Assay Sensitivity Can Be Higher in Single-Site Than Multiple-Site Acute Pain Studies: A Case Study

Neil Singla,[1] Nathaniel Katz,[2] Jonathan Sporn,[3] Paul Goldenheim,[2] Raymond Cheung,[3] Ruoyong Yang,[3] Christian C. Apfel[4] — [1]Lotus Clinical Research, Pasadena, CA; [2]Analgesic Solutions, Natick, MA; [3]Pfizer Inc., New York, NY; [4]UCSF Medical Center, San Francisco, CA

BACKGROUND

- Clinical trials on new analgesics targeting the treatment of acute pain often fail to statistically differentiate active drug from placebo, despite, in many cases, known efficacy of the study product in question
- The reasons for trial failure are most likely multifactorial, including trial design, placebo response rates, and site-to-site variability
- Systematic reviews have shown that increasing numbers of sites increases the risk of study failure[1,2]

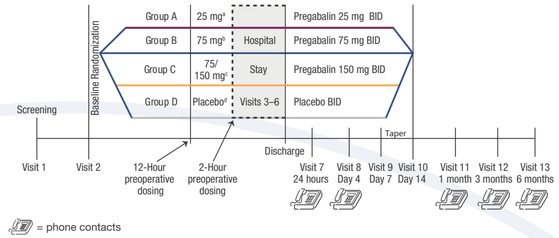
OBJECTIVE

- The purpose of this investigation was to perform a post hoc analysis on a large multicenter acute pain study in which 1 research group accumulated a substantial proportion of the overall study sample, providing an opportunity to compare the assay sensitivity of a study conducted within 1 research group with the assay sensitivity conducted under similar conditions at a large number of sites

METHODS

- Utilizing 26 international sites during a 16-month enrollment period, 403 patients were enrolled in study titled: A randomized, double-blind multicenter dose-ranging study of the efficacy and safety of pregabalin compared to placebo in the adjunctive treatment of postsurgical pain after primary inguinal hernia (ClinicalTrials.gov identifier: NCT00551135). A brief summary of the study appears in **Figure 1**

Figure 1. Study Summary



BID, twice a day
[a] Group A preoperative dosing: pregabalin 25 mg at 12 hours and 2 hours before surgery
[b] Group B preoperative dosing: pregabalin 75 mg at 12 hours and 2 hours before surgery
[c] Group C preoperative dosing: pregabalin 75 mg at 12 hours and 150 mg at 2 hours before surgery
[d] Group D preoperative dosing: placebo at 12 hours and 2 hours before surgery

- The study design of the Pfizer-sponsored clinical trial consisted of 2 preoperative doses of study medication followed by a 7-day treatment period and a 7-day taper
- Study arms included pregabalin 50 mg/d (n=108), 150 mg/d (n=106), 300 mg/d (n=103), or placebo (n=108)
- The primary end point was the worst pain score (question 1 of the modified Brief Pain Inventory–short form[3]) at 24 hours for pregabalin 300 mg/d. After multiple comparisons adjustment, this end point was not statistically significant compared with placebo (Hochberg adjusted P=0.0668)
- The primary outcome measure of this post hoc analysis was the standardized effect size of treatment (mean pain intensity on active drug minus the mean pain intensity on placebo, divided by the pooled standard deviation) for the 2 subgroups of interest: all patients studied at Lotus Clinical Research (n=126) versus all patients studied at all other research sites (n=277)
- Lotus Clinical Research performed this study utilizing 3 closely connected clinical sites, which share staff and conform to internally developed analgesic testing methodologies
- Secondary outcome measures were:
  - The site assay sensitivity as measured by the post hoc sample size requirement to achieve 80% power to detect the observed difference at a 5% significance level
  - The subject enrollment rate expressed as subjects per month
  - The overall performance expressed in terms of number of months required to achieve 80% power (post hoc sample size requirement divided by enrollment rate)

RESULTS

- The key results of the post hoc analysis are reported in **Table 1**

Table 1. Post hoc Analysis Results

	Lotus Clinical Research (n=126)	All 23 Other Sites (n=277)
Primary end point: mean pain intensity at 24 hours on active drug (300 mg/d) minus the mean pain intensity at 24 hours on placebo (Δ)	0.81	0.56
Pooled SD	2.25	2.56
Primary outcome measure of post hoc analysis:		
Standardized effect size (Δ/SD)	0.360	0.219
Secondary outcome measures of post hoc analysis:		
Sample size requirement (80% power, α=0.05)	244	658
Subjects enrolled per site per month (mean)	23.20	0.75
Overall performance (time to 80% power)	10.5 months[a]	36.6 months[b]

SD, standard deviation
[a] Utilizing 3 Lotus sites
[b] Utilizing 23 non-Lotus sites in concert

SUMMARY

- A 64% increase in the standardized effect size was seen at the Lotus Clinical Research group when compared with the other sites in the aggregate
- Because sample size varies inversely with the square of the standardized effect size, these results indicate that sample size requirements are almost tripled in the multicenter environment
- Overall site performance depends upon both observed effect size of treatment (clean data) and subject enrollment rate
- Both variables are considered in the overall performance metric (time to 80% power) described above, which indicated that the Lotus Clinical Research group would be able to achieve sufficient information for 80% power in only 10.5 months compared with 36.6 months for all the other sites together

CONCLUSIONS

- Improving the quality and efficiency of clinical research may be better achieved by increasing enrollment rates at sites using strictly standardized research methods rather than attempting to disperse large numbers of subjects over multiple sites
- These data indicate that 80% power to achieve a P value <0.05 for this clinical investigation could have been achieved from either a well-controlled site group in 10.5 months or 23 sites working in concert for 36.6 months

References: **1.** Katz N. *Neurology*. 2005;65(12 Suppl 4):S32–S49. **2.** Katz J, et al. *Neurology*. 2008;70(4):263–272. **3.** Mendoza T, et al. *Eur J Pain*. 2006;10(4):353–361.

Presented at the 39th American College of Clinical Pharmacology Annual Meeting; September 12–14, 2010; Baltimore, MD

Disclosure: This is an independent research study based on Pfizer-supported clinical trial A0081171. Editorial support for the production of this poster was provided by Beth Young, PhD, of UBC Scientific Solutions and was funded by Pfizer Inc. Pregabalin (Lyrica®) is not approved for postoperative pain.