CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319Orig1s085, 086, 087

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA	125319/85, 86, 87
Submission Date:	3/23/2016
Brand Name	Ilaris®
Submission Type	Efficacy Supplement
Generic Name	Canakinumab
OCP Reviewer	Jianmeng Chen, M.D., Ph.D.
Team Leader	Anshu Marathe , Ph.D.
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OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Pulmonary, Allergy and Rheumatology Products (DPARP)
Sponsor	Novartis
Formulation; Strength(s); Administration Route	Powder for Solution for Injection; 150 mg; Subcutaneous (SC) injection
Approved Indication	Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), systemic juvenile idiopathic arthritis(SJIA)
Proposed Indication	TRAPS, HIDS/MKD, and FMF patients
Approved Dosage Regimen	150 mg for CAPS patients with body weight greater than 40 kg, and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg; for children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. ILARIS is administered every eight weeks 4 mg/kg (with a maximum of 300mg) administered every 4 weeks for SJIA patients with a body weight greater than or equal to 7.5 kg.
Proposed Dosage Regimen	>40kg, 150mg, <40kg, 2mg/kg SC Q4W; up titration to 300 mg and 4mg/kg SC Q4W.

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1. Executive Summary

1.1 Recommendations

From a Clinical Pharmacology perspective, the application is acceptable.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Canakinumab is a high-affinity human monoclonal antibody against interleukin-1β (IL- 1β), developed to bind and neutralize the excess IL-1β produced in some inflammatory diseases. ILARIS® is currently approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older (including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)) and for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older. Three efficacy supplements (S85, S86, S87) were submitted to the BLA125319 to seek approval for the additional indications [tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and familial Mediterranean fever (FMF)] for ILARIS® (canakinumab) in adults and children 2 years of age and older.

The proposed dose is "*150 mg for TRAPS, HIDS/MKD, and FMF patients with body weight greater than 40 kg and 2 mg/kg for patients with body weight less than or equal to 40 kg.* [redacted] (b) (4)

Canakinumab Dose Selection

The dose selection for Phase 3 study is supported by the results of the dose- ranging Phase II studies. A dosing schedule of 150 mg or 2 mg/kg sc q4w was demonstrated to be effective in 3 open - label Phase 2 studies in crFMF and TRAPS patients (Studies DTR01, D2204 and D2203). In a Phase 2 study, a higher dose with a longer interval (300 mg or 4 mg/kg q6w) was demonstrated to be effective in HIDS/MKD patients (Study D2402).

The results of the Phase 3 study (Study N2301) showed a statistically significant benefit of canakinumab compared over placebo with respect to the primary endpoint, the proportion of complete responders in crFMF, HIDS/MKD and TRAPS patients (See section 2.2.1 and medical review for details). However, due to a complicated titration based study design, the exposure-response analyses provided limited information regarding dose selection, and the benefit of dose up-titration (see section 2.2.6).

Canakinumab PK

The exposure of canakinumab was not influenced by disease. The PK parameters of Canakinumab remain constant with time and are dose proportional. In patients with TRAPS, HIDS/MKD, and crFMF:

- The PK of canakinumab is linear and the exposure parameters, AUC and Cmax, increased in proportion to dose over the dose range from 150 mg to 300 mg (or 2 mg/kg to 4 mg/kg in patients ≤40kg) when administered as a subcutaneous injection.

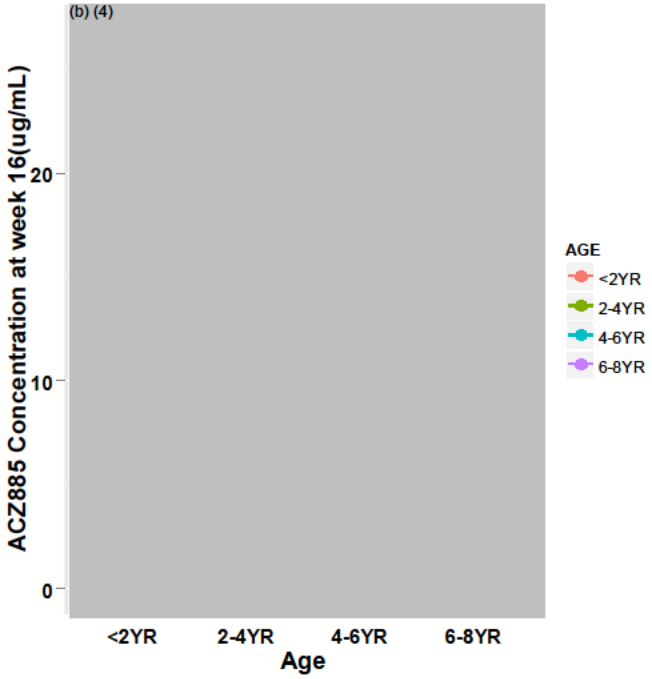
- Serum clearance of canakinumab and its volume of distribution were dependent on bodyweight at baseline. For a typical 70 kg person, the estimated clearance of canakinumab was 0.16 L/day. The corresponding volume of distribution at steady state was 5.82 L. The half-life (T1/2) of canakinumab was approximately 25.2 days.

- The key pharmacokinetic parameters of canakinumab such as clearance and volume of distribution were not impacted by age (≥ 2 yrs) and albumin level at baseline after correction for the subject's bodyweight.

- Pop PK analysis suggested that exposure parameters (such as AUC and Cmin) were comparable across age groups (≥2 yrs) following subcutaneous administration of canakinumab 2 mg/kg or 4 mg/kg every 4 weeks in Periodic Fever Syndrome (PFS) patients with body weight ≤40kg.

Canakinumab exposure in pediatric patients younger than 2 years of age

The exposure of canakinumab in pediatric patients younger than 2 years of age was assessed in response to a clinical consult. Since observed serum concentration of canakinumab in PFS patients younger than 2 years of age was not available (Table 9), pediatric data from previous submissions in CAPS and SJIA was utilized. The observed Ctrough values of canakinumab at Week 16 for CAPS and SJIA patients younger than 2 years were collected and compared with those from other age groups (2 to < 4 years, 4 to < 6 years and 6 to < 8 years) as shown in Figure 1. The results showed the observed Ctrough values of canakinumab were comparable across age groups. It appears that the PK of canakinumab in patients younger than 2 years is not significantly different from those older than 2 years under the same weight based dosing regimen (see section 2.3.2 for details). The numbers of CAPS and SJIA patients in <2 years group, 2 to < 4 years group, 4 to < 6 years group and 6 to <8 years group are 5, 9, 10 and 7 respectively. Note that there is only 1 subject who is less than 6 months old. For additional information regarding safety and disease progression in pediatric patients younger than 2 years, see medical review.



Note: Circles represent individual observed concentration at week 16 for each subject from the pooled database of CAPS and sJIA patients. The solid line represents the median concentration value for each age group (0.2 to 7 years old). The numbers of CAPS and SJIA patients in <2 years group, 2 to < 4 years group, 4 to < 6 years group and 6 to <8 years group are 5, 9, 10 and 7 respectively.

Figure 1. Observed Ctrough values (Dose normalized) at week 16 across ages in CAPS and SJIA population

(Source: The Reviewer's analysis)

The clinical service formulation is bridged to the current-marketed formulation

For development of the Periodic Fever Syndrome (PFS) indications TRAPS, HIDS/MKD, and crFMF, the currently marketed presentation (powder in vial) was used in the four Phase II Periodic Fever Syndromes (TRAPS, HIDS/MKD, and crFMF) trials. Solution for injection in vial is a new presentation (b) (4) and was used in the Phase III study N2301. (b) (4) Therefore, the presentation (solution in vial) used in the phase 3 study was bridged to the current marketed presentation (powder in vial).

2 Question-Based Review (QBR)

2.1 General Attributes

2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Chemistry and Physico-Chemical Properties: Canakinumab (INN) is a fully human monoclonal antibody (IgG1/κ) directed against human interleukin-1 beta (IL-1β), developed to bind and neutralize the excess IL-1β produced in some inflammatory diseases. It does not cross-react with human IL-1α or with IL-1 receptor antagonist (IL-1Ra). Canakinumab prevents the binding of endogenous human IL-1β to its cognate receptor on the surface of its target cells, thus functionally neutralizing its pro-inflammatory bioactivity in diseases like Muckle-Wells Syndrome.

It is comprised of two 447-(or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145k Daltons. Both heavy chains of ACZ885 contain N-linked oligosaccharide chains attached to the protein backbone at Asn(298).

Formulation: Sterile, single-use 6-mL, glass vial containing 180 mg of ILARIS as a lyophilized powder for reconstitution.

2.1.2. What are the approved therapeutic indication, dosage and route of administration?

Indication:
ILARIS® is currently approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older (including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)) and for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

Dosage and Route of Administration:

- 150 mg for CAPS patients with body weight greater than 40 kg and 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Administer subcutaneously every 8 weeks.

- 4 mg/kg (with a maximum of 300 mg) for SJIA patients with a body weight greater than or equal to 7.5 kg. Administer subcutaneously every 4 weeks.

- The proposed dose in this submission for the new indications is "*150 mg for TRAPS, HIDS/MKD, and FMF patients with body weight greater than 40 kg and 2 mg/kg for patients with body weight less than or equal to 40 kg.* [redacted]

(b) (4)

2.2 General Clinical Pharmacology

2.2.1. What are the clinical pharmacology and clinical trials used to support the proposed claims?

Three efficacy supplements were submitted to the BLA125319 to seek approval for the additional indications for ILARIS® (canakinumab) in adults and children 2 years of age and older. Phase II and III studies conducted primarily to determine the appropriate canakinumab dosing regimen and to establish the efficacy and safety of canakinumab in patients with the Periodic Fever Syndromes TRAPS (Supplement 85), HIDS/MKDS(Supplement 86), and crFMF(Supplement 87) and also included evaluation of canakinumab serum concentrations.

The supplements contain the following clinical pharmacology studies in addition to the clinical studies in PFS patients (Table 1):

- Updated popPK (ACZ885n-popPK) and exposure-response analysis (ACZ885N-PKPD) based on study N2301.
- Study 2104 to demonstrate bioequivalence (b) (4)

Three open - label Phase 2 studies in crFMF and TRAPS patients (Studies DTR01, D2204 and D2203) were conducted where a dose of 150 mg or 2 mg/kg sc q4w was shown to be effective. In a Phase 2 study, a higher dose with a longer interval (300 mg or 4 mg/kg q6w) was demonstrated to be effective in HIDS/MKD patients (Study D2402). See Table 2 and medical review for details.

