and Analysis (DMEPA) were requested during this BLA review. The DSI inspection results from pending site visits at three foreign clinical centers will not be available until mid-May 2009. The completed consult from DMEPA for review of the proposed proprietary name, Ilaris, concludes that ILARIS is acceptable. The consult from DDMAC has not been completed at the time of completion of this review.

9.5 Review of Individual Study Reports

BLA 125319 is supported by a single, adequate and well-controlled pivotal Study D2304 and by two uncontrolled, open label trials, Studies A2102 and D2306. There was to have been no data pooling in these analyses. The pivotal study only included patients with MWS. The two uncontrolled studies included patients with FCAS, MWS and overlap MWS/NOMID.

Study D2304

The following description of this Phase 3 protocol for Study D2304 is based upon the original protocol (16January2007). The first patient was enrolled 04June2007 and the data cut-off date for the interim report was 29August2008. There have been no publications from this study to-date. There were no protocol amendments, no changes in the study conduct and planned analyses.

I. Protocol

A. Title

A three-part, multi-center study with a randomized, double-blind, placebo-controlled, withdrawal design in Part 2 to assess efficacy, safety and tolerability of canakinumab (ACZ885, anti-interleukin-1β monoclonal antibody) in patients with Muckle-Wells Syndrome (MWS).

B. Objectives

1. Primary Objective

a. To assess the efficacy of canakinumab based on the primary efficacy endpoint, the percentage of patients with MWS who experienced disease flare, compared with placebo in Part 2 as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers (C-Reactive Protein, CRP, and/or Serum Amyloid A, SAA).

2. Secondary Objectives

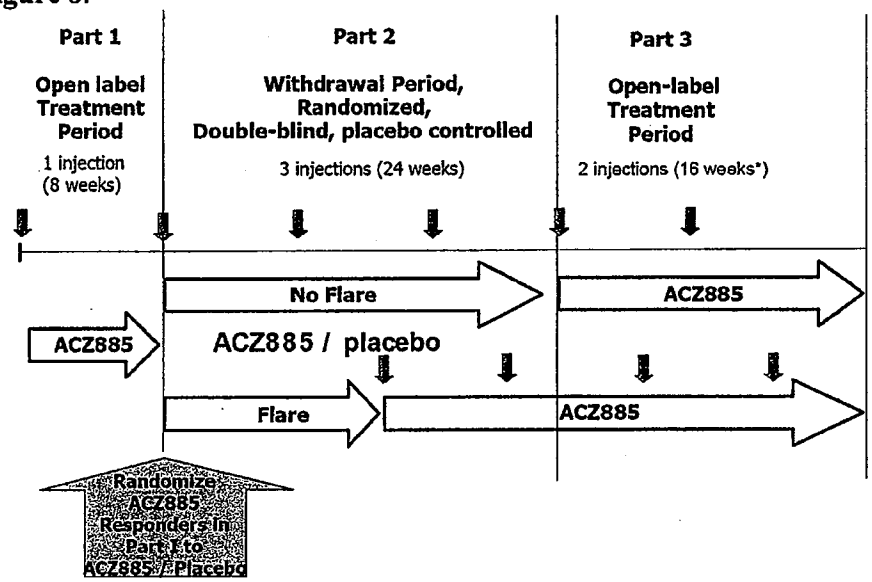
a. To assess the safety, tolerability and immunogenicity of canakinumab,
b. To assess the efficacy (response rate) of canakinumab in Part 1 and Part 3 based upon the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease and inflammation markers,
c. To evaluate the PK and PD of canakinumab, and
d. To assess the effect on disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms.

C. Study Design

Study D2304 was to have been a Phase 3, three part study starting with an open-label treatment period in Part 1, followed by a double-blind, placebo controlled, withdrawal period then followed by a second open-label period, Part 3 (see **Figure 8**). Study D2304 was intended to evaluate the safety and efficacy of canakinumab in patients (adult and pediatric) with Muckle Wells Syndrome (MWS).

All of the enrolled patients were to have first received canakinumab in Part 1, with only the responders, assessed as complete response, randomized into Part 2. Patients were to have then entered Part 3 upon completion of Part 2 or would have had disease flare. Patients were to have been randomized into Part 2 in a 1:1 ratio, canakinumab or placebo.

Figure 8.



