EMA EFPIA M&S Workshop
Break-out session no. 4
Theme 3 - M&S to characterize risk-benefit and support label claims

Decisive support of Modeling & Simulation for getting drug approval of non-tested dosing scheme : 2 examples

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BOS4 : Position statement and associated questions

Successful approval of non-tested dosing scheme using M&S techniques without further dedicated prospective studies

- Would in general the EMA accept the principle of relying on M&S approaches to label an unstudied dose or dosing regimen?
- What information and evidence are needed by the EMA to consider to label an unstudied dose or dosing regimen based on M&S approaches?
- In what circumstances would the EMA accept exposures in a sub-population outside the range of previously tested exposures in that subpopulation but within the range of previously tested exposures in an other sub-population?

BOS4 : Extended Questions

- If the Sponsor demonstrates that:
  - The pharmacology and the mechanism of action of the drug are well known,
  - The exposure-response relationships for efficacy and safety in the target population are adequately characterized,
  - The covariate effects are known,
  - Enough confidence in the models to simulate response in a specific sub-population within the range of previously studied exposure:
    - All of the proof of the model robustness using classical technique (gof plots, SE, VPC, PPC…) are provided
- In which cases
  - The EMA would only rely on the simulations to label an unstudied dose or dosing regimen ?
  - The EMA would still ask to confirm in an additional study ?

BOS4 : Extended Questions

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	Significant Benefit in life-threatening disease	Prevention or delay of long term disease with high morbidity mortality	Symptomatic treatment
AEs that can be monitored and treated	M&S only?	M&S only?	M&S only?
Safety signals with clear predictive indicators	M&S only?	M&S only?	M&S only?
Safety signals without clear predictive indicators	M&S + Additional data?	M&S + Additional data?	??

Background

What has triggered the changes in dose (and dose adjustment rules) compared to the original plan?

- Changes of regulatory recommendation on endpoint target range: **the example of C.E.R.A** (Continuous Erythropoietin Receptor Activator), a new erythropoietin stimulating agent (ESA) for the treatment of anemia in patients with chronic kidney disease (CKD).
  - BLA and MAA were submitted to both FDA and EMA based on an hemoglobin (Hb) target range of 11 to 13 g/dL.
  - After submission, FDA modified the Hb target range to 11 to 12 g/dL (as optimal target range) and avoid Hb > 13 g/dL for safety concern.

Background

What has triggered the changes in dose (and dose adjustment rules) compared to the original plan?

- Less efficacy in an identified sub-population: **the example of ribavarin** in HCV genotype-1 patients with normal transaminases (ALT)
  - A lower dose than the recommended one for HCV genotype-1 infected patients with elevated ALT was used in patients with normal ALT
  - Less efficacy i.e. sustained virologic response (SVR) was observed in this population compared to the patients with elevated ALT

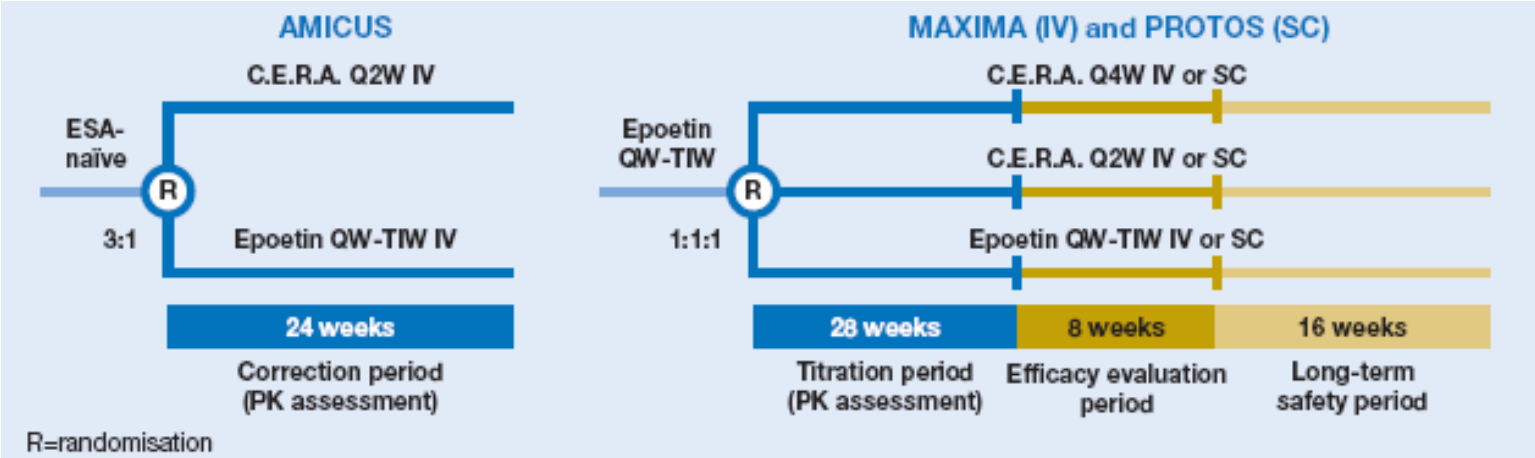
Rationale and objectives of the M&S analyses

