Extrapolation in paediatric juvenile idiopathic arthritis: case study

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Inspired by patients.
Driven by science.

Extrapolation in juvenile idiopathic arthritis (JIA)

Certolizumab pegol (CZP) case-study

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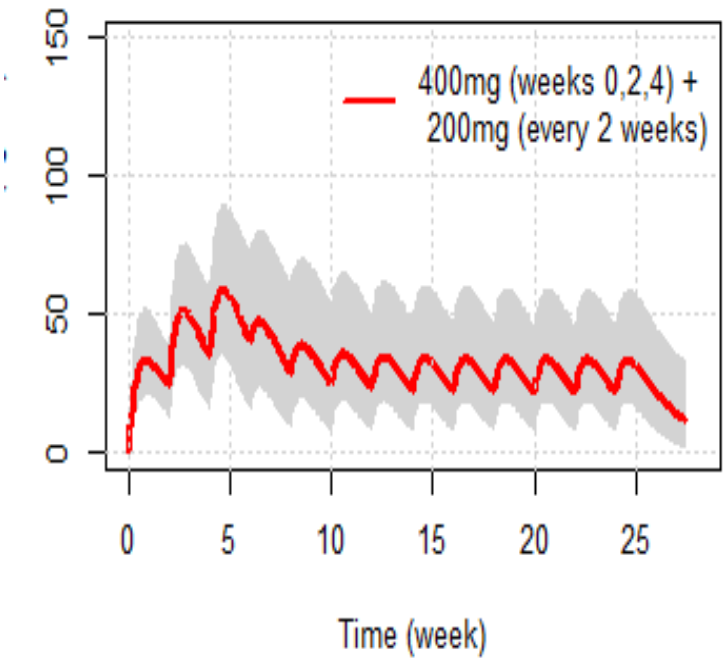
CZP overview

Certolizumab pegol

- A humanized antibody antigen-binding fragment (Fab') with high specificity for human TNFα
  - Linear PK, elimination $T_{1/2}$ of 14 days
  - Administered via subcutaneous injection

- Approved in Europe for treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (AxSpa) including ankylosing spondylitis (AS) in adults.
  - Posology – 400 mg (week 0,2,4) followed by 200 mg every 2 weeks thereafter or an alternative 400mg every 4 weeks dose regimen can be considered



Summary of Product Characteristics: available online at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001037/WC500069763.pdf

JIA overview

Juvenile idiopathic arthritis

Persistent arthritis of unknown aetiology with onset prior to 16 years of age

- Most commonly diagnosed paediatric rheumatic disease, prevalence ~100 in 100,000
- Symptoms of limping, stiffness, irritability, weight loss, delayed maturation etc.
- Depending on severity, treatment typically includes disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, and may progress to include biologic agents

International League of Associations for Rheumatology (ILAR) JIA Categories[1]

Systemic arthritis	
Oligoarthritis, persistent	
Oligoarthritis, extended	**>4 joints/ polyarticular-course**
Polyarthritis, rheumatoid factor +/-	
Psoriatic arthritis (PsA)	
Enthesitis-related arthritis (ERA)	
Undifferentiated	

[1] **Perry RE *et al,*** , *J Rheumatol* ***2004***; 31(2):390-2

CZP JIA clinical trial programs overview

- **JIA study RA0043 'PASCAL'[1] – enrollment completed, dosing ongoing**
  - FDA postmarketing requirement
  - Open-label investigation of CZP PK, safety, and efficacy
    - Moderately to severely active polyarticular-course JIA, 2-17 years old
    - Inadequate response/intolerance to prior DMARDs
    - Enrollment in North America, South America, Russia

- **JIA study JA0002 – planned**
  - As described in agreed PIP (EMEA-001071-PIP02-12-M01)
  - Similar in design to RA0043

