Similar clinical outcomes in patients with systemic juvenile idiopathic arthritis and adult-onset Still's disease treated with canakinumab: Bayesian and population model-based analyses

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SUPPLEMENTARY MATERIALS

METHODS

Bayesian analysis

- The MAP approach was used for this analysis to account for between-study heterogeneity through a hierarchical random effects model [6,7,9,14]
  - Since the data per study is assumed to be independent, the MAP approach required that the data of every sJIA patient was allocated to a single study to justify their independence. During the sJIA clinical study program, patients could participate in several studies (patients could roll-over from studies β-SPECIFIC 1 to β-SPECIFIC 2, β-SPECIFIC 2 to β-SPECIFIC 3, β-SPECIFIC 1 to β-SPECIFIC 3, and from β-SPECIFIC 3 to β-SPECIFIC 4); no rollover occurred with patients participating in NCT02396212
    - For the MAP analysis, patients were evaluated in the study in which they started
    - In β-SPECIFIC 3, not all the parameters of interest were assessed at week 12. β-SPECIFIC 3 was therefore pooled with β-SPECIFIC 2, as it was the core study from which patients would move directly into the extension
- For the binary data (adapted ACR30 response, absence of fever), the observed response rates were transformed using binomial distribution with the logit link function. For the intercept beta (the mean effect) on the log odds scale, a non-information prior with mean equal to 0 and standard deviation (SD) equal to 2 was used. For the between-study heterogeneity parameter tau (the variability in mean response across studies), a conservative half-normal (0,1) prior distribution was assigned
- For the continuous data (continuous adapted ACR response, number of active joints, CRP), the prior distribution for tau was defined as a half-normal (0, sigma/2), where sigma was the SD assumed for the continuous data,
based on the SD observed in the sJIA studies. The prior distribution for the intercept beta (mean effect) for continuous data was set to a normal distribution with mean 0 and SD equal to sigma

- Forest plot graphs were produced displaying the mean by sJIA study, the meta-analytic prior and the (estimated by the medians and presented as “mean” and “predicted” in the forest plot), and the posterior median for the AOSD study with 95% credible intervals

**Exposure-response analyses**

- Data from continuous efficacy variables were plotted versus the corresponding individual predicted canakinumab concentrations by age groups
  - For consistency with the CONSIDER study, the baseline value was obtained as the average of the Screening and Baseline (day 0) visits for DAS28-CRP
  - Exposure-response boxplots were created using tertiles of individual predicted canakinumab concentrations of patients with AOSD at week 8 and 12, resulting in 3 concentration categories: 0.0–15.8 μg/mL, 15.8–23.8 μg/mL, and 23.8–60.0 μg/mL
- For binary efficacy variables, response rates were calculated for each concentration category (as defined above) and the corresponding CI obtained by means of exact method, ignoring the within-patient correlations between measurements obtained at weeks 8 and 12; missing data were imputed as non-response. Imputation of missing data was not applied to continuous variables.
Supplementary Figure 1. Bayesian analysis of continuous ACR response at week 12 using data from the AOSD study and data borrowed from the pooled sJIA studies. Dashed lines refer to the means (filled triangles) and 95% confidence intervals for each individual study; The solid line “Mean” is the meta-analytic median (dot) for the mean response from sJIA studies and 95% credible interval; The solid line “Predicted” shows the prediction median (dot) derived from the MAP prior distribution from the sJIA studies and the corresponding 95% credible interval; The solid line “CONSIDER” shows the posterior median (dot) from the Bayesian update of the robustified meta-analytic prior from the sJIA data and 95% credible interval.

ACR American College of Rheumatology; AOSD adult-onset Still’s disease; LoM limitation of movement; MAP meta-analytic predictive; sJIA systemic juvenile idiopathic arthritis.
**Supplementary Figure 2.** Individual predicted steady-state metrics of canakinumab exposure for patients with sJIA patients (stratified by age) and AOSD patients. The lower and upper ends of boxes represent the 25th and 75th percentiles of the individual predicted PK metrics for the 3 age subgroups of SJIA patients, the bold line in the box represents the median, and the whiskers extend to 1.5 times the interquartile range. Blue dots represent the individual predicted PK metrics for the AOSD patients. N represents the number of patients.

