GI adverse event rate is based on a study in OA patients (New England Journal of Medicine 325; 87-91:1991) for 4 weeks comparing acetaminophen 4000 mg/day (n=61), ibuprofen 1200 mg/day (n=62) and ibuprofen 2400 mg/day (n=61). The GI adverse event rates were 10/61 (16.4%) for acetaminophen, 7/62 (11.3%) for ibuprofen 1200 mg/day, and 14/61 (22.6%) for ibuprofen 2400 mg/day. In the proposed protocol, the duration of study is 10 days and the OTC patient population is generally healthier than OA patients. Thus, the GI event rate could be much lower than the 11% estimated. Moreover, it is unusual that the GI adverse event rate for acetaminophen was higher than the ibuprofen 1200 mg/day. Thus, the estimated GI rate based on this small study in OA patients for four weeks may not be reliable for the projected OTC population over 10 days.

2. Statistical considerations in GI adverse event rate

If the GI event rate is low, it will require a large sample size to show a small difference. The following are some numbers to consider when claiming equivalence in GI rates between the test and control drugs.

<u>Control</u>	<u>Test</u>	<u>Diff.</u>	<u>95% CI Diff.</u>	<u>N/Group</u>

Except for the first row in the table above, the general scheme of the table is that the observed rate of the test drug is 20% more than the control and the upper 95% confidence bound of the difference is within 50% of the observed control rate. The criteria for the first row are relaxed somewhat because the control rate is small. Because of the short duration of the study, the GI adverse event rate will probably be small, making it difficult to demonstrate equivalence without enrolling a large number of patients. Alternatively, one can lump all GI symptoms together to boost the observed rate or relax the upper 95% confidence bound of the difference to make the study more feasible than the requirements above.

If the sample size is fixed at 400 patients per treatment group in the protocol and the power is at least 70% ($\alpha = 0.05$ 2-sided), then the difference which can be detected with power of at least 70% is as follows:

<u>Control</u>	<u>Test</u>	<u>Difference</u>	<u>Power</u>

Thus, this study would have adequate power to detect a two to three-fold increase in GI rate if the control rate is low and can detect a 50% or more increase if the control rate is over 10%.

/S/

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CC:
Archival NDA 20-402

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