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APPLICATION NUMBER:

125319

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 125319	Submission Date(s): 12/17/2008
Brand Name	ILARIS
Generic Name	Canakinumab
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Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Novartis Pharmaceuticals Corporation
Relevant IND(s)	100,040
Submission Type; Code	Original BLA; Priority
Formulation; Strength(s)	Lyophilized powder for injection; 150 mg
Indication	Treatment of Cryopsin Associated Periodic Syndrome (CAPS)
Proposed Dosage Regimen	The recommended dose for CAPS patients with body weight >40 kg is 150 mg, and for patients with body weight ≥ 15 kg and ≤ 40 kg is 2 mg/kg, administered as a subcutaneous injection every eight weeks

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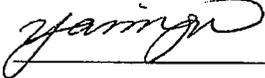
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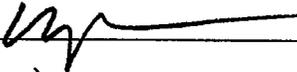
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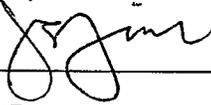
Concurrence:

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Hao Zhu, Ph.D.  5/12/09

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Suresh Doddapaneni, Ph.D.  5/13/09

1 Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology (OCP), the information contained in this submission is acceptable, provided that a mutually acceptable agreement can be reached between the Agency and sponsor regarding the language in the package insert.

In addition, a higher dose (3 mg/kg) should be considered for low body weight subjects who do not demonstrate adequate clinical efficacy with 2 mg/kg dose, provided safety and tolerability are acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Novartis Pharmaceuticals Corporation submitted this original BLA for ILARIS (Canakinumab or ACZ885) injection for the treatment of Cryopsin Associated Periodic Syndrome (CAPS). CAPS, an orphan indication, are group of systemic autoinflammatory diseases including Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal-onset Multisystem inflammatory Disease (NOMID). Ilaris is not approved for CAPS or any other indications outside of US.

Ilaris is a recombinant human monoclonal anti-human interleukin- β (IL-1 β) antibody of the IgG1/k isotype. Ilaris is supplied in sterile, single-use 6 ml glass vial as a 150 mg white, preservative-free lyophilized powder and requires reconstitution with 1 mL of preservative-free sterile for injection via subcutaneous administration.

In addition to the adults, the current submission also seeks marketing approval of ILARIS for use in treatment of CAPS in children over 4 years of age. The recommended dose for CAPS patients with body weight >40 kg is 150 mg, and for patients with body weight \geq 15 kg and \leq 40 kg is 2 mg/kg, administered as a subcutaneous injection every eight weeks.

Priority review has been granted on the basis of this products' potential to serve the unmet medical need in treating children with CAPS diseases.

Clinical Pharmacology and Clinical study data results from three clinical studies form the basis for canakinumab safety and efficacy in CAPS patients.

Study A2102 was an open-label dose-titration study in CAPS (also providing long-term safety data). Study D2304 was a placebo-controlled efficacy trial in patients with Muckle-Wells Syndrome (MWS) including an uncontrolled element in both the run-in (Part I) and extension period (Part III), and Study D2306 is an uncontrolled long-term safety and efficacy trial in CAPS. Additional details of these studies can be found in the attached synopses.

Canakinumab PK and PD, measured as total IL-1 β levels (free and antibody bound), have been characterized in CAPS patients in the following studies (see discussion below and attached study synopses):

- SC Dose titration study in CAPS patients [CACZ885A2102]
- Randomized withdrawal study in CAPS [CACZ885D2304]

Proposed dosing regimen was prospectively studied

Additionally, pharmacokinetics of canakinumab was also studied in healthy volunteers and other patient populations in the following studies (see attached study synopses):

- Single and multiple dose (150 mg) SC administration in _____ patients [CACZ885 _____]
- In healthy subjects and _____ as IV infusion [CACZ885 _____]
- In healthy Japanese volunteers as IV infusion [CACZ885A1101]
- In RA patients as IV infusion [CACZ885A2101]

b(4)

The PK parameters were determined in serum using non-compartmental analysis as well as a compartmental modeling approach described by a population based PK model in ACZ885 CAPS Modeling Report.

In pivotal clinical trial # D2304, CAPS patients meeting the following inclusion criteria were recruited:

- Males and females aged 4-75 years.
- Molecular diagnosis of NALP3 mutations and clinical picture resembling MWS (patients who participated in the CACZ885A2102 study had the option to participate in this study upon disease relapse).
- Body weight ≥ 15 and < 100 kg.

During the lead-in period or Part I of the study, 97.1% of patients (n=35) had a complete response to canakinumab, with 71.4% of patients having complete response by the first scheduled time point (Day 8). Four patients discontinued before entering Part II (DB, PC, random-withdrawal period) because of insufficient efficacy in Part I (open-label, active treatment period). Two are from the 17 - 41 year group and two from >41 yr old group.

Although the clinical endpoints CRP (n=3) and SAA (n=4) improved over baseline, these patients were noted as having minimal disease activity by the physician's global assessment of disease activity (PGADA); whereas treatment success would require "absence" of disease as assessed by PGADA.

Pharmacodynamics of canakinumab

Canakinumab binds to human IL-1 β , and blocks the interaction of this cytokine with its receptors. Sponsor evaluated the changes in several serum and pharmacogenetic markers in CAPS patients following canakinumab treatment (Study D2304, see pharmacometrics review by Dr. Hao Zhu and Genomics review by Dr. Mike Pacanowski). Following the administration of canakinumab, the total (free + canakinumab bound) plasma IL-1 β levels were elevated.

Objective clinical endpoints such as CRP and SAA decreased in response to canakinumab treatment during all stages of the clinical trial. As shown in the figure below, the clinical response was noted within one to two weeks of treatment initiation in the open-label lead-in period. During the randomized withdrawal period, both CRP and SAA increased in placebo group, whereas they remained low in canakinumab treatment group.

Among 35 subjects enrolled in the pivotal trial (Study #2304), only 1 subject received less than 150 mg dose. The primary efficacy variable was the number of subject who experienced flare during Part II. Subject CACZ885D2304_0002_00001 was randomized into the treatment group and experience no flare during the entire part II. In addition, the CRP and SAA levels for subject

Sponsor evaluated the effect of age, race, gender and disease on the pharmacokinetics of canakinumab. There were limited number (n=69) of CAPS patients in the clinical and clinical pharmacology database because CAPS is an orphan disease. However, clinical PK database included healthy volunteers and patients that received canakinumab for the experimental treatment of rheumatoid arthritis. The randomized withdrawal clinical trial had a high success rate (85%) compared to placebo. However, it was noted that clearance of canakinumab was dependent on bodyweight of patient.

Based on the population PK analysis, the PK parameters were comparable between CAPS patients and other study populations (Japanese healthy volunteers or JHV and non-Japanese volunteers or NJHV(predominantly Caucasian)), except for the non-Japanese healthy volunteers, which differed from CAPS patients in that they had approximately 20% slower clearance. However, it was discovered that clearance of canakinumab is dependent on patient bodyweight. The appropriateness of the proposed bodyweight based dosing is discussed below.

Evaluation of body weight based dosing

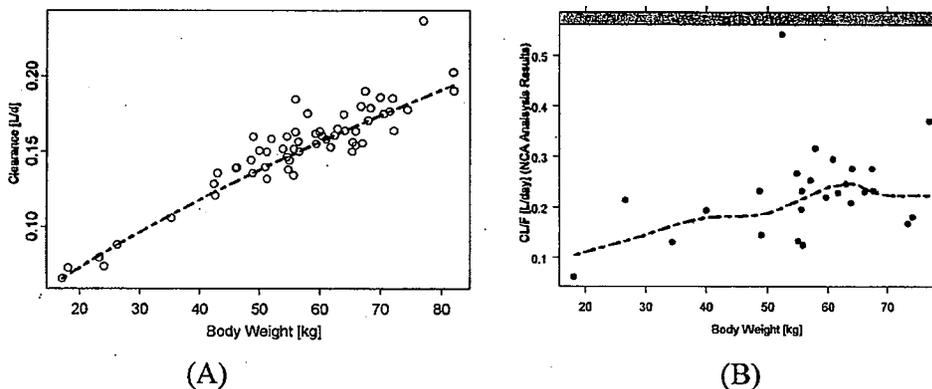
The body weight based dosing proposed by the sponsor is acceptable (see Table below). However, a higher dose (3 mg/kg) should be considered for low body weight subjects (i.e., ≥ 15 kg and ≤ 40 kg) who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable.

The Sponsor Proposed Dose

Patients	Proposed Dose
> 40 kg	150 mg
≥ 15 kg and ≤ 40 kg	2 mg/kg

Body weight based dose adjustment is necessary because large body weight is associated with high clearance of canakinumab. The sponsor's population binding and kinetic model identified body weight as a significant covariate for clearance (Figure below left -A). We confirmed it by checking the relationship between the clearance obtained from Study 2102 using non-compartmental analysis and body weight (Figure below right - B). The results indicated that body weight based dosing is necessary to achieve similar exposure for CAPS patients with different body weights.

Figure Legend: Body Weight and Clearance Relationship

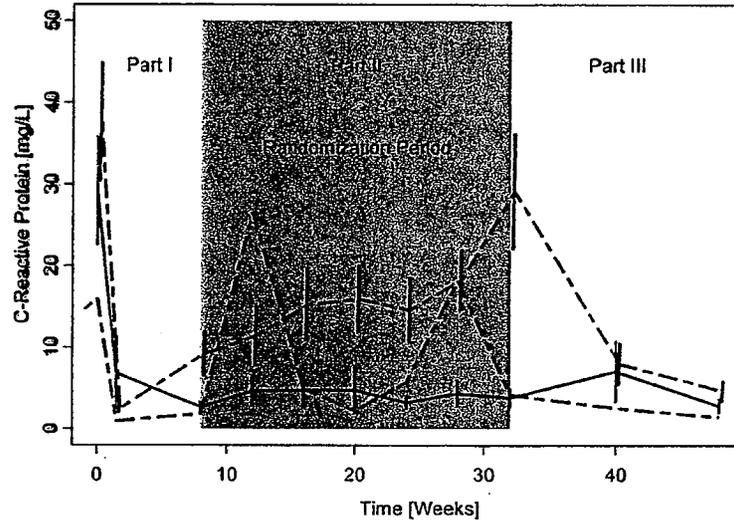


Note: (A) based on binding and kinetic modeling results in all CAPS patients
(B) based on non-compartmental analysis results from Study 2102.

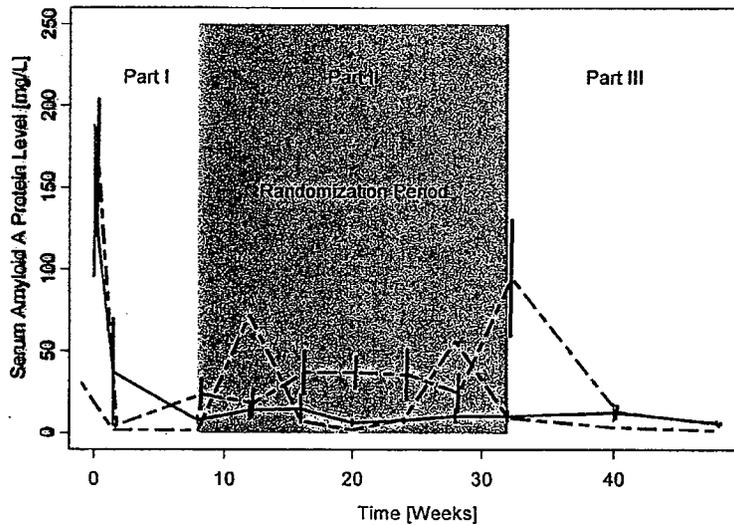
Based on the clinical (relapse of flare) and biomarker (SAA and CRP levels) observations in the pivotal clinical trial (Study 2304), the sponsor proposed body weight adjusted dose is acceptable. However, only 1 subject (subject CACZ885D2304_0002_00001) received 2 mg/kg dose while all other subjects received 150 mg (N=34). The primary efficacy variable was the number of subjects who experienced flare during Part II of the trial. Subject CACZ885D2304_0002_00001 was randomized into the treatment group and experienced no flare during the part II. In addition, the major biomarker values for subject CACZ885D2304_0002_00001 were similar to the rest of the subjects in the treatment group by the end of part I, II and III of the trial (Figure below).

Figure Legend: Biomarkers in the Treatment Group and the Observation from

Subject CACZ885D2304_0002_00001



(A)



(B)

Note: (A) CRP level and (B) SAA level from Study 2304

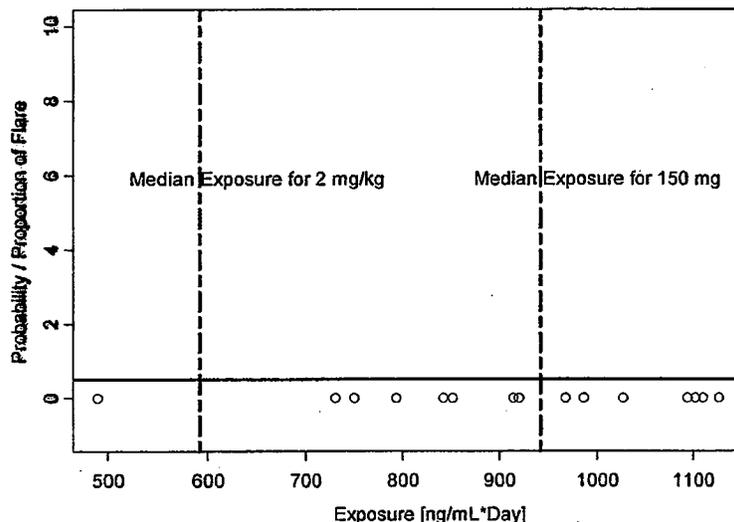
blue line = Treatment Group (Mean ± SE)

Red line = Placebo Group (Mean ± SE)

Green line = Observation from Subject CACZ885D2304_0002_00001 (on treatment).

In addition, we identified a flat exposure-response relationship following canakinumab treatment, where response is defined as the incidence of flare by the end of part II in the trial (See Figure below). In summary, a similar clinical and biomarker response can be seen in low body weight patient receiving 2 mg/kg dose as compared to high body weight (> 40 kg) patients receiving 150 mg dose.

Figure Legend: Exposure-Response Relationship for Subjects in Study D2304



At a clinical pharmacology briefing held on 5/4/2009, the appropriateness of the proposed bodyweight based dosing in patients between 15 kg – 40 kg bodyweight was discussed. During the briefing, the utility of exploring exposure-response relationship to a different clinical endpoint such as time-to-flare was raised. Most of the subjects in study D2304 did not show disease flare during treatment with canakinumab. Hence, data from the study A2102 which also employed the most number of patients in the 15 – 40 kg body weight range was utilized (See table below).

Table Legend: Efficacy Outcomes for Pediatric Patients Receiving 2 mg/kg Dose

Patient, Condition	Age	1st Trial	Dosage	Response/Relapse
2 mg/kg s.c. scheduled dose, (rescue dose), weight ≤40 kg				
0002-05123 (MWS)	4 yr	A2102	2mg/kg s.c. (x10) 5 mg/kg i.v.. (x3)	responder, 1 st relapse at 10 days, then time to relapse approx 30 days
0504-00001 (FCAS)	5 yr	D2306	2mg/kg s.c.	responder at cut-off
0022-05127 (MWS)	6 yr	A2102	2mg/kg s.c. (x4)	responder, 1 st relapse at 70 days, time to relapse approx 70 days
0002-05116 (MWS)	6 yr	A2102	2mg/kg s.c. (x7)	responder, 1 st relapse at 72 days, then approx 38 days post dose
0002-05108 (MWS)	7 yr	A2102	2 mg/k s.c. (x10) 125 mg iv (x10)	responder, 1 st relapse at 3 days, then partial/no response to 2 mg/kg response to high dose, relapse at 7 th relapse approx 34 days after high d
0501-00003 (MWS/NOMID)	8 yr	D2306	2mg/kg s.c.	responder at cut-off
0002-00001 (MWS)	9 yr	D2304	2mg/kg s.c. (x5)	responder, no relapses, D/C on Day 229 for SAE (UTI)
0002-05113 (MWS)	13 yr	A2102	2mg/kg s.c. (x6)	responder, 1 st relapse at Day 63, then approx 59 days post-dose.

Upon further investigation of canakinumab exposure (dose) and time-to-flare (a different efficacy variable), we found a noticeable difference between patients receiving 2 mg/kg dose and 150 mg dose. In terms of the proposed route of administration, i.e., subcutaneous administration, data indicated a shorter median time to relapse in patients receiving 2 mg/kg dose as compared to 150 mg dose (e.g. median values for time to relapse are 48.6 and 115 days for patients receiving 2mg/kg and 150 mg doses, respectively). Two of the patients receiving 2 mg/kg dose received an IV rescue of canakinumab. This suggests that a dose higher than 2 mg/kg may be considered for low body weight patients who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable. It is noteworthy that the 10 mg/kg IV dose of canakinumab showed the longest median time-to-relapse among all cohorts, 1 mg/kg IV dose showed lower median time-to-flare, albeit in limited number of subjects (see Table below).

Figure Legend: Cumulative Probability of Time-to-Relapse by Dose Group

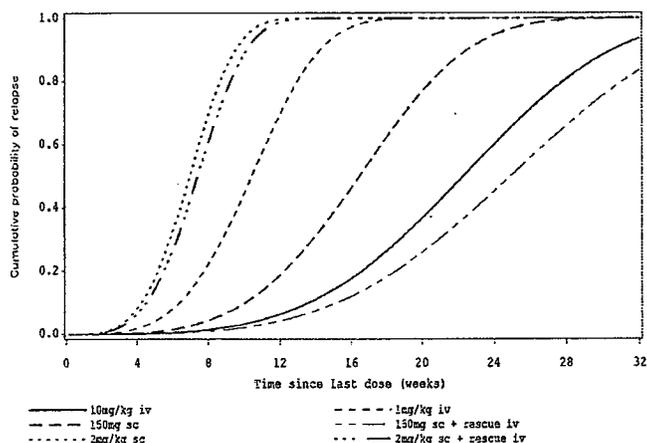
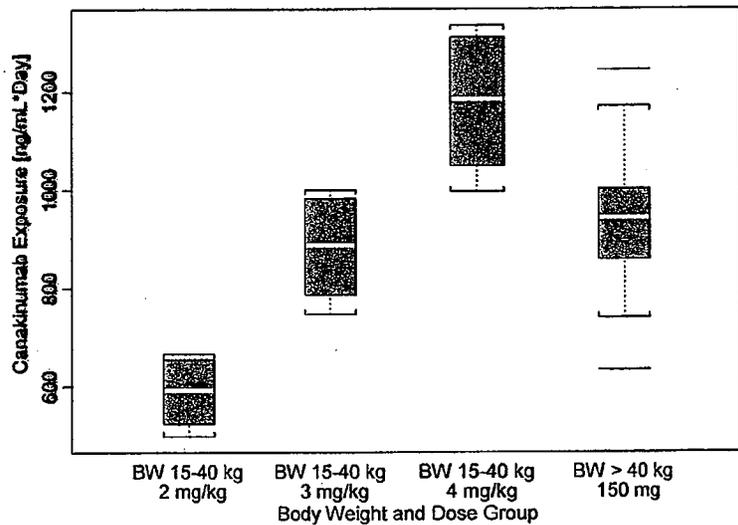


Table Legend: Median Time-to-Relapse Stratified by Different Dose Regimen

Dose regimen	Number of unique subjects who received dose regimen	Number of periods	Median Time-to-Relapse (days)	95% Confidence Interval
10 mg/kg i.v.	4	4	156.2	102.5 - 209.8
1 mg/kg i.v.	4	4	72.8	48.0 - 97.7
150 mg s.c.	29	96	115.2	94.1 - 136.4
150 mg s.c. + rescue i.v.	4	5	174.5	90.5 - 258.5
2 mg/kg s.c.	4	22	48.6	29.3 - 67.9
2 mg/kg s.c. + rescue i.v.	2	11	51.7	27.0 - 76.5

As discussed before, clearance of canakinumab is dependent on bodyweight; hence, bodyweight based dosing is appropriate. We also noted that the median canakinumab exposure for low body weight patients receiving 2 mg/kg dose is 37% lower than the high body weight patients receiving 150 mg dose. Simulations exposure of 2 mg/kg, 3 mg/kg and 4 mg/kg in patients with 15 – 40 kg bodyweight were compared to that noted in patients of >40 kg bodyweight receiving 150 mg dose. We propose that the dose should be increased to 3 mg/kg in patients with 15 – 40 kg bodyweight (Figure below) who do not demonstrate adequate clinical efficacy with 2 mg/kg dose, provided safety and tolerability are acceptable.

Simulated Exposure Distribution for Low Body Weight Patient (≥ 15 kg and ≤ 40 kg) and High Body Weight Patient (> 40 kg) Following Different Doses



Overall, adequate Clinical Pharmacology information has been provided by the sponsor in support of this BLA.

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2.1 General Attributes

Novartis Pharmaceuticals Corporation submitted this original BLA for ILARIS (Canakinumab or ACZ885) injection for the treatment of Cryopsin Associated Periodic Syndrome (CAPS). CAPS, an orphan indication, are group of systemic autoinflammatory diseases including Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal-onset Multisystem inflammatory Disease (NOMID). Ilaris is not approved for CAPS or any other indications outside US.

Ilaris is a recombinant human monoclonal anti-human interleukin- β (IL-1 β) antibody of the IgG1/k isotype. Ilaris is supplied in sterile, single-use 6 ml glass vial as a 150 mg white, preservative-free lyophilized powder and requires reconstitution with 1 mL of preservative-free sterile for injection via subcutaneous administration.

In addition to the adults, the current submission also seeks marketing approval of ILARIS for use in treatment of CAPS in children over 4 years of age. The recommended dose for CAPS patients with body weight >40 kg is 150 mg, and for patients with body weight \geq 15 kg and \leq 40 kg is 2 mg/kg, administered as a subcutaneous injection every eight weeks. Priority review has been granted on the basis of this products' potential to serve the unmet medical need in treating children with CAPS diseases.

2.2 General Clinical Pharmacology

Clinical Pharmacology and Clinical study data results from three clinical studies form the basis for canakinumab safety and efficacy in CAPS patients. Study A2102 was an open-label dose-titration study in CAPS (also providing long-term safety data). Study D2304 was a placebo-controlled efficacy trial in patients with Muckle-Wells Syndrome (MWS) including an uncontrolled element in both the run-in (Part I) and extension period (Part III), and Study D2306 is an uncontrolled long-term safety and efficacy trial in CAPS.

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A general overview of the clinical trial design, study population and clinical endpoints are tabulated below.

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Study objective, population	Treatment duration	Dosage	Efficacy endpoint
Study A2102 (n= 34)			
Dose selection in CAPS (MWS, FCAS, NOMID + MWS)	Up to 28 months	(Multiple doses, re-dosing upon relapse) initially 10 mg/kg IV (first 4 patients only) then 1 mg/kg IV (first 4 patients only) next 150 mg SC (age >16) or 2 mg/kg (age ≤16)	Induction of clinical response and time to relapse. Clinical response was as assessed by physician's global assessment of disease activity, skin disease activity, and serum inflammatory markers (C-reactive Protein or CRP and serum amyloid A or SAA).
Study D2304 (n=35)			
Safety / efficacy in MWS (Parts I & III: uncontrolled) (Part II: placebo-controlled withdrawal)	48 wks in total: Part I: 8 weeks Part II: 24 weeks Part III: 16 weeks	Part I 150 mg SC single dose (>40kg) or 2 mg/kg SC (15 -40kg) Part II 150 mg SC q 8wk (>40kg) or 2 mg/kg SC (15 -40kg) or placebo Part III 150 mg SC q 8wk (>40kg) or 2 mg/kg SC (15 -40kg)	Part I: At the end of week 8 (Day 57), all patients who were complete responders by Day 8 or Day 15 and did not flare entered Part II. In the withdrawal period in Part II of the study, the primary efficacy variable was the proportion of patients with disease flare.
Study D2306 (n=57)			
Safety / efficacy in CAPS (MWS, FCAS, NOMID + MWS)	6 months-2 years	150 mg SC q 8wk (>40kg) or 2 mg/kg SC (15 - 40kg)	Maintenance of response (absence of relapse)

2. What are the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

In study D2304, complete response to treatment was defined as:

- Physician global assessment of autoinflammatory disease activity ≤ **minimal** (using a 5-point scale ranging from absent to severe)

AND

- Assessment of skin disease ≤ **minimal** (using a 5-point scale ranging from absent to severe)

AND

Normal serum values of C-reactive protein (CRP) and/or serum amyloid A (SAA) (< 10 mg/L)

For complete responders, relapse was defined as the following criteria (to be assessed on the same day):

- CRP and/or SAA value > 30 mg/L

AND EITHER

- Physician global assessment of autoinflammatory disease activity > minimal

OR

- Physician global assessment of autoinflammatory disease activity = minimal AND assessment of skin disease > minimal

3. Exposure-response and pharmacodynamics of canakinumab

We identified that there was no exposure-response relationship following canakinumab treatment when considering “incidence of flare” as the primary efficacy endpoint from the pivotal trial. Upon further investigation of canakinumab exposure (dose) and time-to-flare (a different efficacy variable), a noticeable difference between patients receiving 2 mg/kg dose and 150 mg dose was observed. A 3 mg/kg should be considered for low body weight subjects who do not demonstrate adequate clinical efficacy with 2 mg/kg dose, provided safety and tolerability are acceptable.