Table 1. List of clinical studies

Study	Phase	Design and Objectives	Dose Regimen	Age	Total number of subjects
D2203	II	OL, efficacy, S&T, Immunogenicity and PK/PD in TRAPS	150 mg (2 mg/kg for ≤ 40 kg) sc q4w, option of a single up-titration of 300 mg (4 mg/kg for ≤ 40 kg) sc at Day 8	7 to 77	20
D2402	II	OL, efficacy, S&T, Immunogenicity and PK/PD in HIDS/MKD	300 mg (4 mg/kg for ≤ 40 kg) sc q6w, option to up-titrate to 450 mg sc q6w	5 to 29	9
D2204	II	OL, efficacy, S&T, Immunogenicity and PK/PD in crFMF	150 mg (2 mg/kg for ≤ 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for ≤ 40 kg) sc q4w	7 to 15	7
DTR01	II	OL, efficacy, S&T, Immunogenicity and PK/PD in crFMF	150 mg (2 mg/kg for ≤ 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for ≤ 40 kg) sc q4w	12 to 34	9
N2301	III	DB, R, PC, efficacy, S&T, Immunogenicity and PK/PD in TRAPS, HIDS/MKD, crFMF	EPOCH II: 150 mg (2 mg/kg for ≤ 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for ≤ 40 kg) sc q4w	2 to 76	TRAPS (46), HIDS/MKD (72), crFMF (63)

PC=placebo controlled; OL=open label; R=Randomized; DB=Double blind; S&T=safety and tolerability; PK=pharmacokinetics; PD=pharmacodynamics

(Source: Table 2-1, Summary of Clin Pharm)

Table 2. Efficacy summary of open label, uncontrolled phase 2 studies

Study	Indication	Dose regimen	Efficacy summary
D2203	TRAPS N=20	150 mg (2 mg/kg for < 40 kg) sc q4w, option of a single up titration of 300 mg (4 mg/kg for < 40 kg) sc at Day 8	**19/20(95%)** patients achieved a complete or almost complete response on Day 15
D2402	HIDS/MKD N=9	300 mg (4 mg/kg for < 40 kg) sc q6w, option to up-titrate to 450 mg sc q6w	**9/9(100%)** patients achieved primary outcome. The median number of flares per patient decreased from 5 (range: 3-12) during the 6-month historical period to 0 (range: 0-2) during the 6-month treatment period
D2204	CrFMF N=7	150 mg (2 mg/kg for < 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for < 40 kg) sc q4w	**6/7(85.7%)** patients achieved ≥50 % reduction in attack rate in the 3 month treatment phase
DTR01	CrFMF N=9	150 mg (2 mg/kg for < 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for < 40 kg) sc q4w	**9/9(100%)** patients achieving ≥50 % reduction in attack rate in the 3 month treatment phase

(Source: Reviewer summary)

The clinical data pivotal to the current application is derived from study N2301, a double blind, randomized, placebo controlled study in patients with TRAPS, HIDS/MKD, or cfFMF. A total of 181 patients, with 56 pediatric patients (2 to 18 years) were randomized to treatment.

The phase 3 study (N2301) consists of 3 randomized cohorts (crFMF, HIDS/MKD and TRAPS) and 4 study epochs. Epoch 2 is a randomized treatment epoch of 16 weeks (patients were randomized to canakinumab 150 mg Q4W or to placebo) which provided efficacy and safety data in double-blind placebo-controlled parallel-arm setting. The patients received the first sc injection at baseline and returned to the site every 4 weeks to receive injection for total of 16 weeks. Between Day 8 and 28, if experienced persistent "mild", "moderate", or "severe" disease activity for both treatment and placebo arms, the patient had the option to have add-on sc injection of canakinumab (150 mg for patients > 40 kg or 2 mg/kg for patients ≤ 40 kg). Afterwards, the patients randomized to canakinumab 150 mg (or 2 mg/kg for patients ≤ 40 kg) Q4W who received add-on injection received 300 mg Q4W (or 4 mg/kg for patients ≤ 40 kg), and the patients randomized to placebo arm received add-on injection received 150 mg Q4W (or 2 mg/kg for patients ≤ 40 kg). Overall, approximately one-third of HIDS/MKD and TRAPS patients and 16% of crFMF patients required up-titration to canakinumab 300 mg q4w between Day 8 and 28 for resolution of their index flare.

Canakinumab provided statistically significant benefit over placebo with respect to the primary endpoint, the proportion of complete responders as defined by patients who resolved their index disease flare at Day 15 and had no new disease flare over 16 weeks of treatment from the time of resolution of index flare (Table 3).

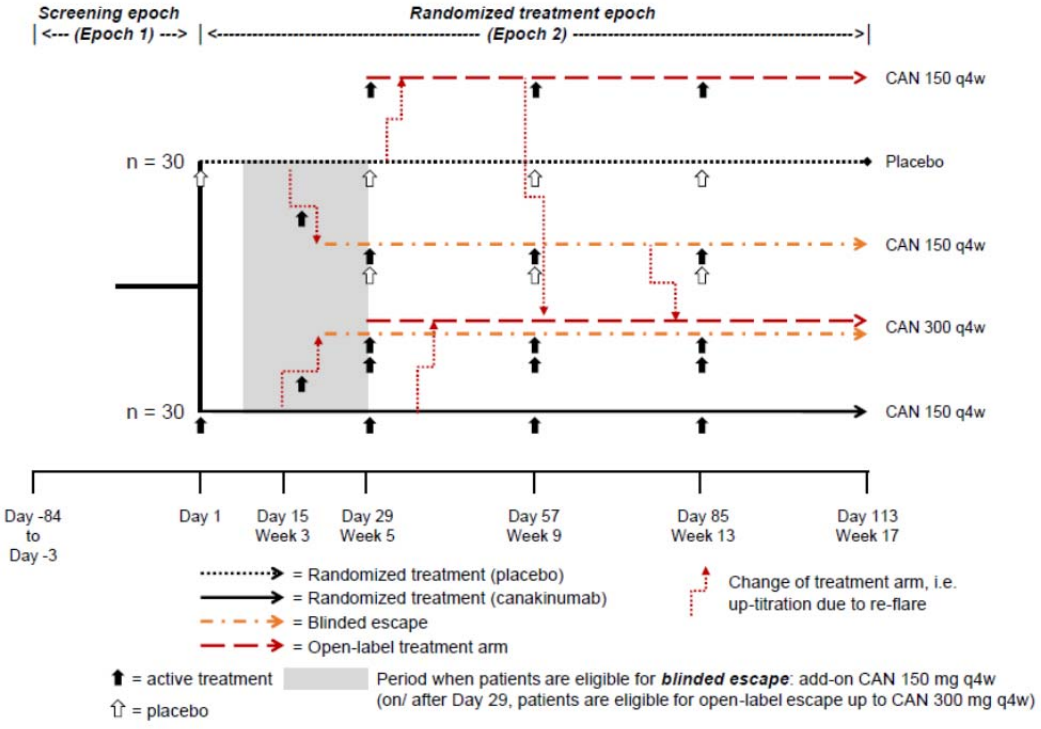


Figure 2. Study design for N2301 screening (Epoch 1) and randomized treatment (Epoch 2)
(Source: Figure 9-2, CSR N2301)

Table 3. Primary analysis: comparison between treatment groups for the proportion of responders after 16 weeks by cohort (Full analysis set)

	ACZ885 150 mg q4w		Placebo		Treatment comparison		
Cohort	n/M (%)	95% CI	n/M (%)	95% CI	Risk difference (95% CI)	Odds Ratio (95% CI)	One-sided p-value
crFMF	19/31 (61.29)	(42.19, 78.15)	2/32 (6.25)	(0.77, 20.81)	0.55 (0.31, 0.73)	23.75 (4.38, 227.53)	<0.0001*
HIDS	13/37 (35.14)	(20.21, 52.54)	2/35 (5.71)	(0.70, 19.16)	0.29 (0.06, 0.50)	8.94 (1.72, 86.41)	0.0020*
TRAPS	10/22 (45.45)	(24.39, 67.79)	2/24 (8.33)	(1.03, 27.00)	0.37 (0.08, 0.61)	9.17 (1.51, 94.61)	0.0050*

n=number of responders; M=number of evaluable patients; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

(Source: Table 4-1, clinical overview)

2.2.3. What are the PK characteristics of Canakinumab in PFS patients?

The pharmacokinetics characteristics of Canakinumab in healthy volunteers, CAPS, and SJIA patients were previously reviewed by Dr. Srikanth Nallani, Dr. Hao Zhu and Dr. Liang Zhao in the original BLA submission and supplement 062.

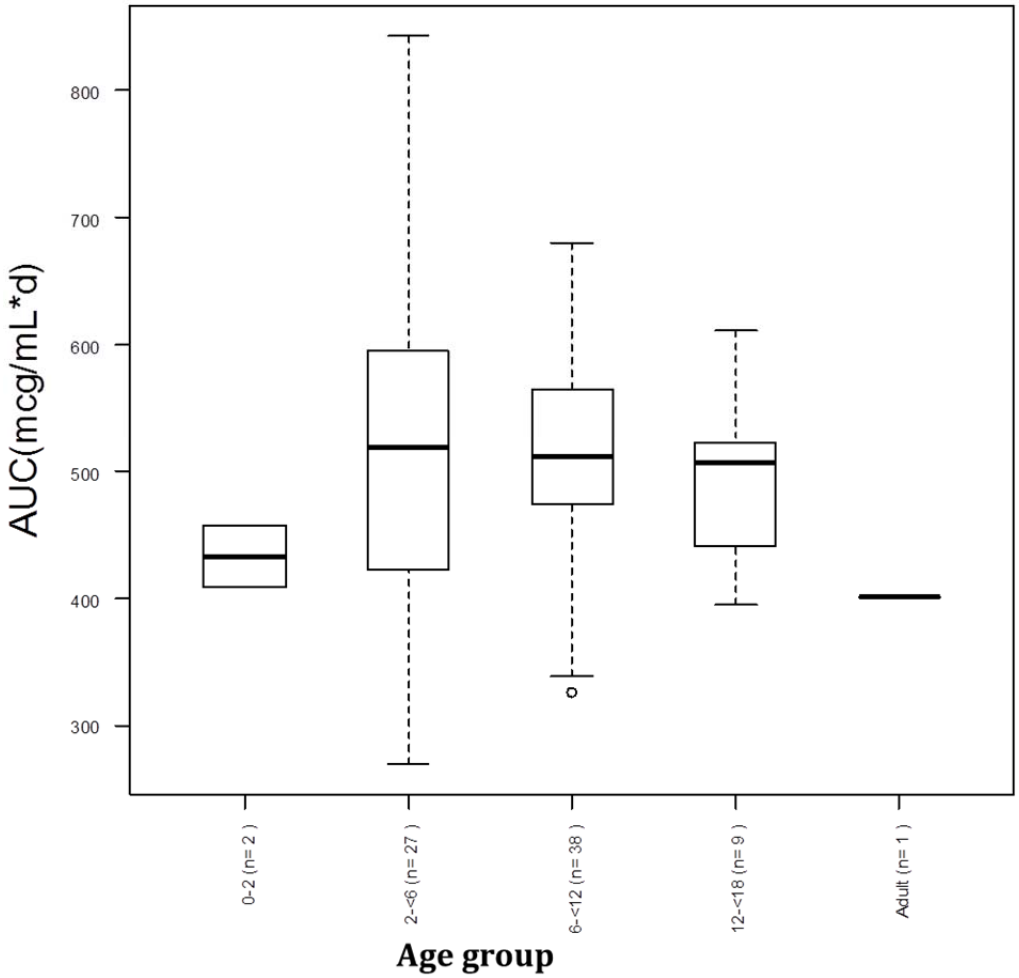
In this current submission, it was found that canakinumab pharmacokinetics was similar across different disease population including, CAPS, SJIA and PF Syndromes when comparing their bodyweight-normalized clearance.