* Part 3: The time point for entering Part 3 was based upon disease flare or completion of Part 2. Part 3 was 16 weeks for patients who completed Part 2, but for patients who withdrew from Part 2 early and entered Part 3, it could be as long as 40 weeks. Patients could enter Part 3 at any point from Day 58 to Day 225.

1. Duration

Part 1 (single dose) was to have been 8 weeks, followed by 24 weeks in Part 2 (multiple doses), and 16 weeks in Part 3. The duration of Part 2 was to be either 24 weeks or until the patient would have flared.

2. Study Population

Selection of Patients, Sample Size and Power Calculations

It was planned that a minimum of 20 patients with MWS would have been randomized into Part 2 of Study D2304. At least 8 patients were to have been newly enrolled into this study with no prior exposure to canakinumab. MWS patients who would have participated in Study A2102 would have had the option to transition/ rollover into Study D2304 upon relapse.

The sample size was calculated to show superiority of canakinumab relative to placebo for the proportions of patients with disease flare. A sample size of 10 patients per group would have 90% power to detect a difference between disease flare rate of 15% for the study drug group and 90% for the placebo group, based on Fisher's exact test with a 0.05 two-sided significance level.

3. Inclusion Criteria

a. Male and female patients aged 4 to 75 years
b. Molecular diagnosis of NALP3 mutation and clinical signs and symptoms resembling MWS (patients who participated in Study A2102 were to have been given the option to participate in Study D2304 upon relapse of CAPS disease, specifically, MWS).
c. Body weight ≥ 15 and < 100 kg.
d. MWS patients requiring medical management either untreated or treated (e.g., under canakinumab, anakinra, or any other investigational IL-1 blocking therapy).

4. Exclusion Criteria

a. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation with the exception of clinical trials with anakinra, other IL-1 blocking therapy, and canakinumab Study A2102.
b. Use of the following therapies:

- Etanercept in the 4 weeks prior to the baseline visit (Day 1)
- Adalimumab in the 8 weeks prior to the baseline visit (Day 1)
- Infliximab in the 12 weeks prior to the baseline visit (Day 1)
- Any other investigational biologics in the 8 weeks prior to the baseline visit (Day 1) (with the exception of anakinra and IL-1 blocking therapies)
- Patients who were on IL-1 blocking agents, including anakinra, would need to discontinue this treatment. As soon as the criteria for relapse would be fulfilled, patients could enter Study D2304 and receive canakinumab treatment. The run-in phase reduces the typical washout phase to a clinically meaningful time and would avoid unnecessary suffering for patients in case a pre-defined wash-out period per protocol would be too long for an individual patient.
- Leflunomide in the 4 weeks prior to the baseline visit (Day 1)
- Thalidomide in the 4 weeks prior to the baseline visit (Day 1)
- Cyclosporine in the 4 weeks prior to the baseline visit (Day 1)
- i.v. immunoglobulin (i.v. Ig) in the 8 weeks prior to the baseline visit (Day 1)
- 6-Mercaptopurine, azathioprine, cyclophosphamide or chlorambucil in the 12 weeks prior to the baseline visit (Day 1)
- Colchicine, dapsone, mycophenolate mofetil in the 3 weeks prior to the baseline visit (Day 1)
- Corticosteroids ≥20 mg/day or >0.4 mg/kg, whichever applies, 1 week prior to the baseline visit (Day 1), and
- No live vaccinations.

c. Live vaccinations within 3 months prior to the start of the trial, during the trial and up to 3 months following the last dose.

5. Study Treatments

Patients were to have remained in the study site for observation for at least 1 hour following study drug administration by subcutaneous injection (sc). **Table 44** presents the number of study drug injections to have been administered in each patient.

Part 1: All patients with body weight > 40 kg received one injection of canakinumab 150 mg sc. Patients with body weight ≥ 15 kg and ≤ 40 kg received a dose of 2 mg/kg sc.

Part 2: Patients were assigned to one of the following two treatment arms in a ratio of 1:1
- Canakinumab 150 mg sc injection or 2 mg/kg sc every 8 weeks. All patients with a body weight > 40 kg received one injection of canakinumab 150 mg sc. Patients with a body weight ≥ 15 kg and ≤ 40 kg received 2 mg/kg sc.

Part 3: All patients with body weight > 40 kg received canakinumab 150 mg sc injection every 8 weeks. Patients with body weight ≥ 15 kg and ≤ 40 kg received 2 mg/kg sc every 8 weeks.

Table 44.