In pivotal clinical trial # D2304, CAPS patients meeting the following inclusion criteria were recruited:

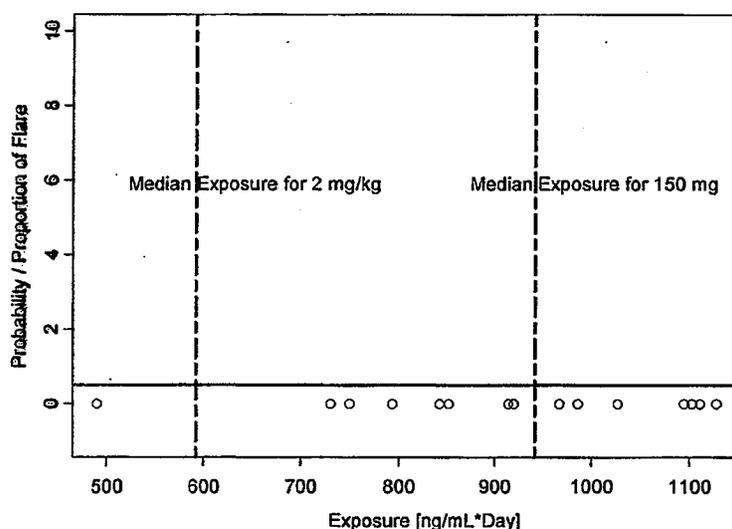
- Male and female patients aged 4 to 75 years.
- Molecular diagnosis of NALP3 mutations and clinical picture resembling Muckle-Wells Syndrome (MWS) (patients who participated in the CACZ885A2102 study, had the option to participate in this study upon disease relapse).
- Body weight ≥ 15 and < 100 kg.

During the lead-in period or Part I of the study, 97.1% of patients (n=35) had a complete response to canakinumab, with 71.4% of patients having complete response by the first scheduled time point (Day 8). Four patients discontinued before entering Part II (double-blinded, placebo-controlled, random-withdrawal period) because insufficient efficacy was demonstrated in Part I (open-label, active treatment period). Two are from the 17 - 41 year group and two from >41 yr old group. Although the clinical endpoints CRP (n=3) and SAA (n=4) improved over baseline, these patients were noted as having minimal disease activity by the physician’s global assessment of disease activity (PGADA); whereas treatment success would require “absence” of disease as assessed by PGADA.

Exposure-response with respect to “incidence of flare” as primary endpoint:

A flat exposure-response relationship was noted following canakinumab treatment, where response is defined as the incidence of flare by the end of part II in the trial (See Figure below). In summary, a similar clinical and biomarker response can be seen in low body weight patient receiving 2 mg/kg dose as compared to high body weight (> 40 kg) patients receiving 150 mg dose.

Figure Legend: Exposure-Response Relationship for Subjects in Study D2304



Exposure-response with respect to “time to flare” as a clinical endpoint:

At a clinical pharmacology briefing held on 5/4/2009, the appropriateness of the proposed bodyweight based dosing in patients between 15 kg – 40 kg bodyweight was discussed. During the briefing, the utility of exploring exposure-response relationship to a different clinical endpoint such as time-to-flare was raised. Most of the subjects in study D2304 did not show disease flare during treatment with canakinumab. Hence, data from the study A2102 which also employed the most number of patients in the 15 – 40 kg body weight range was utilized (See table below).

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0002-05116 (MWS)	6 yr	A2102	2mg/kg s.c. (x7)	responder, 1 st relapse at 72 days, then approx 38 days post dose
0002-05108 (MWS)	7 yr	A2102	2 mg/k s.c. (x10) 125 mg iv (x10)	responder, 1 st relapse at 3 days, then partial/no response to 2 mg/kg response to high dose, relapse at 7 relapse approx 34 days after high d
0501-00003 (MWS/NOMID)	8 yr	D2306	2mg/kg s.c.	responder at cut-off
0002-00001 (MWS)	9 yr	D2304	2mg/kg s.c. (x5)	responder, no relapses, D/C on Day 229 for SAE (UTI)
0002-05113 (MWS)	13 yr	A2102	2mg/kg s.c. (x6)	responder, 1 st relapse at Day 63, then approx 59 days post-dose.

Upon further investigation of canakinumab exposure (dose) and time-to-flare (a different efficacy variable), we found a noticeable difference between patients receiving 2 mg/kg dose and 150 mg dose. In terms of the proposed route of administration, i.e., subcutaneous administration, data

indicated a shorter median time to relapse in patients receiving 2 mg/kg dose as compared to 150 mg dose (e.g. median values for time to relapse are 48.6 and 115 days for patients receiving 2mg/kg and 150 mg doses, respectively). Two of the patients receiving 2 mg/kg dose received an IV rescue of canakinumab. This suggests that a dose higher than 2 mg/kg may be considered for low body weight patients who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable. It is noteworthy that the 10 mg/kg IV dose of canakinumab showed the longest median time-to-relapse among all cohorts, 1 mg/kg IV dose showed lower median time-to-flare, albeit in limited number of subjects (see Table below).

Figure Legend: Cumulative Probability of Time-to-Relapse by Dose Group

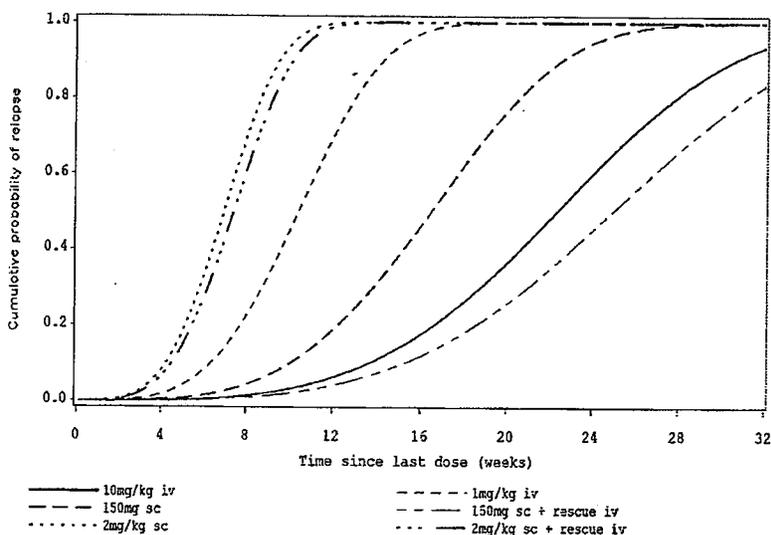


Table Legend: Median Time-to-Relapse Stratified by Different Dose Regimen

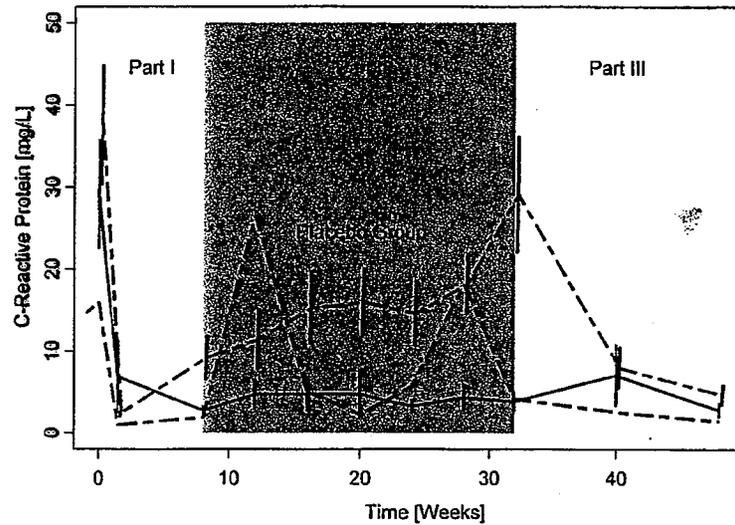
Dose regimen	Number of unique subjects who received dose regimen	Number of periods	Median Time-to-Relapse (days)	95% Confidence Interval
10 mg/kg i.v.	4	4	156.2	102.5 - 209.8
1 mg/kg i.v.	4	4	72.8	48.0 - 97.7
150 mg s.c.	29	96	115.2	94.1 - 136.4
150 mg s.c. + rescue i.v.	4	5	174.5	90.5 - 258.5
2 mg/kg s.c.	4	22	48.6	29.3 - 67.9
2 mg/kg s.c. + rescue i.v.	2	11	51.7	27.0 - 76.5

Pharmacodynamics of canakinumab

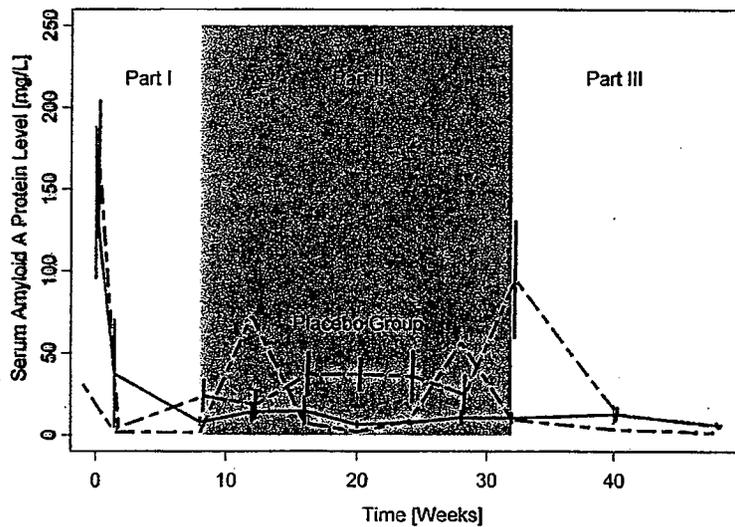
Canakinumab binds to human IL-1 β , and blocks the interaction of this cytokine with its receptors. Sponsor evaluated the changes in several serum and pharmacogenetic markers in CAPS patients following canakinumab treatment (Study D2304, see pharmacometrics review by Dr. Hao Zhu and Genomics review by Dr. Mike Pacanowski). Following the administration of canakinumab, the total (free + canakinumab bound) plasma IL-1 β levels were elevated. Objective clinical endpoints such as CRP and SAA decreased in response to canakinumab treatment during all stages of the clinical trial. As shown in the figure below, the clinical response was noted within one to two weeks of treatment initiation in the open-label lead-in period. During the

randomized withdrawal period, both CRP and SAA increased in placebo group, whereas they remained low in canakinumab treatment group.

Figure: Change in Clinical Endpoints, C-Reactive protein and Serum Amyloid A, with canakinumab treatment over the entire clinical trial # 2304



(A)



(B)

Note: blue line = Treatment Group (Mean ± SE)

Red line = Placebo Group (Mean ± SE)

Green line = Observation from Subject CACZ885D2304_0002_00001.

Among 35 subjects enrolled in the pivotal trial (Study #2304), only 1 subject received less than 150 mg dose. The primary efficacy variable was the number of subject who experienced flare during Part II. Subject CACZ885D2304_0002_00001 was randomized into the treatment group and experience

no flare during the entire part II. In addition, the CRP and SAA levels for subject CACZ885D2304_0002_00001 were similar with the rest of the subjects in the treatment group (see figure above) by the end of part I, II and III.

Apart from subject CACZ885D2304_0002_00001, seven other subjects received 2 mg/kg dose during the clinical development in study# 2102. See clinical review by Dr. Carolyn Yancey for information on canakinumab efficacy in pediatric CAPS patients.

4. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Canakinumab PK and PD, measured as total IL-1 β levels (free and antibody bound), have been characterized in CAPS patients in the following studies (see discussion below and attached study synopses):

- SC Dose titration study in CAPS patients [CACZ885A2102]
- Randomized withdrawal study in CAPS [CACZ885D2304] Proposed dosing regimen was prospectively studied

Additionally, pharmacokinetics of canakinumab was also studied in healthy volunteers and other patient populations in the following studies (see attached study synopses):

- Single and multiple dose (150 mg) SC administration in patients [CACZ885
- In healthy subjects and as IV infusion [CACZ885'
- In healthy Japanese volunteers as IV infusion [CACZ885A1101]
- In RA patients as IV infusion [CACZ885A2101]

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The PK parameters were determined in serum using non-compartmental analysis as well as a compartmental modeling approach described by a population based PK model in ACZ885 CAPS Modeling Report. Review of population PK modeling and simulation report by Dr. Hao Zhu is appended to the review.

5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

In adult CAPS patients peak serum levels of 15.9 (\pm 3.52) μ g/mL were reached by approximately 7 days. Apparent half-life following the single SC dose administration was 26.1 (\pm 7.31) days. The low apparent clearance (average CL/F was 0.228 \pm 0.0597 L/d) and a low apparent volume of distribution (V_z /F was 8.33 \pm 2.62 L) noted for canakinumab appeared typical for a human IgG molecule.

Pharmacokinetics of single dose SC administered canakinumab were investigated in adult CAPS patients in study #A2102 and in

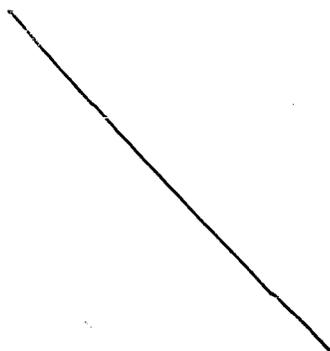
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In study A2102, CAPS patients received canakinumab in two stages. In dosage stage 1, first dose was a single administration of 10 mg/kg IV, the 2nd dose was a single administration of 1 mg/kg IV upon relapse. On second relapse, single administration of 150 mg SC Dosage Stage 2: single administration of 150 mg SC followed by repeat administration upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg SC). If needed: rescue dose of 5 or 10 mg/kg IV Twenty five subjects received single 150 mg SC dose of canakinumab in stage 2 of the study. Since they did not require additional doses due to lack of disease relapse, single dose PK were calculated by noncompartmental analysis (see PK parameters below).

Table: PK parameters of canakinumab a single SC dose of 150 mg in adult CAPS patients are shown in the table below.

	C_{max} [µg/mL]	T_{max} (day)	AUC_{last} [µg*d/mL]	AUC_{0-∞} [µg*d/mL]	F (%)	t_½ [d]	CL/F [L/d]	V_z/F [L]
n	25	25	22	22	4	22	22	22
Mean	15.9		674	708	66.5	26.1	0.228	8.33
SD	3.52		189	206	22.2	7.31	0.0597	2.62
Median	16.2	6.98	634	656	69.7	25.6	0.229	7.97
Min	10.4	1.92	387	405	37.3	13.1	0.125	4.38
Max	21.7	14.0	1124	1204	89.3	39.2	0.370	13.9
CV%	22.2		28.0	29.1	33.5	28.0	26.2	31.4

Figure: Serum PK concentration-time profiles in adult patients [n = 25] after single (initial) SC dose of 150 mg canakinumab (ACZ885)*



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The protocol (study #2102) allowed repeated drug administration only if the disease relapsed in the patients. In patients receiving 150 mg SC, the median time to relapse was about 115 days (95% CI 94 – 136 days). Hence, multiple dose administration and the PK profile varied in different CAPS patients. Following repeat administration, accumulation or change in serum half-life of canakinumab was not noted.

Population PK analysis indicated that steady-state canakinumab levels were achieved in approximately 130 days (5 half-lives, 26.1 days), and a 30% accumulation was estimated-fold for any SC dosing regimen administered every 8 weeks in a typical adult CAPS patient weighing 70 kg. Based on the same model, following multiple doses of 150 mg every 8 weeks in the CAPS patients, the estimated steady state C_{max} and AUC_{tau} were 17.5 µg/mL and 537 µg·day/mL, respectively.

Following IV infusions of 10 mg/kg canakinumab, the maximum serum concentrations were observed within 1 or 2 days after the end of the infusion and were on average 148.7 (SD ± 45.4) µg/mL. After a short distribution phase the serum levels decreased with a mean (± SD) terminal half-life of 31.2 (± 3.39) days. Serum clearance (CL) of canakinumab averaged 0.182 (± 0.053) L/d with

a low total volume of distribution (V_{ss}) (7.08 ± 2.12 L). After dose normalization, the SC dose had an absolute bioavailability of 67%.

Single and multiple dose pharmacokinetics of canakinumab were investigated in patients with _____ following treatments:

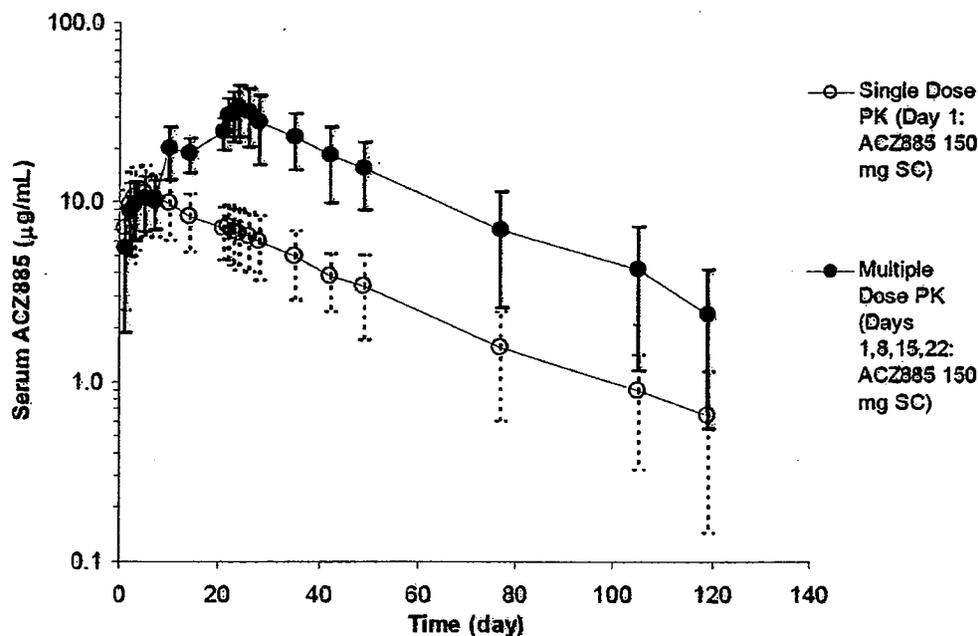
Single dose Cohort - Day 1: Canakinumab 150mg SC, Days 8,15,22: Placebo SC.

Multiple dose Cohort – Day 1, 8, 15, 22 Canakinumab 150 mg SC.

Table: PK parameters of canakinumab in adult patients with _____ receiving 150 mg SC are described in the table below.

Summary Statistics	C _{max} (µg/mL)	T _{max} (day)	AUC _{tlast} (µg.day/mL)	t _{1/2} (day)	AUC _{∞i} (µg.day/mL)	V _z /F (L)	CL/F (L/day)
n	10	10	10	10	10	10	10
Mean	11.9	6.1	451	26.2	479	15.0	0.430
SD	4.89	3.62	177	5.16	197	9.96	0.341
CV%	40.9	59.4	39.2	19.7	41.1	66.3	79.3
Median	13.5	5.0	510	25.6	527	10.6	0.286
Minimum	3.1	2.0	120	19.9	123	9.6	0.209
Maximum	18.5	14.0	624	36.2	717	39.8	1.22

Figure: Mean (SD) serum concentration-time profile of ACZ885 following single and multiple sc ACZ885 dose (150 mg) in patients with _____



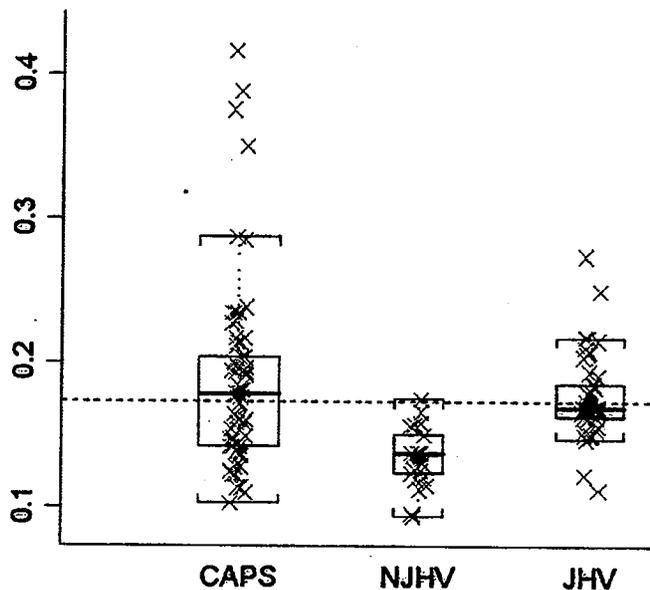
b) How does the PK of the drug in healthy volunteers compare to that in patients?

Based on the population PK analysis, the PK parameters were comparable between CAPS patients and other study populations (Japanese healthy volunteers or JHV and non-Japanese volunteers or NJHV (predominantly Caucasian)), except for the non-Japanese healthy volunteers, which differed from CAPS patients in that they had approximately 20% slower clearance.

Compared to CAPS patients, pharmacokinetics (C_{max} , AUC and $t_{1/2}$) of canakinumab appear to be similar in healthy volunteers. The non-compartmental $t_{1/2}$ estimate in adult CAPS patients, — patients, and in healthy adult Japanese subjects following a single 150 mg SC dose of canakinumab, estimated by non-compartmental analysis were 26.1, 26.2, and 26.3 days respectively.

As noted in the discussion above, in adult CAPS patients peak serum levels of $15.9 (\pm 3.52) \mu\text{g/mL}$ were reached by approximately 7 days. Apparent half-life following the single SC dose administration was $26.1 (\pm 7.31)$ days. The low apparent clearance (average CL/F was 0.228 ± 0.0597 L/d) and a low apparent volume of distribution (V_z/F was 8.33 ± 2.62 L) noted for canakinumab appeared typical for a human IgG molecule (see figure below). Based on the population PK analysis, the PK parameters were comparable between CAPS patients and other study populations (Japanese healthy volunteers or JHV and non-Japanese volunteers or NJHV (predominantly Caucasian)), except for the non-Japanese healthy volunteers, which differed from CAPS patients in that they had approximately 20% slower clearance.

Figure Legend: Clearance (L/day) in CAPS patients and in healthy volunteers



c) What are the characteristics of drug absorption?

Absolute bioavailability of subcutaneously administered canakinumab is approximately 70%.

As discussed above in the single dose PK studies, absolute bioavailability of SC canakinumab is 67% in CAPS (n=4, study#A2102), and ~70% in healthy Japanese subjects (n=10, study#A1101).

d) What are the characteristics of drug distribution?

Canakinumab acts by binding to IL-1 β . No specific studies were conducted to determine the serum/plasma protein binding of canakinumab.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not conducted for this biologic.

f) What are the characteristics of drug metabolism?

Canakinumab, a biologic, is not suspected to undergo metabolism as in the case noted with small molecules.

g) What are the characteristics of drug excretion?

Exact pathway of canakinumab excretion is unknown.

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Pharmacokinetics of canakinumab appears to be linear following IV administration of 0.3 to 10 mg/kg doses in healthy volunteers, RA patients and CAPS patients. A dose-proportional increase in PK parameters (C_{max} and AUC) was noted when 150 mg and 300 mg SC dose was administered in healthy volunteers.