*AOSD* adult-onset Still's disease; *AUCss* area under the curve; *CMAXss* maximum serum concentration; *CMINss* minimum serum concentration; *PK* pharmacokinetic; *sJIA* systemic juvenile idiopathic arthritis; *ss* steady state; *Yrs* years.
## Supplementary Table 1. sJIA pooled studies and AOSD study overviews

| Study | Description | Patient population | Planned (actual) patients | Treatment duration | Canakinumab dosage | Endpoints | Analyses study was included |
|-------|-------------|---------------------|---------------------------|--------------------|-------------------|-----------|-----------------------------|
| NCT00426218 (13) | Phase II, repeat dose range finding study to assess the clinical safety, tolerability, immunogenicity, pharmacokinetics and efficacy of canakinumab in patients with active sJIA | Male and female patients aged ≥ 4 and ≤ 19 years with active sJIA | 26 (23) | > 24 months | Dose ranging study (0.5–9 mg/kg) | **Primary endpoint:** Safety, tolerability and immunogenicity of subcutaneous canakinumab **Key secondary endpoints:** PK-PD relationships to derive a dose and dosing regimen | Exposure-response |
| β-SPECIFIC 1 (6) (NCT00886769) | Placebo-controlled, single-dose study to assess the efficacy and safety of canakinumab in patients with sJIA | Male and female patients aged ≥ 2 and ≤ 19 years who were naïve to canakinumab | 122 (84) | 29 days | Single 4 mg/kg (up to 300 mg) s.c. injection | **Primary endpoint:** Adapted JIA ACR30 response at day 15 **Key secondary endpoints:** Adapted JIA ACR responses at day 15 and day 29, Physician’s Global Assessment of disease activity (PGA) and CRP level up to day 29 | Bayesian, exposure-response |
| β-SPECIFIC 2 (6) (NCT00889863) | Two-part study to assess the practical impact of tapering corticosteroids and the sustained efficacy of canakinumab in patients with sJIA | Rollover patients from β-SPECIFIC 1 and another Phase II study (NCT00426218), and canakinumab-naïve patients | Part 1: 214 (177) Part 2: 58 (100) | Part 1: 32 weeks Part 2: Event-driven (37 flare events) | Part 1 and 2: 4 mg/kg (up to 300 mg) s.c. Q4W | **Primary endpoints:** Part 1 – Tapering of corticosteroids as per protocol in ≥25% of patients at the end of Part 1c Part 2 – Time to flare **Key secondary endpoints:** Adapted JIA ACR responses in Part 1 and Part 2, proportion of patients able to taper corticosteroids in Part 1 | Bayesian, exposure-response |
| β-SPECIFIC 3 (7) (NCT00881046) | Open-label, active treatment extension study of canakinumab in patients with sJIA who participated in studies β-SPECIFIC 2 and/or β-SPECIFIC 1 | Patients who participated in studies β-SPECIFIC 2 and/or β-SPECIFIC 1 who achieved an adapted JIA ACR30 response 15 days after the initial dose of canakinumab but lost this response after day 15, and canakinumab-naïve patients | (144) | Up to 2 years (until β-SPECIFIC 4 was ready at the site) | 4 mg/kg s.c. (up to 300 mg) or 2 mg/kg s.c. (up to 150 mg) Q4W | **Primary endpoints:** Adapted JIA ACR responses, proportion of patients able to taper corticosteroids, the proportion of patients achieving clinical remission or inactive disease, and Juvenile Arthritis Disease Activity Score 71 (JADAS) up to five years | Bayesian, exposure-response |
| Study                        | Description                                                                 | Patient population                                                                 | Planned (actual) patients | Treatment duration | Canakinumab dosage                  | Endpoints                                                                 | Analyses study was included |
