

Label extension for canakinumab NOVARTIS in Adult Onset Still's Disease (AOSD) – Extrapolation from pediatrics to adults

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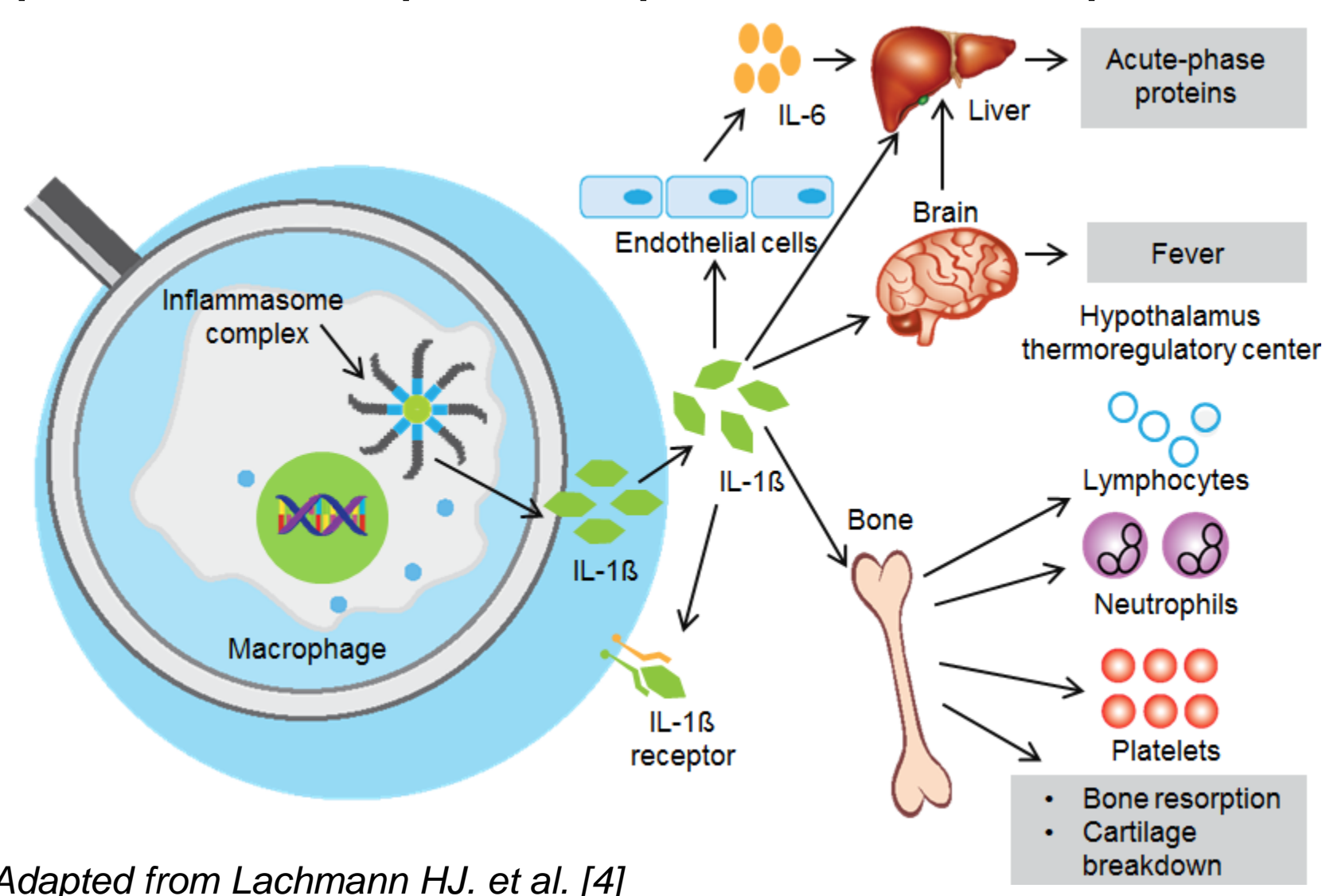
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Canakinumab

Canakinumab (Ilaris®) is a high-affinity fully human monoclonal anti-human interleukin-1 β (IL-1 β) antibody. IL-1 β is recognized as one of the principal pro-inflammatory cytokines, in a variety of inflammatory conditions [1][2].

IL-1 β in AOSD

Dysregulated production of IL-1 β may have a pivotal role in the pathogenesis of AOSD, and anti-IL-1 β treatments such as canakinumab may be an important therapeutic option for those patients.



