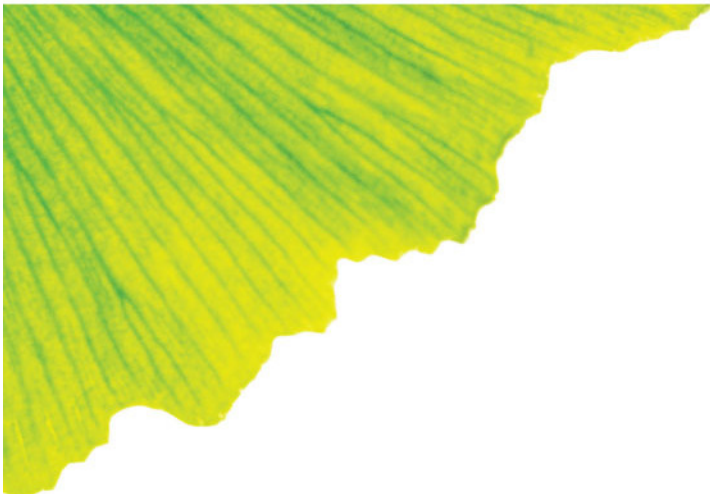


*“Designing clinical trials in a  
multiregional regulatory  
environment”*

*Jørgen Selstrup, Quintiles*



**Basler Biometric Section**  
Current Topics in Pharmaceutical Statistics:  
Dose Finding and Multiregional Trials  
*Basel, Friday, September 16, 2011*

clinical | commercial | consulting | capital

- Introduction: Development of Guidance Documents
  - Harmonisation?
- Regulatory Advice Opportunities
- Case Study 1
  - Setting the Scene
  - 'Negotiating' with the Regulator
- Case Study 2
  - Regulatory Guidelines
  - Regulatory Advice
- Some Concluding Remarks



# Introduction: Development of Guidance Documents (1/3)



- ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  - North America, Europe, Japan
  - Efficacy (E1-E12, E14-E16)
    - **E9: Statistical Principles for Clinical Trials (1998)**
  - Safety (S1-S9)
  - Quality (Q1-Q10)
  - Multidisciplinary (M1-M5)



# Introduction:

## Development of Guidance Documents (2/3)



- Regional guidances
  - **MCA (MHRA)/CPMP: "Biostatistical methodology in clinical trials in applications for marketing authorisations for medicinal products" (1994)**
  - EMA, Points to Consider/Guidelines
    - Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection
    - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2011/07/WC500108672.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500108672.pdf)
  - FDA, Guidance for Industry

# Introduction: Development of Guidance Documents (3/3)



- Disease areas (diagnosis and treatment)
  - National/International societies (e.g., the Kidney Disease Outcomes Quality Initiative (K/DOQI))
  - Acute Kidney Injury Network



## In Need of Harmonisation? (1/2)



- Whatever happened to harmonisation?
  - Statistical/clinical issue
  - ISBS presentation/SiM paper
- Are regional regulators talking to each other?
  - They say they are!
  - Perhaps they should talk more!



## In Need of Harmonisation? (2/2)



- MCP conference
  - Does the FDA care if EMA wants something different (Stockbridge: "No") - or visa-versa
  - Panel: 'As there is only one way to win in a region it is not a multiplicity issue'
  - That's OK if e.g., T v. P v. C and one region wants T v. P as primary and the other wants T v. C, but what if?
  - However, Yi Tsong, FDA: "Designing multiregional clinical trials with different regional required primary endpoints"

## Regulatory Advice (relative to case studies) QUINTILES®

- **FDA - End of Phase 2 (EOP2) meeting / Special Protocol Assessment**
  - Opportunity to discuss and (potentially) reach agreement on clinical studies to support efficacy and safety in a NDA. Review a mock-up label
  - Steps: Request meeting, schedule meeting, submit briefing document, preliminary response, (meeting), final minutes
- **EMA - Scientific Advice (SA) meeting**
  - Steps: Letter of intent and draft briefing package, pre-submission meeting, submission of final briefing package, Scientific Advice Working Party (SAWP) procedure starts, CHMP formal adoption of EMA position, schedule meeting if needed, final advice letter

# The Briefing Package (typical)



- Introduction – drug and disease
- Meeting specifics
- Non-clinical summary
- Clinical summary
  - Pharmacology
  - Pharmacokinetics
- Questions and company position
  - Pre-clinical questions
  - Clinical questions
  - Appendices
    - IB, outlines of completed studies, study reports, references

Remember:  
You only get answers to the questions  
you ask!