- In both examples, the knowledge of the exposure-response relationship was considered sufficient to rely on M&S approaches to investigate new doses

- Clinical trial simulations were conducted to assess efficacy and safety clinical outcomes of non-tested dosing scheme (and dose adjustment) proposed in the SmPC (Summary of Products Characteristics)

Available Data for C.E.R.A.

- Data from 400 patients of 3 open-label, randomized, multicentre, parallel-group Phase III studies, **AMICUS**, **MAXIMA** and **PROTOS**
- The PK assessment period in **AMICUS** was the 24-week correction period. The PK assessment period in both **MAXIMA** and **PROTOS** was the 28-week dose titration period.
- The Hb assessments were performed weekly in the three Phase III studies during the correction or titration periods.



Available Data for Ribavirin

- For model development, SVR and Hb data from genotype-1 infected CHC patients with elevated ALT levels receiving a ribavirin treatment of 48 weeks were used:
  - 817 patients for GAM development of SVR
  - 1233 patients for GAM development of incidence of anaemia

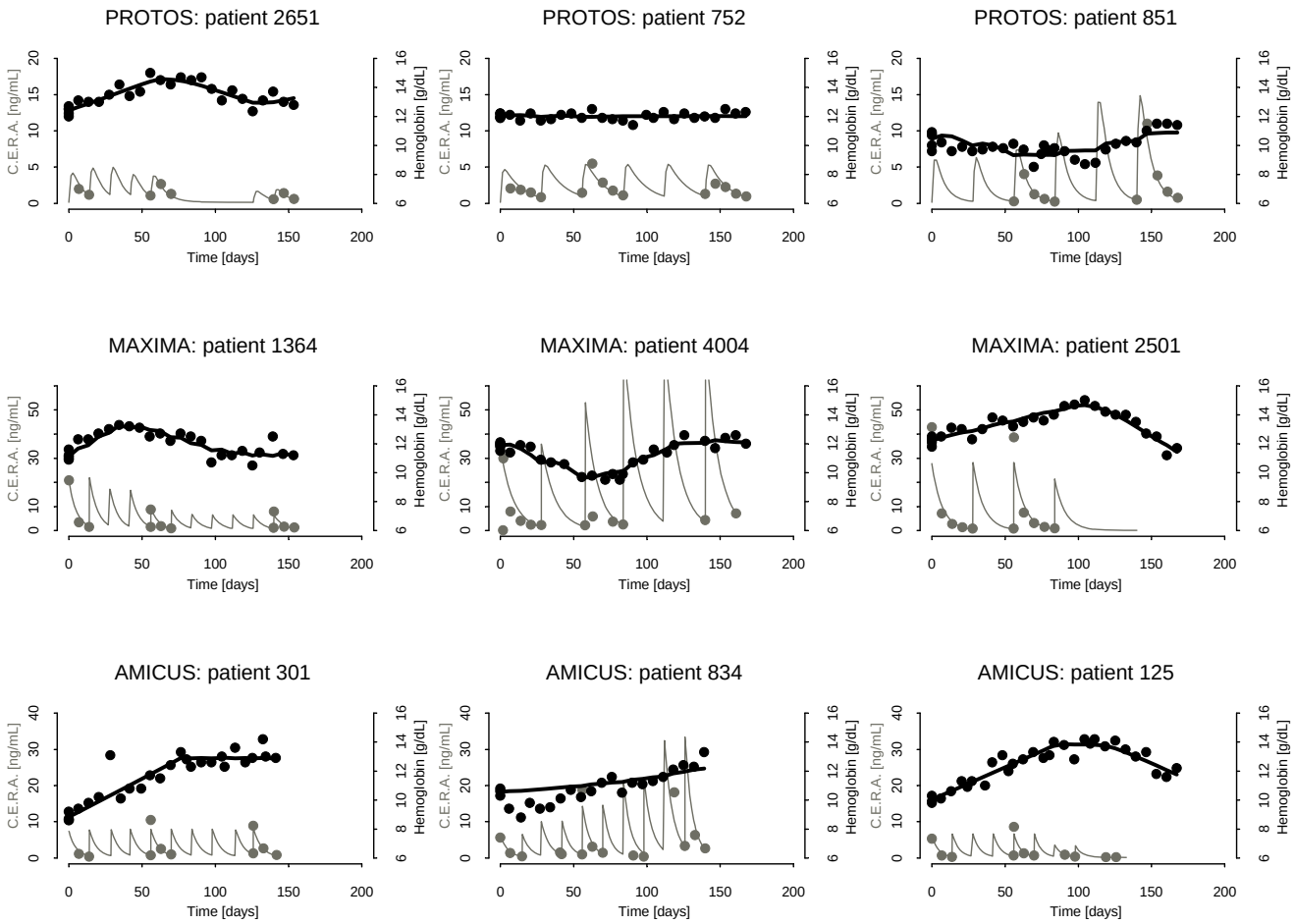
- For the assessment of dose in genotype-1 infected patients with normal ALT levels receiving a daily dose of 800 mg ribavirin for 48 weeks, SVR data from 138 patients and Hb data from 206 patients were used

