Reviewer's report

Title: First administration to man of Org 25435 a new intravenous anaesthetic: A Phase 1 Clinical Trial

Version: 1 Date: 22 December 2009

Reviewer: Evan Kharasch

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This manuscript reports the first-in-man study of a new intravenous propofol analogue anaesthetic, with the stated aim of assessing safety, tolerability, and efficacy, although in actuality the major emphasis is on the pharmacokinetics of the drug. The drug did not behave as anticipated based on the animal studies, and was considered unacceptable for further development due to slow emergence and toxicity (cardiovascular)

Comments

Table 1 and Figure 2 show data from previous publications. They are not appropriate for this manuscript and should be deleted.

P4, last 2 lines. What do the authors mean by ORG 25435 is potent compared with propofol? The doses of the 2 compounds are similar, suggesting similar potencies. Also, what is the relevance of the statement in the add-on clause, regarding water solubility?

P6. What is a "unit" of alcohol? What was the "aqueous vehicle"? The TCI infusion scheme is not at all clear as written.

P9. Please provide complete information on the LCMS assay for ORG. There should be enough detail for the assay to be replicated from the information provided. Why were both arterial and venous blood samples analyzed?

P10. Were arterial or venous samples used for the modeling?

P11. The effect modeling is incompletely described. Also, how was ke0 determined?

Results. The organization of this section is puzzling. The material in the last 2 paragraphs on P13 should come later. After the demographics, the section on induction/maintenance should follow.

In the PK Tables, what is meant by "typical value"?

Since a primary aim of the study was safety, and the drug program was terminated due to safety concerns, please show the relevant safety data (HR, BP).
Table 3. What do the negative confidence intervals say about the quality of the data?

What were the PK parameters which were used in STANPUMP to drive the TCI?

Fig 5. What is "theta"?

Where are the ke0 data?

The Discussion is unfortunately not at all well written. It is loose, poorly organized, lacks focus, and is relatively uninformative. The stated purpose of the study was to determine safety and efficacy. Organize the Discussion around Safety and Efficacy. Why as recovery slow? The drug failed. So what is the lesson? Why did it fail? How can lessons learned be applied to other animal data to prevent a similar failure with another drug? Many drugs fail and their stories are not published. Why is it important to publish this failure story?