# Case Study 1



# Case Study 1



## Chronic Kidney Disease (CKD)

- Common cause of CKD: diabetes and hypertension
- End Stage Renal Disease (ESRD) is the final stage of CKD
- ESRD treated by dialysis and/or kidney transplantation
- Hyperphosphataemia (high concentrations of phosphate in the blood) is a complication of ESRD
- Need for new treatments to improve management of disease (few/old registered compounds)

## Setting the Scene (1/2)



- Regulatory guidance on development of drugs in CKD - *None*
- National Kidney Foundation (USA) - *K/DOQI guideline*
- Transcripts of FDA Advisory Committee meetings
  - Drug 1 (1998): Phase III, 2 trials, open label; one cross-over against active (50 patients), one test group (< 200 patients)
    - Deficiencies: No primary efficacy variable, no sample size calculation, analysis population not pre-specified
  - Drug 2 (2002): Phase II, 2 trials (one of < 50 patients, the other appr 150 patients [4 dose groups and placebo]); Phase III, 1 trial (< 100 patients); all randomised double-blind placebo controlled studies
    - Deficiencies: Phase III, co-primary variables (last serum phosphate on maintenance, control of serum phosphate); Phase II (small), control of serum phosphate (primary); Phase II (larger), change from baseline (primary)

## Setting the Scene (2/2)



- Successful Phase II
- Efficacy evaluation using both change from baseline of serum phosphate and serum phosphate control
- Design a Phase III programme

### **2 (almost) identical Phase III protocols**

- One in a US population and one in a non-US population
- Randomised, open label (for reasons of formulation/size of tablet/labelling of faeces), active-controlled (placebo no more ethical) parallel group, multicentre
- Different comparators in the two trials
- Primary objective: Demonstrate the efficacy of test drug
- Primary efficacy variable: Control of serum phosphate (responder analysis)

## Phase III (2/2)



- Non-inferiority design
- 6 months treatment phase (including wash-out, titration and maintenance)
- $\alpha$  (2-sided) = 5%,  $\beta$  = 10%
- $\delta$  (margin) = 15% ( $M_1$  = total effect of active comparator, from (few) historical trials;  $M_2$  = the margin of interest  $\leq M_1$ ; discounting, i.e., retain a fraction of the effect of the comparator)
- Provision for switching to superiority

# Regulatory Advice Issues



# 1. Choice of NI Design (1/2)



## FDA position

***The non-inferiority design is inadequate for establishing efficacy***

### Reasons:

- Definition of 'responder' favours non-inferiority (Sponsor modified definition)
- Non-compliance favours non-inferiority (Sponsor defined non-compliance as a failure)
- Danger of excluding patients as the trial was open label (Sponsor: excluded patients would be treated as failures)
- Responder analysis is not acceptable as response makes the non-inferiority design less sensitive
- Margin – "the smaller the better"

### Advice:

- Design: A double-blind placebo comparison in a superiority setting

# 1. Choice of NI Design (2/2)



## EMA position

*The non-inferiority design is in principle acceptable*

... but:

- Underlying reasoning ('effect retention' and clinical justification) for the choice of margin may not be adequate ("according to the European standard it is not necessarily sufficient to retain 50%")
- Effect retention is not 'universally' 50% (placebo: 20%-25%, active comparator: 50%-60%)

????????????????????????????????



What had happened to harmonisation?