Number of Injections in Study D2304				
	Part 1 8 weeks	**Part 2** 24 weeks		**Part 3** 16 weeks
# Injections (sc)	ACZ885 N =35	ACZ885 n = 15	Placebo N =16	ACZ885 N = 31
Median	1	3	2	2
(Min, Max)	1, 1	3, 3	1, 3	1, 5

6. Schedule of Events

Table 45.

Study Part	Screening		Part I Open-label treatment period						Part II Withdrawal period							Part III Open-label treatment period				
Visit	1	1.1[1]	2[2]	3A[3]	3B[3]	4	5A[10]	5B	6	7	8	9	10	11A	11B	12	13	14	15*
Week			0	1	2	4	8	8	12	16	20	24	28	32	32	36	40	44	48
Day (visit window ±3 days for dosing visits. For non-dosing visits, visit window was ±1 week except Visits 3 and 4 where it was ±1 day)	-15 to -2		1	8	15	29	57	57	85	113	141	169	197	225	225	253	281	309	337
Informed Consent [D]	X																		
Inclusion/exclusion criteria [S]	X		X																
Relevant medical history/ current medical conditions [D]	X		X																
Molecular diagnosis of NALP3 mutation[D]	X																		
Demography [D]	X																		
Physical examination[S]	X		X				X			X		X		X			X		X
Purified protein derivative tuberculin skin test [D]	X																		
PPD tuberculin skin test check [D] (to be read within 48-72 hours & before entering Part II)		X																	
Chest X-ray [D S]	X																		
Hepatitis and HIV exam[D]	X																		
Pregnancy test [D]	X													X					X
Vital signs, incl. weight[D]	X		X				X			X		X		X			X		X
Height [D]	X													X[11]					X[11]
Body Temperature[D]	X		X	X	X	X	X		X	X	X	X	X	X		X	X	X	X
ECG evaluation [D]	X						X							X[4]					X
Hematology, blood chemistry urinalysis[D]	X		X	X			X			X		X		X			X		X
Blood collection for efficacy (CRP, SAA)[D]	X		X	X	X		X		X	X	X	X	X	X			X		X

Table 45 *(continued)*

Study Part	Screening		Part I Open-label treatment period					Part II Withdrawal period							Part III Open-label treatment period				
Visit	1	1.1[1]	2[2]	3A[3]	3B[3]	4	5A[10]	5B	6	7	8	9	10	11A	11B	12	13	14	15*
Week			0	1	2	4	8	8	12	16	20	24	28	32	32	36	40	44	48
Day (visit window ±3 days for dosing visits. For non-dosing visits, visit window was ±1 week except Visits 3 and 4 where it was ±1 day)	-15 to -2		1	8	15	29	57	57	85	113	141	169	197	225	225	253	281	309	337
Anti-nuclear antibodies (ANA) screen			X				X							X					X
Randomization							X[9]												
Administration of medication [D 6]			X					X[8]		X		X			X		X		
Prior/Concomitant medication/significant non-drug therapies[D]	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X
Adverse events/infections [D]			X	X		X	X		X	X	X	X	X	X		X	X	X	X
Investigator's clinical assessment of auto-inflammatory disease activity [D]			X	X	X		X		X	X	X	X	X	X			X		X
Review of patient's assessment of symptoms (diary review)[D]			X	X	X		X		X	X	X	X	X	X			X		X
SF-36[Φ] (adults)[D]			X	X			X			X		X		X			X		X
FACIT-F[Φ] (adults)[D]			X	X			X			X		X		X			X		X
HAQ[Φ] (adults)[D]			X	X			X			X		X		X			X		X
CHQ-PF28[Φ] (children)[D]			X	X			X			X		X		X			X		X
Patient reported outcomes (languages)[D]			X																
Patient reported outcomes (Administrative – for all questionnaires) [D]			X	X	X		X		X	X	X	X	X	X			X		X
Audiogram [D]			X											X					X
Magnetic resonance imaging (MRI) of brain [D]			X											X					X
Neurological assessment [D]			X											X					X
Ophthalmological assessment [D]			X											X					X