|-----------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------------|--------------------|-------------------------------------|---------------------------------------------------------------------------|----------------------------|
| **Studies in sJIA (cont’d)** |                                                                             |                                                                                     |                           |                    |                                     |                                                                           |                            |
| β-SPECIFIC 4 (9) (NCT02296424) | Open-label, two-part study to assess the efficacy and safety of canakinumab in patients with sJIA | Patients with sJIA receiving canakinumab with inactive disease at the last visit in study β-SPECIFIC 3, and canakinumab-naive patients | Part 1: 166 patients Part 2: 76 patients from Part 1 | 216 weeks         | 4 mg/kg (up to 300 mg) Q4W s.c.; then Treatment group 1: 2 mg/kg Q4W s.c. (followed by taper to 1 mg/kg s.c. Q4W and drug discontinuation if appropriate) Treatment Group 2: 4 mg/kg Q8W s.c. (followed by taper to 4 mg/kg s.c. Q12W and drug discontinuation if appropriate) | Primary endpoint: ≥ 40% of patients were able to maintain clinical remission for ≥ 24 consecutive weeks on either a reduced canakinumab dose (2 mg/kg Q4W) or a prolonged dose interval regimen (4 mg/kg Q8W) | Bayesian                     |
| NCT02396212 (8)             | Open-label, single-arm, active-treatment, efficacy and safety study of canakinumab administered for at least 48 weeks in Japanese patients with sJIA | Japanese patients aged ≥ 2 and ≤ 20 years who were canakinumab-naive                 | 19 (19)                   | 48 weeks           | 4 mg/kg (up to 300 mg) s.c. Q4W     | Co-primary endpoints: Adapted JIA ACR30 response at week 8, proportion of patients able to taper corticosteroids at week 28 | Bayesian                     |
| **Study in AOSD**            |                                                                             |                                                                                     |                           |                    |                                     |                                                                           |                            |
| CONSIDER (NCT02204293) (4)   | Phase II, investigator-initiated multicenter, placebo-controlled study to investigate the efficacy and safety of canakinumab in patients with AOSD and active joint involvement | Patients aged 18–75 years with AOSD and active joint involvement (tender and swollen joint counts of ≥4 each) | Part 1: Baseline to week 12; Part 2: Week 12 to 24 | 68 (36)            | Part 1: 12 weeks Part 2: Responders at week 12 continue Randomized treatment for 12 weeks up to week 24. Non responders at week 12: Canakinumab patients exit study, placebo patients switch to open label canakinumab 4 mg/kg Q4W LTE: 24 months (open label canakinumab 4 mg/kg Q4W) | Part 1 and Part 2: 4 mg/kg (up to 300 mg) or placebo Q4W. LTE: 4 mg/kg optional down-titration to 2 mg/kg Q4W | Primary endpoint (Part 1): Proportion of patients with an improvement > 1.2 in DAS28 (ESR) at week 12 | Bayesian, exposure-response |