- The PK of canakinumab was linear with no evidence of time dependency in clearance in patients with TRAPS, HIDS/MKD, and crFMF.

- Serum clearance of canakinumab and its volume of distribution were dependent on bodyweight at baseline. The estimated serum clearance of canakinumab was 0.16L/day in patients with TRAPS, HIDS/MKD, and crFMF (with typical bodyweight of 70 kg). The corresponding volume of distribution at steady state was 5.82 L. The half-life (T1/2) of canakinumab in patients with TRAPS, HIDS/MKD, and crFMF was approximately 25.7 ± 6.5 days.

- The key pharmacokinetic parameters of canakinumab such as clearance and volume of distribution were not impacted by age above 2 years old and albumin level at baseline in patients with TRAPS, HIDS/MKD, and crFMF after correction for the subject's bodyweight (see section 2.2.5, albumin and age are not covariates in the final PK model).

- Pop PK analysis suggested that exposure parameters (such as AUC and Cmin) were comparable across age groups following subcutaneous administration of canakinumab 2 mg/kg or 4 mg/kg every 4 weeks in PFS patients with body weight ≤40kg (Figure 3).



**Serum concentration of canakinumab was not collected in the two patients <2 yrs (ID 16053, 16086). Only IL-1ß information was collected for these two patients in the study. The estimated AUCtau is based on model prediction.*

Figure 3. Estimated steady state AUCtau in PFS patients ≤40kg, by age group, under 2mg/kg dose

(Source: Reviewer analysis based on sponsor's data

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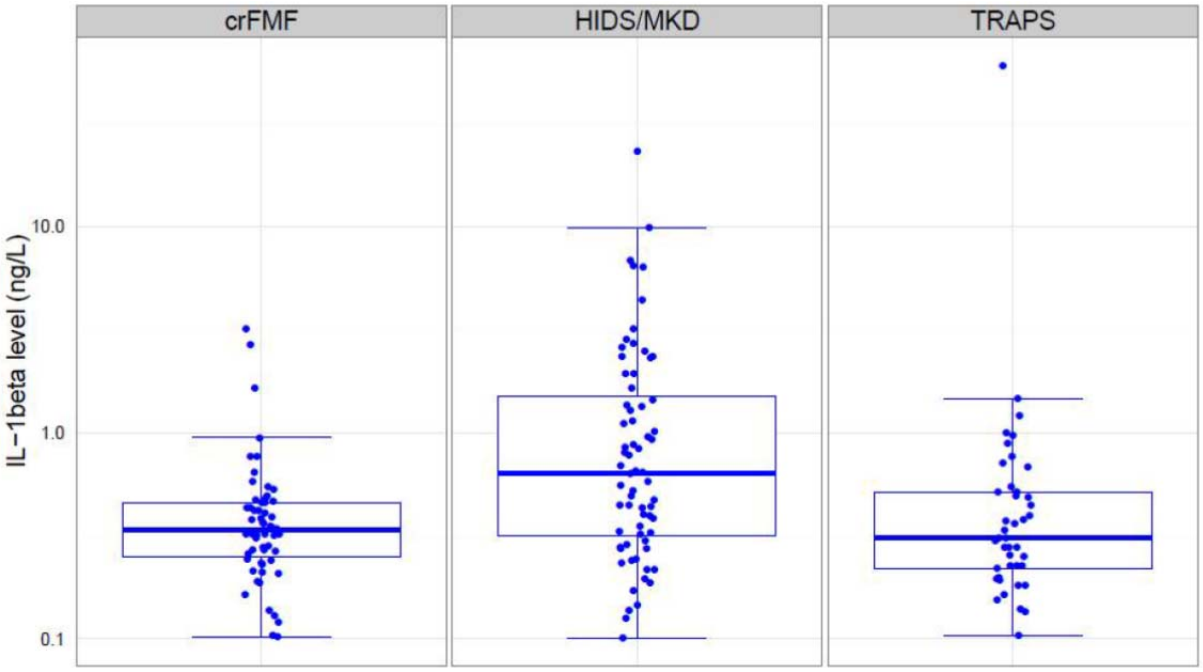
2.2.4. What are the PD characteristics of canakinumab in patients?

Canakinumab binding to human IL-1β neutralizes its bioactivity and results in the formation of a canakinumab-IL-1β complex. Since the complex is cleared slower than the free IL-1β, an increase in total IL-1β indicating successful binding is observed in crFMF, HIDS/MKD and TRAPS patients in Study N2301 (Figure 5).

Baseline IL-1β levels were generally higher in HIDS/MKD patients (Figure 4). There was an observed separation between the 150 mg (2 mg/kg) and 300 mg (4 mg/kg) dose levels of median IL-1β levels

(Figure 5). With the small sample size, variability in time to up titration and up-titration being driven by clinical responsiveness, direct assessment of the doses against each other is not appropriate in this trial.

Canakinumab treatment was associated with a decrease of IL-1β-induced downstream mediators including the acute phase proteins CRP and SAA (Figure 6, Figure 7). This adds to the evidence that canakinumab neutralizes the activity and down - regulates the production of IL-1β in vivo.



The lower and upper end of boxes represent the 25th and 75th percentiles of distribution, the bold line in the box represent the median, and the whiskers 5th and 95th percentiles of the data. Dots represent the observed IL-1β concentrations.
Source: [SCP-Figure 3-4]

Figure 4. Total IL-1beta level at randomization visit

(Source: Figure 3-1, Clinical overview)

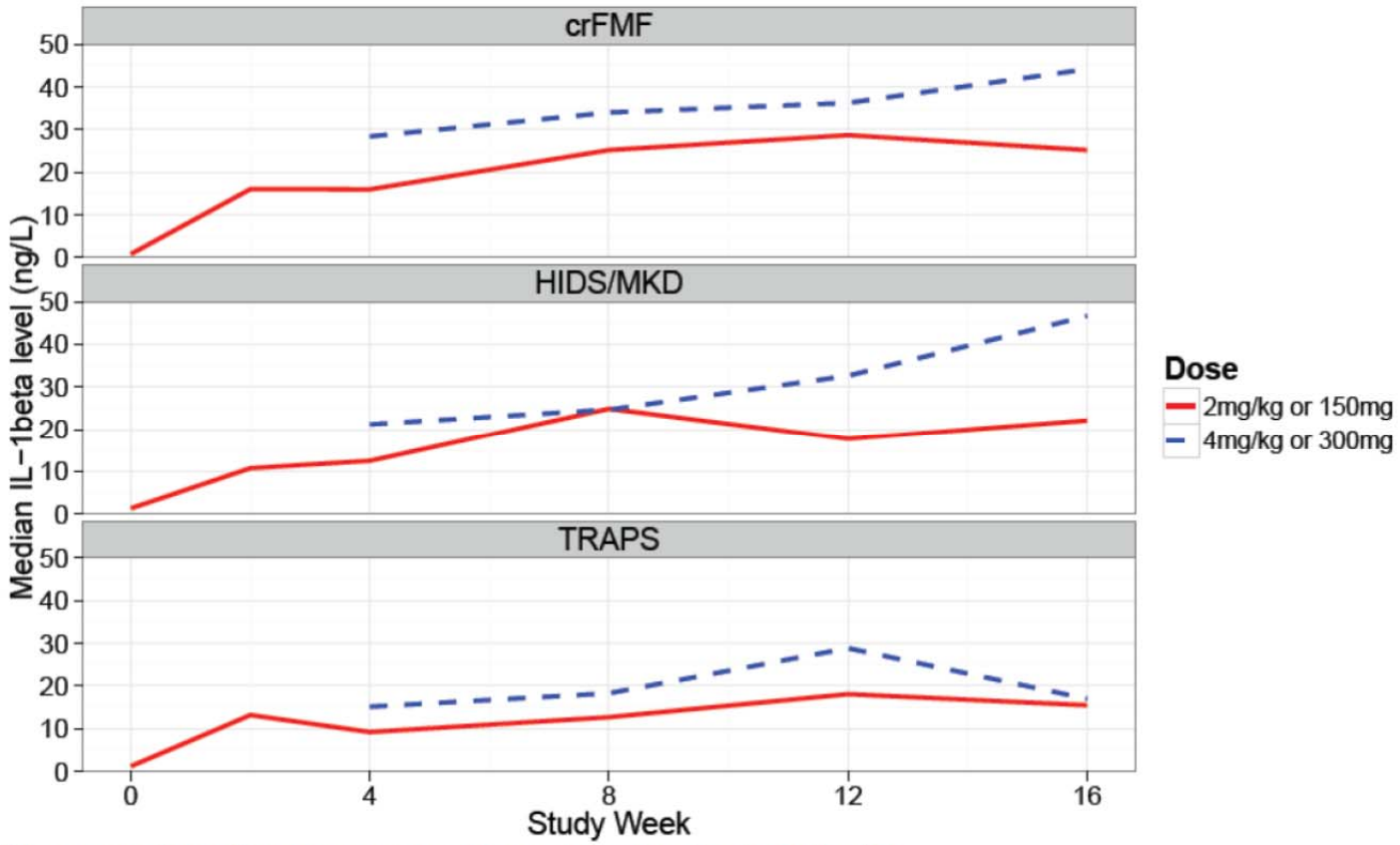


Figure 5. Total IL-1beta median level over time for initially randomized canakinumab patients

