EMA EFPIA workshop
Break-out session no. 2

Case Study Title:

Improvement of clinical benefit for a sub-group of pediatric systemic Juvenile Idiopathic Arthritis (sJIA) patients utilizing model-based dose adjustment optimization (Roche #4)

BOS2: Position statement

Thorough M&S analyses regarding safety and efficacy allows selection of late phase doses (interpolation and extrapolation) without previous testing

Background & Rationale

- Tocilizumab is a recombinant humanized anti-human interleukin-6 receptor (sIL-6R) monoclonal antibody which specifically inhibits the binding of human interleukin-6 (IL-6) to its receptor.

- In sJIA Japanese pediatric patients dosed with 8 mg/kg body weight every 2 weeks for 6 weeks, it was observed that the clinical response (JIA50 and JIA70) was lower in children with a body weight lower than 30 kg compared to patients with a higher body weight.

- This noticeable difference in effectiveness was associated with a visible trend towards lower systemic exposure to tocilizumab in subjects with lower body weight due to the body-weight based dosing.

Objective of the M&S work

Identify the phase III dose regimens that would result in an homogeneous exposure across a wide range of body weights in pediatric sJIA patients

Available Data / Prior Models

- Population PK analysis:
  - A total of 517 serum concentration from 74 sJIA patients were available for this analysis
  - Population PK model (TMDD approximation with linear and non-linear clearances) established from adult RA PK database

- Exposure-response analysis:
  - JIA core set improvements (JIA50 and JIA70) measured at the end study (week 6) in 56 sJIA patients (MRA316JP)