Study Part	Screening		Part I Open-label treatment period					Part II Withdrawal period							Part III Open-label treatment period				
Visit	1	1.1[1]	2[2]	3A[3]	3B[3]	4	5A[10]	5B	6	7	8	9	10	11A	11B	12	13	14	15*
Week			0	1	2	4	8	8	12	16	20	24	28	32	32	36	40	44	48
Day (visit window ±3 days for dosing visits. For non-dosing visits, visit window was ±1 week except Visits 3 and 4 where it was ±1 day)	-15 to -2		1	8	15	29	57	57	85	113	141	169	197	225	225	253	281	309	337
Local tolerability assessment of injection site [D]			X	X		X	X		X	X	X	X	X	X		X	X	X	X
PK blood collection [D]			X	X		X	X		X	X	X	X	X	X		X	X	X	X
Immunogenicity blood collection [D 4]			X				X			X		X		X			X		X
PD (Total IL-1β) blood collection [D]			X	X		X	X		X	X	X	X	X	X		X	X	X	X
PD (Soluble protein markers panel) [D 7]	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X
Pharmacogenomics blood collection [D 7]	X		X	X		X	X		X	X	X	X	X	X		X	X	X	X
CACZ885A2102 patients: First Visit in this study [2]			X																
Study Part completion							X							X					X

[1] The PPD skin test was performed at any time during the screening period but it was read within 48 - 72 hours and prior to randomization.
[2] For patients entering Part I from the CACZ885A2102 study, the assessments performed at the last visit in CACZ885A2102 were the first visit for this study, assessments should not have been repeated twice. Informed consent was obtained prior to conducting any study related activities for patients entering from CACZ885A2102.
[3] Patients who were partial responders at Day 8 (Visit 3A) were to come back to the site to be re-assessed at Day 15 (Visit 3B). Visit 3B was not for all patients, it was only for patients who were partial responders at Day 8 (Visit 3A) in Part I.
[4] Samples for immunogenicity were collected 8 weeks after last dose of study medication.
[5] A chest x-ray should have been obtained if one had not been taken in the 12 months prior to randomization to assess the tuberculosis status and/or history of the patient.
[6] Dosing was to occur in the morning in order to coordinate sample collection times for pharmacokinetic, pharmacodynamic and exploratory assessments.
[7] Pharmacogenomic and soluble protein marker samples were only to be collected after separate consent was signed (these assessments are exploratory). Children (4 – 16 years of age) did not participate in this portion of the study.
[8] Only patients who completely responded to treatment without disease relapse in Part I were administered study medication on Day 57 and entered Part II (Day 57 is the first day of Part II).
[9] The time point for entering Part III was based upon disease flare or completion of Part II. Therefore, patients could enter Part III at any point from Day 58 to Day 225.
[10] If the patient had symptoms of relapse on Day 57 (Visit 5A), the Investigator was to wait for the CRP/SAA results before proceeding to Visit 5B.
[11] Height in adults was obtained at screening only. In children from 4 -16 years of age, height was obtained at screening, Visit 11A, and Visit 15 (EOS).
* End of Study (EOS) or in the event of premature termination. These assessments should also have been done for patients who prematurely discontinued. This visit should have occurred 8 weeks after the last injection.

Source: Sponsor Table 9.2, pp. 59-61.

7. Study Visits: Protocol Specifications

Study D2304 included a screening visit, followed by Part 1 as an open label treatment period for 8 weeks (1 canakinumab injection), Part 2 as a placebo-controlled, double-blind, withdrawal period for 24 weeks (3 canakinumab injections), and Part 3 as an open-label treatment period for at least 16 weeks or longer (2 canakinumab injections). Eligible patients who completed Part 1 with a complete response were randomized into Part 2. See the Study Schedule of Events for the clinical assessments, including the laboratory and diagnostic tests monitored for each patient.

Screening: Day -15 to -2
Patient eligibility was confirmed at screening (Visit 1, Week 0) including molecular diagnosis of NALP3 mutation, informed consent, physical examination, clinical laboratory and diagnostic tests.

Part 1, Enrollment: Day 1- 57
A patient would enter Part 1 (Visit 2, Week 0) through Visit 5A, Week 8; audiogram, ophthalmological and neurological assessments, and MRI were completed on Day 1 among other assessments listed in the Study Schedule of Events.

Part 1, Administration of Medication: Day 1, (Visit 2, Week 0).

Part 2, Randomization: Day 57;
A patient who would have achieved a complete response in Part 1, was to be randomized 1:1 to ACZ885 or placebo in Part 2 (Visit 5B, Week 8).