(Source: Figure 3-2, Clinical overview)

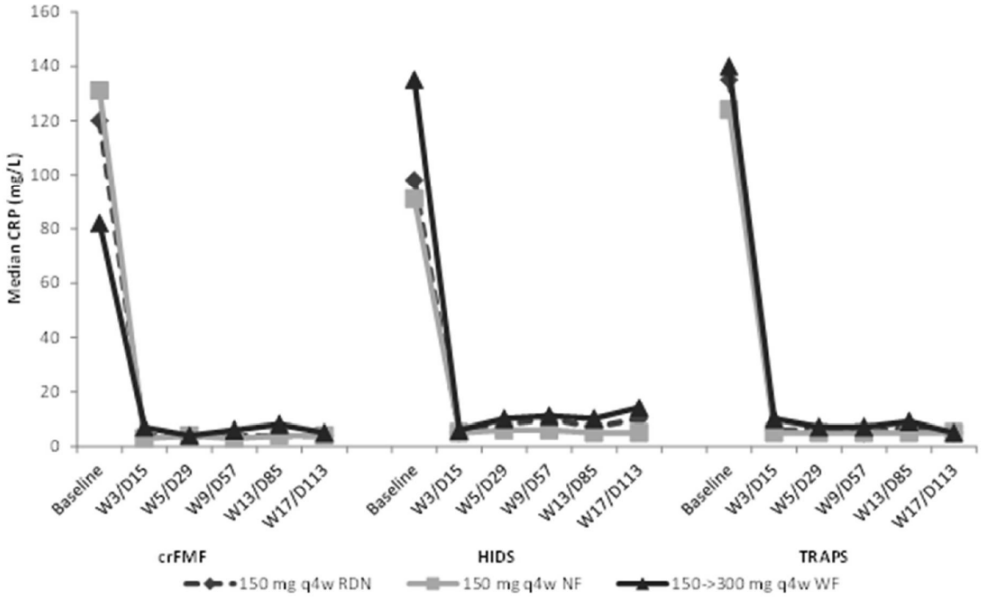


Figure 6. CRP values by visit and cohort, Epoch 2 (Full analysis set)

(Source: Figure 4-2, Clinical overview)

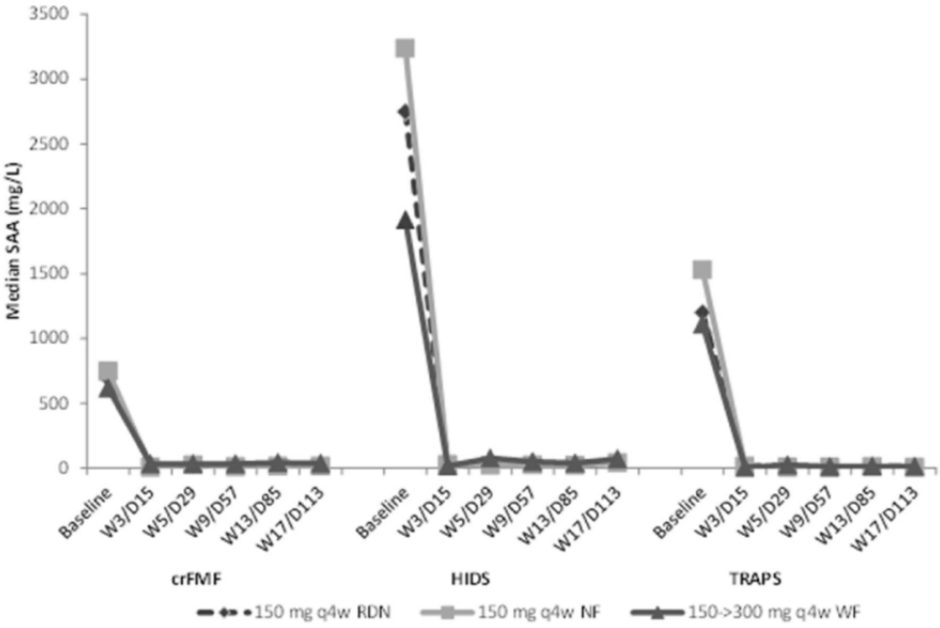


Figure 7. SAA values by visit and cohort, Epoch 2 (Full analysis set)

(Source: Figure 4-3, Clinical overview)

2.2.5. What are the key results from the population PK analysis?

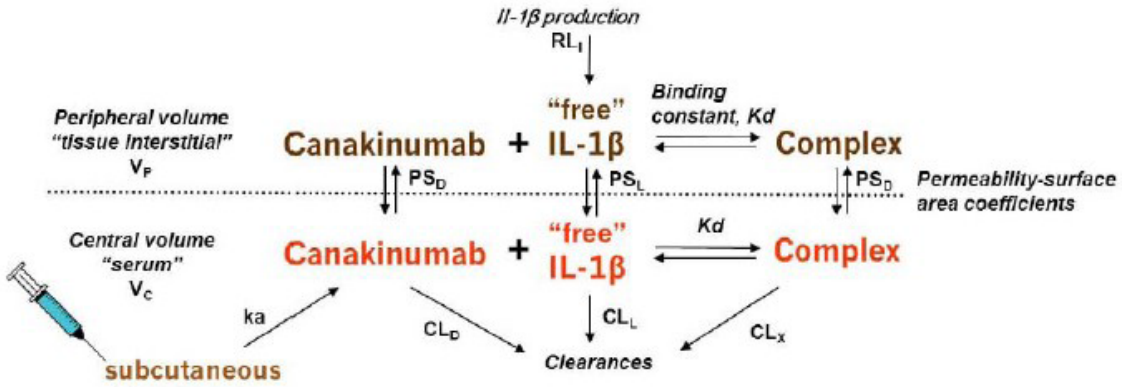
For major conclusions based on the pop PK analysis, see section 2.2.3.

The PK-binding model previously developed in CAPS was used to describe the pharmacokinetics of canakinumab in crFMF, HIDS/MKD, and TRAPS patients based on pooled data from one Phase III study (N2301) in crFMF, HIDS/MKD and TRAPS patients, one proof-of-concept (PoC) study (D2203) in TRAPS patients and previously used data in CAPS patients. The dosing regimens in two studies were 150 mg Q4W for patients > 40 kg and 2 mg/kg for patients ≤ 40 kg with the option of 300 mg or 4 mg/kg in case of flare. The drug was given subcutaneously. The sampling time is predose, 2 weeks, 4 weeks and every 4 weeks after that until the end of the study.

The PK binding model is a dynamic drug-ligand binding and turnover model developed based on the schematic:

ACZ885 + IL-1β ↔ ACZ885-IL-1β complex

This can occur either in the tissue interstitial fluid space, where IL-1β is released, or in the plasma. The model also includes diffusion-exchange of canakinumab and IL-1β between the peripheral and plasma compartments, plus elimination rates for free canakinumab, free IL-1β and the canakinumab -IL-1β complex from the plasma space. A schematic of the PK-binding model is depicted in Figure 8.



CLD Clearance from serum of canakinumab [L/day]
CLX Clearance of complex, in the model, CLX=CLD
VD Volume of distribution of the central, serum compartment of canakinumab or IL-1β [L]
VP Volume of distribution of the peripheral, tissue fluid compartment of canakinumab or IL-1β [L]
PSD Permeability-surface area coefficient for exchange between plasma and peripheral compartment for canakinumab (free and complex) [L/day]
ka Absorption rate constant for s.c. administration [1/day]
F Bioavailability (refers to s.c. bioavailability for canakinumab) [%]
CLL Clearance of uncomplexed ligand, IL-1β [L/day]
RLI Production or release rate of uncomplexed ligand, IL-1β [ng/day]
PSL Permeability-surface area coefficient of uncomplexed ligand, IL-1β [L/day]
KD Equilibrium dissociation constant for binding of ACZ885 to IL-1β [nM]

Figure 8. PK-binding model for canakinumab (ACZ885) and IL-1β.
(Source: Figure 1-1, Sponsor's ACZ885 CAPS extension modeling report)

Due to sparse dataset, only the following parameters were estimated from the model as shown in Table 4 and the rest of the parameters were fixed to the values reported in Table 5 and Table 6 from the Sponsor's ACZ885 CAPS extension modeling report.

Table 4. Estimated values of selected parameters of the PK-binding model in patients with crFMF, TRAPS, and HIDS/MKD (studies D2203 and N2301, n=205)

Name	Estimate	Relative Standard Error [%]
Structural parameters		
Drug clearance, CL [L/day]	0.16	3
Central volume, V_c [L]	5.82	12
Production rate of ligand, RL_I [ng/day]	6.85	6
Covariate effects		
WT0 on CL	0.88	6
WT0 on V_c	1.22	23
HIDS on RL_L	0.40	35
Inter-individual variability(Variance)		
IIV on CL	0.05	35
IIV on V_c	0.28	24
IIV on RL_L	0.15	35
Covariance		
CL-V_c (correlation)	0.05	49
Residual variability (Variance)		
Canakinumab (ng/mL)	0.19	18
IL-1beta (pg/mL)	0.34	13

(Source: Sponsor's response to information request submitted on 06/03/2016, Page 4, Table 2-1)