In study A1101, following IV infusion administration of 1 mg/kg, 3 mg/kg and 600 mg in Japanese healthy volunteers, the C_{max} , $AUC_{0-t_{last}}$, and AUC_{0-inf} increased in a weight-normalized dose-proportional manner.

Pharmacokinetics of canakinumab was investigated in a placebo-controlled single ascending dose safety, tolerability, study (#A1101) following IV infusion and s.c injection administration in healthy Japanese volunteers. Canakinumab or placebo was administered as an IV infusion over approximately 120 minutes in Cohorts 1, 2, and 3, at doses of 1 mg/kg, 3 mg/kg and 600 mg, respectively. In Cohorts 4 and 5, the study drug was administered as SC injection at the dosage of 150 and 300 mg, respectively. Subjects in Cohort 6 received one 600 mg IV dose followed 2 hours later by a 300 mg SC dose.

Table: Pharmacokinetic parameters of canakinumab following SC administration in health Japanese volunteers.

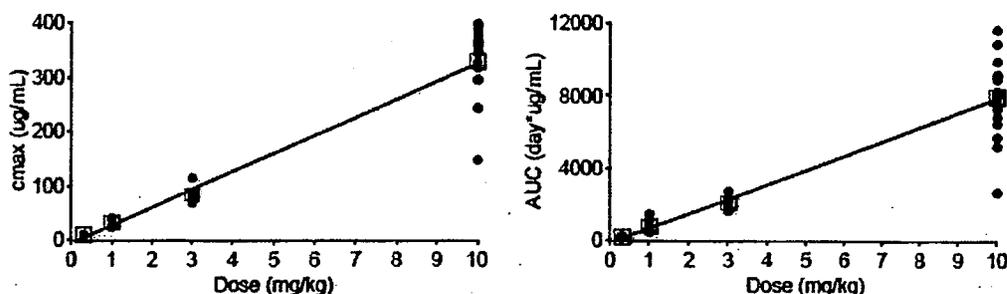
Dose		Tmax (day)	Cmax (day)	AUC0-last ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	AUC0- ∞ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	t _{1/2} (day)
150 mg SC n=6	Mean	-	16.9	15000	15900	26.3
	SD	-	2.62	1750	1910	2.02
	Min	5.00	13.2	12000	12400 16300	24.2
	Median	5.00	17.2	15400	17800	25.9
	Max	9.94	20.2	16900		29.8
	CV%	-	15.5	11.6	12.0	7.67
300 mg SC n=6	Mean	-	34.1	29200	31200	26.9
	SD	-	6.09	4770	6610	8.23
	Min	2.00	25.6	24000	25800	21.7
	Median	5.00	36.0	28800	29700	23.2
	Max	5.00	41.2	37300	43700	42.8
	CV%	-	17.9	16.4	21.2	30.6

Table: Pharmacokinetics of canakinumab following IV administration

Treatment		t_{max} [day]	C_{max} [$\mu\text{g}/\text{mL}$]	$AUC_{0-t_{last}}$ [$\mu\text{g hr}/\text{mL}$]	$AUC_{0-\infty}$ [$\mu\text{g hr}/\text{mL}$]	λ_z [1/day]	$t_{1/2}$ (HL) [day]
1 mg/ kg i.v.	Mean	-	21.0	9390	9770	0.0312	22.6
	SD	-	2.44	1940	2150	0.00454	2.99
	Min	0.0833	18.8	7330	7650	0.0270	18.0
	Median	0.167	20.4	8720	9060	0.0289	24.0
	Max	0.167	25.5	12500	13500	0.0386	25.7
	CV%	-	11.6	20.6	22.1	14.6	13.3
3 mg/ kg i.v.	Mean	-	57.5	24500	26000	0.0262	27.4
	SD	-	5.85	4260	4980	0.00539	5.41
	Min	0.0833	46.7	20200	21800	0.0198	20.1
	Median	0.125	58.5	22600	23400	0.0251	27.6
	Max	0.167	64.4	30700	32600	0.0344	35.0
	CV%	-	10.2	17.4	19.1	20.6	19.8
600 mg i.v.	Mean	-	191	82500	87100	0.0268	27.2
	SD	-	21.2	8880	11300	0.00675	6.61
	Min	0.0833	159	67100	68000	0.0186	18.4
	Median	0.0833	192	83900	87800	0.0255	27.3
	Max	0.167	215	94100	102000	0.0376	37.2
	CV%	-	11.1	10.8	12.9	25.2	24.3

Figure legend:

Canakinumab IV dose-proportionality: 0.3 - 10 mg



ACZ885 Dose-Cmax relationship. Shown are the individual values (filled circles), group means (open squares), and the linear regression line.

As in left panel for ACZ885 Dose-AUC relationship. Regression line:

i) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability in CAPS patients was similar with a coefficient of variation of approximately 22.2% and 29.1% observed in C_{max} and AUC_{∞} values. Patient's bodyweight, disease and race explain the inter-subject variability of canakinumab pharmacokinetics (see discussion below).

2.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure of canakinumab?

Clearance and volume of distribution of canakinumab is related to patients' bodyweight.

Sponsor evaluated the effect of age, race, gender and disease on the pharmacokinetics of canakinumab. There were limited number (n=69) of CAPS patients in the clinical and clinical pharmacology database because CAPS is an orphan disease. However, clinical PK database included healthy volunteers and patients that received canakinumab for the experimental treatment of — rheumatoid arthritis and —. The randomized withdrawal clinical trial employed a single dose and there was high success rate (85%) compared to placebo. Hence, an exposure-response analysis could not be conducted. However, it was noted that clearance of canakinumab was dependent on bodyweight of patient. See Dr. Hao Zhu's review and the discussion below.

Table: Demographics of subjects in different PK studies is tabulated below.

Study	Study pop'n.	Patient numbers		Demographic data for analysis population (mean ± SD & range)					
		# patients analyzed	# placebo	Weight (kg)	Age (years)	Albumin (g/L)	M	F	
A2102	CAPS	Adults	27	0	61.4 ± 8.1 (43 - 77)	35.6 ± 10.6 (18 - 51)	42.3 ± 3.4 (33 - 48)	10	17
		Peds	7	0	31.2 ± 14.3 (17.2 - 52)	9.9 ± 5.3 (4 - 17)	42.6 ± 3.6 (38 - 49)	3	4
		TOT	34*	0	55.2 ± 15.6 (17.2 - 77)	30.3 ± 14.3 (4 - 51)	42.4 ± 3.4 (33 - 49)	13	21
D2304	CAPS	Adults	30	0	59.4 ± 9.7 (42.4 - 81.9)	36.8 ± 13.5 (18 - 74)	42.7 ± 2.9 (37 - 49)	7	23
		Peds	5	0	55.9 ± 20.7 (26.3 - 82)	14.2 ± 3.1 (9 - 17)	40.8 ± 5.5 (34 - 47)	3	2
		TOT	35*	0	58.9 ± 11.5 (26.3 - 82)	33.6 ± 14.8 (9 - 74)	42.4 ± 3.4 (34 - 49)	10	25
B2101	HV, Non-Japanese	25	7	69.6 ± 12.1 (48 - 93.4)	34.6 ± 10.5 (19 - 61)	42.8 ± 2.4 (39.4 - 47.5)	13	12	
A1101	HV, Japanese	48	12	63.8 ± 7.6 (50.5 - 82.7)	24.6 ± 3.9 (20 - 34)	46.1 ± 1.9 (41 - 50)	48	0	
—	—	25	3	76.9 ± 13.5 (57 - 120)	33.2 ± 10.3 (18 - 58)	43.1 ± 2.4 (38.3 - 48.8)	18	7	
A2101	RA adults	52	15	74 ± 13.2 (51 - 100.5)	53.5 ± 10.5 (18 - 74)	40.9 ± 3.1 (33 - 49)	13	39	
—	—	23	4	84.2 ± 11.1 (66.8 - 99.8)	39.3 ± 13.3 (20 - 62)	45.4 ± 3 (42 - 54.2)	23	0	

b(4)

b(4)

Summary of the Final Canakinumab PK Parameter Estimates

Parameter [units]	Population mean [$\theta \pm \text{SEM}$]	Inter-individual variance [$\sigma \pm \text{SEM} (\%CV)$]
Canakinumab parameters		
Clearance for drug (CL_D , L/d at 70 kg and 43 g/L albumin)	0.174 \pm 0.0124	0.0859 \pm 0.0147 (20%)
Central volume of distribution (V_D , L/70 kg)	3.30 \pm 0.135	0.0589 \pm 0.0205 (24%)
Peripheral volume of distribution (V_P , L/70 kg)	2.71 \pm 0.151	0.0817 \pm 0.02 (20%)
Absorption rate constant (k_a , 1/d for 34 year old) for	0.299 \pm 0.0382	0.406 \pm 0.107 (64%)
Logit bioavailability parameter	0.545 \pm 0.227	
BAV after transformation from logit	83.3% \pm 5.26% [‡]	
Intercompartmental permeability flow (PS_D , L/d)	0.429 \pm 0.0529	0.28 \pm 0.107 (53%)
IL-1β parameters		
Clearance for ligand (CL_L , L/d)	14.2 \pm 2.55	0.371 \pm 0.08 (61%)
Production rate of ligand (R_{LI} , ng/d)	9.57 \pm 1.34	0.261 \pm 0.0464 (51%)
Intercompartmental permeability flow f (PS_L , L/d)	0.386 \pm 0.0555	0.254 \pm 0.139 (50%)
Binding constant (K_d , nM)	1.07 \pm 0.173	0.395 \pm 0.13 (63%)
Covariates		
Weight on CL_D ^{**}	0.695 \pm 0.09	
Albumin on CL_D ^{**}	-0.916 \pm 0.185	
Weight on V_D ^{**}	0.684 \pm 0.0921	
Weight on V_P ^{**}	0.798 \pm 0.238	
Age on k_a ^{**}	-0.555 \pm 0.151	
on k_a (ratio from — /	0.899 \pm 0.178	
Absorption rate constant (k_a , 1/d for 34 year old) for	0.269 \pm 0.0634 [‡]	
Logit ratio parameter for cell line on F	1.6 \pm 0.337	
Bioavailability of — material	70.0% \pm 8.25% [‡]	
Study population on CL_D	see table 8-3	
Study population on CL_L	see table 8-3	
Study population on R_{LI}	see table 8-3	
Study population on K_d	see table 8-3	
Covariances in OMEGA matrix		
CL_D - V_D		0.0485 \pm 0.0142
V_P - PS_D		0.0808 \pm 0.0414
V_P - PS_L		0.0408 \pm 0.0408
PS_D - PS_L		0.216 \pm 0.105
CL_L - R_{LI}		0.181 \pm 0.0425
Residual variances		
Canakinumab (ng/mL)	0.0527 \pm 0.00572 (23%)	
IL-1 β (pg/mL)	0.084 \pm 0.0113 (20%)	
Objective function	-10007.83	

^{*} Logit transformation: $F = \exp(X)/(1+\exp(X))$

^{**} Exponent for power model on centered covariate

[‡] Computed using simulation (see section 5.3)

Is the body weight based dosing justified?

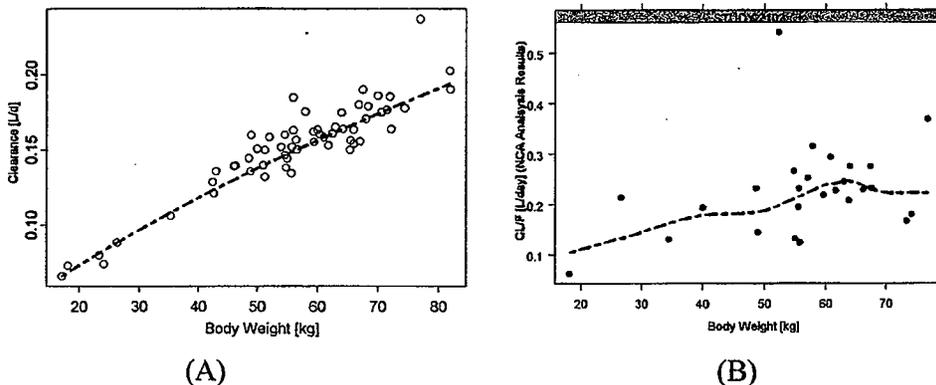
The body weight based dosing proposed by the sponsor is acceptable (see Table below). However, a higher dose (3 mg/kg) may be considered for low body weight subjects (i.e., ≥ 15 kg and ≤ 40 kg) who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable.

The Sponsor Proposed Dose

Patients	Proposed Dose
> 40 kg	150 mg
≥ 15 kg and ≤ 40 kg	2 mg/kg

Body weight based dose adjustment is necessary because large body weight is associated with high clearance of canakinumab. The sponsor's population binding and kinetic model identified body weight as a significant covariate for clearance (Figure below left -A). We confirmed it by checking the relationship between the clearance obtained from Study 2102 using non-compartmental analysis and body weight (Figure below right - B). The results indicated that body weight based dosing is necessary to achieve similar exposure for CAPS patients with different body weights.

Figure Legend: Body Weight and Clearance Relationship



Note: (A) based on binding and kinetic modeling results in all CAPS patients
 (B) based on non-compartmental analysis results from Study 2102.

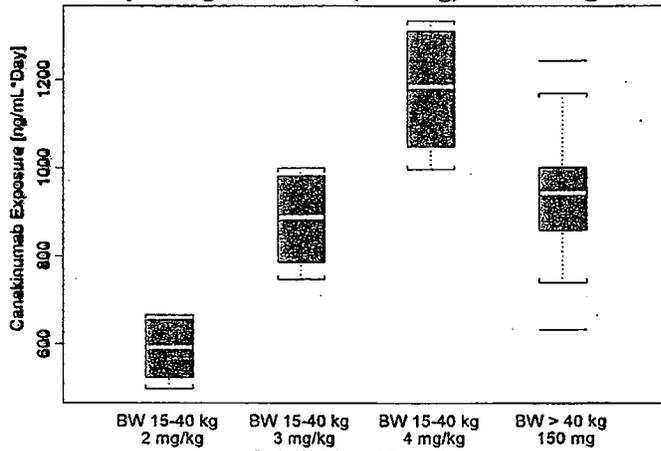
As discussed in the analysis above (see Section 2.3 General Clinical Pharmacology Bullet 3):

- a) A flat exposure-response relationship was noted following canakinumab treatment, where response is defined as the incidence of flare by the end of part II in the clinical trial D2304.
- b) A similar clinical and biomarker response was seen in low body weight patient receiving 2 mg/kg dose as compared to high body weight (> 40 kg) patients receiving 150 mg dose.

Hence, sponsor proposed dosing is acceptable, in general.

Upon further investigation of canakinumab exposure (dose) and time-to-flare (a different efficacy variable), we found a noticeable difference between patients receiving 2 mg/kg dose and 150 mg dose. We noted that the median canakinumab exposure for low body weight patients receiving 2 mg/kg dose is 37% lower than the high body weight patients receiving 150 mg dose. Simulations of exposure of 2 mg/kg, 3 mg/kg and 4 mg/kg in patients with 15 – 40 kg bodyweight were compared to that noted in patients of >40 kg bodyweight receiving 150 mg dose. We propose that the dose can be increased to 3 mg/kg for the patients with 15 – 40 kg bodyweight to match the exposure observed in >40 kg bodyweight patients receiving 150 mg (Figure below).

Simulated Exposure Distribution for Low Body Weight Patient (≥ 15 kg and ≤ 40 kg) and High Body Weight Patient (> 40 kg) Following Different Doses



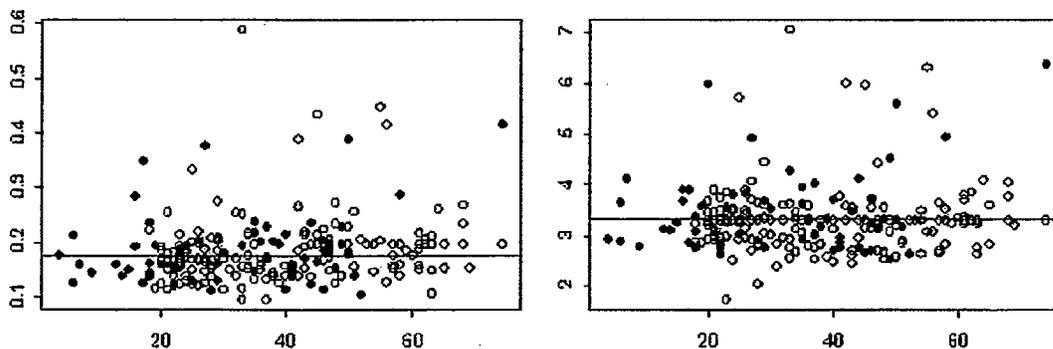
2. Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups?

a) **Elderly**

Dose adjustment is not necessary in elderly patients. Pharmacokinetics of canakinumab when administered subcutaneously does not seem to be different in elderly compared to young adults.

Population PK database consisted of one CAPS patient (receiving canakinumab via SC route) and seven rheumatoid arthritis patients (receiving canakinumab via IV route) who were older than 65 years (range: 68-74). Population PK analysis showed that upon bodyweight normalization, clearance and volume of distribution (central) of canakinumab were not significantly different between elderly and young adults.

Figure: Canakinumab clearance vs. Age after body weight normalization (to 70 kg)
ACZ885 CL, L/d at 70 kg and 43 g/L Alb: Central volume of distribution, L/70 kg

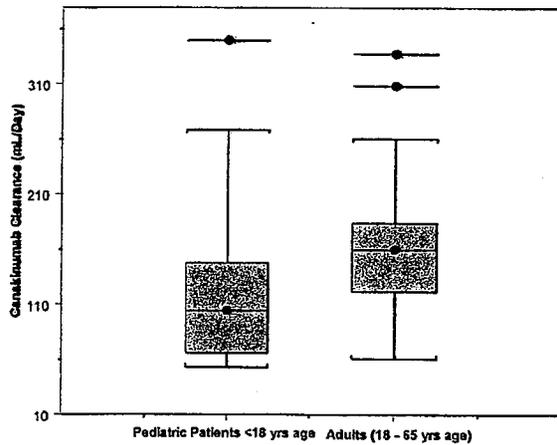


b) **Pediatric patients**

The proposed dose of 2 mg/kg subcutaneous canakinumab is appropriate for pediatric CAPS patients in the bodyweight range of 15kg and 40 kg.

Twelve children were recruited in CAPS clinical trial A2304 and study A2102. Children in the studies were 4 years and older and their bodyweights were in the range of 15 – 40 kg. It should be noted that all of the pediatric CAPS patients responded to treatment in both clinical studies. As mentioned above, population PK analysis evaluated the effect of age (4 – 74 yrs) on clearance and volume of distribution (central) of canakinumab. After bodyweight normalization, canakinumab clearance was not significantly different across patients of different age.

Figure: Clearance of canakinumab in pediatric and adult CAPS patients.



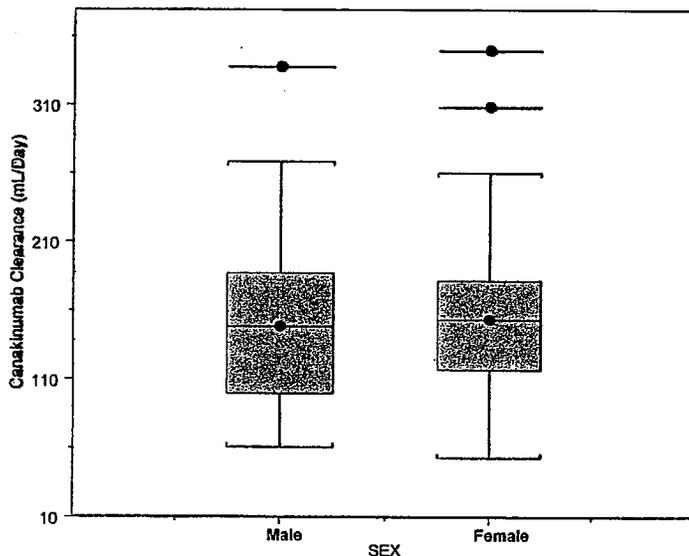
See Dr. Hao Zhu's review for additional discussion above on appropriateness of bodyweight based dosing of canakinumab.

c) Gender

Canakinumab dose adjustment is not needed with regard to gender of the patient.

PK and PD data from 135 males and 98 females were included in the population PK analysis. Population PK analysis indicated that after taking patients body weight into account, PK of canakinumab was similar in males compared to females (see figure below).

Figure: Box-plot of canakinumab clearance in male (n=20) vs. female (n=40) CAPS patients.



d) Race

Canakinumab dose adjustment is not needed with regard to race or ethnicity of patient.

Pharmacokinetics of canakinumab are not significantly different between Caucasian and Asian subjects.

The database for population PK analysis included 175 Caucasians, 54 Asians (of which 48 were Japanese and 3 Indian), 1 black, 1 Native American, 1 “other”. In population PK analysis, after taking body weight into account, non-Japanese and Japanese healthy volunteers differed in canakinumab clearance by about 17%, with the non-Japanese having the slower clearance. However, this difference is not significant to warrant dose adjustment (See discussion in healthy vs. patient PK differences above).

e) Renal impairment

Adequate data is not available to recommend dosage adjustment in patients with renal impairment.

In study # 2102, pharmacokinetics of canakinumab was evaluated in four CAPS patients with varying degree of renal impairment (see table below). Canakinumab (150 mg sc dose) PK parameters from the CAPS patients with renal impairment vs. normal renal function are tabulated below. Although canakinumab Cmax is comparable, AUC levels were very low in patients with decreased renal function is compared to normal renal functions subjects.

Patient #	Creatinine clearance (mL/min)	Cmax (µg/L)	Tmax (days) median	AUC (µg.day/mL)	Vd (L)	T _{1/2} (days)	CL/F (L/day)
CAPS patients	~80	15.9	7	674	8.33	26.1	0.228
5132	40	20.7	7	78.04	5.66	17	0.23
5135	56	13.3	7	110.99	12.35	34.8	0.25
5118	27	11.7	7	76.96	10.94	34	0.223
5136	27 (GFR)	11.1	7	168.96	9.55	33.8	0.196

f)

Hepatic impairment

Pharmacokinetics of

canakinumab were not evaluated in patients with hepatic impairment.

g) Pharmacogenomics?

Canakinumab produces modest changes in IL1-beta pathway gene expression. The efficacy of canakinumab in patients without a molecular diagnosis of NLRP3 mutations (25% of MWS and 50% of NOMID patients) has not been established. Treatment response does not appear to vary according to the different mutations in NLRP3.

Pharmacogenomic aspects of the BLA were reviewed by Dr. Mike Pacanowski (see appended review). CAPS is generally attributed to numerous heterozygous gain-of-function mutations in the gene encoding cryopyrin, NLRP3, which results in constitutive IL-1beta production. NLRP3 mutations are detectable in approximately 75% of FCAS and MWS patients, but less than 50% of NOMID patients.

The sponsor conducted 3 studies to support the efficacy of canakinumab in CAPS: ACZ885A2102, ACZ885D2304, and ACZ885D2306. A molecular diagnosis of presence of NLRP3 mutations was required for entry into A2102 and D2304. This does not represent the distribution of mutations in the to-be-treated population. While some CAPS patients demonstrate low-level mosaicism (i.e. presence of both mutant and non-mutant cells), 25-50% are not characterized as having NLRP3 mutations using conventional sequencing methods.

In both of these studies, the sponsor collected RNA on a voluntary basis from consenting patients at baseline and at various time points following treatment with canakinumab to assess changes in gene expression (genome-wide and focused microarray). RNA samples were collected from a large proportion of study participants. However, gene expression data were incomplete in study # A2102, and not available for analysis to be verified by the reviewer. The gene expression results of study

D2304 were confirmed by the reviewer, and suggested a modest effect of canakinumab on IL-1 beta pathway gene expression (approximately 1.5-fold change); these findings are exploratory.

Two patients with the V198M mutation required frequent use of rescue therapy in study A2102. Since patients with other mutations relapsed in A2102 and D2304, it cannot be concluded based on the available data that NLRP3 mutation status affects treatment response.

h) What pregnancy and lactation use information is there in the application?

Canakinumab pharmacokinetics, safety or efficacy were not evaluated in pregnant and lactating women.

i) Immunogenicity

What is the incidence of formation of antibodies to canakinumab during and after the treatment?

