BOS 4

Rob Hemmings preliminary comments

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Longitudinal model as primary
  - What is of primary relevance?
    - A ≠ B, or A = B
    - Time to event
    - Incidence
  - Statistical vs Clinical relevance

- High impact
  - ≠ controversy, but on reg decision

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Basic questions:
  - Why model? ↓ patient numbers (feasibility) – what level of 'risk' for the decision is acceptable for this benefit.
  - Where has model come from?
  - Is Type I error controlled?
  - In what ways can I make a bad decision? What bias toward demonstrating equivalence?
    - same assumption on time dependency for each treatment group
    - Otherwise different parameters - ok

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Basic questions:
  - Will estimates differ to data observed?
    - Point estimates
    - Variability / confidence intervals
  - Why and how (↓ var)?
    - gains in efficiency must necessarily come from models which have built-in constraints on evolution of the response over time. Are the constraints appropriate? Why?
  - Sources of bias?
    - Handling patient withdrawals? 'Treat as failures' in 'standard' analysis. How handled by Markov? Can we assess influence of withdrawals?

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Assumptions
  - Only mathematical assumptions listed?
  - How are candidate models formed?
  - Missing data – assumptions?
  - Assumptions from literature?
    - Mixture of settings / patients – is same model appropriate for all types of patient (based on disease, demog and response?)
    - Applicability to current trial?
  - Markov model – response depends only on response at previous timepoint?
    - ? AEs and w/d from treatment – how should data from that patient contribute?
  - Equivalence limit same – stat vs clinical considerations.

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Questions → dialogue
- What if model and observed data inconsistent – because of non-completers?
- "A single model incorporating further assumptions has increased risk of bias and poor performance due to model misspecification."
  - Analysis of incidence makes fewer assumptions (depending how you define the question)
- Pre-spec – ok
- Sensitivity analyses – simulations of differences – how would they be exhibited?

Novartis 5, Longitudinal model-based test as primary analysis in phase III

- Is it acceptable?
  - Discussion as above
  - Reg position is understandable from an assessment p.o.v.
  - Was level of detail / dialogue adequate?
  - Intuitively easier to accept for biosimilar: comparability exercise, not establishing efficacy / safety
  - If so, door open to line extensions, difficult to study areas

- If not, what to do?
  - Type I error control by simulation – little experience, but little else to do (simulate extreme scenarios, plan for extreme results)
  - Qualification procedure!
  - Model vs Observed incidence

Sample size for safety!

Holford, Karlsson, Mixed Effect Models for Trials Disease Modifying Treatments

- Need for model clear
  - Parkinson / Alzheimer GL ‘slope analysis’
- Basic questions:
  - How model constructed?
    - Applicability / Comprehensiveness of available epidemiology?
    - Does treatment change underlying profile of disease timecourse?
    - Impact of AEs? Any patients contributing to benefit who withdraw?
  - How does model partition effects into S and DM?

Holford, Karlsson, Mixed Effect Models for Trials Disease Modifying Treatments

- Basic questions:
  - What data available? Why limited duration (feasibility, withdrawals – AE, trt switch?)
  - Simulations – how much extrapolation?
  - In what ways can I make a bad decision?
  - Handling patient withdrawals?
  - Type I error, Pre-spec – ok

Holford, Karlsson, Mixed Effect Models for Trials Disease Modifying Treatments

- Extrapolation – is uncertainty adequately reflected from
  - Parameter estimates
  - Disease model

- Other information on disease progression
  - biomarkers, scans? Developing field “effect on underlying pathological process should be established”
  - Multivariate model?

Both examples

- Communication
  - Stats / PK / PM → Stats / PK / PM
  - Stats / PK / PM → Clin
  - Clin → Clin