  - ***NOTE: CZP is not indicated for use in pediatric patients***

[1]ClinicalTrials.gov identifier: NCT01550003

Evidence to support efficacy extrapolation

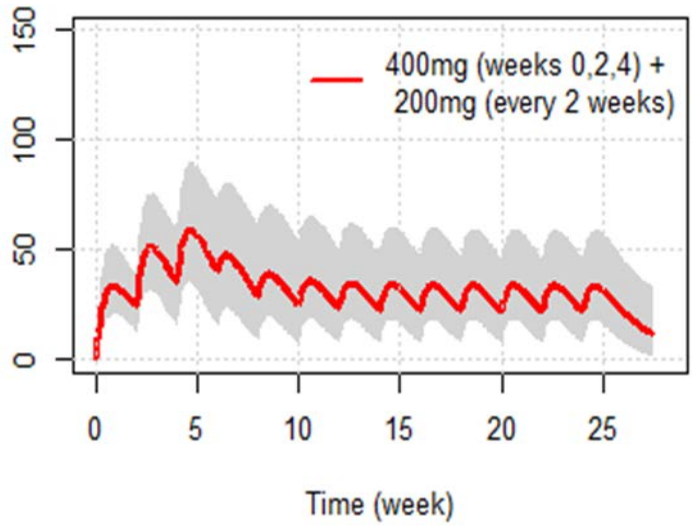
In keeping with EMA guidance documents:
2012 extrapolation (129698) and 2015 JIA (239770)

- Children with polyarticular-course JIA are expected to respond to treatments comparably to adults with RA
  - Adults and paediatric conditions represent inflammatory arthritis
  - Efficacy studies can potentially be waived *"in well-studied pharmacological classes", or when considerable amount of data has been collected in adults (eg licensed indication in one or more of the corresponding adult arthritis categories)"*
- When the paediatric development plan was negotiated:
  - Two other TNF-antagonists (etancercept and adalimumab) were approved in US and EU for the treatment of both RA and JIA
    - Although no direct quantitative similarity between key efficacy scales (ACR and PedACR respectively)
  - CZP was approved for RA

Extrapolation of exposure

Data from two phase 3 studies and a population PK and PK-PD model[1] were used for the extrapolation approach

- Recommended dosing regimen in adults with RA is 400 mg at weeks 0, 2 and 4 followed by 200 mg Q2W thereafter
- Cavg50= average concentration leading to 50% of the maximum ACR20 response was 16.8 ug/mL [95% CI:10.2 to 23.4]
- Assumed that the target therapeutic concentration required in paediatrics was similar to that in adults
- Applied allometric scaling to propose dose/regimen for children >2 years with BW >10 kg using the relationship:



$$V_{ped}=V_{adult}*(Wt_{ped}/70)$$

$$CL_{ped}=Cl_{adul}t*(Wt_{ped}/70)^{0.75}$$

[1]Lacroix BD, *et al*. *Pharmacol Ther*. **2009 Oct;86(4):387-95**

Allometric scaling results

Initial predictions suggested that a dose reduction in subjects <40 kg should achieve the target concentrations

	Loading dose (weeks 0,2 and 4)	Treatment dose (week 6 onwards)
10 to < 20 kg	100 mg (0,2,4)	50 mg Q2W
20 to < 40 kg	200 mg (0,2, 4)	100 mg Q2W
≥ 40 kg	400 mg (0,2,4)	200 mg Q2W

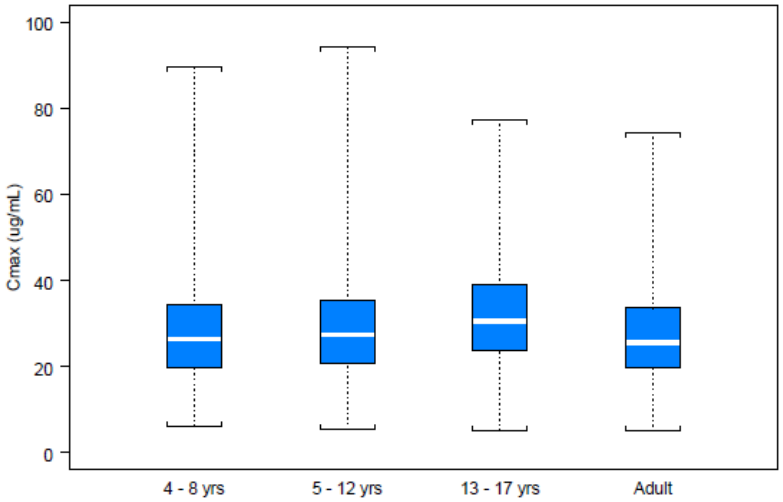
Trial simulations (TS) were performed in TS2, to evaluate:

