Memorandum of Statistical Review

Submission: NDA 20239/S-023 (Pediatric Supplement)
Product: Kytril (granisetron HCl) Injection
Sponsor: Roche Laboratories
Indication: PONV
Medical Div: DGP
Reviewer: M. Welch, DB3

The purpose of this memorandum is to document the statistical conclusion regarding sponsor Study ML16633, "Intravenous Granisetron (Kytril®) in the Prevention of Post-operative Nausea and Vomiting (PONV) in Pediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy."

The primary objective of Study ML16633, as stated in the protocol, was to "..to estimate the effectiveness of 2 dose levels of IV granisetron (20 µg/kg and 40 µg/kg) in preventing PONV defined as total control (no nausea, no vomiting, no use of rescue medication) during the 0-2 hour interval following time of extubation (end of surgery) in children aged 2-16." The protocol and statistical plan note that the sample size for each dose group was chosen to achieve a pre-specified length of the 95% confidence-interval for the true proportion of subjects with total control. (CI half-width = 0.12.)

Thus this study's statistical objective was only to estimate the group proportions with a pre-stated level of *precision,* not to test any hypothesis comparing the two treatment groups. In fact, the clinical study report (page 38) states, "There was no formal hypothesis for this exploratory trial." However, as indicated in the analysis plan, the CI's for each group and for the group differences were to be presented for the primary and secondary endpoints. These results are shown below.

Table te_tcon_t5: Proportion of Subjects with Total Control
Protocol: ML16633
Analysis Population: Evaluable Subjects

	Granisetron 20 ug/kg N= 70	Granisetron 40 ug/kg N= 73	Difference
Proportion of subjects with total control (0-2 hr)			
n	60	66	
%	(85.7)	(90.4)	4.7
95% CI*	0.75 - 0.93	0.81 - 0.96	-0.09 - 0.23
Proportion of subjects with total control (0-24 hr)			
n	46	45	
%	(65.7)	(61.6)	-4.1
95% CI*	0.53 - 0.77	0.50 - 0.73	-0.20 - 0.12

Total control is defined as no nausea, no vomiting and no use of rescue medication
* 95% confidence interval for within group proportion
% is calculated as n/N
Difference in percentages is for Granisetron 40 ug/kg minus Granisetron 20 ug/kg

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From these data, the confidence intervals of the treatment differences cover zero, so it cannot be concluded that one dose is (potentially) statistically superior to the other. Moreover, there is no clear dose-response, since both endpoints do not show a consistent directional effect. Without knowledge of placebo response from appropriate historical data, the effectiveness of either dose is difficult to ascertain.

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/s/

MICHAEL E WELCH
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