None of the 192 subjects treated with canakinumab in the six different clinical studies developed anti-canakinumab antibodies.

Immunogenicity assessments were done in single and multiple dose PK, safety and efficacy studies in different patient populations.

- SC Dose titration study in CAPS patients [CACZ885A2102]
Blood samples for immunogenicity were collected in each treatment period on Day 1 at predose, on Day 8 and at relapse before re-treatment.
- Randomized withdrawal study in CAPS [CACZ885D2304].
Blood samples for immunogenicity were collected pre-dose 1, pre-dose Day 57, pre-dose Day 113, pre-dose Day 169 and pre-dose Day 120.
- Single and multiple dose (150 mg) SC administration in — patients [CACZ885/ —
Blood samples for immunogenicity were collected at pre-dose 1, pre-dose Day 15, pre-dose Day 22 and at Day 50, 78 and 120.
- In healthy Japanese volunteers as IV infusion [CACZ885A1101]
Blood samples for immunogenicity were collected at pre-dose, day 29, day 57 and day 113.

b(4)

2.4 Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

None evaluated

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, albeit a subtype IL-1 β , such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

2.5 General Biopharmaceutics

During development of canakinumab several drug substance manufacturing changes were introduced. A summary of manufacturing changes and corresponding comparability exercises conducted by the sponsor are listed in the table below. CMC reviewer, Dr. Ruth Cordoba-Rodriguez, addressed the

adequacy of the physico-chemical comparability testing and results supporting the introduction of the final commercial material (Product type D). The final commercial product of canakinumab, referred to as Product type D, will be available as 150 mg powder for solution for injection, as a lyophilisate form, that is reconstituted with Water for Injections (WFI) intended for SC administration.

Summary of the main manufacturing changes for drug substance and drug product during development, the corresponding comparability exercises and the material used per clinical study or program

Item	Process A	Process B	Process C	Process D
Production cell line				
Drug substance concentration				
Drug product strength				
Drug substance manufacturing site				
Drug product manufacturing site				
Drug substance scale (approximate working volume)				
Drug substance manufacturing change				
Comparability exercise	Physicochemical testing	Physicochemical testing PK marmosets Tissue cross-reactivity (human /marmosets)	Physicochemical testing PK marmosets Tissue cross-reactivity (human /marmosets)	Physicochemical testing
PKPD Comparison in Humans	Population based PK-binding model ⁶	Population based PK-binding model ⁶	No data available	No data available
Toxicology Test	-Marmosets: 4, 26 wks i.v., 13 wks s.c. toxicology and EFD ⁷ -Tissue cross-reactivity Study	-Single dose local intra-articular marmoset -Tissue cross-reactivity Study	-Tissue cross-reactivity Study	No data available
Material per clinical study	CACZ885A2101 CACZ885A2102 CACZ885 / CACZ885 CACZ885A2101	CACZ885D2304	CACZ885D2306	intended for market, and intended to be used for clinical trials
Use of ACZ885 batches	Clinical trials	Clinical trials	Clinical trials	Clinical trials, market

b(4)

b(4)

2.6 Analytical

1) Is the method employed for detection of canakinumab adequately validated?

Total canakinumab, i.e. free canakinumab plus canakinumab bound to IL-1 β (canakinumab : IL-1 β complex), was analyzed in human serum using a specific competitive ELISA method with an LLOQ of 100 ng/mL. This method is based on a purified anti-idiotypic anti-canakinumab antibody coated on microtiterplates. Total IL-1 β is determined in human serum using a sandwich ELISA method based on a commercially available kit with a lower limit of detection of 0.1 pg/mL.

b(4)

APPEARS THIS WAY ON ORIGINAL

Summary of analytical method validation for canakinumab or ACZ-885 detection

<i>Method</i>	Competitive ELISA
	A purified anti-idiotypic anti-ACZ885 antibody is coated on the microtiterplate. Serum samples (calibration, quality control or unknown samples) and biotin-labeled 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 O-phenylenediamine dihydrochloride (OPD) as substrate.
<i>Detection</i>	Optical density at 490/650 nm
<i>Calibration curves</i>	4-Parameter Logistic (4PL) fit. The acceptance criteria for the mean accuracy was met: Deviation $\leq 15\%$ (from nominal concentration) within the working range for at least two-third of the non-zero calibration samples.
<i>LLOQ</i>	42.6 pg/mL serum
<i>ULOQ</i>	2130 pg/mL serum
<i>Intra-day accuracy and precision</i>	Intra-day Accuracy within the range 89.1 % to 117 %. Intra-day Precision within the range 3.9 % to 25.9 %.
<i>Inter-day accuracy and precision</i>	Inter-day Accuracy within the range 100.6 % to 105 %. Inter-day Precision within the range 9.6 % to 14.9 %.
<i>Stability</i>	Stable in spiked human serum after 3 freeze-thaw cycles
	Stable in spiked human serum for at least 4 weeks storage at or below -18°C

Immunogenicity Assay:

The method used to screen the human samples for anti-ACZ885 antibodies was a _____ method validated for human serum. The principle of the method is the interaction of anti-ACZ885 with ACZ885 based on plasmon resonance spectroscopy _____, ACZ885 is

b(4)

Biologic product quality reviewer, Dr. Lixin Xu, from the division of monoclonal antibodies has observed several deficiencies in the validation of the immunogenicity assay, particularly regarding the sensitivity of the assay.

20 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2 Individual Study Reviews

4.2.1 Pharmacometrics Review

See Next Page

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the body weight based dosing justified?

The body weight based dosing proposed by the sponsor is acceptable (Table 1). However, a higher dose (3 mg/kg) should be considered for low body weight subjects (i.e., ≥ 15 kg and ≤ 40 kg) who do not demonstrate adequate clinical efficacy with 2 mg/kg dose, provided safety and tolerability are acceptable.

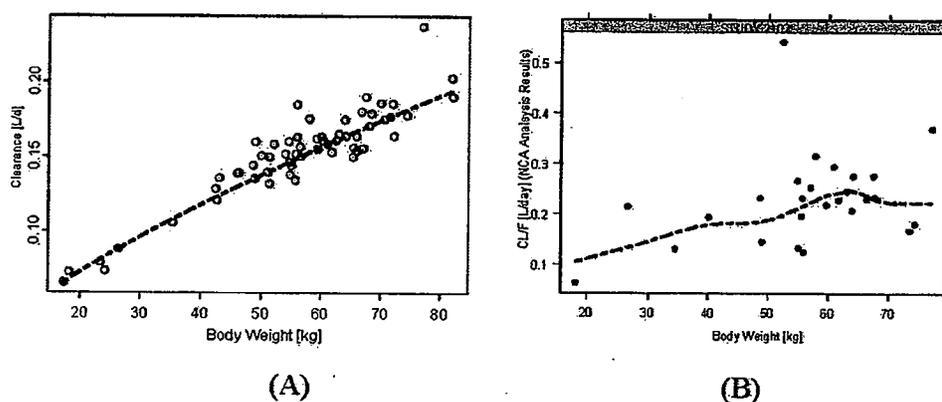
Body weight based dose adjustment is necessary because large body weight is associated with high clearance of canakinumab. The sponsor's population binding and kinetic model identified body weight as a significant covariate for clearance (Figure 1A). We confirmed it by checking the relationship between the clearance obtained from Study 2102 using non-compartmental analysis and body weight (Figure 1B). The results indicated that body weight based dosing is necessary to achieve similar exposure for CAPS patients with different body weights.

Based on the clinical (relapse of flare) and biomarker (SAA and CRP levels) observations in the pivotal clinical trial (Study 2304), the sponsor proposed body weight adjusted dose is acceptable. However, only 1 subject (subject CACZ885D2304_0002_00001) received 2 mg/kg dose while all other subjects received 150 mg (N=34). The primary efficacy variable was the number of subjects who experienced flare during Part II of the trial. Subject CACZ885D2304_0002_00001 was randomized into the treatment group and experienced no flare during the part II. In addition, the major biomarker values for subject CACZ885D2304_0002_00001 were similar to the rest of the subjects in the treatment group by the end of part I, II and III of the trial (Figure 2). In addition, we identified a flat exposure-response relationship following canakinumab treatment, where response is defined as the incidence of flare by the end of part II in the trial (Figure 4). In summary, a similar clinical and biomarker response can be seen in low body weight patient receiving 2 mg/kg dose as compared to high body weight (> 40 kg) patients receiving 150 mg dose.

However, by investigating canakinumab exposure and time-to-flare (a different efficacy variable), we found a noticeable difference between patients receiving 2 mg/kg dose and 150 mg dose. Figure 4 showed that the median canakinumab exposure for low body weight patients receiving 2 mg/kg dose is 37% lower than the high body weight patients

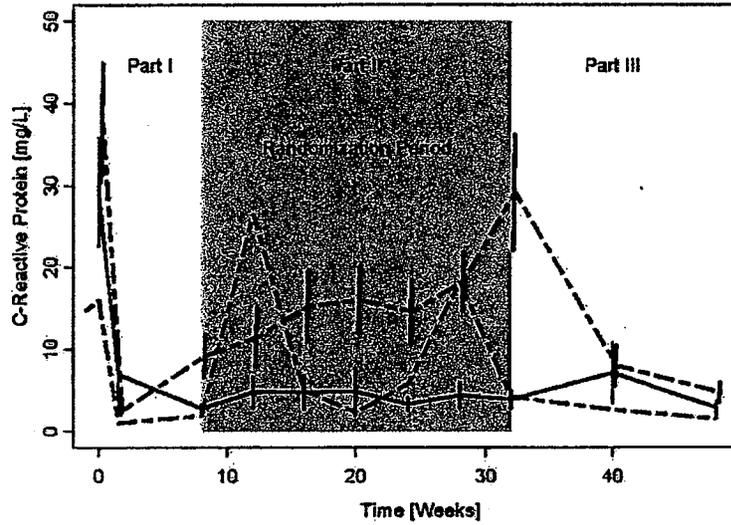
receiving 150 mg dose. Furthermore, the observation from Study 2102 indicated a shorter median time to relapse in patients receiving 2 mg/kg dose as compared to 150 mg dose (e.g. median values for time to relapse are 48.6 and 115 days for patients receiving 2mg/kg and 150 mg doses, respectively). This suggests that a higher dose than 2 mg/kg can be considered for low body weight patients who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable. We proposed that the dose can be increased to 3 mg/kg for these patients to match the exposure observed in high body weight patients receiving 150 mg (Figure 3).

Figure 1. Body Weight and Clearance Relationship

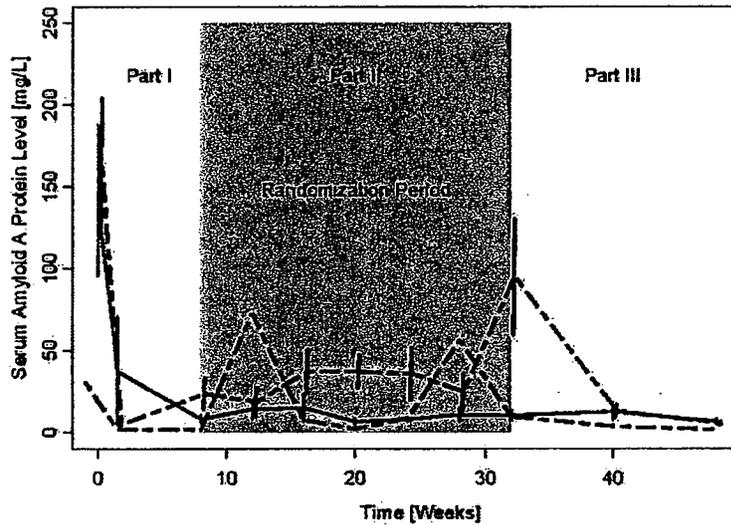


Note: (A) based on binding and kinetic modeling results in all CAPS patients
(B) based on non-compartmental analysis results from Study 2102.

Figure 2 Biomarkers in the Treatment Group and the Observation from Subject CACZ885D2304_0002_00001



(A)



(B)

Note: (A) CRP level and (B) SAA level from Study 2304
Blue line = Treatment Group (Mean \pm SE)
Red line = Placebo Group (Mean \pm SE)
Green line = Observation from Subject CACZ885D2304_0002_00001 (on treatment).

Figure 3. Simulated Exposure Distribution for Low Body Weight Patient (≥ 15 kg and ≤ 40 kg) and High Body Weight Patient (> 40 kg) Following Different Doses

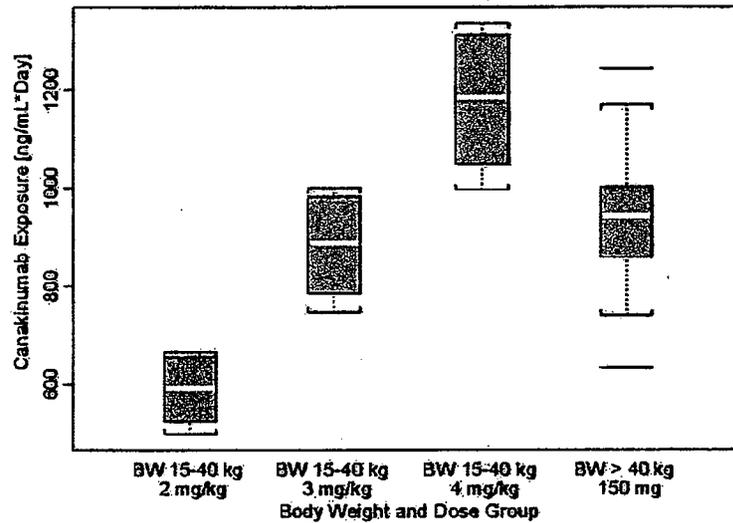


Figure 4 Exposure-Response Relationship for Subjects in Study D2304

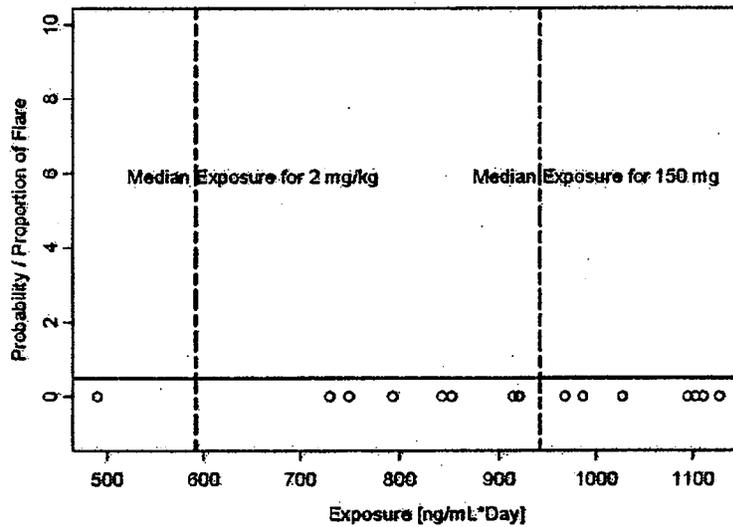


Table 1 The Sponsor Proposed Dose

Patients	Proposed Dose
> 40 kg	150 mg
≥15 kg and ≤ 40 kg	2 mg/kg

1.2 Recommendations

The sponsor proposed dosing regimen is acceptable from clinical pharmacology perspective. However, a higher dose (3 mg/kg) should be considered for low body weight subjects who do not demonstrate adequate clinical efficacy under 2 mg/kg dose, provided safety and tolerability are acceptable.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2.2 Recommended Dose

The recommended dose of Ilaris is 150 mg for CAPS patients with body weight >40 kg.

For CAPS patients

with body weight ≥ 15 kg and ≤ 40 kg, the recommended dose is 2 mg/kg, and dose can be increased to 3 mg/kg for patients who do not demonstrate adequate clinical efficacy with 2 mg/kg dose.

b(4)

Ilaris is administered every eight weeks as a single dose via subcutaneous injection.

b(4)

2 PERTINENT REGULATORY BACKGROUND

This is the original submission that the sponsor is seeking marketing approval of canakinumab (BLA 125319) for the treatment of Cryopyrin Associated Periodic Syndrome (CAPS) in adults and pediatric patients aged 4 and above.

3 RESULTS OF SPONSOR'S ANALYSIS

In the modeling report (Modeling report for the pharmacokinetics and pharmacodynamics of canakinumab or ACZ885, an anti-interleukin-1 β monoclonal antibody for cryopyrin associated periodic syndromes, CAPS), the sponsor applied the binding and kinetic model to simultaneously describe the canakinumab and IL-1 β concentration time profiles

(Figure 5). Total canakinumab concentration and total IL-1 β concentration from 223 subjects in 6 different clinical trials (CACZ885A2102, CACZ885D2304, CACZ885 — , CACZ885A1101, CACZ885A2101, and CACZ885 — were included in the analysis. Patient population included healthy subjects and patients with CAPS, — , rheumatoid arthritis, — s (Table 2).

b(4)

Table 2 Summary of the Subjects Included in the Analysis

Study	Study pop'n.	Patient numbers		Demographic data for analysis population (mean \pm SD & range)					
		# patients analyzed	# placebo	Weight (kg)	Age (years)	Albumin (g/L)	M	F	
A2102	CAPS	Adults	27	0	61.4 \pm 8.1 (43 - 77)	35.6 \pm 10.6 (18 - 51)	42.3 \pm 3.4 (33 - 48)	10	17
		Peds	7	0	31.2 \pm 14.3 (17.2 - 52)	9.9 \pm 5.3 (4 - 17)	42.6 \pm 3.6 (38 - 49)	3	4
		TOT	34*	0	55.2 \pm 15.6 (17.2 - 77)	30.3 \pm 14.3 (4 - 51)	42.4 \pm 3.4 (33 - 49)	13	21
D2304	CAPS	Adults	30	0	59.4 \pm 9.7 (42.4 - 81.9)	36.8 \pm 13.5 (18 - 74)	42.7 \pm 2.9 (37 - 49)	7	23
		Peds	5	0	55.9 \pm 20.7 (26.3 - 82)	14.2 \pm 3.1 (9 - 17)	40.8 \pm 5.5 (34 - 47)	3	2
		TOT	35*	0	58.9 \pm 11.5 (26.3 - 82)	33.6 \pm 14.8 (9 - 74)	42.4 \pm 3.4 (34 - 49)	10	25
B2101	HV, Non-Japanese	25	7	69.6 \pm 12.1 (48 - 93.4)	34.6 \pm 10.5 (19 - 61)	42.8 \pm 2.4 (39.4 - 47.5)	13	12	
A1101	HV, Japanese	48	12	63.8 \pm 7.6 (50.5 - 82.7)	24.6 \pm 3.9 (20 - 34)	46.1 \pm 1.9 (41 - 50)	48	0	
			25	3	76.9 \pm 13.5 (57 - 120)	33.2 \pm 10.3 (18 - 58)	43.1 \pm 2.4 (38.3 - 48.8)	18	7
A2101	RA		52	15	74 \pm 13.2 (51 - 100.5)	53.5 \pm 10.5 (18 - 74)	40.9 \pm 3.1 (33 - 49)	13	39
			23	4	84.2 \pm 11.1 (66.8 - 99.8)	39.3 \pm 13.3 (20 - 62)	45.4 \pm 3 (42 - 54.2)	23	0

* Overlap of 9 patients between the two CAPS studies

b(4)

Based on the sponsor's model, the major parameters derived from the final model were listed in Table 3. The major diagnostic plots for the base model and final model were shown in

Figure 6 and Figure 7 respectively.

Figure 5 Schematic Presentation of the Model for Canakinumab and IL-1 β

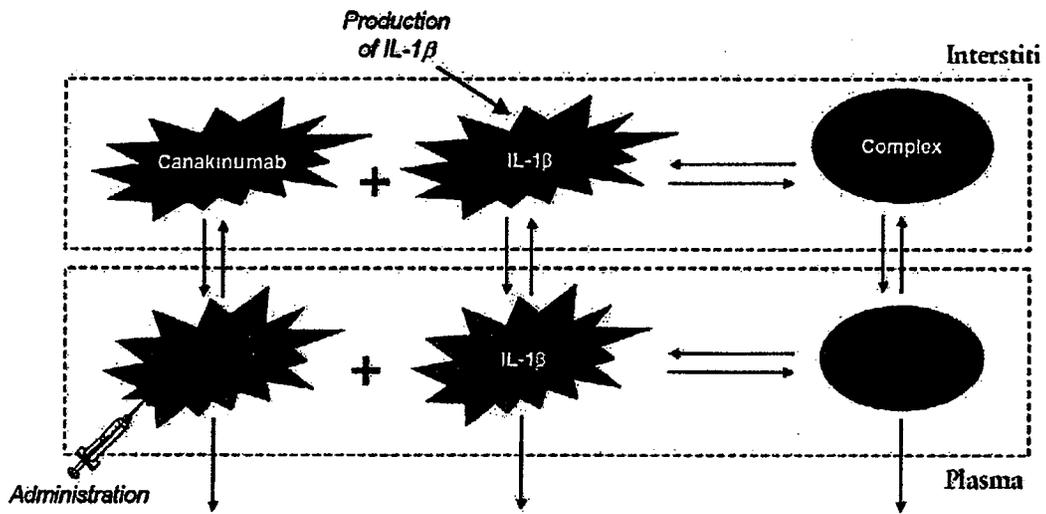


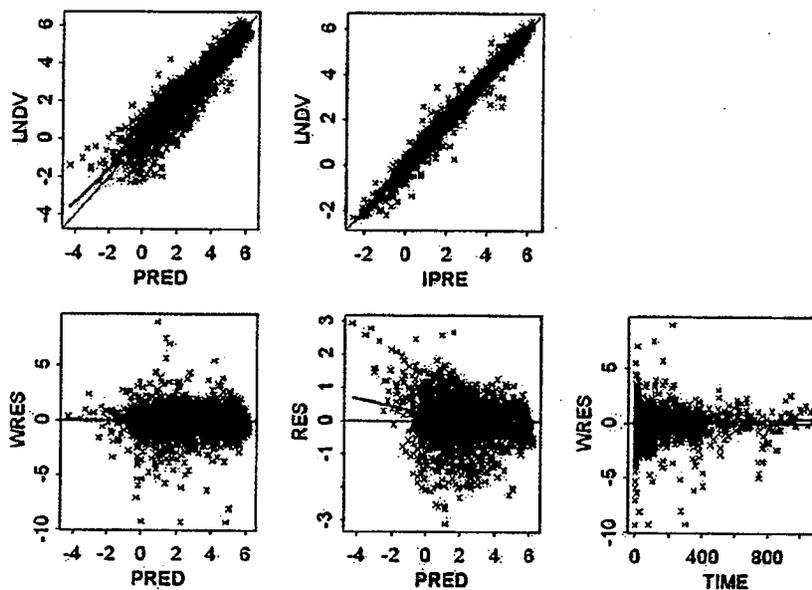
Table 3 Summary of the Final Parameter Estimates for CAPS Patients