Part 2, Administration of Medication: Day 57 (Visit 5B, Week 8); Day 113 (Visit 7, Week 16); Day 169 (Visit 9, Week 24); Day 225 (Visit 11A, Week 32).

Part 3, Administration of Medication: Day 225 (Visit 11B, Week 32); Day 281 (Visit 13, Week 40). Follow-up audiogram, ophthalmological and neurological assessments, and MRI were to be repeated on Day 225.

End of Study: Day 337 (Visit 15, Week 48)
Follow-up audiogram, ophthalmological and neurological assessments, and MRI were to be repeated on Day 337 (Visit 15, Week 48).

Additional Special Assessments in CAPS Patients

Special assessments, including MRI of the brain, audiogram testing, neurological and ophthalmological testing, were to have been performed as part of the efficacy/disease status evaluations and were to have been recorded in the electronic case report forms (eCRF). A definition of *normal, clinically insignificant abnormality* or *clinically significant abnormality* was not provided in the original protocol. This information was submitted to the Agency in response to an Information Request (09Feb2009). The response from the applicant was acceptable.

The definition of the special assessment was to have been based on clinical assessments by the specialist who was to have been making the assessment. The term *"clinically significant"* was to have been used to describe a finding that required:

- Medical intervention/treatment, or
- Further diagnostic evaluations to exclude a condition warranting treatment, or
- Further monitoring of its course, or
- Was a finding that unequivocally differentiated from a normal result.

Health-related quality of life assessments were to have been completed at baseline:

- Medical Outcome Short Form (36) Health Survey (SF-36), physical and mental component summary scores (PCS and MCS). Summary scores of 50 represent the mean in the US population. Higher scores represent better mental and physical quality of life. (10 points above/below 50 reflect one standard deviation difference in either direction).
- Functional disability as measured by the Health Assessment Questionnaire (HAQ-DI). Higher values up to a maximum of 3 indicate increased functional disability.
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score measures fatigue. Lower values, from a maximum of 52, suggest increased fatigue, e.g. 40 would be fatigued, and 30 would be more fatigued.
- In children/adolescent patients, 5 years to 17 years, the Child Health Questionnaire-Parent Form (CHQ-PF28) was employed to assess quality of life. This is a parent administered questionnaire. This instrument has two components (physical and psychosocial health) scores for a 14-concept health status and for well-being concepts. This instrument employs a 0 to 100 visual analogue scale (VAS), 0 the worst possible score and 100 the best possible score. Scoring is analogous to the SF-36 scoring.

Table 46

Study Part	Screening		Part I Open-label treatment period					Part II Withdrawal period							Part III Open-label treatment period				
Visit	1	1.1[1]	2	3A	3B	4	5A	5B	6	7	8	9	10	11A	11B	12	13	14	15*[2]
Week			0	1	2	4	6	8	12	16	20	24	28	32	32	36	40	44	48
Day The visit window was +/- 3 days for dosing visits. For non-dosing visits, the visit window was +/- 1 week except for Visit 3 and 4 where it was +/- 1 day	-15 to -2		1	8	15	29	57	57	85	113	141	169	197	225	225	253	281	309	337
Randomization								X											
Administration of medication			X					X		X		X			X		X		

Treatment ACZ885/placebo.

Part I: One s.c. injection of ACZ885; duration of 8 weeks.

Part II: Three s.c. injections, i.e. one injection of ACZ885 or placebo approximately every 8 weeks; duration of 24 weeks (unless disease flare, then the patient entered Part III).

Part III: Injections every other month, i.e. one s.c. injection of ACZ885 approximately every 8 weeks; duration of 48 weeks after the first injection in Part I. The time point for entering Part III was based upon disease flare or completion of Part II. Therefore, patients could enter Part III at any point from Day 58 to Day 225.

*End of Study (EOS) or in the event of premature termination. All assessments listed under Visit 15 should also have been done for patients who prematurely discontinued. This visit was to occur 8 weeks after the last injection.

[1] Visit 1.1: Patients had to return to the site within 48-72 hours of the PPD skin test for proper evaluation of the test site.

[2] Samples for immunogenicity were collected 8 weeks after last dose of study medication.

8. Removal of Patients from Treatment or Assessment

Patients would have been discontinued from the study for withdrawal of informed consent, pregnancy, study drug discontinuation or any prespecified medical condition requiring discontinuation. Patients could voluntarily withdraw from the study for any reason at any time. In addition, the investigator could have withdrawn a patient from the study if a patient was not compliant with study visits or the investigator concluded that it would be in the patient's best interest for any reason. Patients who did not achieve partial response by Day 8 or complete response by Day 15 were to be discontinued from the study. All patients who would have relapsed in Part 1 were discontinued from the study.