Methods

- Development of PKPD models using available data.
- Evaluation of the predictive performance of the PKPD models by visual predictive check and posterior predictive check on defined metrics
- Simulations to evaluate the efficacy and safety of alternative dosing scheme.

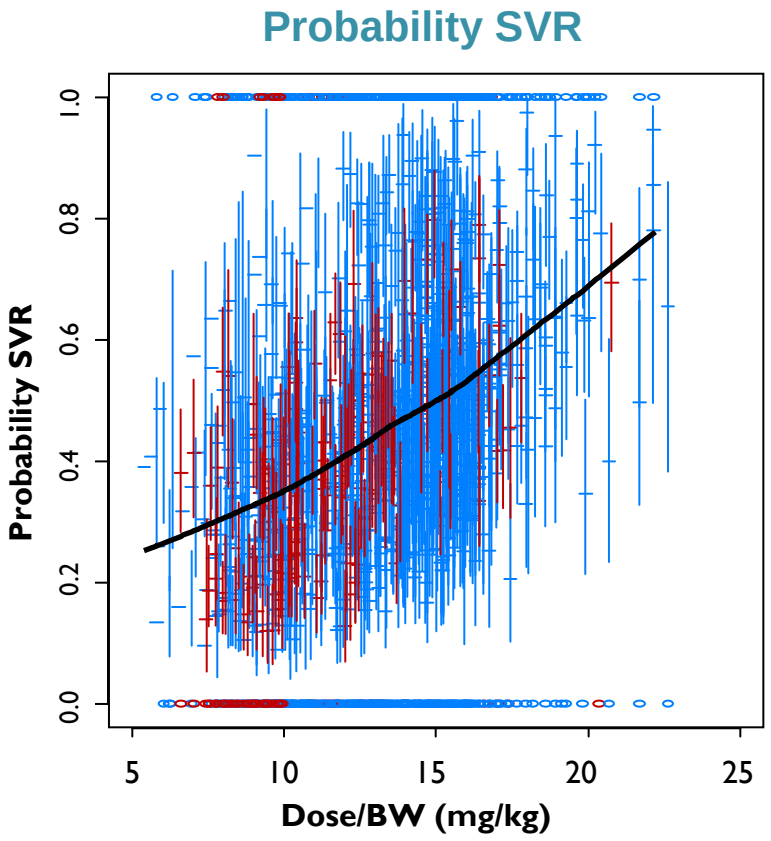
The Exposure-Response Analysis for C.E.R.A.