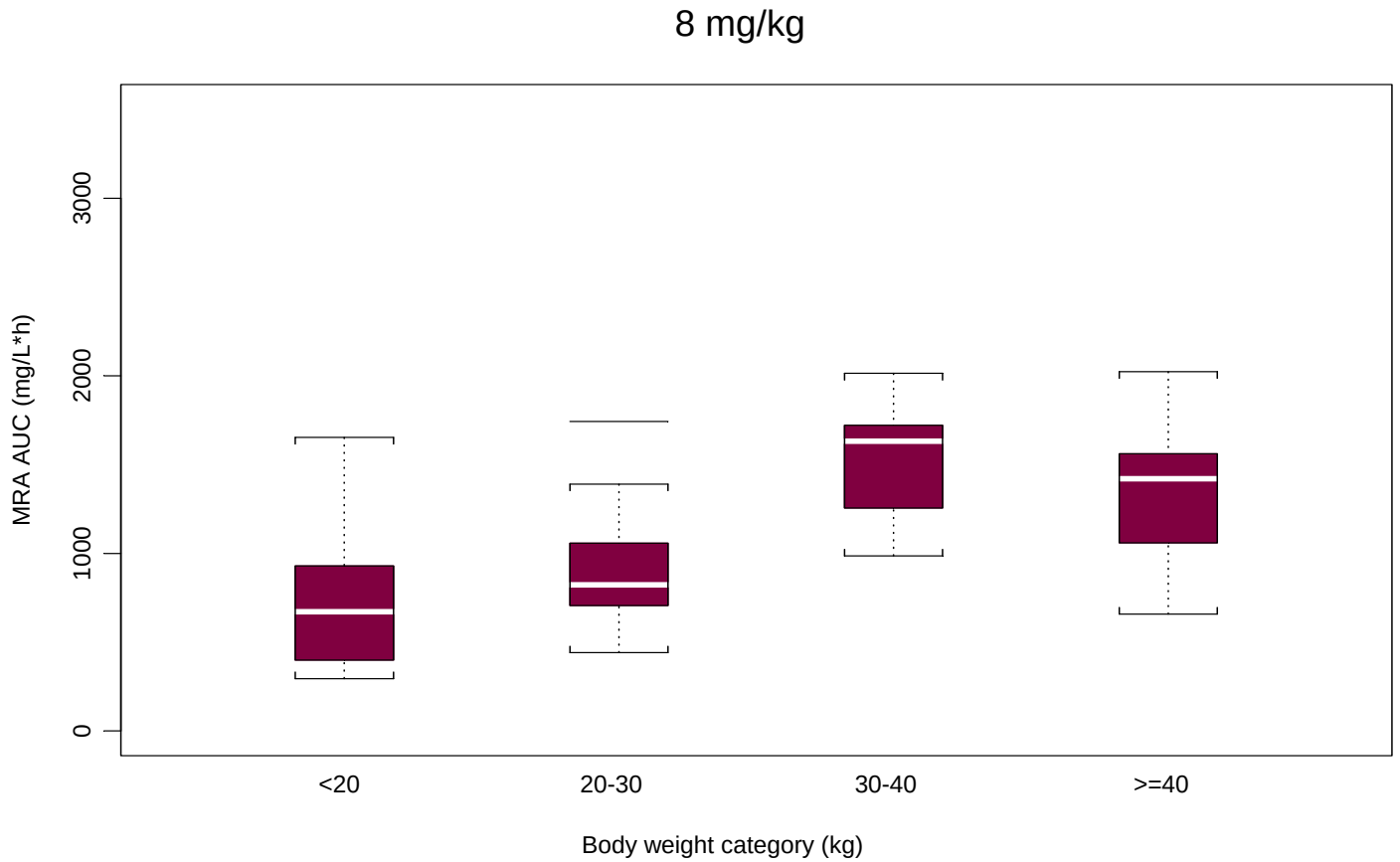
Methods

- A two-compartment model with a combined saturable (Michaelis-Menten elimination) and a non-saturable elimination pathway was developed in NONMEM.

- The relationship between tocilizumab systemic exposure and efficacy has been investigated with a logistic regression model in SPLUS.

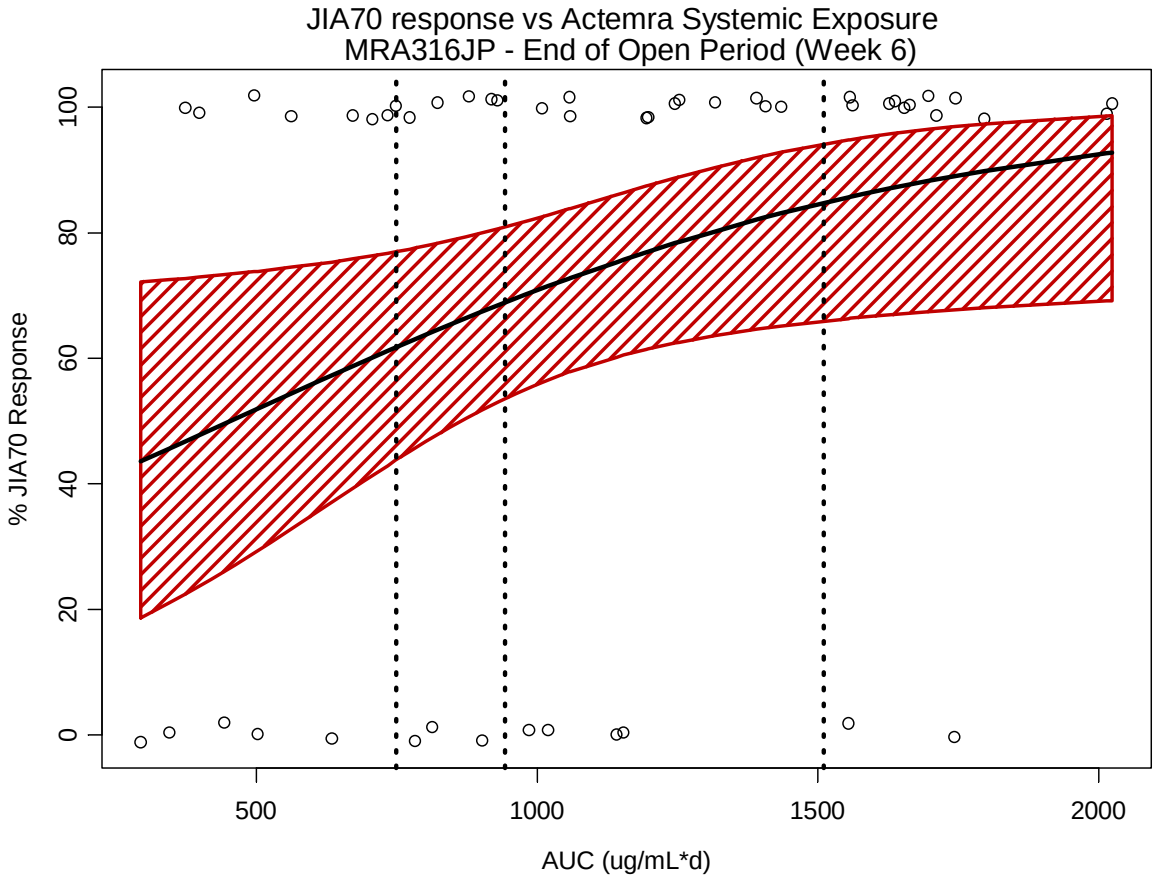
M&S Results

The tocilizumab linear clearance was found to be higher than expected in low body weight resulting in an under exposition of the children with low body weight…