SJIA and AOSD

- Extensive literature review complemented by biomarkers and gene expression profiling analyses showed superimposable systemic clinical features for systemic juvenile idiopathic arthritis (SJIA) and AOSD.
- Both clinical phenotypes represent a disease continuum ranging from pediatric (SJIA) to older, adult-onset (AOSD) patients [3].
- Canakinumab is already approved for the treatment of SJIA.

Objective

In the absence of any data in AOSD patients, evaluate the pharmacokinetics and exposure-response relationships by age groups to support extrapolation of the efficacy of canakinumab from SJIA to the adult population of AOSD patients.

Conclusions

- Ranges of individual canakinumab exposures were overall comparable across age groups, including young adult SJIA patients and a simulated population of “SJIA-like” adult patients.
- No significant trend with age was seen in baseline values of IL-1 β , DAS28 and CRP.
- DAS28 and CRP responses to treatment and corresponding exposure-response relationships, were comparable across age groups.
- Overall, these analyses supported extrapolation of the efficacy of canakinumab from SJIA to AOSD.

EMA approval

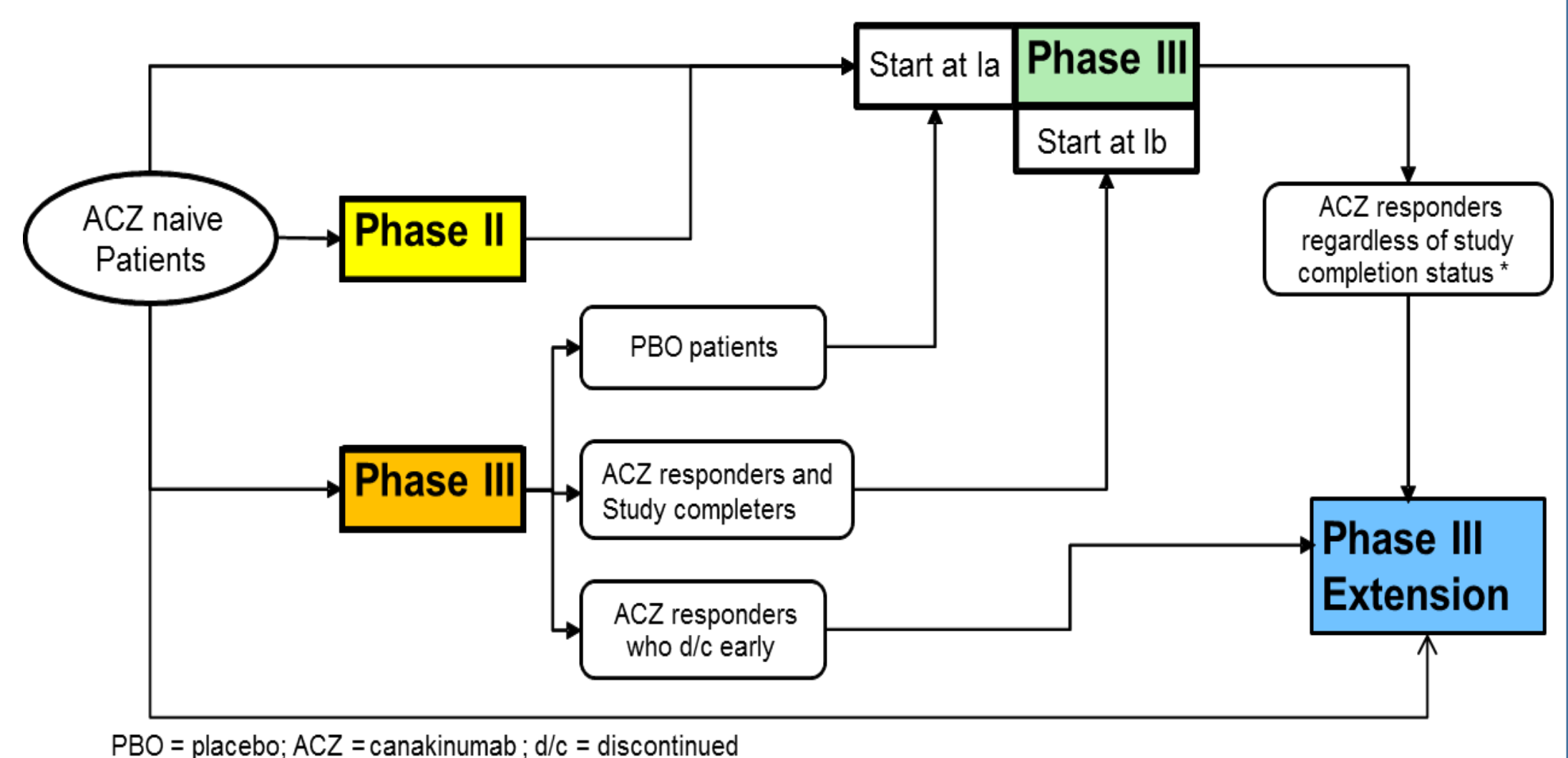
- In August 2016, EMA adopted the decision amending the marketing authorization of canakinumab to extend the scope of the SJIA indication to the treatment of Still's disease (including SJIA and AOSD).
- First time that such extrapolation from pediatric to adult patients was used for label extension (adaptation pathway).