- Adequacy of the proposed dosing regimen in terms of matching exposure measures (Cmax, Ctrough, and AUC)
- Expected incidence of anti-CZP-antibodies relative to adults
- Precision of CL/F and V/F depending on overall sample-size

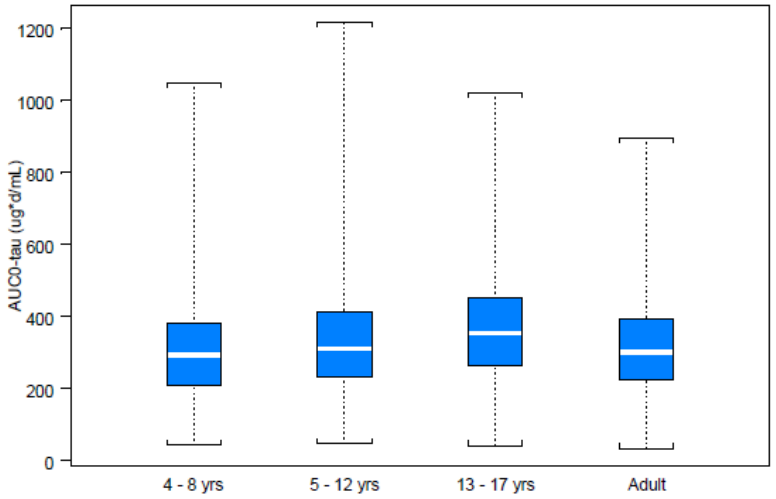
Predicted steady-state (week 14-16) PK parameters

Stratified by age group

Box-and-whisker plots of C_{max} by age group



Box-and-whisker plots of AUCτ by age group



Expected precision of parameters based on a sample-size of 125 across the entire age/weight range was high, <10 % for CL/F and V/F

Predicted C_{trough} and expected anti-drug antibody incidence

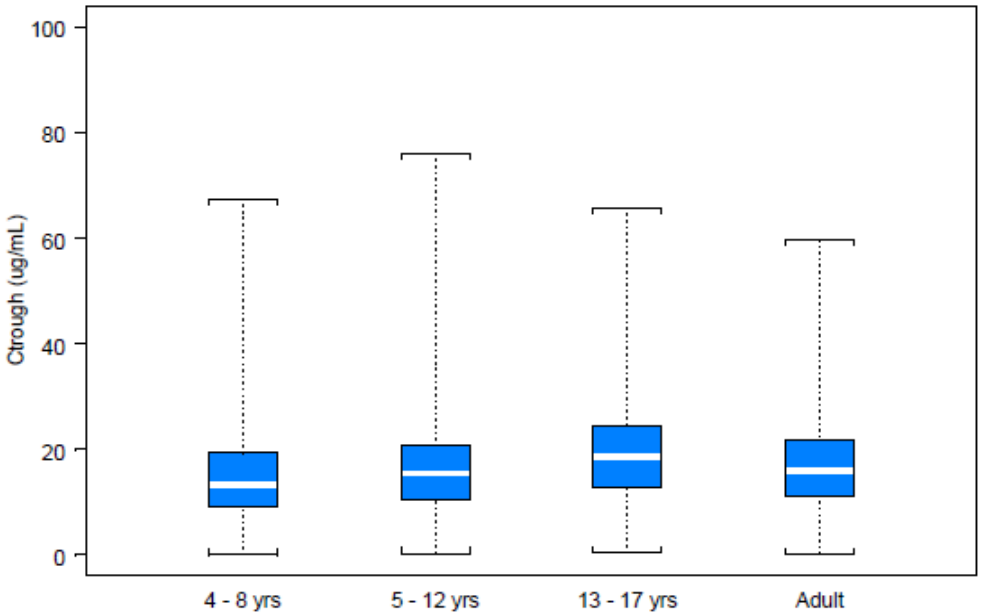


Table 9:3 Summary of C_{trough} values and anti-body incidence

Age Group	C_{trough} (µg/mL)			% Anti-body Positive (ratio[(a)])
	Median (ratio[(a)])	Range	% < 10 µg/mL (ratio[(a)])	
4 - 8 yrs	13.4 (0.84)	0.011 - 67.5	31.1 (1.59)	7.7 (1.01)
5 - 12 yrs	15.4 (0.96)	0.265 - 76.1	22.3 (1.14)	6.1 (0.80)
13 - 17 yrs	18.5 (1.16)	0.426 - 65.8	14.8 (0.76)	6.7 (0.88)
Adult	16	0.234 - 59.8	19.5	7.6