Table 5. Final estimates of model parameters for CAPS patients

Parameter [units]	Population mean [Θ ± SEM]	Inter-individual variance [ω^2 ± SEM] (CV%)	Shrinkage (%)
Canakinumab parameters			
Clearance, drug	0.169 ± 0.0122	0.0933 ± 0.0139 (31%)	3 %
Central distribution volume (V_D, L)	3.48 ± 0.219	0.0855 ± 0.0283 (29%)	23 %
Peripheral distribution volume (V_P, L)	2.72 ± 0.172	0.0849 ± 0.0183 (29%)	34 %
Intercompartmental permeability flow (PS_D, L/d)	0.453 ± 0.0682	0.224 ± 0.103 (47%)	45 %
Absorption rate constant (k_a, 1/d)	Table 9-2	0.308 ± 0.108 (55%)	29 %
Logit bioavailability	Table 9-2		
IL-1β parameters			
Clearance for ligand (CL_L, L/d)	9.47 ± 1.51	0.446 ± 0.0895 (67%)	19 %
Production rate of ligand (R_{LI}, ng/d)	8.17 ± 1.03	0.294 ± 0.0378 (54%)	7 %
Intercompartmental permeability flow (PS_L, L/d)	0.332 ± 0.0542	0.262 ± 0.13 (51%)	30 %
Binding constant (K_d, nM)	1.56 ± 0.166	0.331 ± 0.0752 (58%)	20%
Covariates			
Weight on CL_D	0.792 ± 0.0489		
Albumin on CL_D	-0.629 ± 0.209		
Weight on V_D	0.898 ± 0.0636		
Weight on V_P	0.896 ± 0.0999		
Age on k_A	-0.449 ± 0.187		
Weight on R_{LI} in CAPS population	0.284 ± 0.117		
Age on R_{LI} for Muckle-wells in CAPS population	-0.363 ± 0.107		
Age on R_{LI} for NOMID in CAPS population	-0.714 ± 0.109		
Age on CL_L in CAPS population	-0.174 ± 0.0778		
Covariances in OMEGA matrix			
CL_D:V_D		0.0613 ± 0.0161	
V_P:PS_D		0.0676 ± 0.0371	
V_P :PS_L		0.0283 ± 0.0356	
PS_D:PS_L		0.14 ± 0.0951	
CL_L:R_{LI}		0.238 ± 0.0408	
Residual variances			
Canakinumab (ng/mL)	0.0548 ± 0.0045 (23%)		
IL-1β (pg/mL)	0.104 ± 0.0123 (32%)		
Objective function	-13977.188		

* Logit transformation: F = exp(X)/(1+exp(X))

(Source: the Sponsor's ACZ885 CAPS extension modeling report, Page 21, Table 9-1)

Table 6. Absorption rate and bioavailability parameters for all product types (mean ± SEM)

Parameter [units]	Product type A	product type B	Product type C	Product type D
Logit bioavailability	0.529 ± 0.24	0.853 ± 0.294	1.18 ± 0.351	0.663 ± 0.258
Bioavailability (%)*	62.7 ± 5.54	69.8 ± 6.11	75.9 ± 6.3	65.8 ± 5.73
Relative bioavailability*			0.873 ± 0.1088	
Absorption rate constant (k_a, 1/d)	0.319 ± 0.05	0.275 ± 0.048	0.289 ± 0.067	0.379 ± 0.214

(Source: the Sponsor's ACZ885 CAPS extension modeling report, Page 22, Table 9-2)

The exposure of canakinumab was not influenced by disease. For a typical 70 kg person, the estimated clearance of canakinumab was estimated to be 0.16 L/day in PFS patients, comparable to that in other indications. The corresponding volume of distribution at steady state was ~ 5.82 L. The estimated half-life (T1/2) of canakinumab was ~25 days. The clearance and volume of distribution were dependent on body weight in an allometric relationship.

2.2.6. Is the proposed dosing regimen justified by the exposure-response for both efficacy and safety?

The canakinumab starting dose (150 mg or 2 mg/kg sc q4w for patients ≤ 40 kg) selected for Phase III study N2301 was reasonable. The dose selection is supported by the results of the dose- ranging Phase II studies. Further evidence supporting this dosing regimen, particularly with respect to safety, was provided from approved indications including CAPS, which also belongs to the group of periodic fever syndromes.

A dosing schedule of 150 mg or 2 mg/kg sc q4w was demonstrated to be effective in 3 open - label Phase 2 studies in crFMF and TRAPS patients (Studies DTR01, D2204 and D2203, Table 7). In a Phase 2 study, a higher dose with a longer interval (300 mg or 4 mg/kg q6w) was demonstrated to be effective in HIDS/MKD patients (Study D2402, Table 7).

Table 7. Efficacy summary of open label, uncontrolled phase 2 studies

Study	Indication	Dose regimen	Efficacy summary
D2203	TRAPS N=20	150 mg (2 mg/kg for < 40 kg) sc q4w, option of a single up titration of 300 mg (4 mg/kg for < 40 kg) sc at Day 8	**19/20(95%)** patients achieved a complete or almost complete response on Day 15
D2402	HIDS/MKD N=9	300 mg (4 mg/kg for < 40 kg) sc q6w, option to up-titrate to 450 mg sc q6w	**9/9(100%)** patients achieved primary outcome. The median number of flares per patient decreased from 5 (range: 3-12) during the 6-month historical period to 0 (range: 0-2) during the 6-month treatment period
D2204	CrFMF N=7	150 mg (2 mg/kg for < 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for < 40 kg) sc q4w	**6/7(85.7%)** patients achieved ≥50 % reduction in attack rate in the 3 month treatment phase

DTR01	CrFMF N=9	150 mg (2 mg/kg for < 40 kg) sc q4w, option to up-titrate to 300 mg (4 mg/kg for < 40 kg) sc q4w	**9/9(100%)** patients achieving ≥50 % reduction in attack rate in the 3 month treatment phase

(Source: Reviewer summary)

Canakinumab provided statistically significant benefit over placebo with respect to the primary endpoint, the proportion of complete responders as defined by patients who resolved their index disease flare at Day 15 and had no new disease flare over 16 weeks of treatment from the time of resolution of index flare (Table 8).

No new risks were identified for canakinumab in the Study N2301 patient population. The profile of the identified and potential risks in crFMF, HIDS/MKD, and TRAPS cohorts in Study N2301 Epoch 2 and Epochs 2-4 is consistent with that of the known safety profile in CAPS patients. See medical review for details for efficacy and safety assessment.

Table 8. Primary analysis: comparison between treatment groups for the proportion of responders after 16 weeks by cohort (Full analysis set)

	ACZ885 150 mg q4w		Placebo		Treatment comparison		
Cohort	n/M (%)	95% CI	n/M (%)	95% CI	Risk difference (95% CI)	Odds Ratio (95% CI)	One-sided p-value
crFMF	19/31 (61.29)	(42.19, 78.15)	2/32 (6.25)	(0.77, 20.81)	0.55 (0.31, 0.73)	23.75 (4.38, 227.53)	<0.0001*
HIDS	13/37 (35.14)	(20.21, 52.54)	2/35 (5.71)	(0.70, 19.16)	0.29 (0.06, 0.50)	8.94 (1.72, 86.41)	0.0020*
TRAPS	10/22 (45.45)	(24.39, 67.79)	2/24 (8.33)	(1.03, 27.00)	0.37 (0.08, 0.61)	9.17 (1.51, 94.61)	0.0050*

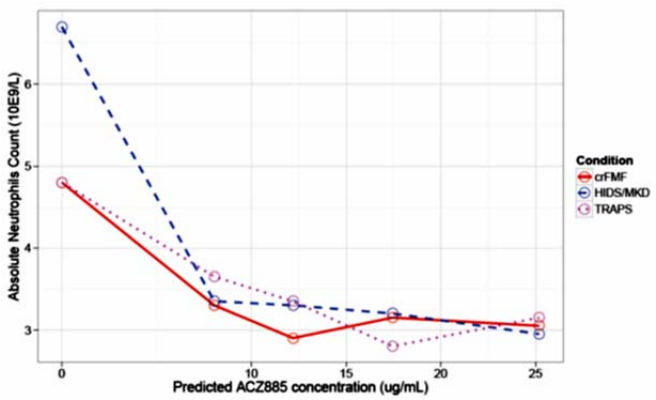
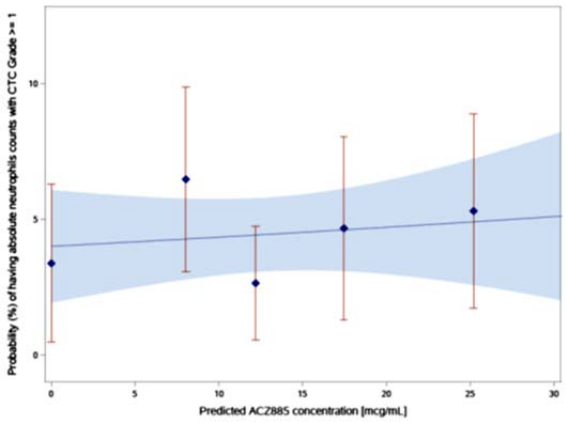
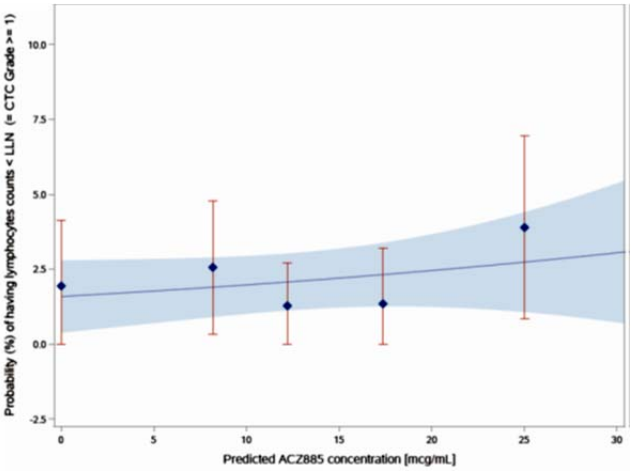
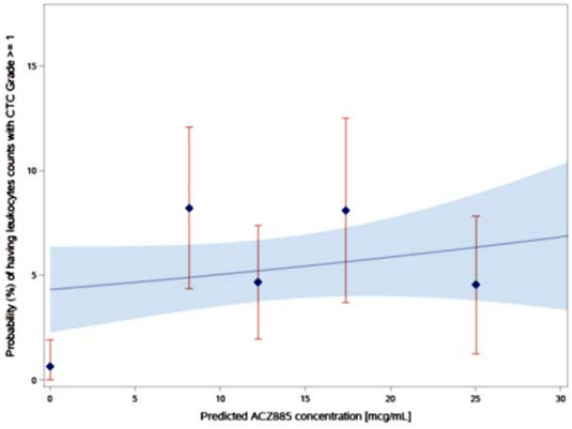
n=number of responders; M=number of evaluable patients; CI=confidence Interval.
* indicates statistical significance (one-sided) at the 0.025 level based on Fisher exact test.

(Source: Table 4-1, clinical overview)

The sponsor performed some exposure response analyses for efficacy and safety endpoints for the treatment phase (Epoch 2) of the phase 3 study N2301. However, due to the complicated study design, the PK metrics used in the analysis may not reflect the exposure at the time of events (such as flare). The response guided dose up-titration happens before the PK reaches steady state, and the analysis cannot differentiate the time effect (longer duration of therapy) vs the dose effect (up-titration of dose).