M&S Results

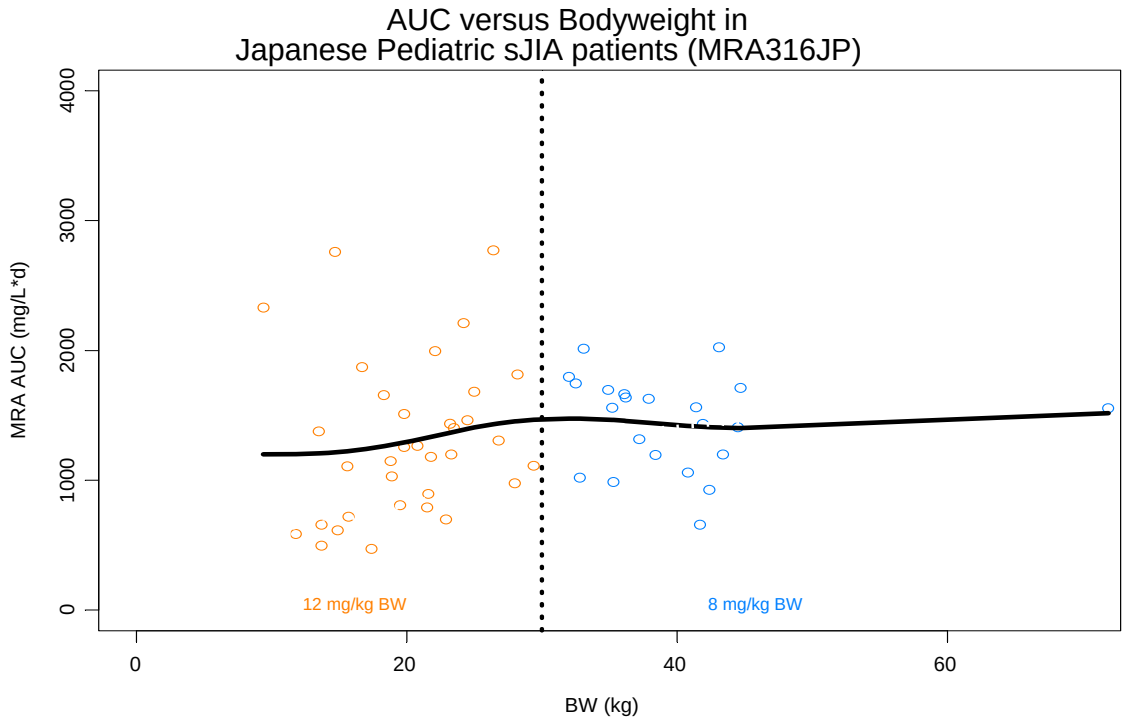
...and explaining why less response is observed in children with low body weight.



Legend: The open circles = the individual data (data jittered). The black line = the estimated curve. The dashed region = twice the standard errors of the estimated curve. The vertical dotted lines = average tocilizumab systemic exposure in children with BW < 20 kg, between 20 and 30 kg and > 30 kg, from left to right, respectively.

M&S Recommendations

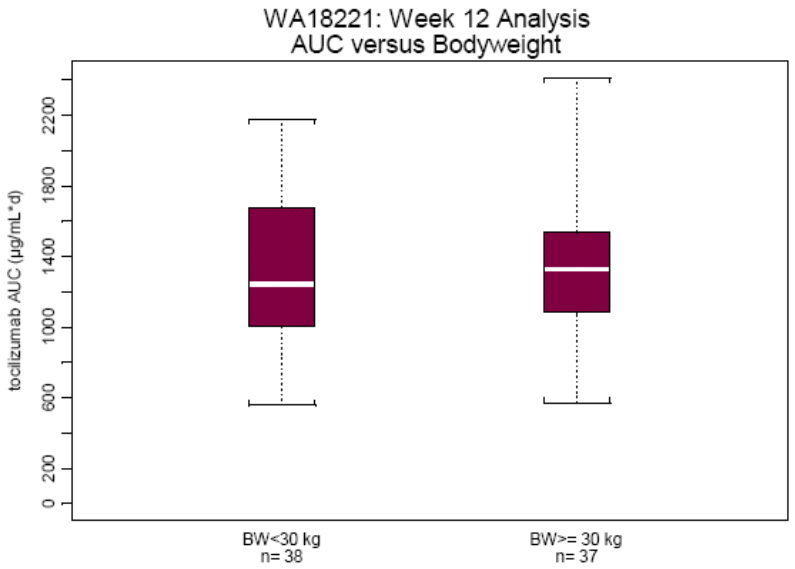
- A dose of 12 mg/kg in patients with a body weight below 30 kg was found to result in an homogeneous systemic exposure and was proposed for Phase III.
- The safety of this systemic exposure range in children has been evaluated in more than 60 sJIA patients (some treated for up to 6 years).
- Regularly scheduled monitoring of adverse events and laboratory parameters in Phase III were proposed.