Parameter [units]	Population mean [$\theta \pm \text{SEM}$]	Inter-individual variance [$\omega \pm \text{SEM} (\%CV)$]
Canakinumab parameters		
Clearance for drug (CL_D , L/d at 70 kg and 43 g/L albumin)	0.174 \pm 0.0124	0.0859 \pm 0.0147 (29%)
Central volume of distribution (V_D , L/70 kg)	3.30 \pm 0.135	0.0589 \pm 0.0205 (24%)
Peripheral volume of distribution (V_P , L/70 kg)	2.71 \pm 0.151	0.0817 \pm 0.02 (29%)
Absorption rate constant (k_a , 1/d for 34 year old) for	0.299 \pm 0.0382	0.406 \pm 0.107 (64%)
Logit bioavailability parameter	0.545 \pm 0.227	
BAV after transformation from logit	63.3% \pm 5.26%*	
Intercompartmental permeability flow (PS_D , L/d)	0.429 \pm 0.0529	0.28 \pm 0.107 (53%)
IL-1β parameters		
Clearance for ligand (CL_L , L/d)	14.2 \pm 2.55	0.371 \pm 0.08 (61%)
Production rate of ligand (R_L , ng/d)	9.57 \pm 1.34	0.261 \pm 0.0464 (51%)
Intercompartmental permeability flow f (PS_L , L/d)	0.386 \pm 0.0555	0.254 \pm 0.139 (50%)
Binding constant (K_d , nM)	1.07 \pm 0.173	0.395 \pm 0.13 (63%)
Covariates		
Weight on CL_D **	0.695 \pm 0.09	
Albumin on CL_D **	-0.916 \pm 0.185	
Weight on V_D **	0.684 \pm 0.0921	
Weight on V_P **	0.798 \pm 0.236	
Age on k_a **	-0.555 \pm 0.151	
cell line on k_a (ratio from	0.899 \pm 0.178	
Absorption rate constant (k_a , 1/d for 34 year old) for cell line	0.269 \pm 0.0634*	
Logit ratio parameter for cell line on F	1.6 \pm 0.337	
Bioavailability of cell line material	70.0% \pm 8.25%*	
Study population on CL_D	see table 8-3	
Study population on CL_L	see table 8-3	
Study population on R_L	see table 8-3	
Study population on K_D	see table 8-3	
Covariances in OMEGA matrix		
$CL_D:V_D$		0.0485 \pm 0.0142
$V_P:PS_D$		0.0808 \pm 0.0414
$V_P:PS_L$		0.0408 \pm 0.0408
$PS_D:PS_L$		0.216 \pm 0.105
$CL_L:R_L$		0.181 \pm 0.0425
Residual variances		
Canakinumab (ng/mL)	0.0527 \pm 0.00572 (23%)	
IL-1 β (pg/mL)	0.084 \pm 0.0113 (29%)	
Objective function	-10007.83	

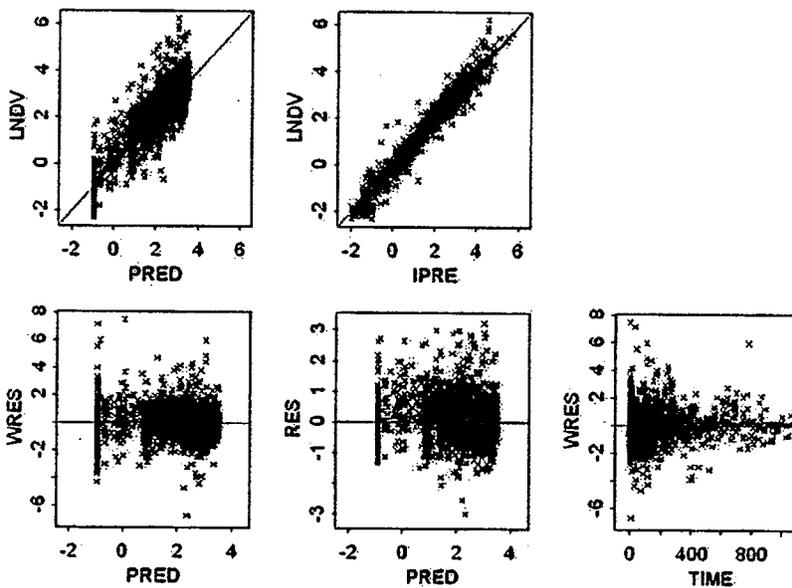
b(4)

b(4)

Figure 6 Diagnostic Plots for Base Model:



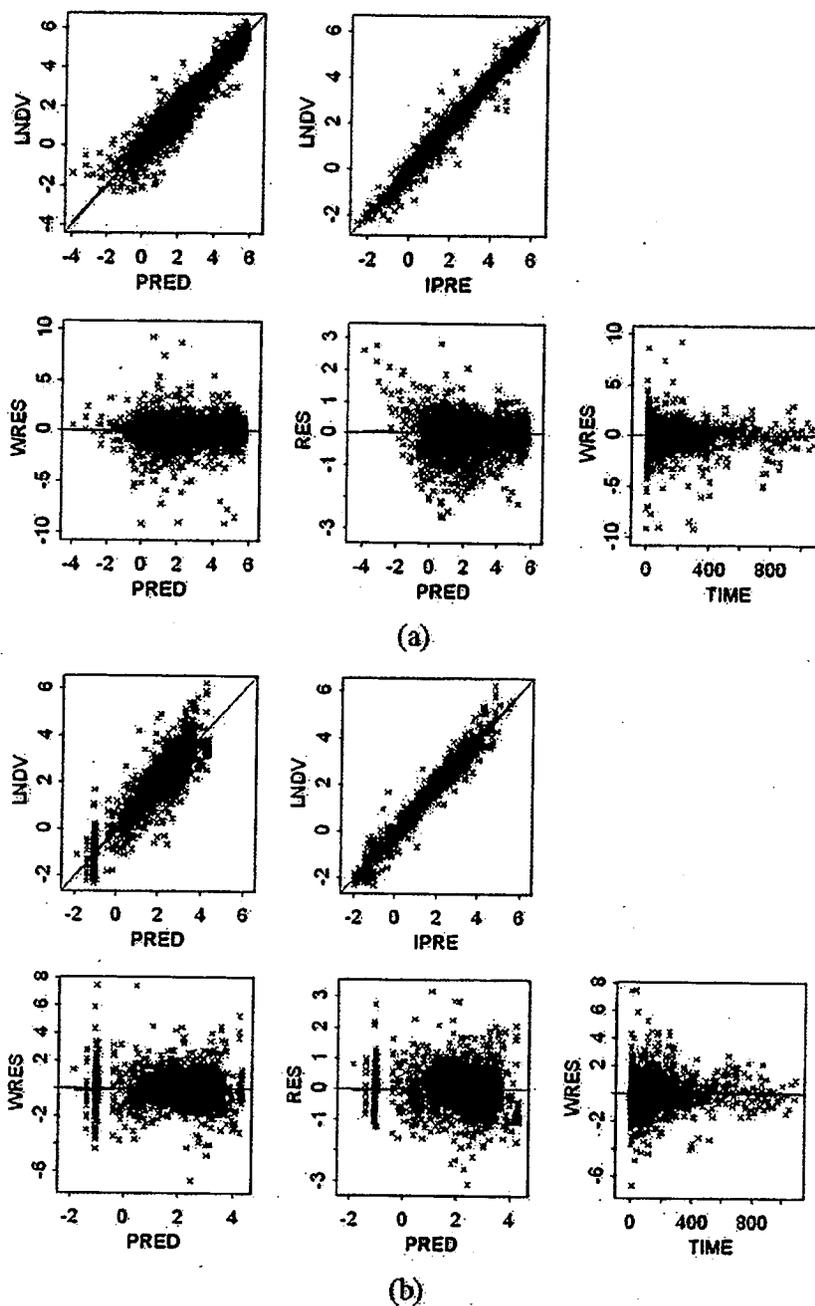
(a)



(b)

(Note: Diagnostic plots for Canakinumab (a) and IL-1 β (b))

Figure 7 Diagnostic Plots for Final Model



(Note: Diagnostic Plots for Canakinumab (a) and IL-1 β (b))

Major assumptions for the binding and kinetics process include,

- 1.) Equilibrium between canakinumab and IL-1 β was achieved at a short time scale in both central and peripheral compartment.

- 2.) The volume of distributions for IL-1 β , canakinumab, and the complex were assumed to be the same.
- 3.) The clearance of canakinumab and complex was assumed to be the same.
- 4.) The exchange rates for canakinumab and complex between the peripheral and central compartment were assumed to be the same. IL-1 β has a different exchange rate.

Typical assumptions in the compartmental analysis, such as first-order absorption and first-order elimination, also applied.

Reviewer's Comments:

1. *The sponsor's model was established based on assumptions for the binding and kinetic process for canakinumab and IL-1 β . These assumptions are difficult to evaluate. In the reviewer's analysis section, however, we applied the standard two-compartment model to assess the canakinumab PK profile.*
2. *The major pharmacokinetic parameter estimates for canakinumab (i.e., Clearance and Volume of Distribution) based on the sponsor's binding and kinetic model are similar to the reviewer's analysis results using 2-compartment model and non-compartmental analysis.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

Based on the sponsor's modeling approach, the reviewer performed additional analysis to evaluate the proposed dose and to confirm the pharmacokinetic parameters derived from the sponsor's model.

4.2 Objectives

Analysis objectives are:

1. to confirm the population PK parameters derived from the sponsor's model, and
2. to evaluate the body weight based dose adjustment proposed by the sponsor

4.3 Summary of the Pivotal Study Design

The sponsor conducted one pivotal trial (Study 2304). The primary objective was to assess the efficacy of canakinumab (percentage of patients who experienced disease flare) compared with placebo in Part II as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers (CRP and/or SAA). This was a three part trial, with an open-label design to Part I for identification of canakinumab responders. Only patients with complete response to treatment and without disease relapse until Week 8 in Part I entered Part II, which was a double-blind, placebo controlled, randomized-withdrawal period. Upon disease flare or completion in Part II, patients entered Part III, which was open-label, active treatment with canakinumab. In part I, 35 patients were enrolled, 4 subjects discontinued due to

unsatisfactory therapeutic effect, with 31 entering into Part II. All patients with a body weight > 40 kg received one injection of canakinumab 150 mg s.c. every 8 weeks. Patients with a body weight \geq 15 kg and \leq 40 kg received an equivalent of 2 mg/kg s.c. dose.

4.4 Methods

4.4.1 Data Sets

Data sets used are summarized in Table 4.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
	Capsms.xpt	\\obsap58\MeCTD_Submissions\STN125319\0003\m5\datasets\pooledpkpd\analysis

4.4.2 Software

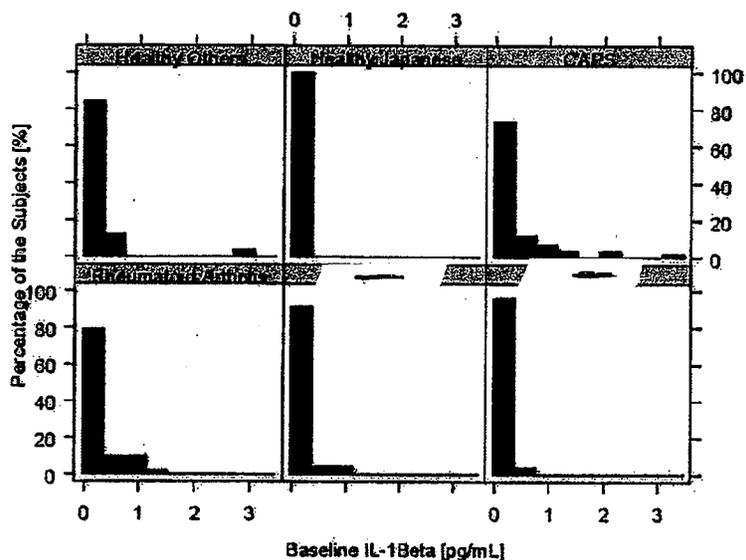
NONMEM (Double Precision Version 6.1.0, Golobomax Inc.) and S_Plus (Version 7.0, Insightful Inc) were used in the analyses.

4.4.3 Models and Results

4.4.3.1 Data Preview

We firstly previewed plasma concentration of IL-1 β . The baseline IL-1 β concentration across different disease populations were shown in Figure 8. It appeared that higher percentage of CAPS and Rheumatoid Arthritis patients were associated with elevated baseline IL-1 β levels in the plasma.

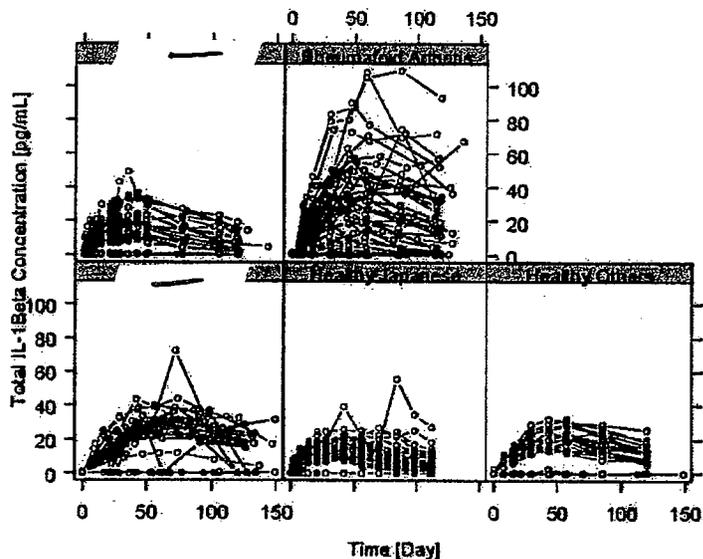
Figure 8. Baseline IL-1 β Concentration Distribution across Different Disease Populations



b(4)

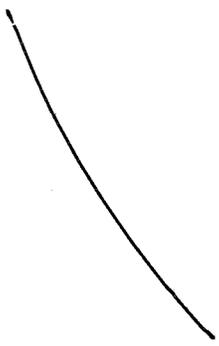
Following the administration of canakinumab, the total plasma IL-1 β levels were elevated. A similar trend was seen in CAPS patients and non-CAPS patients (Figure 9).

Figure 9 Total IL-1 β Concentration vs. Time Profiles in Non-CAPS Patients (A) and CAPS Patients (B) Following Administration of Canakinumab



b(4)

(A)

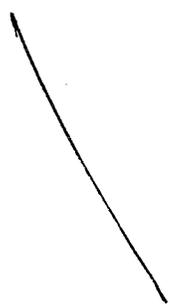


b(4)

(B)

The Canakinumab concentration time profiles in CAPS and non-CAPS patients were shown in Figure 10.

**Figure 10 Canakinumab Concentration Time Profiles
in Non-CAPS (A) and CAPS (B) Patients**



b(4)

(A)

b(4)

(B)

4.4.3.2 Analyses and Results

The reviewer performed population PK analysis using the PK observations from CAPS patients. PK samples were taken from 60 CAPS patients in 2 clinical trials (Study 12102 and Study 2304) (Table 5). Instead of applying the binding and kinetic model with various assumptions on the binding and distribution process between canakinumab and IL-1 β , we applied a standard two-compartment model using NONMEM to characterize the pharmacokinetic profile of canakinumab. The results were shown in Table 6. In addition, pharmacokinetic parameters based on non-compartmental analysis (NCA) using intensive PK observations from Study 12102 were also summarized. All PK parameters using different analyses were similar with the sponsor's results.

Table 5 Summary of the Two Clinical Trials

Study NO	PK Observations	Subjects *	Route of Administration
2102	1075	34	i.m
2304	291	35	i.v. infusion

Note: * Total subject number = 60, with 9 subjects participated both trials

Table 6 Summary of the Major Pharmacokinetic Parameters using Different Methods

Pharmacokinetic Parameters				
Analysis Method	CL (L/Day)	Vd (L)	F (%)	Dataset
Binding and Kinetic Model (NONMEM) ^{#1}	0.174	6.01	70	Combined data from 6 studies in CAPS and non-CAPS patients ^{#2}
2-Compartment Model (NONMEM)				Combined data from Study 12102 and Study 2304 (CAPS patient)
ADVAN 4	0.15	4.14	72	
Non-compartmental Analysis ^{#3}				Study 12102 only (CAPS patient)

Geometric Mean 0.21 6.7 66.4

Note:

#1: The sponsor performed binding and kinetic model. The major PK parameters were included in the label.

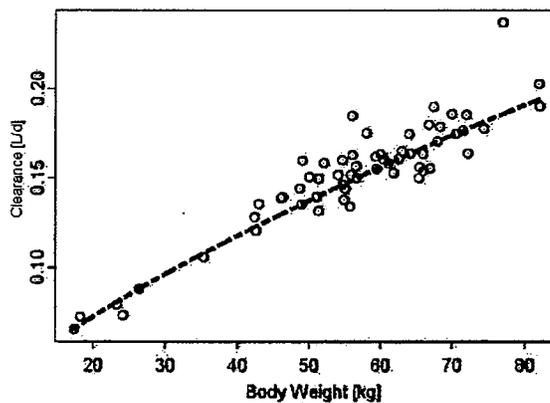
#2: Disease was used as a covariate in the model. Therefore the PK parameters were specifically related to CAPS patients.

#3: Please refer to Dr. Nallani Srikanth's review for detail.

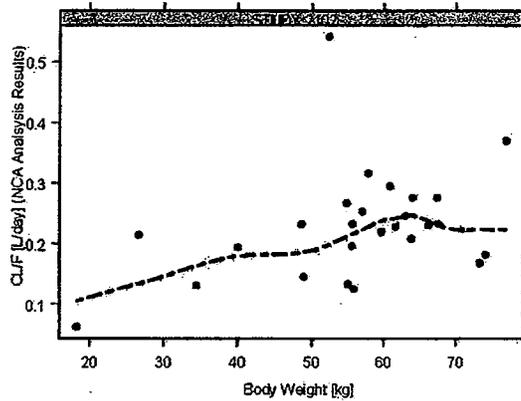
Additional analyses were performed to identify whether body weight based dose adjustment was necessary. According to the sponsor's analysis, body weight is a significant covariate for clearance. The body weight and clearance relationship in CAPS patient (Study 2102 and Study 2304) based on the sponsor's model was shown in

Figure 11 A. A similar trend can be seen from NCA analysis using data in Study 12102 (Figure 11 B). Because larger clearance is associated with higher body weight, body weight based dose adjustment is necessary to maintain similar canakinumab exposure for patients with different body weights.

Figure 11 Body Weight and Clearance Relationship
Based on the Sponsor's Model (A) and the Reviewer's NCA analysis (B)



(A)



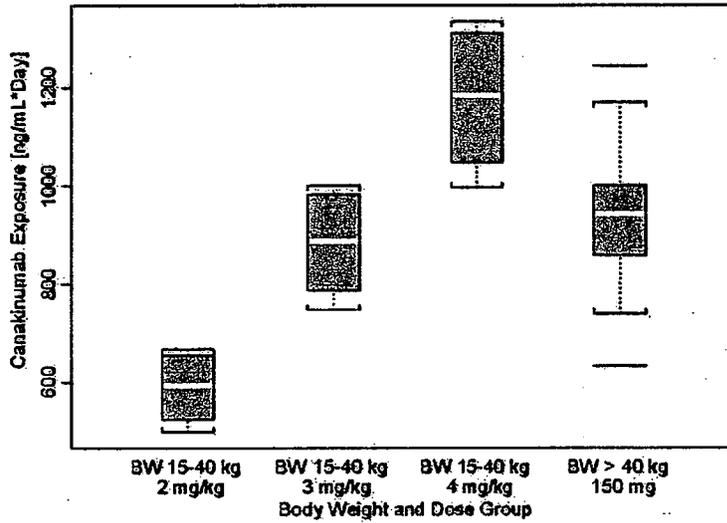
(B)

Note: NCA analysis was conducted based on observations from Study 2102.

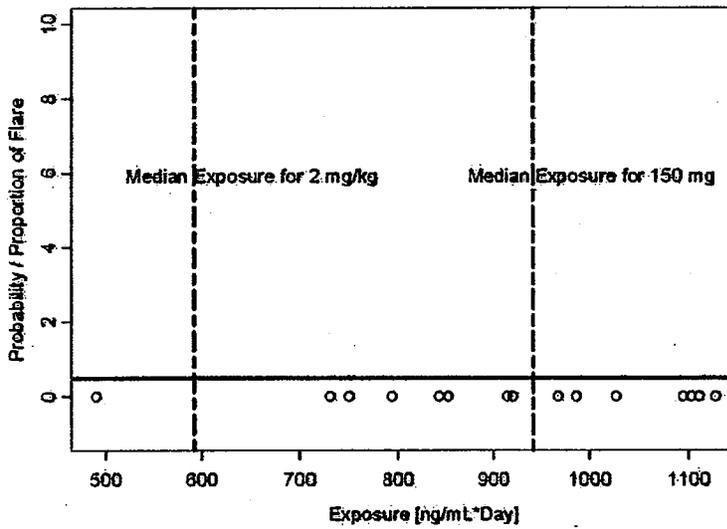
The sponsor proposed 150 mg dose for patients with body weight greater than 40 kg and 2 mg/kg dose for patients with body weight ≥ 15 kg and ≤ 40 kg. We performed simulation to assess the exposure levels for patients with different body weight. The simulation included all subjects enrolled in Study 2102 and Study 2304. Following the proposed dosing regimen, the exposure distributions were shown in Figure 12. The median exposure in patients with low body weight (body weight not greater than 40 kg) was about 37% lower than that obtained from high body weight (body weight greater than 40 kg) patients.

In addition, the exposure-response analysis was performed graphically based on the clinical observations from the pivotal study (Study 2304). Exposure is defined as AUC within a dose interval. Response is the incidence of flare by the end of part II in the treatment group. As shown in Figure 13, the exposure-response relationship is flat. A 30% reduction in exposure did not yield meaningful change in the probability of flare. However, only 1 patient received 2 mg/kg dose.

**Figure 12 Canakinumab Exposure Distributions
Following the Sponsor Proposed Dosing Regimen**



**Figure 13 Exposure-Response Relationship for Patients
in Study 2304**



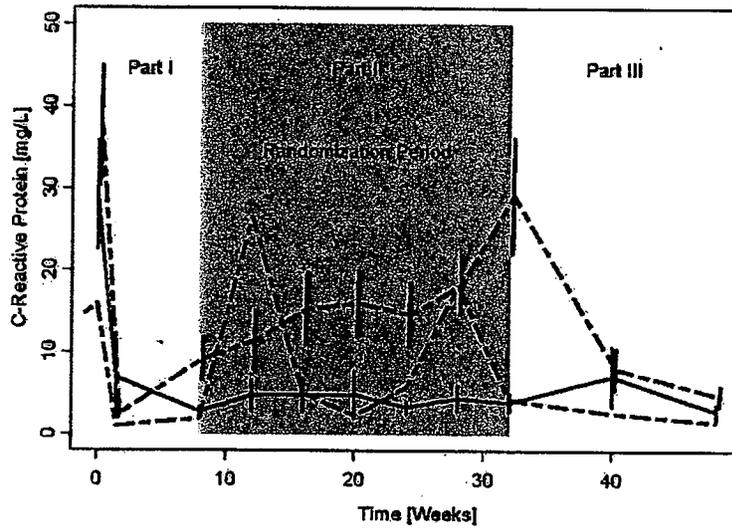
Note: open circle = Clinical Observations

can be increased to 3 mg/kg for these patients to match the exposure observed in high body-weight patients receiving 150 mg (Figure 3).

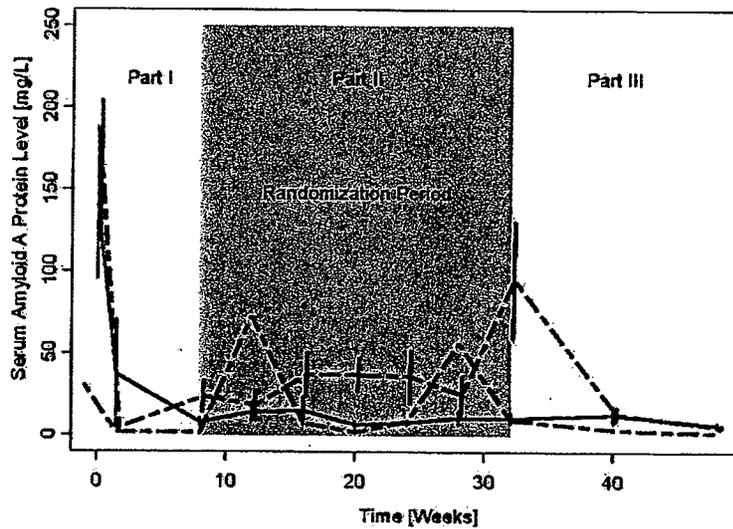
Table 9 Efficacy Outcomes for Pediatric Patients Receiving 2 mg/kg Dose

Patient, Condition	Age	1st Trial	Dosage	Response/Relapse
2 mg/kg s.c. scheduled dose, (rescue dose), weight ≤40 kg				
0002-05123 (MWS)	4 yr	A2102	2mg/kg s.c. (x10) 5 mg/kg i.v. (x3)	responder, 1 st relapse at 10 days, then time to relapse approx 30 days
0504-00001 (FCAS)	5 yr	D2306	2mg/kg s.c.	responder at cut-off
0022-05127 (MWS)	6 yr	A2102	2mg/kg s.c. (x4)	responder, 1 st relapse at 70 days, time to relapse approx 70 days
0002-05116 (MWS)	6 yr	A2102	2mg/kg s.c. (x7)	responder, 1 st relapse at 72 days, then approx 38 days post dose
0002-05108 (MWS)	7 yr	A2102	2 mg/k s.c. (x10) 125 mg iv (x10)	responder, 1 st relapse at 3 days, then partial/no response to 2 mg/kg response to high dose, relapse at 7 relapse approx 34 days after high d
0501-00003 (MWS/NOMID)	8 yr	D2306	2mg/kg s.c.	responder at cut-off
0002-00001 (MWS)	9 yr	D2304	2mg/kg s.c. (x5)	responder, no relapses, D/C on Day 229 for SAE (UTI)
0002-05113 (MWS)	13 yr	A2102	2mg/kg s.c. (x6)	responder, 1 st relapse at Day 63, then approx 59 days post-dose.