In the exposure response analysis for safety, While mean neutrophil levels decreased following canakinumab treatment, this did not translate into a higher occurrence of notable abnormalities (CTC grade ≥1) with increased concentrations of canakinumab. Likewise, the occurrence of notable abnormalities for lymphocytes count, leukocytes and platelets count did not increase with canakinumab concentrations either (Figure 9).

Overall, exposure-response analyses provided limited information regarding dose selection, and the benefit of up-titration is inconclusive.

Neutrophil  **Predicted canakinumab concentration**	Probability of Neutrophil CTC grade≥1  **Predicted canakinumab concentration**
Probability of lymphocyte<LLN  **Predicted canakinumab concentration**	Probability of leukocytes CTC grade≥1  **Predicted canakinumab concentration**

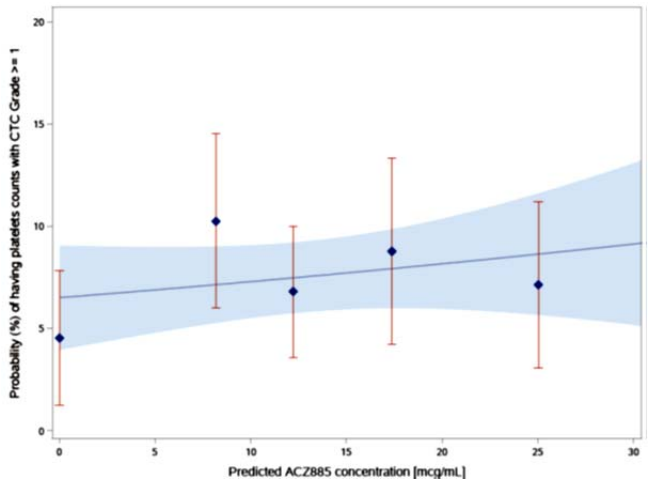


Figure 9. Safety endpoints vs concentration of canakinumab

(Source: Figure 5-8, 5-9, 5-10, 5-11, 5-12)

2.3 Intrinsic Factors

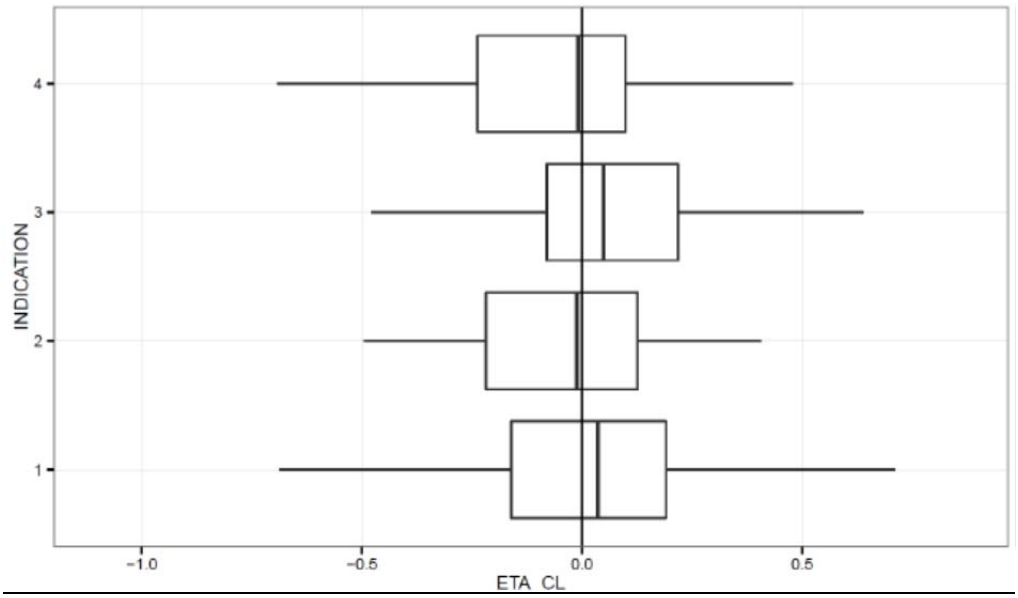
2.3.1. What was the impact of demographic covariates on Canakinumab exposure?

The primary demographic covariates that were explored for correlation with canakinumab exposure were weight, age, sex, ethnicity, albumin, and disease state. Based on the population PK analysis of CAPS, SJIA and PFS patients, weight was found to be a significant covariate. In PFS patients, an increase in bodyweight (from 9.6 to 169.8 kg) yielded an increase in canakinumab clearance. Therefore, dosing based on a per kilogram basis is justified.

There are no other covariates that warrant dose adjustment.

Disease Status

The estimated individual clearances were generally consistent across all disease conditions in Periodic Fevers Syndromes. As shown in Figure 10, the individual estimates of clearance from the population PK model are similar among the indication groups.



Indication: 1=CAPS; 2=crFMF; 3=HIDS/MKD; 4=TRAPS.
"Relative clearance" is based on post-hoc empirical Bayes estimates and is given relative to the clearance of CL=0.14 L/day in a "typical subject" (e.g. a value of 0.1 indicates a 10% relative increase in clearance). The left-most whisker represents 5th and the right-most whisker represents 95th percentile. The left border of the box represents 1st quartile (25%), the middle line is the second quartile (median), and the right border of the box is the 3rd quartile (75%).

Figure 10. Relative clearance by indication group (after adjusting for bodyweight)
(Source: Figure 5-12, POPPK ACZ885N report)

Body Weight

The dosing for patients in higher bodyweight group (>40 kg) was fixed dosing (150 mg q4w) and for patients in lower bodyweight group (≤40 kg) was body weight based dosing (2 mg/kg q4w). When stratified by bodyweight, approximately 20% higher exposure was predicted for trough concentrations at week 16 for the higher bodyweight group (> 40 kg) when given 150 mg q4w vs. the lower bodyweight group (≤ 40 kg) given 2 mg/kg q4w (Figure 11). Comparable Cmin and AUC exposure were expected across all the weight groups in patients (≤ 40kg) using the same weight based dose (such as 2 mg/kg, Figure 12). As the dose of canakinumab can be up- titrated based on clinical response for individual PFS patient, and there is significant overlap in the exposure for patients using fixed dose (>40 kg) and weight based dose (≤ 40kg), the proposed dosing regimen is reasonable.

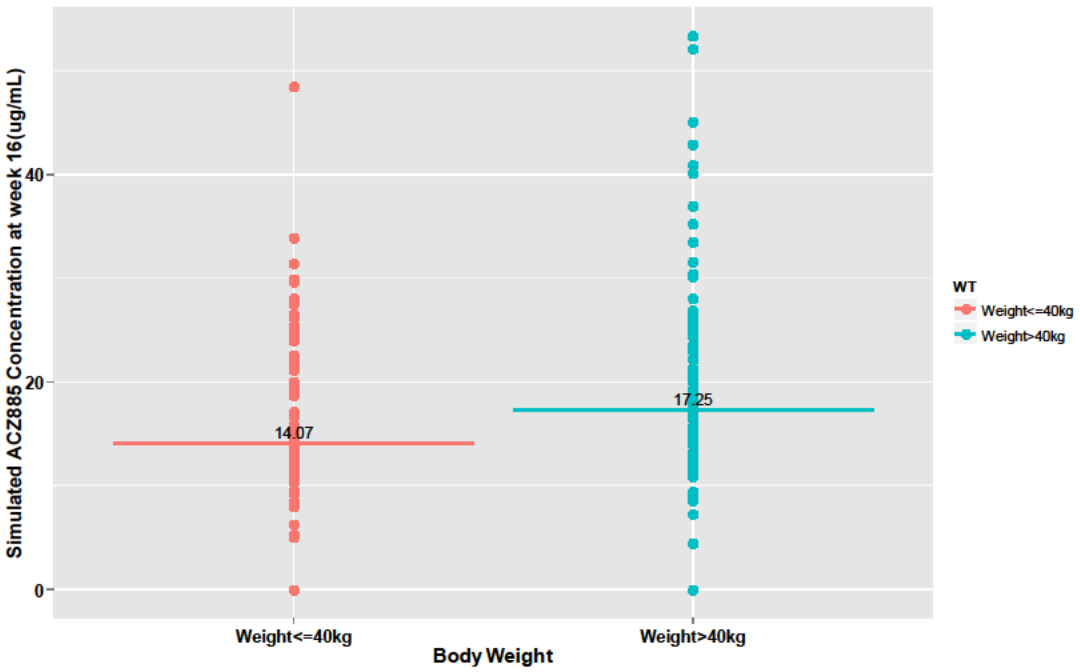


Figure 11. Simulated trough concentrations at week 16 stratified by bodyweight
(Source: Reviewer's analysis)