SJIA Clinical Program

- Dose: 4 mg/kg s.c. q4w (with body weight \geq 7.5 kg, maximum dose of 300mg)
- Total of N=324 patients in dataset

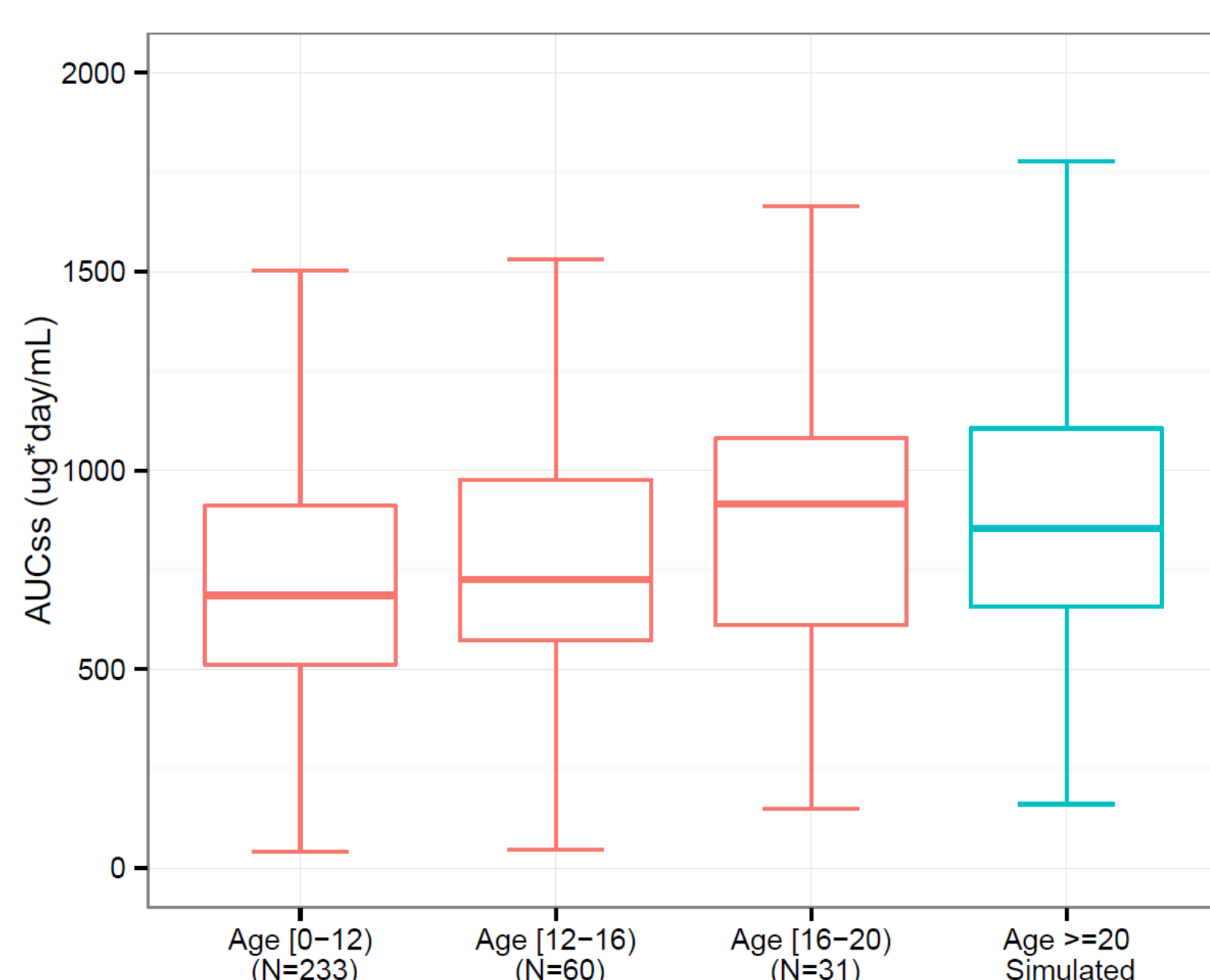
Children	Adolescents	Adults (~AOSD)
[2-12] y.o.	[12-16] y.o.	\geq 16y.o. (max 19 y.o)
N=233	N=60	N=31