Figure 14 Biomarkers in the Treatment Group and the Observation from Subject CACZ885D2304_0002_00001



(A)



(B)

Note: blue line = Treatment Group (Mean \pm SE)

Red line = Placebo Group (Mean \pm SE)

Green line = Observation from Subject CACZ885D2304_0002_00001.

Figure 15 Cumulative Probability of Time-to-Relapse by Dose Group

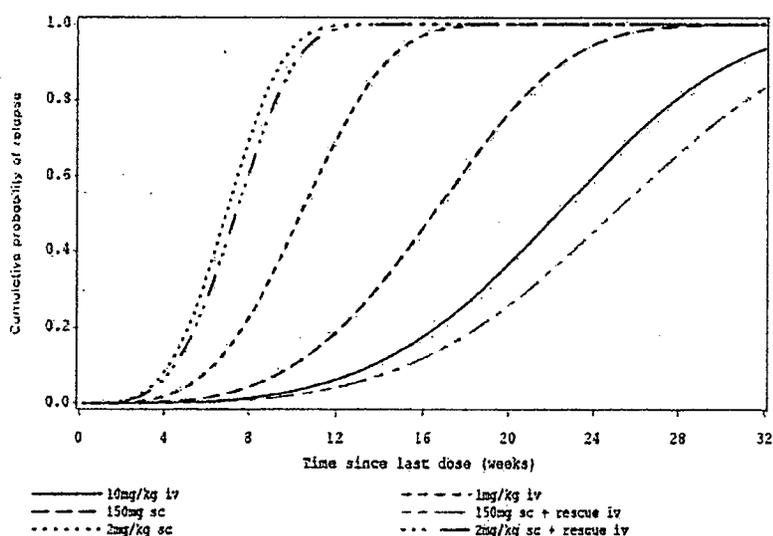


Table 10 Median Time-to-Relapse Stratified by Different Dose Regimen

Dose regimen	Number of unique subjects who received dose regimen	Number of periods	Median Time-to-Relapse (days)	95% Confidence Interval
10 mg/kg i.v.	4	4	158.2	102.5 - 209.8
1 mg/kg i.v.	4	4	72.8	48.0 - 97.7
150 mg s.c.	29	96	115.2	94.1 - 136.4
150 mg s.c. + rescue i.v.	4	5	174.5	90.5 - 258.5
2 mg/kg s.c.	4	22	49.6	29.3 - 67.9
2 mg/kg s.c. + rescue i.v.	2	11	51.7	27.0 - 76.5

Results from statistical analysis of time-to-relapse. Source: Post-text table 14.2-1.1.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Scripts	S_plus Script File	\\cdsnas\pharmacometrics\Canakinumab
NM	NONMEM Code	
Results	Results	

4.2.2 Genomics Review

See Next Page

CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

BLA Number	125319
Submission Type; Code	P
Applicant Name	Novartis
Submission Date	12-16-2008
Brand Name	ILARIS
Generic Name	Canakinumab
Proposed Indication	CAPS
Genomics Reviewer	Mike Pacanowski, Pharm.D., M.P.H.
Associate Director	Issam Zineh, Pharm.D., M.P.H.

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3.2	WHAT IS THE IMPACT OF CANAKINUMAB ON IL-1β PATHWAY GENE EXPRESSION?	4
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1. BACKGROUND

Canakinumab is an anti-IL-1 β antibody (IgG1/k). The applicant is seeking approval of canakinumab for the treatment of Cryopyrin-Associated Periodic Syndrome (CAPS). CAPS encompasses several rare, sometimes overlapping, autosomal dominant, periodic fever disorders: Familial Cold Autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID). CAPS is generally attributed to heterozygous gain-of-function mutations in the gene encoding cryopyrin, *NLRP3*, which results in constitutive IL-1 β production.

From a genomics standpoint, the sponsor's proposed labeling includes comment on CAPS genetics and canakinumab's effect on IL-1 β pathway gene expression.

2. BLA CONTENT RELATED TO GENOMICS

The sponsor conducted 3 studies to support the efficacy of canakinumab in CAPS: ACZ885A2102, ACZ885D2304, and ACZ885D2306. A molecular diagnosis (i.e., presence of *NLRP3* mutations) was required for entry into A2102 and D2304. Also, in both of these studies, the sponsor collected RNA on a voluntary basis from consenting patients at baseline and at various time points following treatment with canakinumab to assess changes in gene expression (genome-wide and candidate gene studies). D2306 represents an extension study of D2304 and A2102, but also recruited new patients without regard to mutational status; exploratory pharmacogenetic aims were not described in this study report.

3. KEY QUESTIONS AND SUMMARY OF GENOMICS FINDINGS

The following key questions were addressed in this review in the context of the sponsor's proposed labeling regarding the effects of canakinumab on IL-1 β pathway gene expression.

3.1 What are the genetic characteristics of CAPS?

Cryopyrinopathies generally result from rare inherited or *de novo* mutations in the gene encoding cryopyrin, *NLRP3* (previously referred to as the Cold-Induced Auto-inflammatory Syndrome 1 gene, or *CIAS1*). Cryopyrin (*NLRP3*, also referred to as *NALP3* or *PYPAF-1*) is an inflammasome constituent that is integral to innate immunity (e.g., cellular responses to pathogenic and other threatening signals). Activation of *NLRP3* by cellular threats results in recruitment of procaspase 1, which is then converted to caspase 1. Caspase 1, in turn, converts IL-1 β precursors to their active form. (Neven 18665151, Ting 15771576, Inohara 15952891)

NLRP3 mutations lead to inflammasome activation, resulting in constitutive expression of IL-1 β and chronic systemic autoinflammation. (Agostini) *NLRP3* mutations are detectable in approximately 75% of FCAS and MWS patients, but less than 50% of NOMID patients. Approximately 60 mutations in *NLRP3* have been described, almost all of which are missense mutations residing in functional domains of the protein. The different mutations may correspond to different levels of disease severity, as shown in the table below. (Aksentijevich 12483741, Feldmann 12032915, Neven 14630794, Aro' stegui 15593220, Goldbach-Mansky 16899778, Aksentijevich 17393462, Dode 11992256, Aganna 12355493, Hoffman 11687797). For instance, the D303N mutation is more commonly seen in patients with the most severe disease group, NOMID, whereas L353P is seldom seen in MWS or NOMID. Conversely, the V198M mutation has been identified in healthy individuals, and as such, the clinical significance of this mutation has been questioned. One report described an anakinra resistant periodic fever patient with V198M. (Aksentijevich 12483741) Furthermore, among patients with the clinical picture of CAPS who are mutation negative, genetic mosaicism has been described. Thus, a portion of patients may actually carry mutations that go undetected by conventional sequencing techniques. Mutation-negative patients respond to anti-IL-1 β therapy. (Aksentijevich 17393462, Saito 18063752, Saito 16255047, Aksentijevich 16871551)

b(4)

Source: Aksentijevich, et al. Arthritis Rheum 2007 (12483741)

Comment

- All of the patients in the sponsor's studies A2102 and D2304 had a molecular diagnosis of CAPS, i.e., *NLRP3* mutation positive, as a requirement for entry. This does not represent the distribution of mutations in the to-be-treated population.
- D2306 is an ongoing supportive study enrolling patients without regard to mutational status; only 2 of the 57 enrolled patients were negative for mutations in *NLRP3*.

- The mutations may be of varying penetrance, and other genetic/environmental factors may contribute to disease activity.

3.2 What is the impact of canakinumab on IL-1 β pathway gene expression?

3.2.1 Study A2102

Objectives

Primary: efficacy (complete response [physician global assessment, skin disease, CRP/SAA])

Secondary: safety, tolerability, immunogenicity, PK, PD (IL-1 β , IL-1 α , IL-1 Ra, IL-6, IL-8, IL-10, IL-12P40, IL-12P70, IL-15, IL-17, IL-18, MCP-1, TIMP, MMP1, MMP2, MMP3, MMP9, RANTES, eotaxin, ferritin, GM-CSF, TNF- β , TNFR2, and VEGF), PK/PD, modification of disease progression (deafness, kidney function, neurological and ophthalmological symptoms), and health-related quality of life.

Exploratory: changes in gene expression patterns (blood, PAXgene; genome-wide microarray) following canakinumab treatment

Design and methods

A2102 was an open label, uncontrolled phase II study of canakinumab in CAPS patients with a molecular diagnosis (included FCAS, MWS, and NOMID) to evaluate efficacy (complete response [CR]), defined by a combined assessment of physician global assessment of disease activity (9 items, 5-point scale of absent to severe) and skin disease, and serum CRP/SAA concentrations. Patients were treated first with first a single administration of 10 mg/kg IV. The 2nd dose was a single dose given following relapse at a dose of 1 mg/kg IV. For subsequent relapses, 150 mg SC was given as needed (children were give 2 mg/kg SC). Rescue with 5-10 mg/kg IV was permitted.

Enrollment in the gene expression study required separate voluntary informed consent if the patient agreed to participate. It was required as part of this protocol that the Investigator presented this option to the patient. Pharmacogenomic samples were to be collected at visits 5-11 (day 1 [3 samples at 0, 4, and 6 hours], 2, 3, 8, 15, 22, 29). Genome-wide expression using the Affymetrix platform was performed on three patients, but the analysis methodology, platform, or target genes were otherwise not described.

Results

Consent/RNA was obtained from 29 of 34 patients in study A2102. Of those, gene expression profiles were completed for only 7 subjects. Raw data were not included in the submission and the data/results tables were not provided for study A2102. Genome-wide expression (Affymetrix) was conducted for the first 3 patients treated with IV canakinumab. In the sponsor's protocol amendment narrative, IL-1 β pathway related genes, such as IL-1R1, NALP3, and MyD88 changed significantly 1 week following canakinumab administration (direction unknown).

A2102 comments

- The findings from this analysis were not presented as a complete report; data were incomplete and not available for analysis to verify the sponsor's conclusions.

3.2.2. Study D2304

Objective

Primary: efficacy (disease flare in Part II [physician's global assessment, skin disease, CRP/SAA])

Secondary: safety, tolerability, immunogenicity of canakinumab, overall efficacy (response rate) of canakinumab in Part I and Part III, PK, PD (IL-1 β), disease progression (deafness, kidney function, neurological and ophthalmological symptoms)

Exploratory: changes in gene expression patterns (blood, PAXgene; IL-1R1, IL-1R2, IL-1RN, TLR2, TLR4, TNF α) and soluble serum protein biomarkers (MMP-1, MMP-3, IL-6, IL-1RA and IL-18) following canakinumab treatment

Design and methods

D2304 was a 3 part study with a double-blind, placebo-controlled, randomized withdrawal study, as shown in the following table:

D2304 Efficacy / safety in MWS			
(part I: uncontrolled)	35	part I (single dose, 8 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c. (15-40kg)	complete response
(part II: placebo-controlled, double-blind, withdrawal)	31	part II (multiple doses, up to 24 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c. (15-40kg)	primary endpoint: proportion with flare
(part III: uncontrolled)	31 (cut off)	placebo (part II only) part III (16 wk if finished part II, or longer) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c. (15-40kg)	complete response

Source: D2304 study report

RNA samples were collected at the following time points: part I – baseline, days 1, 8, 29, 57; part II – days 85, 113, 141, 169, 197, 225; part III – day 253, 281, 309, 337.

The following genes were analyzed using quantitative RT-PCR on a TaqMan low-density microarray (RPS4Y1 and XIST are gender controls):

Gene Symbol	Gene Name
Act- γ 1	Actin, gamma 1
GAPDH	Glyceraldehyde 3 phosphate dehydrogenase
GUS β	Glucuronidase beta
IL1 α	Interleukin 1, alpha
IL1R1	Interleukin 1 receptor, type 1
IL1R2	Interleukin 1 receptor, type 2
IL1RN	Interleukin-1 receptor antagonist
IL1- β	Interleukin 1 beta
RPS4Y1	Ribosomal protein S4, Y linked 1
TINF2	TERF1 (TRF1)-interacting nuclear factor 2
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4
TNF α	Tumor necrosis factor, alpha
XIST	X (inactive)-specific transcript

Source: D2304 study report

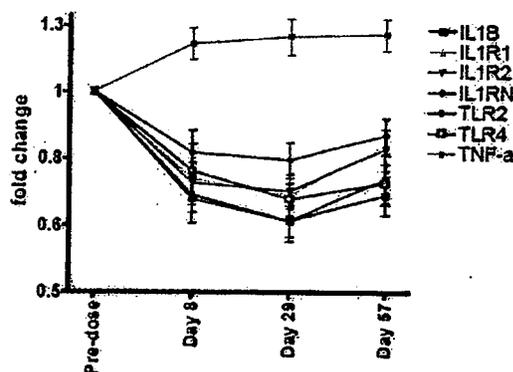
Statistical analysis was performed on the average of ActG1, GAPDH, TNF2, and GUSB normalized Ct values of triplicate reactions by analysis of variance (ANOVA) followed by a Dunnett's post test correction. Values were considered significantly different if the p-value was ≤ 0.05 . In Parts II and III a Mann-Whitney u-test was used to compare the mean values between the placebo and treated groups at the start of Part II, start of Part III and end of Part III.

Sponsor's Results

Consent/RNA sample ascertainment was almost complete at baseline in the open-label phase (28 of 31 patients). Data were available for 23 of the 27 adult patients at the beginning of the randomized treatment period. 24 patients provided samples at the beginning of the second open-label phase. RNA samples were obtained from at least 20 of the 27 patients at each time point (except visit 9).

Summary data/results tables from a low density array of 9 target genes were presented in summary form. IL-1 β , IL-1R1, IL-1R2, IL-1RN, TLR2, and TLR4 gene expression decreased by approximately 1.5-fold by the end of part I, with changes evident as early as the first visit on day 8, as shown in the following figure and table. IL-1 α was not detectable.

Figure 4-2 Part 1 summary of RT-PCR results



Data shown is the average fold change (from day 1 pre-dose) in expression of all of the target genes in the patients in study Part I. The day 1 sample was chosen as the baseline comparator sample for the treatment samples due to the lack of screening samples for all patients.

Table 4-1 Summary Table of Day 1 to day 8 Expression Changes

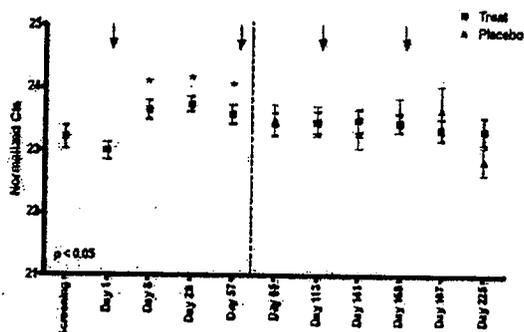
Gene	Avg normalized Ct at Day 1	Avg Normalized Ct @ Day 8	Avg Fold Decrease	Min. Fold Decrease	Max Fold Decrease
IL1 β	22.99	23.60	1.59	0.66	4.65
IL1R1	25.33	25.77	1.42	0.64	2.65
IL1R2	24.44	24.86	1.46	0.68	4.00
ILRN	23.17	23.57	1.29	0.50	2.76
TLR2	22.07	22.55	1.44	0.90	2.55
TLR4	22.68	23.15	1.49	0.46	4.11
TNF- α	26.72	26.51	0.84	0.44	1.33

Data shown is the average normalized Ct value across all patient samples evaluated. The average normalized Ct change from pre-dose, study day 1, to study day 8 was converted to a fold decrease value to demonstrate the magnitude of decrease in expression of the genes with ACZ885 treatment.

Source: D2304 study report

The gene expression profiles diverged toward the end of part II, based on the reported ΔCt , with placebo patients returning to an expression level that approximated baseline. Initiation of canakinumab in Part III again produced a similar change in the expression profile as Part I. The results for IL-1 β reductions in gene expression are depicted in the following figures; the results for other genes outlined above were similar, except for TNF α , which showed no significant change or increased. The gene expression profiles for IL-1 β and the other genes appeared to return to baseline over time as inferred from the lack of significance from the beginning of Part II onward.

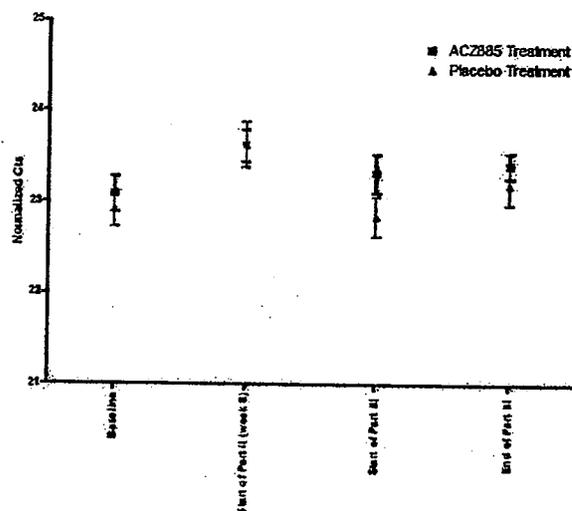
Figure 4-1 IL1-beta : Part I and II



Data shown is normalized Ct. The higher the Ct the lower the expression of the target gene in the sample. An increase of 1 Ct represents a 2 fold decrease in transcript levels. The day 57 time point was the last time point in part I of the study and day 85 was the first time point where samples were available in Part II of the study.

* Indicates a statistically significant difference ($p < 0.05$) in the average value at the time point compared to the day 1, pre-dose value. The arrow indicates dosing with ACZ885. Treat indicates the ACZ885 treated group.

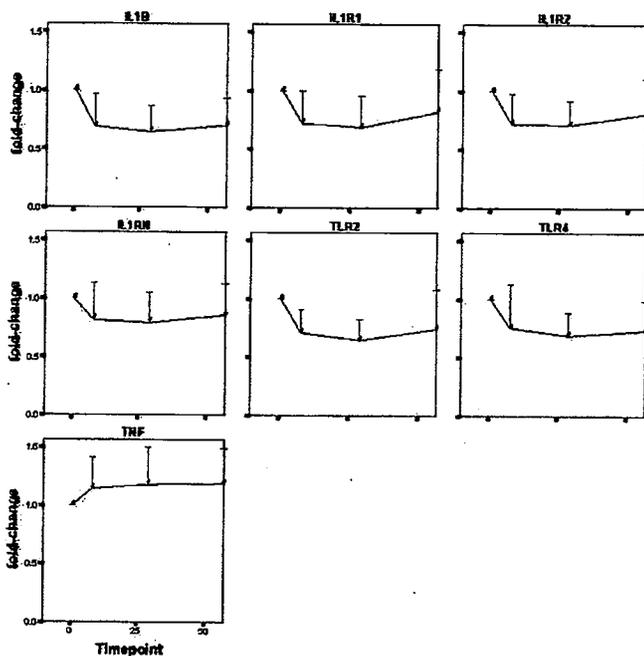
Figure 4-9 IL1-beta : Summary Across Parts I, II and III



Reviewer's Results

The sponsor's analyses were confirmed. Fold-change was calculated using the $2^{-\Delta\Delta\text{Ct}}$ method (Livak 11846609). Mean (SD) changes in the expression of each gene over the course of part I are shown in the following figure. For part I, using a paired t-test,

significant changes were noted at each time point for IL1 β , IL1R1, IL1R2, IL1RN, TLR2, TLR4, as well as TNF. These findings were confirmed using repeated-measures ANOVA with last observation carried forward. Wilcoxon two-sample test for the difference at the end of part II did not reveal any significant difference between canakinumab and placebo, and no significant within-treatment changes were noted for any of the genes.



D2304 comments

- Gene expression changes were modest (<2-fold), and while biologically plausible, the relevance to the overall pharmacological and clinical effect cannot be robustly concluded.

3.3 Do NLRP3 mutations or gene expression differences predict canakinumab treatment response?

3.3.1. Study A2102

Response rates

In study A2102 (n=34), 4/4 patients receiving the initial IV dose responded and 28/29 patients achieved a CR after the first 150 mg SC dose; 24 patients achieved a CR after every subsequent 150 mg SC dose, with only 4 adult patients requiring IV rescue therapy (5117, 5118, 5120, 5133). One adult required regular rescue doses (5133). In the pediatric 2 mg/kg SC group, all patients responded, although patient 5108 needed regular rescue treatment after each injection, and patient 5123 needed a rescue IV treatment three times during the study. The median duration of response following 150 mg SC dosing was 90.5 days (range: 22 to 215 days). At the 2 mg/kg dose, the median duration of

response was 66.5 days (range: 10 to 72 days). The median time to relapse was estimated to be longer in FCAS patients (189.2 days) and shorter in MWS/NOMID patients (95.3 days) as compared to MWS patients (120.3 days).

NLRP3 mutational status and rescue therapy requirements

The most frequent mutations in MWS patients were R260W (33.3%), E311K (29.6%), and T348M (22.2%). As per the sponsor, the frequency of mutations seemed to have a correlation with the geographical location of the site, which is possibly related to the enrollment of members of the same family.

CACZ885A2102

Table 14.1-3.2 (Page 1 of 1)
Summary of molecular diagnosis of NALP3 mutation
Safety Analysis Set

		Adult subjects N=27 n (%)	Pediatric subjects N=7 n (%)	Total N=34 n (%)
Clinical picture				
MWS		22 (81.48%)	5 (71.43%)	27 (79.41%)
FCAS		2 (7.41%)	0	2 (5.88%)
NOMID		1 (3.70%)	0	1 (2.94%)
MWS/NOMID		2 (7.41%)	2 (28.57%)	4 (11.76%)
Genotype				
MWS	E311K	6 (27.27%)	2 (40.00%)	8 (29.63%)
	R260K	2 (9.09%)		2 (7.41%)
	R260W	9 (40.91%)		9 (33.33%)
	T348M	5 (22.73%)	1 (20.00%)	6 (22.22%)
	V198M		2 (40.00%)	2 (7.41%)
FCAS	A439V	2 (100.0%)		2 (100.0%)
NOMID	A439P	1 (100.0%)		1 (100.0%)
MWS/NOMID	G569R	1 (50.00%)	1 (50.00%)	2 (50.00%)
	T348M	1 (50.00%)	1 (50.00%)	2 (50.00%)

Two of the patients requiring rescue therapy had codon 439 mutations (5118, A439P; 5120, A439V). The genotypes for the other patients requiring rescue were as follows: 5117, E311K; 5133, R260W. Both children requiring regular IV rescue therapy (5108 and 5123) had the V198M mutation.

RNA profile and rescue therapy requirements

Data were not available.

Comment

- Two of the three patients that required multiple doses had the V198M mutation, which is consistent with a previous case report (Aksentijevich 12483741), although relapse occurred in patients with other mutations.
- Gene expression data were not available for the adult patients experiencing flares. RNA was not collected for the pediatric non-responder patients, preventing analysis of response predictors.

3.3.2. Study 2304

Response rates

In study D2304 (n=35), open-label phase (Part I) 4 patients discontinued due to lack of efficacy (0010-0002, 0010-0003, 0501-0003); only 1 of the 35 patients relapsed (0501-0003; 97.1% CR rate). In the randomized withdrawal phase (Part II), 15 patients received canakinumab and none had a flare, while 13 of the 16 patients that received placebo experienced a disease flare. In the last open-label phase (Part III), only 1 of the 31 patients relapsed (0008-0006).

Mutational status and disease flare

The distribution of NLRP3 mutations was as follows: R260W, 50%; T348M, 21%; A439V, 3%; D303N, 12%; M662T, 3%; T436I, 3%; E311K, 6%; T436N, 3%. The mutational statuses for relapsing patients were as follows: 0010-0002, T348M; 0010-0003, T348M; 0501-0003, T436I; 0502-0003, D303N; 0008-0006, T436N. Both patients with codon 436 mutations experienced a flare. No patients had the V198M mutation which was present in two patients in study A2102.