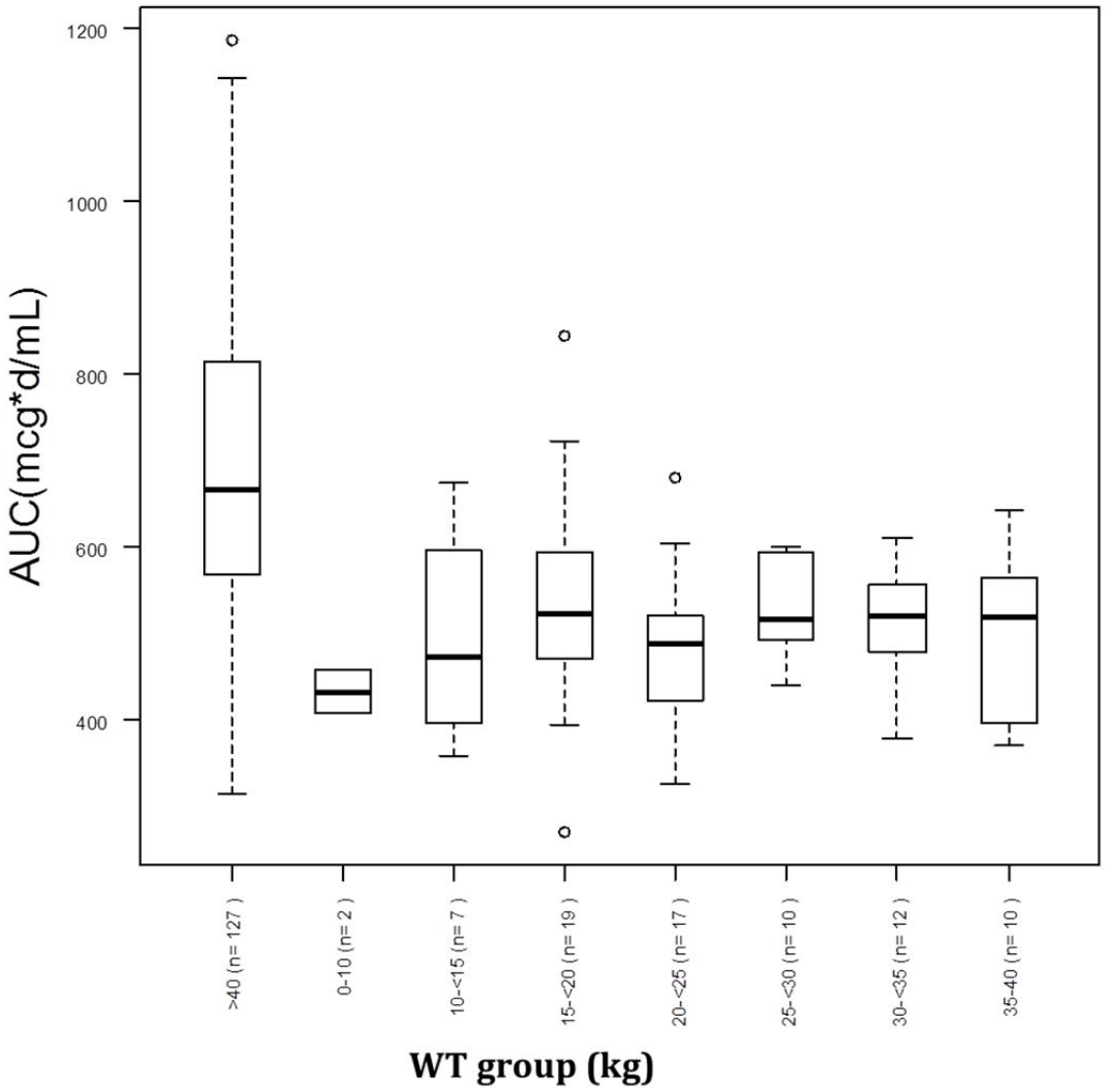


Figure 12. Estimated steady state AUCtau in PFS patients by weight group. AUCtau is estimated for 150mg dose in patents >40kg, and 2mg/kg in patients ≤40kg

(Source: Reviewer analysis based on sponsor's data \\cdsesub1\evsprod\bla125319\0224\m5\datasets\acz885n-poppk\analysis\legacy\programs\project-indiv.txt)

Pediatric patients

The body-weight normalized canakinumab clearance did not show any significant trend under different age groups. Comparable exposure were expected across all the age groups (≥2 yrs) with body weight ≤ 40 kg, with the weight based dosing regimen (Figure 3).

Renal Impairment and Hepatic Impairment patients

No formal PK study was performed in patients with impaired hepatic or renal function, as it is known that the majority of IgG elimination occurs via intracellular catabolism.

There were no severely renal impaired subjects included in the Periodic Fever Syndromes (TRAPS, HIDS/MKD, and crFMF) studies. Prior clinical data in CAPS showed that no dose adjustment is needed in patients with renal impairment.

2.3.2. What was the Canakinumab exposure in pediatric patients younger than 2 years of age compared to pediatric patients older than 2 years of age?

The Canakinumab exposure in pediatric patients younger than 2 years was comparable to that in pediatric patients older than 2 years. The conclusion was drawn based on the comparison of observed concentrations at week 16 across different age ranges by pooling all the PK information from current and previous submission.

In current submission, the Applicant proposed to give canakinumab to patients 2 years of age and older based on the phase 3 study, in which the majority of the patients are equal to or older than 2 years. To investigate the pharmacokinetics of canakinumab in patients younger than 2 years, the information from CAPS, SJIA patients and non-randomized patients from current submission were pooled together assuming no PK difference across indications. The baseline characteristics of these patients are listed in Table 9.

Table 9. Baseline characteristics of patients younger than 2 years taken canakinumab

Patient ID	Weight (kg)	Age (Years)	Dosing Regimen	Indications	PK information
42002	8.1	0.5	2 mg/kg Q8W	CAPS	Yes
42004	11.4	1.2	2 mg/kg Q8W	CAPS	Yes
42007	6.2	0.2	2 mg/kg Q8W	CAPS	Yes
42012	7.5	0.5	2 mg/kg Q8W	CAPS	Yes
42016	8.3	1.0	2 mg/kg Q8W	CAPS	Yes
42017	7.5	0.5	2 mg/kg Q8W	CAPS	Yes
73030	9.7	1	4 mg/kg Q4W	SJIA	Yes
16053	6.4	1	4 mg/kg Q4W	HIDS/MKD	No
16086	9.8	1	2 mg/kg Q4W	HIDS/MKD	No

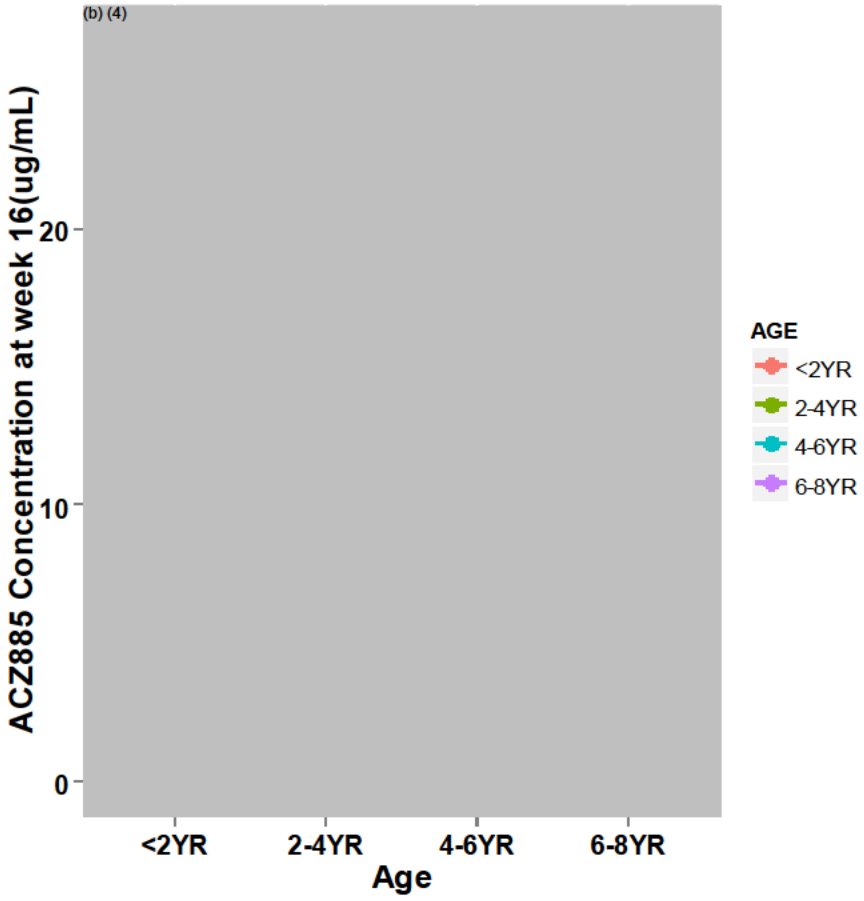
(Source: The Reviewer's analysis)

The observed C_{trough} values of canakinumab at Week 16 for CAPS and SJIA patients younger than 2 years were collected and compared with those from other age groups (2 to < 4 years, 4 to < 6 years and 6 to < 8 years) as shown in Figure 13. The concentrations were dose normalized concentrations (normalized to dose of 2 mg/kg) according to the dosing regimen given last visit as patients may have dose adjustment during the treatment. Although there were 7 patients younger than 2 years had PK information but only 5 of them have observed concentrations at week 16. The numbers of CAPS and SJIA patients in 2 to < 4 years group, 4 to < 6 years group and 6 to <8 years group are 9, 10 and 7 respectively (Table 10). The results showed the observed C_{trough} values of canakinumab were comparable across age groups. It appears that the PK of canakinumab in patients younger than 2 years is not significantly different from those older than 2 years under the same weight based dosing regimen.

Table 10. Number of patients with observed concentration at week 16 in each age group of CAMPS and SJIA patients

Age group of CAPS and SJIA patients	No. of patients with observed concentration at week 16
<2 Years	5
≥2 Years and < 4 Years	9
≥4 Years and < 6 Years	10
≥6 Years and < 8 Years	7

(Source: The Reviewer's analysis)



Note: Circles represent individual observed concentration at week 16 for each subject from the pooled database of CAPS and sJIA patients. The solid line represents the median concentration value for each age group.

Figure 13. Observed C_{trough} values (Dose normalized) at week 16 across ages in CAPS and SJIA population

(Source: The Reviewer's analysis)

However, it is worth noting that the variability of canakinumab concentrations is relative big in some age groups. A possible explanation is that the dose may be adjusted not long before Week 16 and steady state was not achieved yet for those patients.

To conclude, the PK of canakinumab in patients younger than 2 years shows similar behavior as compared to that in patients with older. See medical review for additional information for patients younger than 2 years, such as safety, and disease progression.

2.3.3. What were the immunogenicity findings for Canakinumab? What was the impact of immunogenicity on exposure and/or safety?

Overall the incidence of ADA is low in PFS patients. The incidence of treatment related anti-canakinumab antibodies was < 1% in crFMF, HIDS/MKD and TRAPS patients across all Phase 2 and 3 studies. No patient had neutralizing antibodies. No anti-drug antibodies (ADA) were detected in any patient in Study N2301. Two patients (1 crFMF and 1 TRAPS) in the Phase 2 studies had treatment-emergent ADA, with no link to adverse events (AEs), loss of efficacy or change in PK.

2.4 Extrinsic Factors

2.4.1 What are the drug-drug interactions?

No formal clinical drug interaction studies between canakinumab and other medicinal products have been performed. Based on pop-PK analysis, Colchicine co-medication had no impact on pharmacokinetics of canakinumab in patients with Periodic Fever Syndromes.

There were approximately 87% of crFMF patients who took colchicine co-medication during Epoch 2 in study [Study N2301]. Effect of concomitant colchicine was assessed by estimating relative changes on canakinumab clearance in the final population PK model. The ratio of the two estimated clearances were 0.98 and the corresponding 95% CI was within 20% (0.9-1.07).