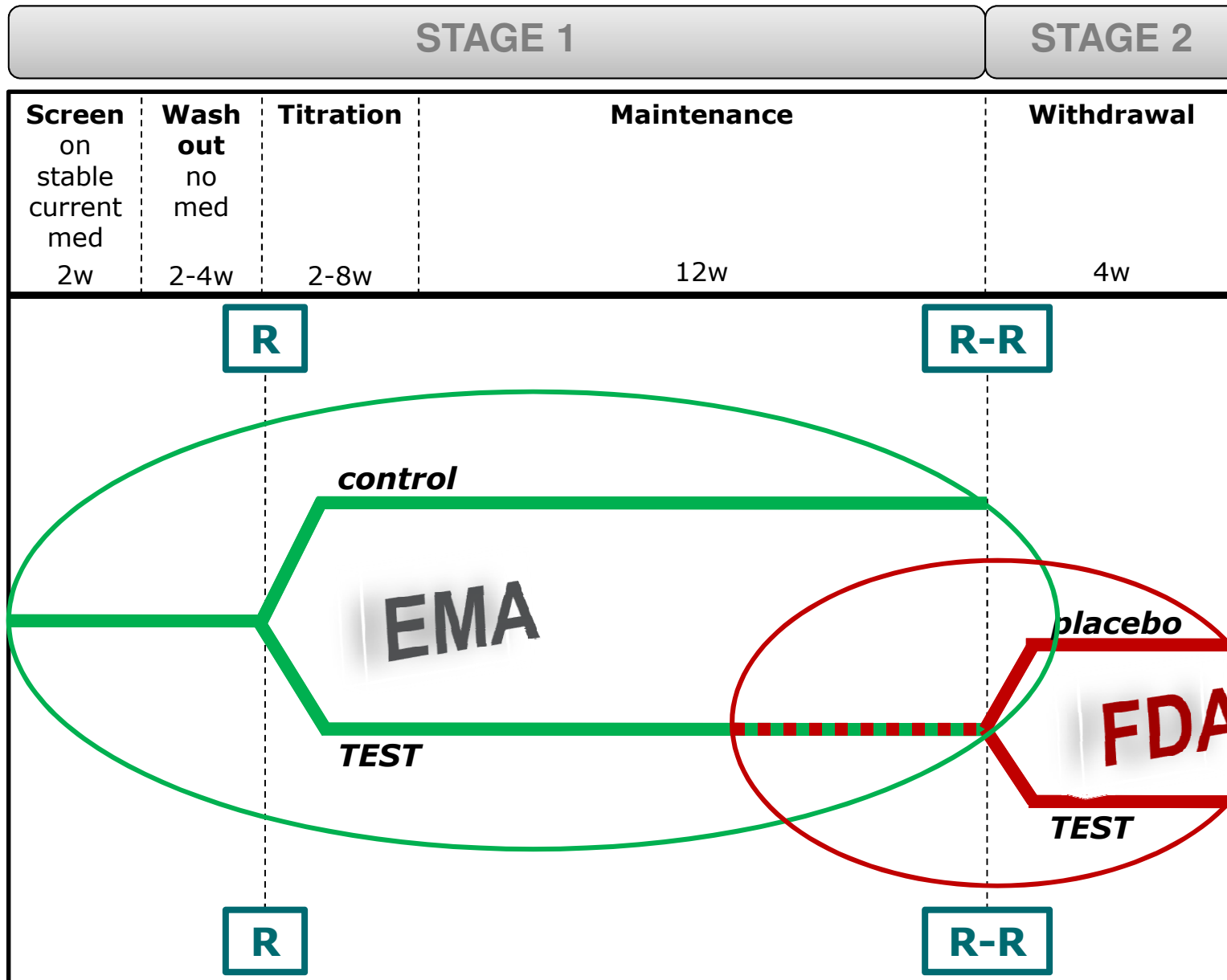
One set of studies for the FDA and a different set of studies for the EMA?

**Sponsor's solution:**

*2-stage re-randomisation design where stage 1 is the original non-inferiority design (acceptable to FDA for safety) and stage 2 is a re-randomisation of patients on the test drug to either continue on the drug or be given a placebo*



# Final Design



## 2. Switching to Superiority



### **Sponsor position**

- *If non-inferiority is established proceed to test for superiority (no statistical penalty)*
- *Secondary variables to be hierarchically tested to create the most favourable labeling opportunity*

### **FDA position**

- *It may not be possible to test secondary variables if switching to superiority has happened and failed (sequential gate-keeping strategy – more research need to bridge the gap between logical statistical restrictions and sensible clinical hypotheses)*

### **EMA position**

- *No particular comments*



## 3. Responder Analysis



### **FDA position**

- *Not acceptable*
- *Wants evaluation of continuous endpoint*

### **EMA position**

- *Acceptable*

## 4. ITT Definition



### **Sponsor position**

- *ITT = All subjects randomised, taking at least one dose and having at least one serum phosphate measurement on treatment*

### **FDA position**

- *No particular comment*

### **EMA position**

- *Generally all randomised patients who receive at least one dose should be included in the ITT population. However, in open label studies all randomised patients should be included*