RNA profile and disease flare

No significant differences were noted between relapsing/discontinuing patients in phase I as compared to responders based on the reviewer's analysis.

Comment

- No patients had the V198M mutation; patients with other mutations relapsed in D2304. On a descriptive level, no obvious trend for lack of efficacy appears to be associated with mutational status.
- The nonresponse rate was too low to permit meaningful statistical analysis of gene expression.

4. COMMENTS

The efficacy of canakinumab in patients without a molecular diagnosis of NLRP3 mutations, representing approximately 25% and 50% of MWS and NOMID patients, respectively, has not been evaluated.

The gene expression study should be regarded as descriptive and exploratory for the purpose of understanding the drug's pharmacodynamics.

Canakinumab decreased expression of IL-1 β pathway-related genes modestly, while TNF α expression tended to increase.

b(4)

CAPS is genetically heterogeneous. The available data do not suggest that NLRP3 mutation status affects treatment response. Gene expression as a response predictor was not evaluable.

5. RECOMMENDATIONS

The sponsor's proposed labeling concerning the genetic etiology of CAPS and the pharmacodynamics of canakinumab as related to IL-1 β pathway gene expression is acceptable provided that the sponsor and the Agency come to an agreement regarding the labeling language.

The sponsor should refer to the following guidance documents for recommendations on sample preparation and molecular methodologies for future submissions.

- Pharmacogenomic Data Submissions
<http://www.fda.gov/Cder/guidance/6400fml.pdf>
- Pharmacogenomic Data Submissions-Companion Guidance
<http://www.fda.gov/cder/guidance/7735dft.pdf>

5. LABEL RECOMMENDATIONS

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [CIAS1]). CAPS disorders are

inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

b(4)

the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1 β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1 β that drives inflammation.

b(4)

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 β) antibody of the IgG1/ κ isotype. Canakinumab binds human IL-1 β and neutralizes its activity by blocking its interaction with IL-1 receptors.

b(4)

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2.3 Synopsis of Study A1101

Title of Study A1101: A randomized, double-blind, placebo-controlled, single ascending dose study to demonstrate the safety, tolerability, pharmacokinetics and pharmacodynamics of ACZ885 administered as intravenous infusion and subcutaneous injection in Japanese healthy volunteers

Objectives:

Primary objective:

- To evaluate the safety and tolerability of ACZ885 administered as intravenous infusion and subcutaneous injection to Japanese healthy volunteers

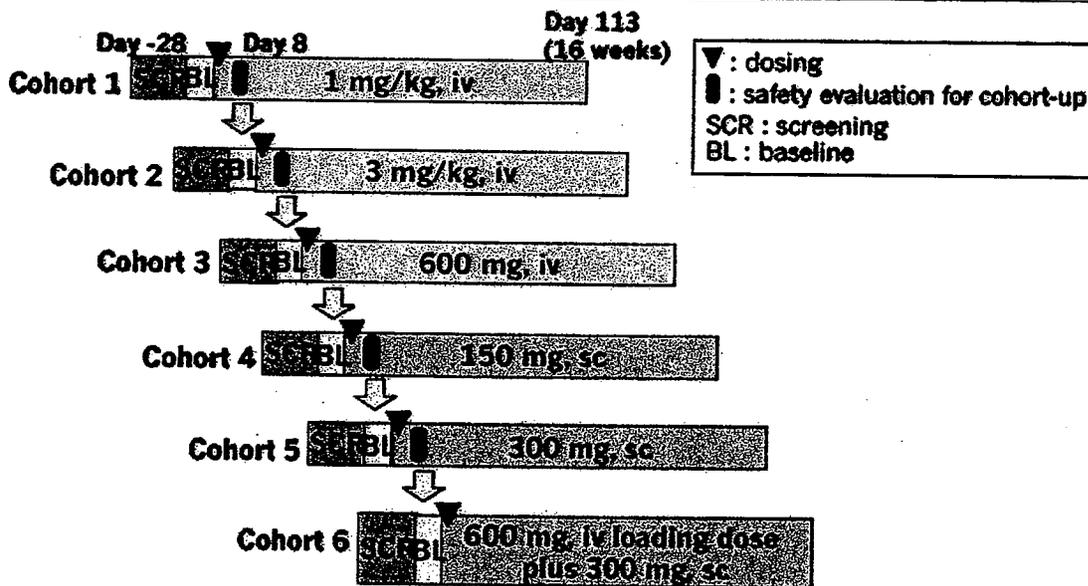
Secondary objective:

- To evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of ACZ885 administered as intravenous infusion and subcutaneous injection to Japanese healthy volunteers

Methodology

This study employed a randomized, double-blind, placebo-controlled, 6-cohort, single ascending dose design. A total of 48 Japanese healthy male subjects were enrolled in the study. Eight subjects participated in each of 6 cohorts. In each cohort, 8 subjects were randomly assigned to the active drug (6 subjects) or placebo (2 subjects).

Each subject participated in a screening period (Days -28 to -2), a baseline period to evaluate the criteria (Day -1), a 16-week treatment period and a study completion period (Day 113). Forty-eight subjects were randomized into six cohorts. ACZ885 or placebo was administered as an intravenous (i.v.) infusion over approximately 120 minutes at the dosage of 1, 3 mg/kg and 600 mg/body in Cohorts 1, 2, and 3, respectively. In Cohort 4 and 5, the study drug was administered as a subcutaneous (s.c.) injection at the dosage of 150 and 300 mg, respectively. In Cohort 6, the study drug was administered as a 600 mg i.v. loading dose plus a 300 mg s.c. injection as the total dose of 900 mg. Each subject was domiciled on Days -1 to 8 during which the blood samples were collected for PK (serum ACZ885 concentrations), PD assessments (serum total and free IL-1 β , IL-1 Receptor antagonist (IL-1Ra), IL-6 and TNF- α) and the safety assessments. Following the discharge from study center (Day 8), each subject came to the study site for the follow-up evaluations every 1 - 2 weeks. The term from screening to last visit was approximately 20 weeks.



Number of subjects (planned and analyzed):

A total of 48 subjects were planned to be randomized as 6 subjects for ACZ885 administration and 2 subjects for placebo administration in each of 6 cohorts. A total of 170 subjects were screened in this study. Forty-eight eligible subjects were randomized and took the study drug. All 48 subjects completed the study.

Bioanalytics:

For PK evaluation, serum ACZ885 concentrations were measured by an ELISA method.

For PD evaluation, serum cytokines (total IL-1 β , free IL-1 β , IL-1Ra, IL-6 and TNF- α) concentrations were measured by an ELISA method.

For immunogenicity evaluation, serum anti-ACZ885 antibody titers were measured by a — method.

b(4)

Statistical methods:**Pharmacokinetic evaluation:**

All subjects with evaluable PK measurements were to be included in the pharmacokinetic data analysis. Pharmacokinetic parameters (AUC_{0-tlast}, AUC_{0-inf}, λ_z , C_{max}, t_{max}, t_{1/2} (HL), CL, CL/F, V_{ss}, V_{z/F}) were to be determined using non-compartmental methods. ACZ885 concentrations and PK parameters were summarized using plots and descriptive statistics. Dose proportionality of AUC_{0-tlast}, AUC_{0-inf} and C_{max} were assessed graphically.

Pharmacodynamic evaluation:

All subjects with evaluable PD measurements were to be included in the data analysis. Cytokines concentrations were summarized using plots and descriptive statistics.

PK-PD evaluation:

ACZ885 and cytokines individual concentrations were to be only presented together in plot.

Bioanalytical results:**Pharmacokinetics**

- The PK characteristic properties of ACZ885 were in line with expectation and typical of human IgG-type immunoglobulin.
- Peak serum ACZ885 concentration was achieved shortly after end of the i.v. administration, while the concentration increased smoothly and the peak concentration was reached at 5 days after the s.c. administration.
- When the 600 mg i.v. administration was followed by the 300 mg s.c. administration, the peak serum concentration was achieved as shortly after end of the administration as the case with the i.v. administration. The C_{max} in both 600 mg i.v. followed by 300 mg s.c. administration was almost the same as that in only 600 mg i.v. administration, whereas the AUC was 1.3-fold larger.
- C_{max} and AUC increased in a weight-normalized dose-proportional manner within the whole range of i.v. administration.
- Serum ACZ885 concentration decreased following the peak concentration was achieved and the mean t_{1/2} was 22.6 to 27.4 days in each administration route.
- The mean apparent distribution volume at steady state following i.v. administration was 5.44 to 5.77 liter, suggesting that the ACZ885 did not distribute beyond the serum and interstitial space.
- The absolute bioavailability in the s.c. administration was 0.7, which is comparable with the expectation from the nonclinical findings (marmoset data).

Pharmacodynamics

- Serum concentration values for total IL-1 β in **almost all** samples from placebo treatment groups were below the LOD throughout the study period. Similarly, concentration values at pre-dose time point for all subjects were below the LOD.
- Total IL-1 β **increased after administration of ACZ885.**
- The total IL-1 β concentration immediately after ACZ885 i.v. treatment increased at the similar speed among different doses and more rapidly compared with s.c. treatment. The total IL-1 β concentration after ACZ885 i.v. followed by s.c. treatment increased in a similar manner with only i.v. treatment groups.
- The duration of the increased total IL-1 β after ACZ885 treatment was longer with higher dose of ACZ885 in i.v. treatment groups.
- After the peak, the total IL-1 β concentrations decreased gradually, and the concentrations at the last time point (112 days after the administration) did not return to the pre-dose in ACZ885 treatment groups.
- Serum concentration values for free IL-1 β in **all samples from all ACZ885 or placebo treatment groups** were below the LOD throughout the study period.
- No significant change from baseline in IL-1Ra, IL-6 or TNF- α was shown after ACZ885 treatment.

Conclusion:

- ACZ885 was safe and well tolerated in Japanese healthy volunteers with ACZ885 exposure up to 900 mg administration by 600 mg i.v. plus 300 mg s.c. treatment.
- There was no immunogenicity throughout the study period in Japanese healthy volunteers.
- The PK characteristics were typical of human IgG molecules in Japanese healthy volunteers.
- The C_{max} and AUC increased in a weight-normalized dose-proportional manner within the whole range of i.v. administration.
- The mean t_{1/2} was 22.6 to 27.4 days in each administration route.
- The absolute bioavailability in the s.c. administration was 0.7.
- Total IL-1 β increased after ACZ885 treatment, however, no free IL-1 β was detected even after ACZ885 treatment in Japanese healthy volunteers. These were indicative of sufficient capture of IL-1 β by ACZ885 in serum.
- ACZ885 did not significantly affect IL-1Ra, IL-6 or TNF- α in Japanese healthy volunteers.

4.2.4 Synopsis of Study A2101:

Title of Study A2101: A randomized, double-blind, placebo-controlled, cohort dose escalation study of the safety, tolerability, pharmacokinetics and pharmacodynamics of ACZ885 (anti-interleukin-1 β monoclonal antibody) in patients with active rheumatoid arthritis (RA) despite ongoing treatment with methotrexate (MTX) 15 mg or more weekly for at least 3 months.

Objectives:

Primary objective

- To evaluate the safety and tolerability of ACZ885 administered as an intravenous infusion

Secondary objectives

- To assess the preliminary biologic activity/pharmacodynamics of ACZ885 using measurements to include ACR20, Disease Activity Score (DAS); quantification of IL-1 β , IL-6, and C-reactive protein (CRP), matrix metalloproteinases (MMPs) 1 and 3, C-telopeptide of Type I collagen (serum CTX-1, Crosslaps) and C-telopeptide of Type II collagen (urinary CTX-II, CartiLaps), at Week 7, as well as week 4, versus baseline
- To evaluate the pharmacokinetics of intravenously infused ACZ885
- To develop initial data to assist in the selection of biologically active doses for subsequent phase II studies of ACZ885
- To examine the potential immunogenicity of ACZ885 in RA patients receiving concomitant methotrexate, with or without oral corticosteroids.

Design: This was a multi-center, double-blind, randomized, placebo-controlled, cohort dose escalation study, with an expansion phase to explore safety and efficacy of intravenously administered ACZ885 in patients with active rheumatoid arthritis despite ongoing treatment with methotrexate 15 mg or more weekly for at least 3 months prior to randomization.

There was a 14 day screening period (Day -19 to Day -5), a baseline evaluation to assure active arthritis (Day -4 to Day -1), a single treatment period consisting of two dosing days, Day 1 infusion (with 4 post-dose visits) and Day 15 infusion, with an observation period of 14 weeks following this second dose administration (with 10 visits including a completion visit in Week 17).

Each dose group in the dose escalating phase consisted of 6 patients receiving active ACZ885 and 2 receiving a placebo infusion (comparable to vehicle). As sites recruit patients, randomization across the centers and allocation of patient numbers were controlled centrally. Each patient's participation was about 17 weeks from first dosing until last visit. ACZ885 was administered as an i.v. infusion over approximately 120 minutes, on two separate occasions: Day 1 and Day 15. The decision to proceed to the next dose level was based on a review of safety and tolerability data available 5 to 7 days after the administration of the second dose of ACZ885 to 6 out of 8 patients in the dose cohort. Evaluation criteria included absence of treatment-related SAEs and investigation of patient dropouts.

The purpose of increasing the sample size in the expansion phase was to add power to explore the range of antirheumatic activity of ACZ885. Patients in the expansion phase of the study received 10 mg/kg on Day 1 and Day 15.

Special safety assessments included the measurement of anti-ACZ885 antibodies in serum. The pharmacokinetics of ACZ885 in serum was also investigated.

The pharmacodynamic effects of ACZ885 was assessed using

- the ACR components [including joint counts, patient/investigator disease activity and pain assessment, acute phase reactants (ESR and CRP) and a Health Assessment Questionnaire (HAQ)] forming the ACR20, ACR50 and ACR70 definitions
- joint assessments were done by blinded observers at baseline, Day 43 and Day 113
- joint assessments were done by the investigator at screening, baseline, Days 8, 15, 22, 29, 43, 57, 85 and 113.
- the Disease Activity Score (DAS28) derived from joint counts, ESR and patient's global assessment of disease activity).
- changes in IL-1 β (free and total), IL-1ra (receptor antagonist), IL-6, TNF- α , Rheumatoid Factor, C-reactive protein (CRP), C-telopeptide of Type 1 collagen (CTX, Crosslaps) and C-telopeptide of Type 2 collagen (CTX-II, CartiLaps). These PD assessments were completed at several visits throughout the study as well as at study completion (Day 113) (see PD assessment section below).

Number of subjects:

Fifty-three (53) patients were planned, entered and completed the trial, as follows:

Phase	Treatment group			Active	Placebo
Escalating	Dose I	0.3 mg/Kg	n = 8	6	2
	Dose II	1.0 mg/Kg	n = 8	6	2
	Dose III	3.0 mg/Kg	n = 8	6	2
	Dose IV	10.0 mg/Kg	n = 8	6	2
Expansion	Dose IV	10.0 mg/Kg	n = 21	14	7

In total, 15 patients received placebo and 20 received the active maximum dose (10 mg/kg).

Investigational drug:

- ACZ885 50 mg lyophilisate or powder in vial (variant name: ACZ885 LYVI 50MG 22 GLW.001), batch # Y096 0503

- placebo to match (variant name: ACZ885 LYVI 0MG 22 GLW.001), batch # Y003 0103

Four i.v. doses: 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg and 10.0 mg/kg

Duration of treatment: Two doses (Day 1 and Day 15) with follow-up evaluations until Week 17 (study completion).

Criteria for evaluation:

Safety and tolerability evaluations: physical examination, ECG, vital signs, blood chemistry, hematology, urinalysis and adverse events (including the question "how have treatments affected you?") were monitored during the entire study until the end of study evaluation.

Anti-ACZ antibody was also measured.

Pharmacokinetic evaluations:

Blood samples were collected up to Day 112 postdose for determination of ACZ885 in serum by a validated competitive ELISA assay. Standard noncompartmental pharmacokinetic parameters were derived.

- PK parameters: AUC(0-tz), AUC(0-∞), C_{max}, T_{max}, t_{1/2}, CL and V_z determined from serum concentration-time data.

Pharmacodynamic evaluations:

- ACR Components: Joint Counts / Patient/Investigator Global VAS Disease Activity / Pain Assessment = VAS/HAQ / acute phase reactants (ESR,CRP):

- ESR (Westergren)

- C-reactive protein (CRP) (using Dade-Behring assay or comparable high sensitivity assay)

These assessments form the components of the ACR20, ACR50 and ACR70 definitions for improvement of rheumatoid arthritis.

- Disease activity score (DAS) (this was in addition derived from swollen joint count, tender joint count, ESR and patient's assessment of disease activity).

- Blinded observer joint assessment

- Free and total IL-1 β quantification, IL-1 Receptor Antagonist (IL-1Ra), IL-6, TNF- α , **Rheumatoid Factor** (performed as part of blood chemistry), C-telopeptide of Type I collagen (CTX-I) (use Serum CrossLaps™ One-Step ELISA) and Ctelopeptide of Type II collagen (CTX-II) (using urine CartiLaps™ ELISA).

The measurement of MMP1 and 3 was also planned, but, due to technical problems not feasible.

Pharmacogenetic evaluations:

A single 18 mL blood sample was collected in EDTA tubes at baseline from each patient who agrees, in writing, to participate in pharmacogenetic evaluations. If the baseline timepoint was missed for any reason, the blood sample was drawn at the next scheduled blood draw.

Statistical methods:

Statistical analyses were performed on the ACR20, ACR50 & ACR70 event rates. Separate statistical analyses were performed on the response rate based on the blinded observer assessment at Week 7 (Day 43) and the response rate based on the investigator assessment at Week 5 (Day 29), Week 7 (Day 43) and up to Day 43.

Fisher's exact test was performed to compare treatment groups. The primary comparison was the comparison between the 10mg/kg treatment group and placebo.

For the analysis of the DAS scores, a mixed model was fitted with treatment group and baseline DAS score and, where applicable, time-point and its interaction with treatment and baseline, as fixed effects. The difference between each active dose and placebo at each time-point (where applicable) was calculated. These differences are presented with their associated 95% confidence interval. The primary comparison of interest is the comparison between the 10mg/kg treatment group and placebo at Week 7 (Day 43).

Similar analyses were performed on the serum CRP, CTX-I and urine CTX-II Concentrations.

Sample size

The inclusion of 6 patients per dose group in each escalation step provided an 80% probability that at least one patient would report an adverse event that has an incidence of 24%.

Twenty patients receiving the highest ACZ885 dose (6 patients in the last escalation step + 14 patients in the expansion phase) and 15 patients receiving placebo (2 patients in each of the 4 escalation steps + 7 patients in the expansion phase) provided at least 80% power to detect an odds ratio of 6 in ACR20 response rate comparing ACZ885 to placebo, assuming a 5% significance level and a one-side test approach. Given a placebo ACR20 response rate of 20%, an odds ratio of 6 would translate into an ACR20 response rate of 60% for the ACZ885 treatment group.

Results:

Pharmacokinetics:

Parameters are tabulated below C_{max} and AUC's rose in a dose proportional manner over the full range from 0.3 mg/kg to 10 mg/kg. The half-life t_{1/2} is similar across dose levels and averaged 21.5 ± 4.9 days. The mean volume of distribution V_z was dose-independent, yielding an average value of 6.27 ± 1.54 L. This value agrees with a distribution into the plasma volume plus additional distribution into the tissue interstitial fluid space in human. The total systemic serum clearance Cl (0.21 ± 0.07L/day) was also similar across dose levels and was extremely low compared to the hepatic blood flow.

Table 1 Pharmacokinetic Parameters

Parameter	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
N	6	6	6	20
t _{max} (days)	14.06 (0.17-14.30)	13.63 (0.09-14.18)	14.12 (14.08-14.19)	14.16 (13.17-21.12)
C _{max} (µg/mL) #	8.8 ± 1.5	32.2 ± 8.5	81.9 ± 16.2	328.9 ± 62.1
AUC(0-t _z) (day*µg/mL)	181 ± 32	751 ± 338	2014 ± 368	7594 ± 1810
AUC _{0-∞} (day*µg/mL)	179 ± 31	807 ± 417	2082 ± 400	7918 ± 2003
V _z (L)	7.89 ± 1.52	6.35 ± 0.87	6.16 ± 1.30	5.87 ± 1.57
Cl (L/day)	0.283 ± 0.064	0.203 ± 0.068	0.199 ± 0.043	0.200 ± 0.066
t _{1/2} (day)	19.6 ± 2.3	23.7 ± 8.8	21.7 ± 3.0	21.2 ± 5.1

Pharmacodynamics:

• ACR criteria

Using the ACR definitions based on blinded observer joint assessments at baseline and Day 43, eleven (11) out of 37 (one subject was excluded from the analysis) subjects treated with ACZ885 achieved an ACR20 response at Day 43. Ten (10) of these responders were in the 3 mg/kg and 10 mg/kg groups. One (1) out of 15 subjects on placebo was classified as an ACR20 responder in the placebo group.

The p-value for the comparison of the 10mg/kg and placebo was 0.085 indicating that there is some evidence that the difference in response rates between these groups was unlikely to be due to chance. When patients from the 3 mg/kg and 10 mg/kg cohorts were pooled, there was a significant difference (p=0.023) to placebo for the outcome parameter ACR20.

In total, four (4) subjects on ACZ885 showed an ACR50 and two (2) subjects showed an ACR70 response at Day 43, while placebo did not induce these response rates.

• DAS28

DAS scores decreased initially in all treatment groups except the 1mg/kg group. From Week 2 (Day 8) to Week 7 (Day 43), the DAS scores remained fairly stable with a slight decrease in the 10mg/kg group. At Week 7 (Day 43), there was a reduction of 0.82 in the 10mg/kg compared with placebo.

• CRP

CRP levels decreased rapidly at Day 8 in the 0.3, 3 and 10 mg/kg cohorts. At Day 43, the reductions were 55%, 41%, 46% and 54% for the 0.3, 1, 3 and 10 mg/kg treatment groups compared with placebo. Due to the small sample sizes in the 0.3, 1 and 3 mg/kg groups, only the reduction in the 10mg/kg group was statistically significant.

• Serum cytokine levels

TNFalpha, IL-6 and IL1RA serum levels were in the range of healthy subjects and no obvious changes during the study were observed. Therefore, no conclusions on the effect of ACZ885 on these cytokine levels in serum could be drawn.

• Serum CTX-I levels

CTX-I levels in subjects treated with ACZ885 or placebo were not different and were in the normal range of 1000 to 5500 pM. There were no changes up to Day 43.

• **Urinary CTX-II levels**

Urinary CTX-II levels (measured only in the placebo and 10mg/kg groups) were in the normal range of 102 to 443 n/mmol (Creatinine corrected) during the entire study. There was a reduction in urine CTX-II levels over placebo of 21% in the 10 mg/kg cohort at Day 43 but this reduction was not statistically significant (95% CI : a 32% increase to a 56% reduction).

• **IL-1 β levels in serum, PK/PD modeling**

Serum total IL-1 β levels at baseline were below 1.2 pg/ml, in many subjects below the level of detection (0.1 pg/ml). Free IL-1 β was not detectable. Upon treatment with ACZ885, there was a dose-dependent increase of total IL-1 β reaching maximal levels of 100 pg/ml. Highest levels were seen between Day 29 and 57 of the study. A mathematical model was created encapsulating an understanding of the mode of action of ACZ885 in binding and thereby reducing levels of free IL-1 β .

Pharmacogenetics:

An optional exploratory retrospective pharmacogenetic analysis was conducted to evaluate potential association between genetic variation and clinical outcome. In total, one baseline sample from 28/38 ACZ885-treated patients and 13/15 placebo-treated patients were analyzed for five known polymorphisms in the IL-1 β and IL-1 receptor antagonist (IL-1RA) genes. Subjects carrying the CT genotype (approximately 1/3 of all patients) at the +3953 polymorphism of IL-1 β showed a trend to greater response to ACZ885 treatment, relative to patients with the CC genotype, as assessed by ACR20 criteria.