2.5 General Biopharmaceutics

2.5.1. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The ACZ885 was assessed based on a based on a competitive Enzymatic Linked ImmunoSorbent Assay (ELISA) with an LLOQ of 100 ng/mL. (validation report BxSD RS710569 / CP105398). A purified anti-idiotype anti-ACZ885 antibody is coated on the microtiterplate. Serum samples (calibration, quality control (QC) or test samples) and biotin-labelled ACZ885 are simultaneously incubated and compete for binding to the anti-idiotype anti-ACZ885 antibody. Non-bound material is removed by washing. Bound biotinylated-ACZ885 is detected by incubating horseradish peroxidase-conjugated Streptavidin with Ophenylenediamine dihydrochloride (OPD) as substrate. The reaction is terminated by addition of acid and absorbance is measured at 490/650 nm.

All bioanalytical PK assays meet the regulatory criterion, with the intra-day or inter-day accuracy and precision did not deviate by more than ± 20.0% (± 25.0% at the lower limit of quantitation (LLOQ, 100 ng/mL) and the upper limit of quantitation (ULOQ, 4000 ng/mL)).

2.5.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

ILARIS® is currently supplied as a 6 mL single-use vial, which contains a sterile, preservative free, white lyophilized powder containing 180 mg of canakinumab. Each vial is to be reconstituted with 1 mL of preservative-free Sterile Water for Injection to make 150 mg/mL solution from which the appropriate amount is to be given by subcutaneous injection. The new ILARIS 150 mg/mL Drug Product configuration is supplied in a single-use, 2 mL clear, colorless, (b) (4) Type I glass vial as a solution for injection for subcutaneous administration.

For development of the Periodic Fever Syndrome indications TRAPS, HIDS/MKD, and crFMF, only drug substance from the final commercial manufacturing process was used (previously referred to (b) (4) Drug product powder for solution for injection (the currently marketed presentation) was used in the four Phase II Periodic Fever Syndromes (TRAPS, HIDS/MKD, and crFMF) trials. Solution for injection in vial is a new presentation (b) (4) and was used in the Phase III study N2301. (b) (4) Based on the above, the presentation (solution in vial) used in the phase 3 study was bridged to the to-current marketed presentation (powder in vial).

3 Labeling Recommendation

The revised labeling language based on the clinical pharmacology review is as below. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font. Refer to the sBLA action letter for the full text of the final labeling.

12.3 Pharmacokinetics

Distribution

Canakinumab binds to serum IL-1β. Canakinumab volume of distribution (Vss) varied according to body weight and was estimated to be 6.01 liters in a typical CAPS patient weighing 70 kg, and 3.2 liters in a SJIA patient weighing 33 kg, and (b) (4) liters for a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing (b) (4) 70 kg. The expected accumulation ratio was 1.3-fold for CAPS patients and 1.6-fold for SJIA patients following 6 months of subcutaneous dosing of 150 mg ILARIS every 8 weeks and 4 mg/kg every 4 weeks, respectively.

Elimination

Clearance (CL) of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a typical CAPS patient weighing 70 kg and, 0.11 L/day in a SJIA patient weighing 33 kg, and (b) (4) L/day in a Periodic Fever Syndrome (TRAPS, HIDS/MKD, FMF) patient weighing (b) (4) 70kg. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. No gender- or age-related pharmacokinetic differences were observed after correction for body weight.

Pediatrics

Pharmacokinetic properties are similar in Periodic Fever Syndromes (CAPS, TRAPS, HIDS/MKD, FMF) and SJIA pediatric populations. In patients less than 2 years of age (b) (4), the exposure of canakinumab were comparable to older age groups with the same weight based dose.

In CAPS patients, peak concentrations of canakinumab occurred between 2 to 7 days following single subcutaneous administration of ILARIS 150 mg or 2 mg/kg in pediatric patients. The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults.

In SJIA, exposure parameters (such as AUC and Cmax) were comparable across age groups from 2 years of age and above following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks.

In TRAPS, HIDS/MKD, and FMF exposure parameter trough concentrations were comparable across age groups from 2 to less than 20 years following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks.

4. APPENDIX

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	125319 (S85, 86, 87, 88)	**SDN**	549, 552, 554, 555
Applicant	Novartis	**Submission Date**	3/23/2016
Generic Name	Canakinumab	**Brand Name**	ILARIS
Drug Class	Interleukin-1β blocker		
Indication	FMF, HIDS/MKD and TRAPS in patients ≥2yrs		
Dosage Regimen	>40kg, 150mg, <40kg, 2mg/kg SC Q4W; up titration to 300 mg and 4mg/kg SC Q4W.		
Dosage Form	Lyophilized powder, solution in vial	**Route of Administration**	SC
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Jianmeng Chen	Anshu Marathe	
Pharmacometrics	Luning Zhuang, Jeffry Florian	Jingyu (Jerry) Yu	
Genomics			
Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	5/22/2016	**74-Day Letter Date**	6/6/2016
Review Due Date	8/29/2016	**PDUFA Goal Date**	9/22/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

Clinical Pharmacology Package

Tabular Listing of All Human ☑ Yes ☐ Clinical Pharmacology Summary ☑

Studies	No		Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		1	Study 2104
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	PK information collected for N2301
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☑ Genetics			Genetic information collected for N2301
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			
Pharmacokinetics/Pharmacodynamics			

☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	1	ACZ885N pop PK
☑ Exposure-Efficacy	1	ACZ885N PKPD
☑ Exposure-Safety		

Total Number of Studies and reports	**In Vitro**		**In Vivo**	4
Total Number of Studies/reports to be Reviewed				4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	The innovator has comparative bioavailability data for different presentations. The innovator proposed that all presentations are valid for all indications.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	The innovator has comparative bioavailability data to support different presentations. It is not a (b)(2) submission.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☑Yes ☐No ☐N/A	

Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

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/s/

JIANMENG CHEN
08/29/2016

JINGYU YU
08/29/2016

ANSHU MARATHE
08/29/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	125319 (S85, 86, 87, 88)	**SDN**	549, 552, 554, 555
Applicant	Novartis	**Submission Date**	3/23/2016
Generic Name	Canakinumab	**Brand Name**	ILARIS
Drug Class	Interleukin-1β blocker		
Indication	FMF, HIDS/MKD and TRAPS in patients ≥2yrs		
Dosage Regimen	>40kg, 150mg, <40kg, 2mg/kg SC Q4W; up titration to 300 mg and 4mg/kg SC Q4W.		
Dosage Form	Lyophilized powder, solution in vial	**Route of Administration**	SC
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jianmeng Chen	Anshu Marathe
Pharmacometrics	Luning Zhuang, Jeffry Florian	Jingyu (Jerry) Yu
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	5/22/2016	**74-Day Letter Date**	6/6/2016
Review Due Date	8/29/2016	**PDUFA Goal Date**	9/22/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		

☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☑ Bioequivalence		1	Study 2104
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	PK information collected for N2301
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☑ Genetics			Genetic information collected for N2301
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		1	ACZ885N pop PK
☑ Exposure-Efficacy		1	ACZ885N PKPD
☑ Exposure-Safety			

Total Number of Studies and reports	**In Vitro**		**In Vivo**	4
Total Number of Studies/reports to be Reviewed				4

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	The innovator has comparative bioavailability data for different presentations. The innovator proposed that all presentations are valid for all indications.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	The innovator has comparative bioavailability data to support different presentations. It is not a (b)(2) submission.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No',	☑Yes ☐No ☐N/A	

has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
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9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

Submission in brief:

Indication and mechanism of action

Three efficacy supplements were submitted to the BLA125319 to seek approval for the additional indications for ILARIS® (canakinumab) in adults and children 2 years of age and older. In addition, a CMC supplement was submitted to seek marketing approval for additional product presentation (ILARIS150mg/mL solution for injection in vial). The supplements are:

- Supplement 85- Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS)
- Supplement 86 -Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)
- Supplement 87- Familial Mediterranean Fever (FMF) patients in whom colchicine is contraindicated, is not tolerated or does not provide an adequate response
- Supplement 88- CMC supplement to seek marketing approval for ILARIS® for the proposed additional product presentation as follows: ILARIS 150 mg/mL solution for injection in vial.

Canakinumab is a high-affinity human monoclonal antibody against interleukin-1β (IL- 1β), developed to bind and neutralize the excess IL-1β produced in some inflammatory diseases. ILARIS® is currently approved for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older (including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)) and for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older.

ILARIS® is currently supplied as a 6 mL single-use vial, which contains a sterile, preservative free, white lyophilized powder containing 180 mg of canakinumab. Each vial is to be reconstituted with 1 mL of preservative-free Sterile Water for Injection to make 150 mg/mL solution from which the appropriate amount is to be given by subcutaneous injection. The new ILARIS 150 mg/mL Drug Product configuration is supplied in a single-use, 2 mL clear, colorless, (b) (4) Type I glass vial as a solution for injection for subcutaneous administration. The pivotal clinical study N2301 for supplement 85, 86, and 87 was conducted with the new presentation (solution in vial).

Summary of information submitted

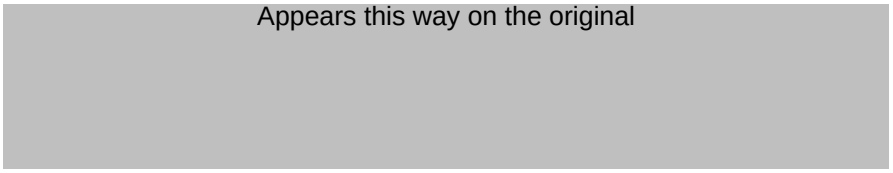
This supplements contain the following clinical study results:

- The pivotal clinical trial, CACZ885N2301, to support this application in periodic fever syndromes included three patient cohorts (HIDS/MKD, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) and Familial Mediterranean Fever (FMF)) for a total of 181 randomized patients. This was a multi-center, randomized, double-bind, placebo controlled trial; the screening phase (Epoch 1) and randomized treatment phase (Epoch 2) are complete and the trial results provided herein to support registration. Epoch 3 (randomized withdrawal) and Epoch 4 (long-term extension) remain ongoing.
- Updated popPK (ACZ885n-popPK) and exposure-response analysis (ACZ885N-PKPD) based on study N2301.
- BE study 2104 was submitted under supplement 85.

As the CMC supplement 88 has a closer PDUFA date of Jul 30, 2016, there will be a separate clinical pharmacology review for this supplement. The efficacy supplements 85, 86, and 87 will be combined in one clinical pharmacology review. During the filing meeting, the division also discussed potential expansion of patient population to include pediatric patients less than 2 years of age, and/or FMF patients who are not colchicine irresponsive/intolerant.

The clinical pharmacology review will focus on:

1. Updated popPK and exposure-response analysis to support dose recommendation.
2. BE study 2104 to support CMC supplement 88.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/s/

JIANMENG CHEN
05/17/2016

ANSHU MARATHE
05/17/2016