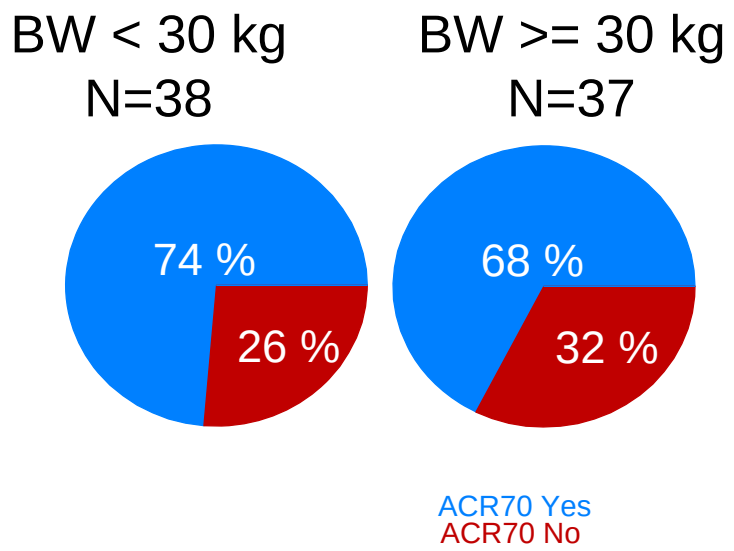
Phase III Results

- Uniform exposure to tocilizumab across the entire range of body weight was accompanied by a comparable ACR70 response in a Phase III confirmatory trial

AUC distribution (Phase III)



ACR70 responders (Phase III)



Conclusions

- Successful use of model-based dose adjustment optimization to improve clinical benefit for a sub-group of pediatric sJIA patients.

- Health authority interactions:
  - The FDA was very supportive of the dosing rationale based on the data interpretation using M&S approaches.
  - The EMA was more conservative by asking to have a pilot study to confirm the M&S predictions before starting Phase III because 12 mg/kg was never tested in this pediatric population.

Question

- What is the minimum data needed and on which set of assumptions would every stakeholder be comfortable to make decisions on M&S results to interpolate and extrapolate for doses to be tested in future trials?

Back-up

SAFETY SUMMARY

- Of the 67 patients who received at least one infusion of tocilizumab in the multiple dose sJIA studies there were 12 SAEs in 9 patients. The outcome was resolved/recovered for all SAEs.
- No association was found between the occurrence of SAEs and exposure or body weight.
- Decrease in neutrophil counts was found to be correlated with concentrations.

MRA316JP study design

Study # Phase Location	Study Design	Treatment Dose/Regimen	Duration	# of Patients Age range
Systemic Juvenile Idiopathic Arthritis (sJIA) studies				
MRA316JP **P3** **Japan**	Multi-center, double-blind, randomized, placebo-controlled, withdrawal study	Tocilizumab: 8 mg/kg q2wks x 3 (open phase) followed by 8 mg/kg or placebo q2wks x 6 (double-blind withdrawal phase)	6 wks followed by 12 wk DB withdrawal phase	(Completed) 56 dosed 10 withdrawn Ages 2 - 19 yrs

- A sparse PK sampling strategy was employed in the open label phase (week 0 to week 6): one sample was collected before the intake of the first dose of the study medication and one sample every week up to week 6 or 2 weeks after withdrawal. Additionally and if possible, one sample was collected at 1 hour post dose in weeks 0, 2 and 4.

M&S Standards Employed

- The work was done according to :
  - Roche Best Practices:
  - Process for data analysis
- The work was done using :
  - Standard computing environment
  - M&S analysis Plan
  - M&S report template