9. Concomitant Therapy

All concomitant medications were to have been recorded in the electronic case report form (eCRF). Patients should have remained on their medication wherever possible for the duration of the study. Anti-hypertensives, gastric protection, folic acid, NSAIDs and analgesics were considered appropriate for this treatment group. Prohibited concomitant medications are presented in **Table 47**

The discontinuation of a medication not permitted per protocol would have been managed as follows: as soon as a prospective patient would have fulfilled criteria for *relapse*, e.g., in ongoing Study A2102, a patient would have entered Study D2304 and would have received canakinumab treatment. The run-in open label period, Part 1, would have allowed reduction of the typical washout phase to a clinically meaningful time period and would have avoided unnecessary suffering for patients in case a pre-defined wash-out period per protocol would have been too long for an individual patient. All concomitant medications taken by a patient were to have been recorded in the eCRF.

Table 47

Prohibited Concomitant Medications Study D2304	
Drug/Biologic	**Restricted Time Period Prior to Baseline Visit**
Etanercept Adalimumab Infliximab	4 weeks prior to baseline visit (Day 1) 8 weeks prior to baseline visit (Day 1) 12 weeks prior to baseline visit (Day 1)
Other investigational biologics	8 weeks prior to baseline visit (Day 1) with the exception of anakinra and IL-1 blocking therapies.
Patients on IL-1 blockers, including anakinra	Needed to discontinue this treatment
Leflunomide	4 weeks prior to baseline visit (Day 1)
Thalidomide	4 weeks prior to baseline visit (Day 1)
Cyclosporine	4 weeks prior to baseline visit (Day 1)
iv immunoglobulins (iv Ig)	8 weeks prior to baseline visit (Day 1)
6-Mercaptopurine, azathioprine, cyclophosphamide or chlorambucil	12 weeks prior to baseline visit (Day 1)
Colchcine, dapsone, mycophenolate mofetil	3 weeks prior to baseline visit (Day 1)
Corticosteroids ≥ 20 mg/day or > 0.4 mg/kg, whichever applies.	1 week prior to baseline visit (Day 1)

D. Rescue Medication

Rescue medication was not to have been allowed during the course of the study as only complete canakinumab responders without disease relapse (identified in Part 1) were to be randomized into Part 2 and subsequently entered into Part 3.

E. Outcome Measures

1. Primary Efficacy Endpoint

The primary efficacy variable was to be the number (proportion) of patients with MWS who experienced a *disease flare* in Part 2, defined as those patients who experienced a *clinical relapse.* For the primary analysis patients who discontinued from Part 2 for any reason were imputed as *disease flare.* In Study D2304, only the complete responders without *disease relapse* (identified in Part 1) were to have been randomized into Part 2 and, subsequently, enrolled into Part 3.

The definition of the primary efficacy endpoints follows:

Primary Efficacy Endpoints by Part of Study D2304:

In Part 1, the patient's *complete response* to canakinumab was determined by daily diary entries on Days 1 through 15. After Day 15 in Part 1, the diary was to have been completed on a weekly basis.

In Part1, *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 CRP and/or SAA (< 10 mg/L).

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

- CRP and/or SAA value > 30 mg/L, AND
- Physician global assessment of autoinflammatory disease activity > minimal, OR
- Physician global assessment of autoinflammatory disease activity ≥ minimal AND assessment of skin disease > minimal.

The investigators clinical assessment of disease activity employed a 5-point scale for the Physician global assessment on autoinflammatory disease activity (categorical variables: absent, minimal, mild, moderate and severe) and for the following assessments:

- Skin disease (urticarial skin rash)
- Arthralgia
- Myalgia
- Headache/migraine
- Conjunctivitis
- Fatigue/malaise

- Other symptoms related to autoinflammatory syndrome, and
- Other symptoms not related to autoinflammatory syndrome.

Partial response to treatment was defined as:

- Absence of complete response but a reduction of CRP and/or SAA from baseline by > 30% but not reaching normal values (< 10 mg/L),

AND

- Physician global assessment of autoinflammatory disease activity improvement form baseline by at least one category.