- Patients in the clinical program could roll over from study to study
- Age was defined at screening at their time of their first enrolment
- **12-week efficacy** was the longest duration that could be analyzed as pooled data across studies



Simulated exposure

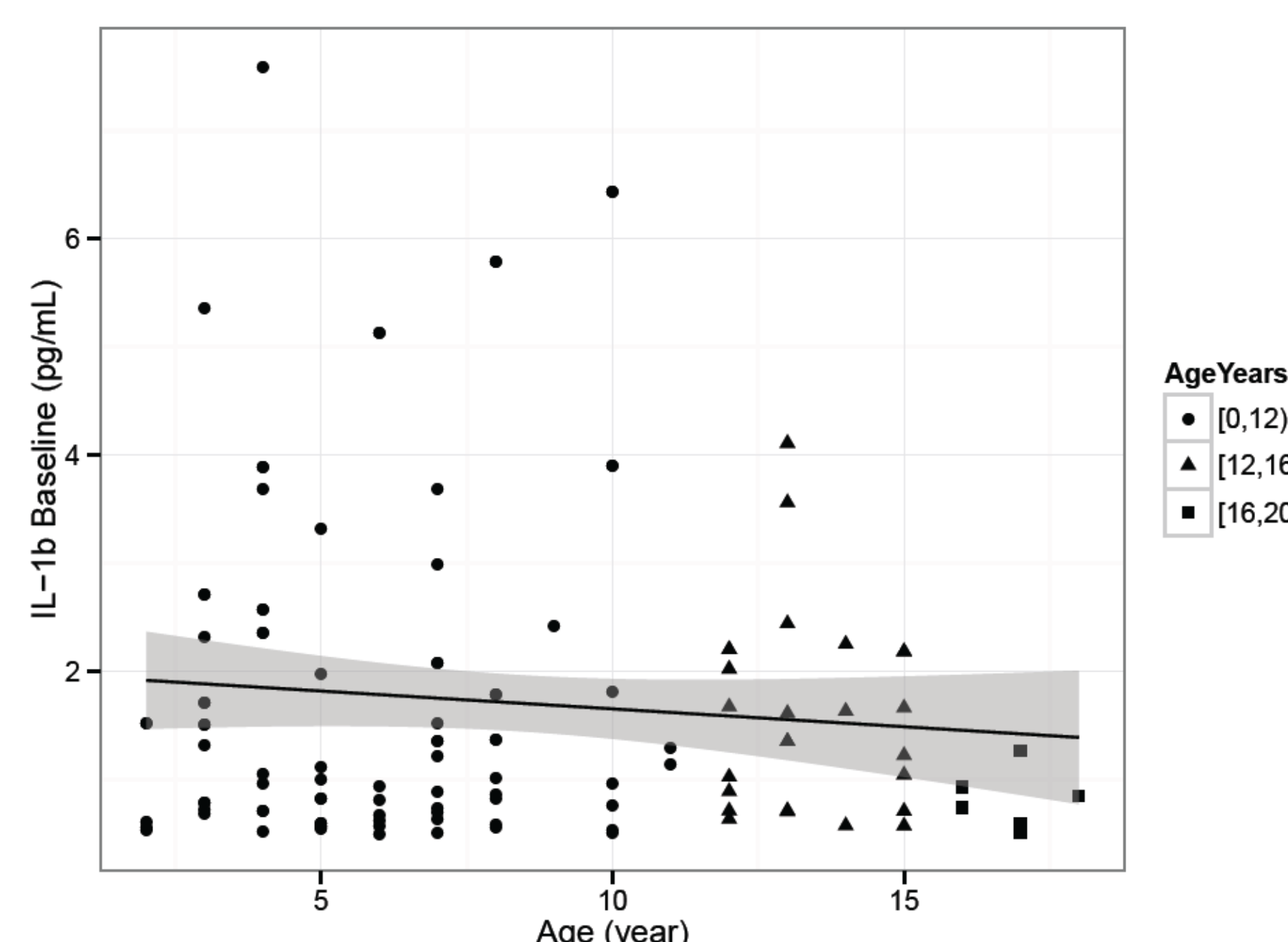
- A population of “SJIA-like” adult patients was simulated using a previously established PK-binding model.
- Predicted exposure in “SJIA-like” adult patients was close to that observed in young adult SJIA patients.