### **Sponsor reaction**

- *E9 is sufficiently pragmatic to allow proposed definition to stand*



## 5. Missing Data



### **FDA position**

- *Pre-specify in the protocol details of handling of missing data*

### **EMA position**

- *Pre-specify in the protocol details of handling of missing data*

... and by the way, submission of the Statistical Analysis Plan at the earliest opportunity will add credibility to the study results (FDA)



# Case Study 2



## Case Study 2



### **Pulmonary Arterial Hypertension (PAH)**

- PAH is a progressive disorder characterized by abnormally high blood pressure (hypertension) in the pulmonary artery
  - PAP (pulmonary arterial pressure)
  - PVR (pulmonary vascular resistance - normally about 14mmHg; in PAH usually > 25mmHg)
- Over time, the heart muscle weakens to such an extent that the heart loses its ability to pump enough blood through the body  
→ Left Ventricular Failure (Heart failure) → Death
- Signs and symptoms of PAH:
  - Shortness of breath (dyspnoea) during exertion
  - Fainting spells (syncope)
  - Dizziness
  - Swelling (edema) of the ankles and/or legs
  - Chest pain
  - Racing pulse /palpitations
- Treatments, but no cure

# Regulatory Guidelines



## EMA

- CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension  
London, 22 October 2009; Doc. Ref.  
EMA/CHMP/EWP/356954/2008  
[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/12/WC500016686.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500016686.pdf) (came into effect 1 May 2010)

## FDA

- None (so far!)

### **Objectives of a new treatment**

- Prolong survival time
- Reduce morbidity
- Ameliorate symptoms
- Improve quality of life

### **Efficacy variables**

- All cause mortality (identify cause of death, CV)
  - At least no detrimental effect on survival
- Morbidity (time to event)
  - Non-planned PAH-related hospitalization
  - Deterioration in functional class
  - Deterioration in exercise capacity
- Clinical symptoms (WHO/NYHA functional classification)
  - Component of the primary endpoints
  - Subjective
  - Not less than 6 months
- Exercise capacity
  - 6MWT (short term, e.g., 15% improvement from BL)

### ■ **Primary efficacy variables**

- Improvement in exercise capacity (6MWT)
  - 'traditional'
- Time to clinical worsening (TCW) – composite endpoint
  - All-cause death
  - Time to non-planned PAH-related hospitalization
  - Time to PAH-related deterioration identified by:
    - » increase in WHO FC
    - » deterioration in exercise testing
    - » signs or symptoms of right-sided heart failure

### ■ **Secondary efficacy variables**

- Haemodynamics
- QOL
- Biomarkers

## Phase III – dilemmas



- One or two studies?
- Primary efficacy: 6MWT or TCW?
  - 6MWT  
PROBLEM: Extrapolation from short term improvements to clinical meaningful changes
  - TCW  
PROBLEM: Length of study

# Regulatory Advice Issues



- One or two studies?
  - Two studies for 6MWT, pooled for TCW
  - Comment: Justification is needed that a meta-analysis is appropriate for a TCW claim
- Efficacy: 6MWT or TCW
  - Minimum: 6MWT at 6 months (with no detrimental effect on morbidity and mortality) as primary with TCW key secondary
  - Comment: TCW is a composite endpoint; negative trends on important components may result in the rejection of a MA application

- One or two studies?
  - Either two successful “phase III” studies ( $p < 0.05$ ) or one successful study with a very low p-value or a relatively low p-value in one study on an unquestionably important endpoint (e.g., mortality)
  - Phase II study could serve as one of two adequate and well-controlled studies (to-be-marketed dose must be used and be statistically significant; adjustment as necessary)
- Efficacy: 6MWT or TCW
  - Two significant 6MWT studies with TCW as secondary pooled across the studies
  - Comment: The statistical significance decision tree will be complex because of such pooling and needs to be proposed for further discussion with the Agency

# Lessons Learned



- Make sure of a statistical strategy which reflects label expectations (e.g., hierarchical ordering of secondary endpoints)
- Specify handling of missing data
- Get clarity on number and design of studies
- When the FDA says 'we recommend', think again about not doing it



# Concluding Remarks



- Whatever happened to harmonisation?
- Talk to the Regulator – the mechanism for doing so exists
- Ensure all relevant regulatory agencies are consulted simultaneously to avoid different development strategies
- Harmonisation is not just (but is also) a statistical issue
- Further discussion and action is needed regarding harmonisation in order that both society (the patient) and the drug developer (the industry) may prosper