2. Subgroup Analyses of Primary Efficacy

Subgroup analyses for the primary efficacy variable were to have been completed for demographic and baseline variables:

a. Cohorts - Cohort 1: Patients who would have been transitioned from Study A2102;
Cohort 2: Canakinumab naïve patients.
b. Age - ≤ 16 years; Age > 16 years.
c. Sex - F/M.

Subgroup analyses were to have consisted of descriptive statistics of the proportion of patients having had disease flare in Part 2.

3. Secondary Efficacy Endpoints

The key secondary efficacy variables were to have included the assessment of safety, tolerability, and immunogenicity of canakinumab in Part 1 and Part 3, and the PK/PD assessment of canakinumab. The effect of canakinumab on CAPS disease progression of co-morbidities was to have included deafness, renal function, neurological and ophthalmological signs and symptoms.

The following secondary efficacy endpoints were to have been analyzed:

- Proportion of canakinumab treatment responders in Part 1;
- Proportion of patients without disease relapse in Part 3;
- Change in inflammatory markers CRP and SAA;
- Physician's clinical assessment of autoinflammatory disease activity;
- Patient's assessment of disease symptoms; and
- Assessment of skin disease.

F. Statistical Analyses

Three populations were to have been used for analysis. The definitions follow:

- Safety Population: All patients who would have received at least one dose of study drug in Parts 1, 2 and 3 and would have had at least one post-baseline safety assessment in Part 1, 2 and 3, respectively. Patients were to have been analyzed according to the treatment received.
- Intent-to-Treat (ITT) Population: The ITT population would have consisted of all patients randomized that would have received at least one dose of study drug in Part 2. Patients would have been analyzed according to the treatment they would have been

assigned to at randomization in Part 2. The ITT populations for Part 1 and Part 3 would have consisted of all patients who received at least one dose of study drug in Part 1 and Part 3, respectively.

- Per-Protocol (PP) Population: The PP population for Part 2 would have consisted of all ITT Part 2 patients without major deviations from the protocol procedures which would have potentially affected treatment results.

Relevant medical history and current medical conditions were to have been assessed and summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. The exposure to study drug (number of injections) and the duration of exposure (days) was to have been summarized and listed.

The number and percentage of patients taking medication and non-drug therapies was to have been summarized by PT according to the WHO Drug Reference List dictionary. Separate summaries were to have been provided for therapies that ended prior to Part 1 (prior therapies) and those that would have been active during the treatment periods in each study part (concomitant therapies).

Efficacy Analysis

The primary efficacy variable in Part 2, the placebo controlled, double-blind, withdrawal period was the proportion of patients with MWS *disease flare*. All patients who would have achieved *complete response* in Part 1 were to have been eligible to be randomized into Part 2. Patients who met the criteria for disease relapse or discontinued Part 2 prematurely due to any reason, were to be considered as patients having disease flare.

The primary efficacy variable was to have been analyzed by comparing the two treatment groups using the exact test about the common odds ratio, adjusting for pre-specified cohorts, e.g., patients transferred from Study A2102, and canakinumab naïve patients. In addition to the Fisher's exact two-sided p-value, the common odds ratio was to have been estimated and an exact 95% CI for the common odds ratio was to have been calculated taking into account the pre-specified cohorts cited above.

The primary efficacy analysis was to have been based on the ITT population of Part 2. In addition, the time to disease flare from Week 8 in Part 2 was to have been analyzed as a supportive efficacy analysis. The differences between treatment groups in the time to disease flare were to have been analyzed using Cox's proportional hazards regression model with treatment and cohort as explanatory variables. In addition, the Kaplan-Meier estimates of the proportion of patients with disease flare, along with 95% CI using Greenwood's formula were to have been calculated.

Part 1

The ITT population in open label Part 1 was to have been used for the secondary efficacy analysis of the complete response to canakinumab treatment. In Part 1, the proportion of patients who would have responded to canakinumab treatment and would not have had a disease flare thereafter until week 8, e.g., the end of Part 1, was to be calculated.

