Reviewer's report

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

Version: 2 Date: 17 February 2010

Reviewer: Harald Ihmsen

Reviewer's report:

The authors have responded adequately to all comments, and the manuscript has been improved markedly.

I have only a few minor essential comments:

1.) page 16: when comparing arterial and venous concentrations it may be reasonable to report not the absolute but the relative difference, i.e (Cv-Ca)/Ca because the magnitude of the concentrations is quite different for the different doses, so that one cannot judge whether the difference given in ng/mL is large or small.

2.) Legend of Figure 7: it may reasonable to explain what context sensitive half-time means

3.) Tables 2,3,4: the NONMEM typical value is the value of the parameter in the population, and this is not in any case the geometric mean of the individual estimates. This is only true if an exponential model for interindividual variability is used. Furthermore, if the mean of the estimated individual ETAs is not exactly zero, the geometric mean of the individual estimates will be different from the typical value which is the main estimate of the NONMEM fit. It may be reasonable to give a short explanation in the Methods section, for example: "Pi=PTV*exp(etai) where Pi is the parameter value in the ith subject, PTV is the typical value of the parameter in the population, and etai is a random variable with a mean of 0 and a variance of omega2."

4.) Table 3, 4: I would suggest to write that the CV% was calculated as the square root of the variance of the eta variable associated with that parameter. In table 4 the header "CV%(*SD)" seems to be a typing error. Probably, it must be simply CV% like in table 3.

5.) Figure 6. For the y-axis, I would suggest to use the label "Theta power" because "Observations/predictions" could mean that a ratio was calculated (as for example in goodness-of-fit plots where the ratio measured/predicted is plotted vs. time). In the legend to this figure I would suggest to write not simply "values for theta" but "values of absolute theta power".

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.