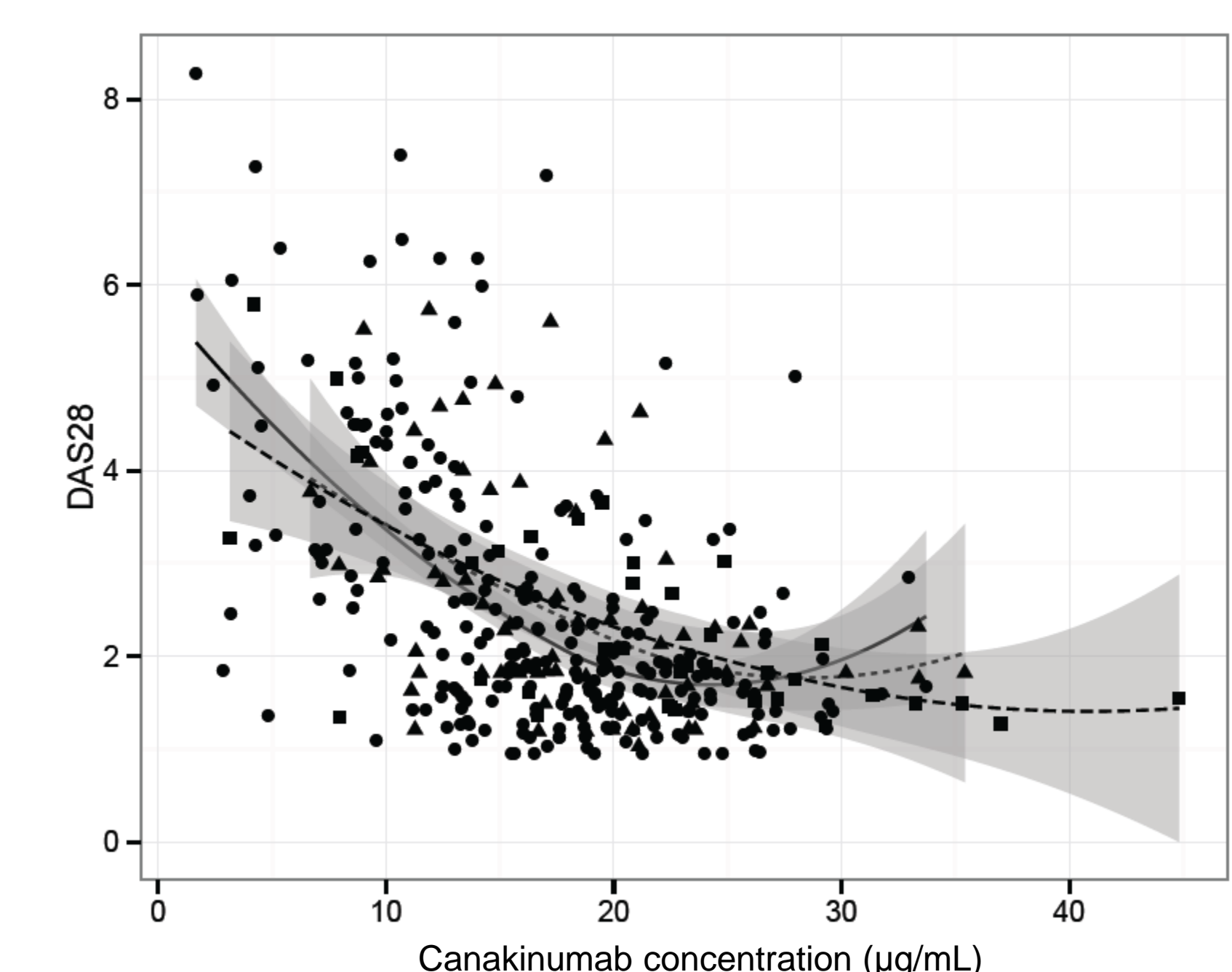
The lower and upper end of ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers the maximum 1.5 IQR.

Extrapolation of exposure-response relationship

- No significant differences in baseline IL-1 β levels is expected between AOSD and SJIA patients.



- Clinical efficacy (DAS28 and CRP) data at week 8 and 12 were pooled.
- Comparable concentration-response relationships were seen across the age groups (DAS28 illustrated below).



The lower and upper end of ends of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represents the median, and the whiskers the maximum 1.5 IQR. Dots represent the outliers.