ACR American College of Rheumatology; AOSD adult-onset Still’s disease; CRP C-reactive protein; DAS28 [ESR/CRP] Disease Activity Score 28-ESR/CRP; ESR erythrocyte sedimentation rate; EULAR European League Against Rheumatism; HAQ Health Assessment Questionnaire; JIA juvenile idiopathic arthritis; LoM limitation of movement; LTE long-term extension; PD pharmacodynamics; PK pharmacokinetic; s.c. subcutaneous; SF-36 36-Item Short Form Survey; sJIA systemic juvenile idiopathic arthritis; Q4W every 4 weeks; Q8W every 8 weeks; Q12W every 12 weeks.
**Supplementary Table 2.** Adaptations to the ACR response parameters for the Bayesian analysis

| Assessment                                      | sJIA pooled studies (6–9)                                                                 | AOSD study (4)                                                        | Adapted ACR response                                                                                   |
|-------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Number of joints with active arthritis          | 75/73 (β-SPECIFIC 4 and NCT02396212) and 78/76 (β-SPECIFIC 1, β-SPECIFIC 2 and β-SPECIFIC 3) joints with pain or tenderness or with swelling available | 68/66 joints with pain or swelling available Part of inclusion criteria for AOSD study: ≥ 4 painful and ≥ 4 swollen joints at screening and baseline | The joints assessed in the AOSD study were used for the sJIA pool for consistency (68/66 joints); LoM was not included in the active joint assessment due to differences in its collection between the studies. Therefore, active joints were defined as joints with swelling or pain |
| Physician Global Assessment (PGA)               | Visual analog scale (VAS) 0–100 mm scale                                                  | Numerical rating scale (NRS) 0–10 scale                               | PGA score from the AOSD study was multiplied by 10                                                                 |
| Patient/Parent Global Assessment (PtGA)         | CHAQ© included as PtGA on VAS 0–100 mm scale                                             | NRS 0–10 scale                                                       | Parents, not the patients, completed the PtGA for younger patients, whereas for patients ≥ 18 years of age, this was self-assessed PtGA score from the AOSD study was multiplied by 10 |
| Functional ability (CHAQ©/HAQ-DI)               | Assessed using CHAQ©                                                                    | Assessed using HAQ-DI                                                | Due to the differences in functional ability questionnaires, CHAQ/HAQ-DI was not included in the Bayesian inference of single parameters, but was used in the calculation of the adapted ACR30 response |
| CRP                                             | Studies NCT02396212, β-SPECIFIC 2, β-SPECIFIC 3 and β-SPECIFIC 1 had an eligibility criterion of CRP > 30 mg/L (normal range < 10 mg/L) and β-SPECIFIC 4 included CRP as one of the criterion to establish active disease | Collected but no eligibility criterion based on CRP                  | Used upon standardization using mg/L                                                                 |
| Absence of intermittent fever                   | Available - absence of intermittent fever in the sJIA studies was clearly defined as oral or rectal body temperature ≤ 38°C in the preceding week | Available - fever was not defined specifically in the AOSD study, which only referenced the Yamaguchi criteria in which fever attacks are defined as 39°C, with a duration > 1 week | The analysis plan for the AOSD study defined missing fever data as a non-response (i.e., fever present); this method was used in the sJIA population for the analysis |

ACR American College of Rheumatology; AOSD adult-onset Still’s disease; CHAQ Childhood Health Assessment Questionnaire; CRP C-reactive protein; HAQ-DI Health Assessment Questionnaire Disability Index; LoM limitation of movement; sJIA systemic juvenile idiopathic arthritis.
Supplementary Table 3. Response to canakinumab treatment according to adapted ACR30 criteria, reduction in number of active joints, and CRP level at week 12 for sJIA pooled group and AOSD group

|                              | sJIA pooled group | AOSD group |
|------------------------------|-------------------|------------|
|                              | 2 to < 12 years   | 12 to < 16 years | ≥ 16 years |                               |
| ACR30 response, n (%)        | 147 (65.9)        | 35 (64.8)  | 20 (87.0)  | 11 (64.7)                      |
|                              | N = 223           | N = 54     | N = 23     | N = 17                         |
| Median reduction in number of | -4 (-66, 4)       | -7 (-66, 4)| -9 (-42, -2) | -5 (-15, 5) |
| active joints from baseline, | N = 175           | N = 43     | N = 21     | N = 17                         |
| (range)                      |                   |            |            |                               |
| Median CRP level, mg/L (range)| 5.0 (0, 386.7)    | 4.6 (0, 458.3) | 4.5 (0.5, 110.6) | 6.7 (N/A) |
|                              | N = 243           | N = 68     | N = 28     | N = 17                         |

*ACR* American College of Rheumatology; *AOSD* adult-onset Still’s disease; *CRP* C-reactive protein; *N/A* not applicable; *sJIA* systemic juvenile idiopathic arthritis.