Conclusions:

ACZ885 was found to be safe and well tolerated at all tested dose levels. No unexpected and clearly drug-related adverse events were discovered. Infections were the most prominent adverse events, consistent with a role of IL-1 β as a cytokine involved in immune defenses. The severity or duration of the infectious episodes including the susceptibility to antibiotic treatment was found to be not altered as compared to what can be expected in this patient population. There was no evidence of immunogenicity.

CRP levels were decreased even at lower doses of ACZ885. Serum cytokine levels, serum CTX-I levels and urinary CTX-II levels were in the normal range. There was only a small reduction of urinary CTX-II in the 10 mg/kg treatment group, while all other parameters did not show a treatment-related change up to Day 43.

4.2.5 Synopsis of Study A2102

<p>Title of Study A2102: An open-label, phase II dose titration study of ACZ885 (human anti-IL-1β monoclonal antibody) to assess the clinical efficacy, safety, pharmacokinetics and pharmacodynamics in patients with NALP3 mutations.</p>
<p>Objectives: <i>The primary objective</i> was to determine the efficacy of canakinumab administered as intravenous (i.v.) infusion and subcutaneous (s.c.) injection to improve the clinical status of patients with NALP3 (CIAS1, PYPAF1) mutations. <i>Secondary objectives</i> were to assess the safety, tolerability, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD) of canakinumab administered as i.v. infusion and s.c. injection, to assess PK/ PD relationships in order to derive a dose and dosing regimen for Phase III, to assess the efficacy of canakinumab to modify disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms, and to modify health-related quality of life. <i>Exploratory objectives</i> were to conduct genomic studies to identify gene expression patterns of blood that are associated with treatment response to canakinumab, or that possibly correlate with the severity or progression of autoinflammatory diseases.</p>
<p>Methodology: This was a non-randomized, open-label, uncontrolled, single group Phase II study, with a first single centre stage and a second multinational, multicentre stage.</p> <p>Number of patients (planned and analyzed): In the first stage of the study it was planned to enrol a total of 4 to 6 adult patients. Additional patients were to be enrolled in the second stage, for a total number of up to 50 patients enrolled in the study. Four patients completed the first stage of the study and continued in Stage 2. Additional 30 patients were newly enrolled in Stage 2 of the study, for a total of 34 patients enrolled in the study and analyzed. 31 patients completed the study, 3 discontinued.</p> <p>Diagnosis and main criteria for inclusion: CAPS patients with a molecular diagnosis of NALP3 mutation and a clinical picture characteristic of Muckle-Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS), or Neonatal Onset Multi-system Inflammatory Disease (NOMID) overlapping MWS, aged 4 to 75 years, of either gender, with no active medical condition preventing participation in the study.</p> <p>The trial included 2 adult FCAS patients, 27 MWS patients (5 of them in the pediatric age range), 2 adult and 2 pediatric patients with MWS/ NOMID overlap, and 1 adult NOMID patient.</p> <p>Test product, dose and mode of administration, batch number: Novartis supplied canakinumab in 6 mL vials each containing 150 mg canakinumab as a lyophilized cake, to be reconstituted with water for injection to obtain solutions for injection or for infusion. Batch nos.: Y043 0504 and Y006 0106.</p> <p>Dosage Stage 1: first dose was a single administration of 10 mg/kg i.v., the 2nd dose was a single administration of 1 mg/kg i.v. upon relapse. On second relapse, single administration of 150 mg s.c.</p> <p>Dosage Stage 2: repeat single administration of 150 mg s.c. upon each relapse (in children from 4 to 16 years an equivalent of 2 mg/kg s.c.). If needed: rescue dose of 5 or 10 mg/kg i.v.</p> <p>Duration of treatment: Re-dosing upon each relapse, until roll-over to Phase III studies CACZ885D2304 or CACZ885D2306, or until study discontinuation.</p>
<p>Criteria for evaluation</p> <p>Efficacy: <i>The primary efficacy variable</i> was the time from each dose administration to relapse. Response to treatment was collected through the Physician's clinical assessment of disease activity, patient's assessment of symptoms, and inflammation markers (C-reactive protein [CRP], serum amyloid A [SAA]) in serum. <i>Secondary efficacy variables</i> were ear nose throat examinations and audiologic assessments, monitoring of creatinine clearance and proteinuria, magnetic resonance imaging (MRI) of brain, neurological assessments, and ophthalmological assessments. The health related quality of life was assessed using the following Patient Reported Outcome (PRO) instruments: Medical Outcome Short Form (36) Health Survey (SF-36$\text{\textcircled{C}}$) (adults), Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F$\text{\textcircled{C}}$) (adults), Health Assessment Questionnaire (HAQ$\text{\textcircled{C}}$) (adults), and Child Health Questionnaire – Child Self-Report Form (CHQ-CF87$\text{\textcircled{C}}$) (for children aged 10 to 18 years).</p> <p>Safety: Collection of adverse events (AEs) with particular focus on occurrence of infections. Regular monitoring of clinical laboratory parameters (including screening for anti-nuclear antibodies and PPD skin test reactivity), vital signs, body weight and height (only for children < 16 years), physical condition, electrocardiogram. Local tolerability assessment of s.c. injections. Evaluation of immunogenicity potential of canakinumab during the study by surface plasmon resonance spectroscopy using a validated — binding assay.</p> <p>Pharmacokinetics: Canakinumab concentrations in serum by competitive ELISA. PK parameters using non-compartmental analysis and compartmental analysis using population (nonlinear mixed effect) PK-binding model in NONMEM (Version VI Level 1.2).</p> <p>Pharmacodynamics: Total IL-1β in serum by ELISA, soluble serum protein markers (TNF-α, IL-6,</p>

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IL-1 α , IL-1Ra, soluble IL-1R, and CTX-1) in serum by commercially available ELISA assays.

Pharmacogenomics: RNA using microarray technology and RT-PCR to examine the effect of canakinumab on gene expression in peripheral blood cells will be reported separately.

Statistical methods: Statistical analyses were performed to assess the time from last dose to relapse for each of the different dose regimens and the impact of certain covariates on time-to-relapse. For each analysis, a Weibull 'gap-time' frailty model was used. Demographic and baseline characteristics, PK and efficacy/ PD variables, safety data were summarized by either age group or dose regimen using descriptive statistics.

Three interim analyses were performed during the course of the study.

Summary - Conclusions

Efficacy results: Canakinumab induced a fast and long lasting response in patients with CAPS.

Within 1 day from first s.c. dosing, the urticarial rash disappeared or decreased to minimal in 94.1% of the patients. Following the first s.c. administration of 150 mg canakinumab, 96.6% of the patients achieved a complete clinical response within 2 to 9 days from dosing. In the 2 mg/kg treatment group, all pediatric patients achieved a complete clinical response within 2 to 8 days from first dosing. However, 2 patients experienced a rapid response loss and received rescue treatment, achieving then a complete response. Throughout the trial, rescue treatment with i.v. canakinumab was administered in 4 adult patients and 2 pediatric patients. The estimated median time to relapse is shown in the table below.

Dose regimen	No. of unique subjects who received dose regimen	Number of periods	Median Time-to-Relapse (days)	95% Confidence Interval
10 mg/kg i.v.	4	4	156.2	102.5 - 209.8
1 mg/kg i.v.	4	4	72.8	48.0 - 97.7
150 mg s.c.	29	96	115.2	94.1 - 136.4
150 mg s.c. + rescue i.v.	4	5	174.5	90.5 - 258.5
2 mg/kg s.c.	4	22	48.6	29.3 - 67.9
2 mg/kg s.c. + rescue i.v.	2	11	51.7	27.0 - 76.5

CRP and SAA as well as serum levels of IL-6 and IL-1Ra, returned to the normal range, while levels of IL-1R, TNF α and sCTX did not change. An improvement was observed in all PROs.

Safety results: No patients died. Three serious AEs were reported: a chest infection in an adult patient, vertigo in a child and pain due to progression of underlying fibromyalgia in a NOMID adult patient. There was one discontinuation due to pregnancy. A total of 308 AEs were reported. For 28 AEs (in 13 patients) a relationship with the study drug was suspected. The majority of AEs was mild to moderate in severity and was transient in nature. The most frequent AEs were infections and infestations (upper respiratory tract infections and nasopharyngitis), in the adult and pediatric population. In the other system organ classes the most frequent AEs in the adult patients group were muscle spasms, headache, pharyngolaryngeal pain, dyspepsia, nausea, and haematoma. In the pediatric patients group the most frequent AEs were rash, vomiting, diarrhoea, sleep disorder, cough, pharyngolaryngeal pain, and acne. None of the patients showed a treatment induced immune response to canakinumab. Canakinumab s.c. injections were well tolerated.

PK/PD results: Non compartmental serum PK parameters of canakinumab after an initial s.c. dose of 150 mg in adult patient are shown in the table below.

	Cmax [μ g/mL]	tmax [d]	AUC _{last} [μ g \cdot d/mL]	AUC _{0-∞} [μ g \cdot d/mL]	F (%)	t $\frac{1}{2}$ [d]	CL/F [L/d]	Vz/F [L]
n	25	25	22	22	4	22	22	22
Mean	15.9		674	708	66.5	26.1	0.228	8.33
SD	3.52		189	206	22.2	7.31	0.0597	2.62
Median	16.2	6.98	634	656	69.7	25.6	0.229	7.97
Min	10.4	1.92	387	405	37.3	13.1	0.125	4.38
Max	21.7	14.0	1124	1204	89.3	39.2	0.370	13.9
CV%	22.2		28.0	29.1	33.5	28.0	26.2	31.4

Peak serum levels were reached by approximately 7 days. Maximum serum concentrations were on average 15.9 (\pm 3.52) μ g/mL. Apparent half-life following the single s.c. dose administration was 26.1 (\pm 7.31) days. Moderate inter-subject variability with a coefficient of variation of approximately 22.2% and 29.1% was observed in Cmax and AUC ∞ values. Correcting for bioavailability of ~67%, the PK of canakinumab was in line with the expected PK characteristics of a human IgG molecule, i.e. low apparent clearance (average CL/F was 0.228 \pm 0.0597 L/d) and a low apparent volume of distribution (Vz/F was 8.33 \pm 2.62 L). In pediatric patients enrolled only in Stage 2, PK inference using non-compartmental analysis could not be drawn from 2

subjects as the length of PK assessment from their first s.c. dose was very short (10 days or shorter). Peak concentrations of canakinumab occurred between 2 to 7 days following s.c. administration of 150 mg or 2 mg/kg s.c. dose of canakinumab.

Apparent half-lives ranged from 22.9 to 25.7 days, in line with the PK properties seen in adults. CL/F and Vz/F values were 0.131 and 0.0621 L/d, and 4.48 and 2.30 L, respectively, for the 2 subjects given 2 mg/kg dose. These parameter estimates are consistent with the relatively smaller body weight of pediatric patients. The older child, subject 5131, had CL/F and Vz/F values of 0.232 L/day and 7.67 L respectively, more in line with the PK characteristics observed in adults. PK/ PD compartmental parameters of canakinumab in patients receiving at least one dose of canakinumab are shown in the table below.

	CLD [L/d]	VD [L]	VP [L]	PSD [L/d]	KA [1/d]	F	CLL [L/d]	RLI [ng/d]	PSL [L/d]	KD nM
Mean	0.154	2.83	2.26	0.376	0.371	0.633	18.6	12.6	0.335	1.14
SD	0.0577	0.74	0.75	0.15	0.21		12.9	14.57	0.12	0.53
Median	0.1540	2.87	2.34	0.36	0.35	0.633	15.3	9.75	0.34	1.10
Min	0.0522	1.12	0.44	0.12	0.09	0.633	6.10	3.76	0.08	0.37
Max	0.319	4.75	4.02	0.90	1.14	0.633	70.0	88.38	0.65	2.31
CV%	37.4	26.2	32.9	41.0	57.4		69.5	115.8	35.8	46.7

There was significant increase in canakinumab bound IL-1 β after dosing which was indicative of capture of IL-1 β by the antibody. The PK parameter estimates from the population PK-binding model are in agreement with the estimates from the non-compartmental PK parameters. For example, the s.c. bioavailability of canakinumab (F) was estimated from the model to be 63.3%, in close agreement with the non-compartmental estimate of 66.5%. Similarly, the CL and total volume of distribution from the model were 0.154 L/d and 5.09 L, compared to CL and Vss values of 0.182 L/d and 7.08 L, respectively, from non-compartmental analysis from the i.v. data. The equilibrium dissociation constant for binding of canakinumab to IL-1 β was estimated to be 1.14 nM based on the population PK/PD binding model. The production or release rate and the clearance of the uncomplexed ligand, IL-1 β were estimated to be 12.6 ng/d and 18.6 L/d, respectively.

A nonlinear mixed effect PK-flare probability model was created to identify a dosing regimen for the phase III study which keeps free IL-1 β production below the threshold associated with clinical evidence of CAPS.

Conclusion:

- Treatment with canakinumab was highly effective achieving fast, complete and sustained response in adult and pediatric CAPS patients. Acute phase serum inflammatory protein markers, white blood cells counts, neutrophils, and platelets counts supported the clinical observations, rapidly reaching normal levels following canakinumab injection.
- Canakinumab was safe and well tolerated. AEs were as expected for this disease and drug class, namely infections and infestations in both the adult and pediatric groups. None of the patients in this study showed a treatment induced immune response to canakinumab. Canakinumab s.c. injections were well tolerated.
- The PK properties of canakinumab are typical of a human IgG1-type antibody. The concentration time profiles indicated that peak concentration of canakinumab occurred around 1 day following i.v. infusion administration and approximately 7 days following s.c. administration in adult patients. The apparent volume of distribution (Vz/F 8.33 \pm 2.62 L) is indicative of the distribution of the drug mainly to the vascular compartment and interstitial space. Low apparent systemic clearance (CL/F averaged 0.228 \pm 0.0597 L/day) contributed to long half-lives averaging 26.1 \pm 7.31 days following s.c. administration of canakinumab. Similarly, the peak concentrations of canakinumab in pediatric patients occurred approximately 2 to 7 days following s.c. administration of 2 mg/kg or 150 mg of canakinumab. Apparent half-life following a single s.c. dose administration was comparable between adult and pediatric subjects, averaging 26.1 \pm 7.31 days in adults, and ranging from from 22.9 to 25.7 days in pediatric patients.
- The equilibrium dissociation constant for binding of canakinumab to IL-1 β was estimated to be 1.14 nM based on the binding model, signifying potent in vivo binding of canakinumab to IL-1 β .
- Based on PK/ PD modeling and simulation, a regimen of 150 mg canakinumab administered s.c. every 8 weeks for patients with a body weight \geq 40 kg should keep patients flare free.
- Data on audiograms, MRI examinations, neurological and ophthalmological examinations and kidney function are sparse at the time of this report to formulate any conclusions on the efficacy of canakinumab to modify long-term disease progression.
- The PROs used in the study reflected an improvement in quality of life following canakinumab.

4 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

4.2.8 Synopsis of Study D2304

Title of Study D2304: A three-part multi-center study, with a randomized, double-blind, placebo controlled, withdrawal design in Part II to assess efficacy, safety and tolerability of ACZ885 (anti-interleukin-1 β monoclonal antibody) in patients with Muckle-Wells Syndrome

Objectives: The primary objective was to assess the efficacy of canakinumab (percentage of patients who experienced disease flare) compared with placebo in Part II as determined by the Physician's global assessment of autoinflammatory disease activity; assessment of skin disease and inflammation markers (CRP and/or SAA).

The secondary objectives were to assess the safety, tolerability and immunogenicity of canakinumab, to assess overall efficacy (response rate) of canakinumab in Part I and Part III as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers, to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of canakinumab and to assess the effect on disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms.

Methodology: This was a three part trial, starting with open-label treatment in Part I, with Part II being double-blind, placebo controlled, withdrawal design, returning to an open-label design in Part III. All patients initially received canakinumab in Part I, with only responders randomized into Part II. Patients then entered Part III upon completion of Part II or disease flare.

Number of patients (planned and analyzed): This was a multinational study and it was expected that a minimum of 20 Muckle-Wells Syndrome (MWS) patients would be randomized in Part II of this study. In Part I, 35 patients were enrolled, four patients discontinued due to unsatisfactory therapeutic effect, with 31 entering into Part II. In total 19 patients completed Part II.

Diagnosis and main criteria for inclusion

The investigator was to ensure that all patients who met the inclusion and none of the exclusion criteria were offered enrollment in the study. No additional exclusions could be applied by the investigator, in order to ensure that the study population be representative of all eligible patients.

Inclusion criteria were:

- Male and female patients aged 4 to 75 years.
- Molecular diagnosis of NALP3 mutations and clinical picture resembling MWS (patients who participated in the CACZ885A2102 study, had the option to participate in this study upon disease relapse).
- Body weight ≥ 15 and < 100 kg

Test product, dose and mode of administration, batch number: Novartis supplied individual vials each containing 150 mg canakinumab or placebo matching powder as a lyophilized cake.

Dosing was to occur in the morning. Patients were to remain at the study site for observation for at least 1 hour following study drug administration.

All patients with a body weight > 40 kg received one injection of canakinumab 150 mg s.c. every 8 weeks.

Patients with a body weight ≥ 15 kg and ≤ 40 kg received an equivalent of 2 mg/kg s.c.

In Part I, all patients received canakinumab.

In Part II, patients were assigned to one of the following two treatment arms in a ratio of 1:1 within each strata (patients > 16 years transitioned from study CACZ885A2102, canakinumab naïve patients > 16 years, and patients ≤ 16 years):

- canakinumab
- placebo

In Part III, all patients received canakinumab.

Identity of investigational product(s)

Canakinumab and placebo were manufactured by Novartis.

Treatment	Variant No.	Batch No.
Canakinumab 150 mg	7004942.005	U23 1006
Placebo to canakinumab 150 mg	7001283.004	Y121 1004

Duration of treatment: Duration of treatment was planned in Part I to be 8 weeks, followed by 24 weeks in Part II, and 16 weeks in Part III. The duration of Part II was determined by patient flare – patients who experienced disease flare prior to the end of the 24 weeks were allowed to enter Part III.

Criteria for evaluation

Efficacy: In the withdrawal period in Part II of the study, the primary efficacy variable was the proportion of patients with disease flare as assessed by the physician's global assessment of autoinflammatory

disease, assessment of skin disease and levels of serum inflammatory markers, or

discontinuation from Part II.

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at the central laboratory (only if the site urine dipstick test was positive) and regular assessments of vital signs, physical condition and body weight. Blood samples were taken to assess anti-nuclear antibodies. Additional tests included audiograms, brain MRI, neurological testing and ophthalmological assessment. Other assessments could be made at the discretion of the investigator.

Pharmacokinetic assessments: Canakinumab was analyzed in serum by means of a competitive ELISA assay.

Pharmacodynamic assessments: Total IL-1 β was analyzed in serum by means of a competitive ELISA assay.

Immunogenicity: Anti-canakinumab antibodies concentrations were assessed in serum by — with detection based on Surface Plasmon Resonance.

Biomarker assessments

Soluble protein marker analysis: Soluble protein analysis was performed using single use ELISAs.

Pharmacogenomics: RNA analysis was performed by RT-PCR.

Statistical methods: In the withdrawal period in Part II of the study, the primary efficacy variable was the proportion of patient with disease flare. Patients who met the criteria for disease relapse or discontinued Part II due to any reason, were considered as patients having disease flare in Part II. The two treatment groups were compared using an exact test (based on hypergeometric probabilities) about the common odds ratio, adjusting for cohort (patients transitioned from CACZ885A2102, canakinumab naïve patients). The following statistical hypothesis was tested:

H0: common odds ratio = 1, i.e. the probability of having disease flare is the same for both groups, versus

HA: common odds ratio \neq 1, i.e. the probability of having disease flare is different for both groups

In addition to the exact two-sided p-value, the common odds ratio was estimated and an exact 95% confidence interval for the common odds ratio was calculated, taking into account cohort.

The primary analysis was based on the ITT population of Part II.

Time to disease flare from Week 8 in Part II was analyzed as a supportive analysis. Differences between treatment groups in time to disease flare were analyzed using Cox's proportional hazards regression model with treatment and cohort as explanatory variables. The Kaplan-Meier estimates of the proportion of patients with disease flare, along with 95% confidence intervals using Greenwood's formula, were provided. The Kaplan-Meier estimates were also plotted against time.

Part I

The ITT population for Part I was used. In the open label Part I of the study, the proportion of patients who did not have a disease relapse thereafter until Week 8 was calculated.

Part II

The secondary efficacy endpoints were assessed from the beginning of the Part II, i.e. Week 8. The analyses of all secondary efficacy variables were performed on the ITT population for Part II. The method of last observation carried forward (LOCF) was used to impute missing values. Change from Week 8 in CRP and SAA was analyzed using a Wilcoxon rank-sum test, stratified by cohort. The frequency distribution of the severity scores for the physician's global assessment of autoinflammatory disease activity was compared between treatment groups using an exact permutation test with equally spaced scores, stratified by cohort. The same analyses were performed for patient's assessment of symptoms. In addition, changes from Week 8 in the total core were analyzed using a stratified Wilcoxon rank-sum test, stratified by cohort. The frequency distribution of the severity scores (absent, minimal, mild, moderate, severe) for the assessment of skin disease was summarized by treatment group. No statistical test was performed.

Part III

In the open label Part III of the study, the proportion of patients without disease relapse was calculated based on the ITT population for Part III.

Other efficacy variables were presented descriptively.

Pharmacokinetic and Pharmacodynamic evaluations: A mixed effects modeling approach was taken in order to analyze the available PK and PD (total IL-1 β) data from the study.

Biomarker evaluations

Soluble protein marker analysis: Analysis of this information was data driven.

Pharmacogenomics: The statistical analyses were performed by analysis of variance (ANOVA) followed by a Dunnett's post test.

Summary - Conclusions

Efficacy results: The results of this interim analysis show that in Part I of the study, 97.1% of patients had a

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complete response to canakinumab, with 71.4% of patients having complete response by the first scheduled timepoint (Day 8).

In Part II, treatment with canakinumab prevented all 15 patients treated from experiencing a disease flare. In contrast, 13 of 16 patients (81.3%) treated with placebo experienced disease flare. This difference was statistically significant ($p < 0.001$). At the time of interim database lock one patient had experienced a disease relapse in Part III.

The levels of inflammatory markers (CRP and SAA) rose by a significantly smaller amount in the canakinumab treated group than placebo over the course of Part II from Week 8 to last assessment in Part II; CRP 1.10 mg/L versus 19.93 mg/L and SAA 2.27 mg/L versus 71.09 mg/L for canakinumab and placebo, respectively). When patients were re-treated with canakinumab in Part III, levels of serum inflammatory markers decreased to levels seen at the start of Part II.

The physician's global assessment of auto-inflammatory disease had statistically significant better outcomes at the last assessment in Part II than the placebo group.

Safety results: Adverse events in all treatment Parts were mainly mild to moderate in severity, and showed a similar overall frequency between canakinumab and placebo treated patients in Part II (100% and 87.5% of patients, respectively). The most commonly affected organ class was infections and infestations (34.3% of patients in Part I, 80.0% in Part II canakinumab treated and 56.3% in Part II placebo treated). In Part II, a higher percentage of patients in the canakinumab treatment arm had infection AEs (according to Investigator's opinion) than in the placebo group (66.7% versus 25.0%).

There was one adverse event discontinuation and two serious adverse events (all reported during Part III). Notably abnormal laboratory and vital sign values were uncommon.

Pharmacokinetic and Pharmacodynamic results: Serum clearance (CL) of canakinumab averaged 0.177 (\pm 0.085) L/d with a low total volume of distribution of 5.62 L. The s.c. bioavailability of canakinumab (F) was estimated to be 70.5%.

The equilibrium dissociation constant for binding of canakinumab to IL-1 β was estimated to be 1.23 nM, signifying potent in vivo binding of canakinumab to IL-1 β . The production or release rate and the clearance of the uncomplexed ligand, IL-1 β were estimated to be 11.6 ng/d and 17.3 L/d, respectively.

Immunogenicity: Results showed that treatment with canakinumab did not result in the production of specific anti-ACZ885 antibodies.

Conclusion: Complete clinical response in Part I was achieved by 97.1% of patients receiving canakinumab. A fast onset of clinical response was observed, with 71.4% of patients having complete response by the first scheduled timepoint (Day 8).

Treatment with canakinumab every 8 weeks effectively prevented disease flare in patients with MWS.