[(a)] pediatric to adult ratio

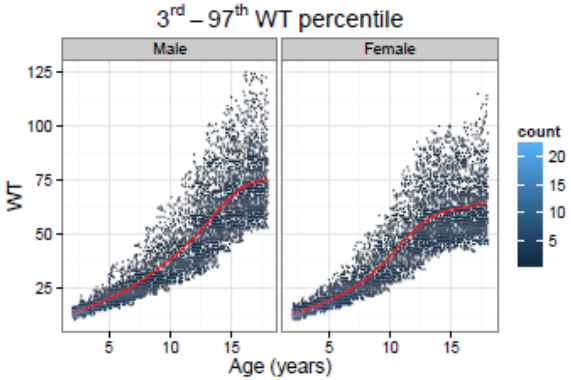
Planned model-based interim analysis

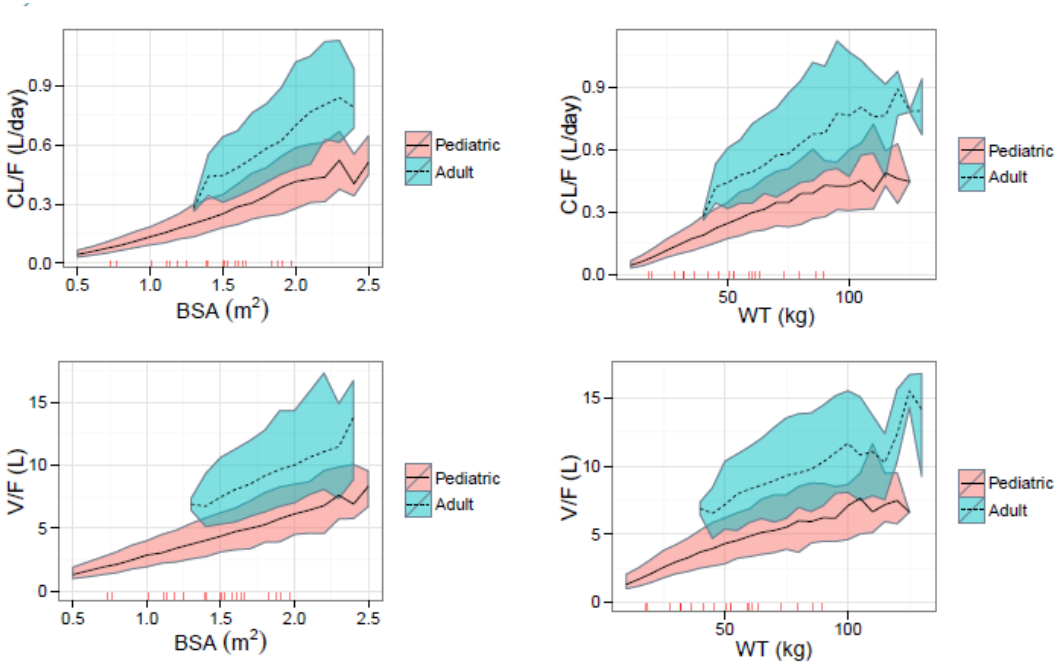
Conducted after 36 subjects had been enrolled

- Overall, the exposure appeared higher in paediatric subjects compared with adults
  - during both the loading phase (weeks 0, 2 and 4),
  - and during the maintenance phase (post-week 6)
- Population analysis performed, combining data from adult RA population in western countries and Japan and available data from RA0043
- Subsequent model was used to perform a series of simulations to evaluate a more optimal dosing algorithm

Simulations

Paediatric population with realistic WT-HT-AGE distribution was constructed based on demographic data from NHANES

