How sponsors could implement new ECG biomarker approaches

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Disclosure & Disclaimer

- I am employed at Novo Nordisk A/S, Denmark
- The opinions expressed in this presentation are mine and do not necessarily reflect the opinion of my employer

What works well today?

- QT interval assessment
  - well established methodology
  - current knowledge based on many decades of experience
- TQT trial
  - timing
  - design
- Well-known regulatory requirements/strategy
  - ICH E14 Guideline
- New opportunity - exposure-response analysis

Why do we need new ECG biomarkers?

- Will provide increased early knowledge about new drugs in clinical development beyond the QT interval
- Will constitute a part of the decision making - stopping/continuing the clinical development programme
- Will ensure increased subject safety in early clinical development

Operational considerations (1/2)

- Trial design
  - increased complexity?
  - compatible with current early phase trial design?
  - variability of new biomarkers – potentially increased trial population?
- ECG recorders
  - do the current Holter devices provide sufficient signal quality?
- Method/algorithm validation
  - e.g. J-point and T-peak determination

Operational considerations (2/2)

- CRO/ECG core lab
  - increased involvement during protocol development
  - validated methodologies implemented
  - timely delivery
- Cost
  - trial conduct
  - suppliers

Analytical considerations (1/2)

- Increased amount of data points
  - time, resources and cost implications
- Analysis of data
  - HR correction method (if needed)?
  - formal stat testing - which model to use?
  - store raw data for later analysis - safety/ethical issue?

Analytical considerations (2/2)

- Interpretation of results
  - consolidation/comparison with pre-clinical data
  - how to weigh the results from different sub-analyses
  - provide a concrete conclusion and its implications for the next steps in clinical development
  - potential risk - increased attrition rate based on uncertainty and lack of knowledge

Regulatory considerations (1/2)

- Regulatory guidance needed
  - should QTc still be assessed as today?
  - assessment of new ECG biomarkers in all situations?
  - new biomarkers only to be analysed when QT is prolonged?
  - in which circumstances could clinical development continue with a QT prolonging drug?
  - when do new biomarkers support a waiver for a TQT trial?
  - should new biomarkers be analysed only in SAD/MAD trials?

Regulatory considerations (2/2)

- Next steps in drug development
  - implications for later stage development?
  - will extensive ECG recording in later stage development be required based on new biomarkers?
- Regulatory interaction/advice important
- Consensus among regulatory agencies - ICH alignment

Conclusion

Overall in favour of new validated biomarkers that support the clinical development and improve the risk/benefit assessment

What sponsors could do to make it happen

- operational readiness
- analytical readiness

Sponsors expectations

- CRO/ECG core lab
  - validated methodology in place

- Regulatory agencies
  - provide clear guidance, rationale and implementation timelines
  - ICH alignment