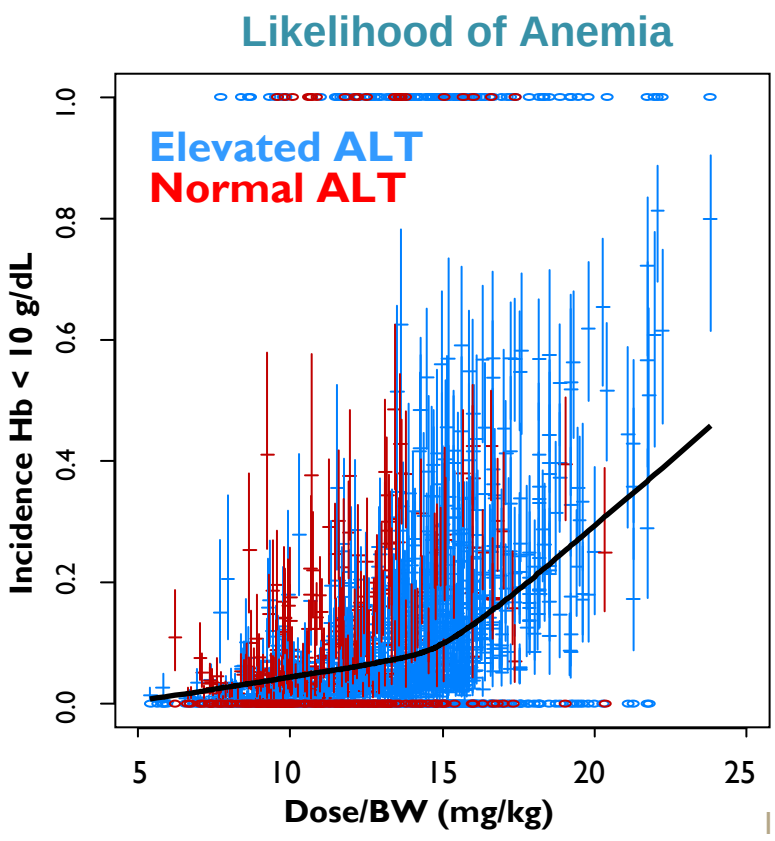
Observed and predicted Hb concentrations in individual patients selected from PROTOS, MAXIMA and AMICUS.



The Exposure-Response Analysis for Ribavirin

- The higher incidence of anemia in patients with normal ALT is due to a difference in percentage of female patients (61% for normal ALT versus 33% for elevated ALT)



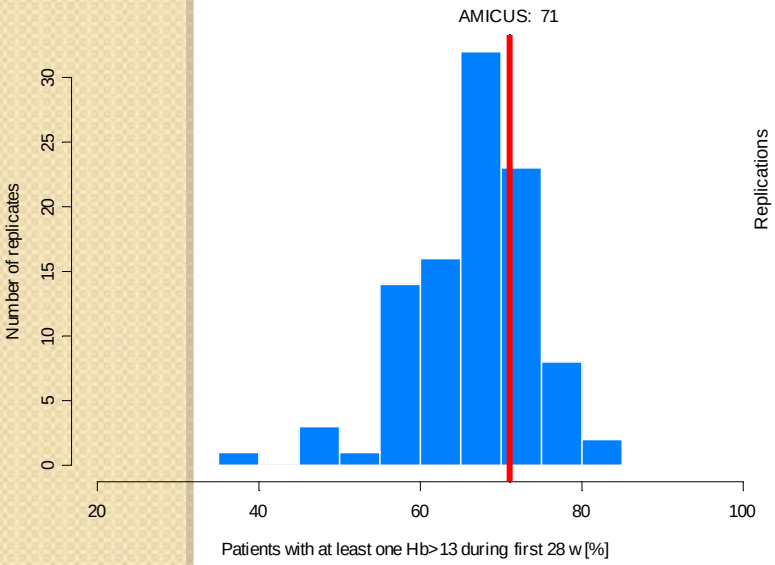


Model qualification

- The PKPD models are qualified to be used in simulation mode

C.E.R.A.

Occurrence Hb>13 g/dL (IV)