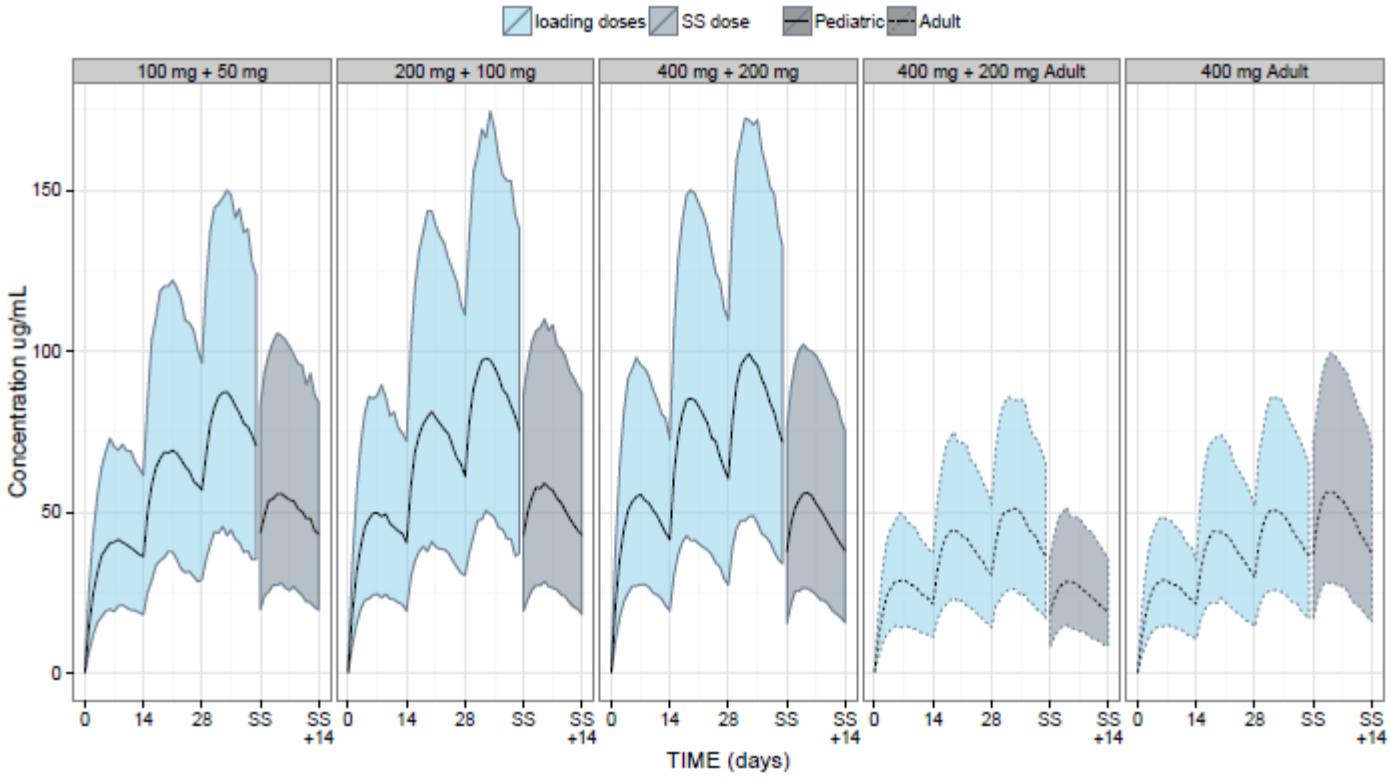




Paediatric subjects appear to have a lower CL/F and V/F compared to adults

Overall predicted exposure ranges based on interim data

Higher exposures during loading and maintenance phase



Dose optimization

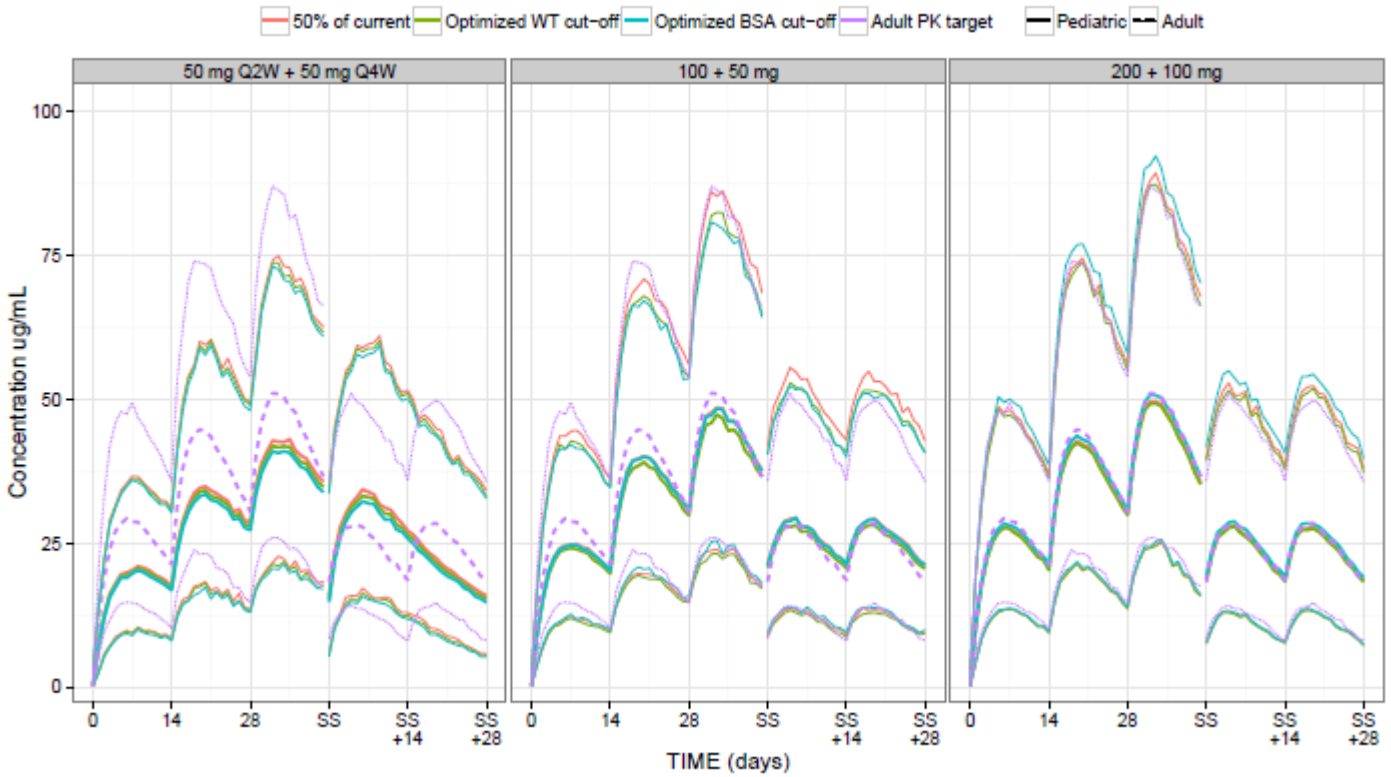
Evaluate optimal dose and weight/BSA cut-off

Weight range	Loading dose	Maintenance dose
50% of current		
10 to < 20 kg	50 mg Q2W	50 mg Q4W[1]
20 to < 40 kg	100 mg Q2W	50 mg Q2W
≥ 40 kg	200 mg Q2W	100 mg Q2W
Optimized WT cut-off		
10 to < 21 kg	50 mg Q2W	50 mg Q4W[1]
21 to < 41 kg	100 mg Q2W	50 mg Q2W
≥ 41 kg	200 mg Q2W	100 mg Q2W
Optimized BSA cut-off		
0.47 to < 0.84 m^2	50 mg Q2W	50 mg Q4W[1]
0.84 to < 1.21 m^2	100 mg Q2W	50 mg Q2W
≥ 1.21 m^2	200 mg Q2W	100 mg Q2W
Adults		
Adults	400 mg Q2W	200 mg Q2W

[1] The optimal dose estimated to be 25 mg Q2W, but the lowest available dose size is 50 mg. A 50 mg Q4W dosing regimen was used instead of 25 mg Q2W

Trial adaptation

All three evaluated dosing regimens could match the target Css average in adults, 50% of current dosing regimen appeared most pragmatic



This interim analysis resulted in a protocol amendment and a reduced dosing was implemented

Data on file

Conclusions

Extrapolation allows program optimization

- **No dose-finding study conducted in paediatric population**
- **No controlled efficacy clinical trial needed**
- **Open label design of pediatric study facilitated recruitment and reduced sample size in this vulnerable population**
- **Health authorities consultation and feedback:**
  - Study design (RA0043) and use of extrapolation agreed by FDA
  - Similar study design (JA0002) and extrapolation plan included in the agreed PIP (EMEA-001071-PIP02-12-M01)