EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Product Development Scientific Support Department

Treatment effect measures when using recurrent event endpoints – Qualification Opinion List of Issues regarding provided simulation exercises

Additional list of issues to be addressed in writing by 23 August 2018:

1) It is noted from slide 29 of the presentation dated 10th July that estimates of estimand 1, the HHF rate while alive, are calculated for each treatment group by dividing the total number of HHF events for patients in that group and dividing that by the total time until death/study end for patients on that group. This would seem to provide an unbiased estimate only under assumptions that are unlikely to be valid in reality and are not valid in the simulations provide, namely that death is independent of HHR. An analysis based on first deriving the HHR for each patient and then calculating from this the average HHR for each treatment group would seem to provide unbiased estimates under less stringent assumptions.

a) Please discuss the reasons why the chosen approach to calculating the HHR was selected.

b) Please repeat the simulations looking at the performance characteristics of recurrent event analysis methods using estimates of estimand 1 and 2 calculated on a per patient basis, and discuss whether this reduces the issue of the estimated treatment effect on HHR being impacted by the treatment effect on CVD.

2) Please provide sample size calculations to show how the sample size and power vary when recurrent event analysis is used as primary compared to time to event analysis in differing scenarios, some of which should be based on past clinical trials.

3) Please discuss the performance characteristics of recurrent event methods in scenarios where the HHR changes over time, i.e. the HHR generally increases over time. Do (or do not) completed clinical trials in different therapeutic areas indicate changing event rate over time in survivors?

4) For estimand 2 please clarify how events are counted when a patient is hospitalised and then dies while hospitalised. Would this be counted as one event or two? Please further discuss the clinical interpretation of results on estimand 2.

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