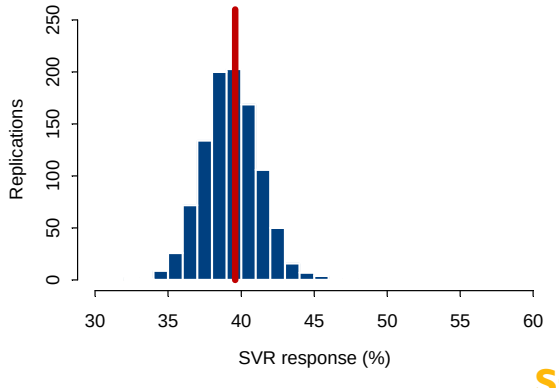


Ribavirin

Patients with normal ALT

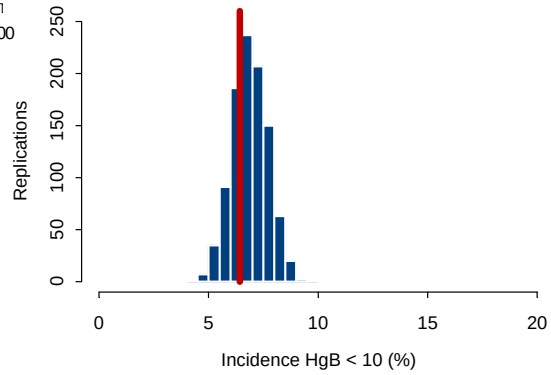
Efficacy

800 mg



Safety

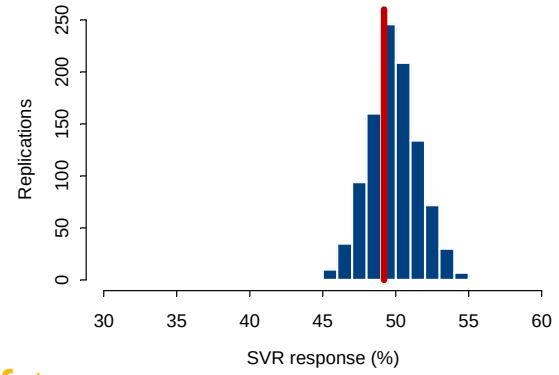
800 mg



Patients with elevated ALT

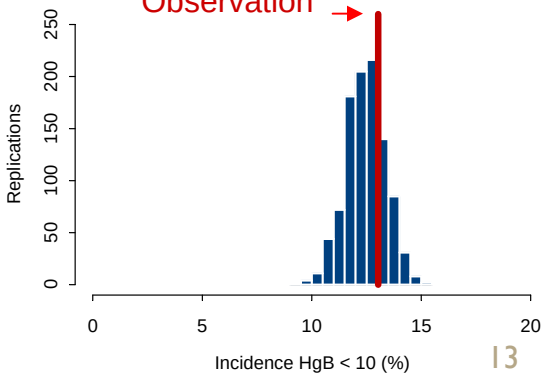
Efficacy

1000/1200 mg



Safety

1000/1200 mg



M&S Results: Simulation of efficacy and safety of non-tested dosing scheme and dose adjustment rules of C.E.R.A.

- With 0.3 µg/kg/w IV or SC every 2 weeks, the median predicted occurrence of Hb>13 g/dL was decreased down to 41% and 26.5% respectively compared to 71% in AMICUS.

- With 0.3 µg/kg/w IV and SC given every 2 weeks, the median response rate (percentage of patients with Hb≥11 g/dL and ΔHb from baseline ≥1 g/dL at least once during the first 24 weeks of treatment) was 92.5% and 83% respectively. The value in AMICUS was 93%.

	0.3 µg/kg/w IV	0.3 µg/kg/w SC
Median predicted incidence >13 g/dL	41.0 %	26.5%
Median simulated response rate	92.5 %	83.0%

M&S Results: Simulation of efficacy and safety of non-tested dosing scheme of Ribavirin

- At 1000/1200 mg, the SVR in patients with normal ALT is predicted to be similar to patients with elevated ALT

	800 mg	1000/1200 mg
Elevated ALT	40% (36%-45%)	49% (46%-53%)
Normal ALT	39% (34%-44%)	48% (42%-53%)

- At 1000/1200 mg/day, the incidence of anaemia in patients with normal ALT is predicted to be higher than in patients with elevated ALT, especially in females

	1000/1200 mg	
	Females	Males
Elevated ALT	23% (19%-27%)	8% (6%-10%)
Normal ALT	31% (24%-38%)	11% (7%-16%)

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Conclusions

1. The trial simulations have shown that new dosing scheme proposed in SmPC ensures good efficacy and manageable the safety risk.

2. Thanks to Modeling and Simulation techniques additional confirmatory trials can be avoided.

Regulatory Feedback

- The new dosing scheme and dose adjustment for C.E.R.A. were approved by EMA and FDA

- EMA accepted the changes in the label
  - The dose of 1000/1200 mg Ribavirin is not limited only to patients with elevated transaminases
  - The risk of developing anemia is higher in the female population

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