Question 1.

From a statistical point of view should the CIs derived from the final analyses be adjusted to take account of the two stage study design and the interim statistical analyses?

Yes, adjustments must occur at each stage, although in the current study, the required adjustment of the second stage CIs will be minimal.

If so what adjustment should be made (e.g. use the 94.13% CIs)?

The sponsor has elected to maintain overall [redacted] Following the general decision sequence of Potvin et al's [redacted] Other approaches to control of Type I error with interim testing are available and widely used in superiority trials (see Schultz and Grimes, 2005). The one used by the sponsors most resembles the most commonly applied approaches in using a stringent significance level at the interim analysis or analyses, leaving the final test significance level little if at all altered while maintain overall Type I error at 5%.

Was this required approach used? If not we need to ask that it be done.

From the decision procedure diagram, it is claimed that the final (second) stage analyses were conducted with α=.049, implying appropriate adjustment was made, assuming that this led to the construction of 90.2% CIs, although, as noted above, the difference between these and conventional 90% CIs is likely to be trivial.

[redacted]

Question 2.

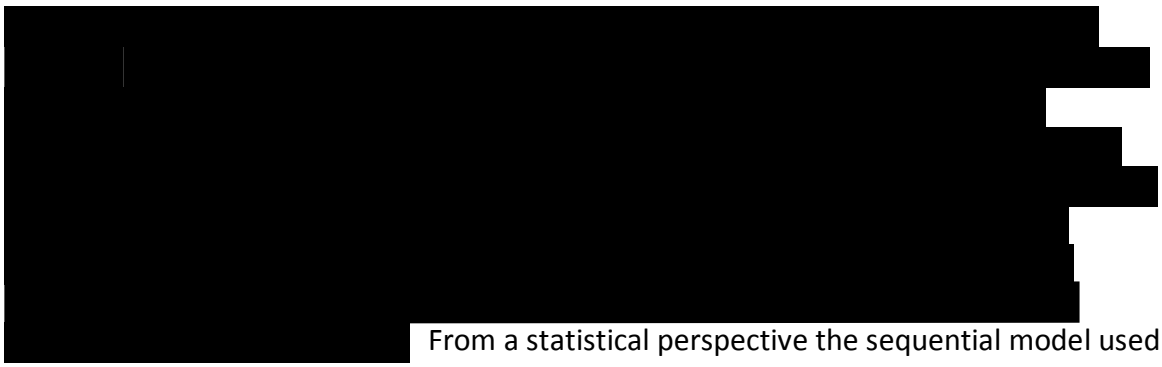
Is the statistical model used valid?

Model terms

At Stage 2, the minimally required terms in ANOVA model are treatment, sequence, stage, and period(stage). The EMA (2013-2015) additionally specifies sequence×stage and subject(sequence×stage) as expected model terms (p. 32). Karalis and Macheras (2014) evaluated the performance of the EMA model using simulation and found that the sequence×stage was almost always non-significant. They also pointed out that the consequences of this term being significant were unspecified. Their conclusion was that this term is unnecessary [redacted]

Decision tree/Sequential model

This two-stage approach to evaluating BE is widely accepted. The principal requirements are that the two-stage design is pre-specified and that Type I error is constrained to 5%. Regulatory authorities differ in their preference for Potvin et als (2008) Method B or C.



From a statistical perspective the sequential model used in this BE study appears to contain Type I error to 5% and thus to be valid.

References

EMA (2010) *Guideline on the Investigation of Bioequivalence*, CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, London, 20 January 2010.

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