Part 2

The secondary efficacy endpoints were to have been assessed from the beginning of Part 2, e.g., Week 8 and would be analyzed using the ITT population. The method of last observation carried forward (LOCF) was to have been employed to impute missing values. The change from Week 8 in CRP and SAA was to be analyzed using a Wilcoxon rank-sum test, stratified by cohort. The frequency distribution of the severity scores for the physician's global assessment of auto-inflammatory disease activity was to have been compared between treatment groups using an exact permutation test with equally spaced scores, stratified by cohort. The same analyses were to have been performed for the patient's assessment of symptoms. In addition, changes from Week 8 in the total score were to be analyzed using a stratified Wilcoxon rank-sum test, stratified by cohort. The frequency distribution of the severity scores (e.g., absent, minimal, mild, moderate or severe) for the assessment of skin disease was to be summarized by treatment. No statistical test was to have been performed on these data.

Handling of Missing Values/Discontinuations

For the primary efficacy variable, patients who discontinue prematurely in Part 2 due to any reason were considered as having disease flare.

Part 3

In the open label Part 3 period, the proportion of patients without disease relapse was to have been calculated based upon the ITT population for Part 3. The protocol did not contain provisions for imputation of missing data. All other efficacy variables were presented descriptively.

Pharmacokinetic / Pharmacodynamic Evaluations

Canakinumab was to have been analyzed in serum by a competitive ELISA assay.
Total IL-1β was to have been analyzed in serum by a competitive ELISA assay.

Immunogenicity Assessments

Anti-canakinumab antibodies concentrations were to have been assessed in the serum.

G. Safety Evaluation

Safety assessments consisted of all adverse events (AEs) and serious adverse events (SAEs) with their severity and relationship to the study drug. The AEs were to be reported in two parts: AEs (including infections) and, separately, as infectious AEs. The AEs were summarized for each treatment group, including the number and percentage of patients who had any AE in each primary system organ class and each individual AE based on the preferred term (PT). Deaths, SAEs and AEs that led to discontinuation of the study drug were to be summarized by the primary organ system and PT.

Safety assessments were to have included the regular monitoring of hematology, blood chemistry and urine tests, and regular assessments of vital signs, ECG data, physical condition and body weight. Descriptive statistics for the absolute values, changes from baseline and change from Week 8 by treatment group in Part 2 were to be reported. In addition, shift tables were to have been based on the normal ranges and incidence rates of notable abnormalities.

Special tests were to have included audiogram testing, brain MRI, neurological and ophthalmological assessment. The interpretation, e.g. *normal, clinically insignificant abnormality, or clinically significant abnormality,* was to have been summarized descriptively by shift tables from baseline to each study visit.

Local injection site tolerability was to have been assessed at the injection site and classified in four pre-specified categories:

1. No tolerability reactions at any time in the study;
2. Mild reaction observed on at least one occasion but no moderate or severe reactions.
3. Moderate reaction observed on at least one occasion but no severe reaction;
4. Severe reaction observed on at least one occasion.

The analysis of safety was to have been provided for each study Part, separately, and combined, as appropriate.

II. Study Conduct

This protocol involved one initial uncontrolled, open label period (Part 1) followed by the pivotal portion designed as a randomized, double-blind, placebo-controlled withdrawal period (Part 2). Part 2 was then to have been followed by a second uncontrolled, open label period (Part 3).

Patients who would have had *complete response* in Part 1 were to have been randomized in a 1:1 allocation into Part 2 to canakinumab or placebo treatment. If a patient would have had *disease flare* in Part 2, the patient would have been transitioned into Part 3, and continued in Study D2304. The duration of each Part of Study D2304 and the planned study drug treatment was explained in the study design section of this report.

A. Protocol Amendments

There were no protocol amendments or any other amendments in this protocol.

B. Treatment Compliance

All patients received all injections during the scheduled visits. Compliance was assured by patient and physician attendance.

C. Protocol Deviations

In Parts 1 and 2, the majority of protocol deviations as detailed below were minor. In Part 2, 14 of 15 patients (92%) in the canakinumab treatment group, 15 of 16 patients (93%) in the placebo treatment group and 29 of 31 patients (94%) had protocol deviations.

Part 1

In Part 1, three patients were excluded from the per protocol analysis: one patient (USA-0501-00003, 25 yr old/F) was excluded because this patient received anakinra treatment. A second patient (FRA-0008-00005, 41 yr old/F) was excluded from the per protocol analysis of Part 1 because of missing primary endpoint data (e.g., investigator's global assessment of auto-inflammatory disease activity and skin assessment, CRP and SAA) and a third patient (USA-

0502-00003) was excluded from the per protocol analysis because the patient did not have at least partial response at Day 8 or did not have complete response by Day 15 or flared in Part 1.

Part 2

In Part 2, among a total of 31 patients, one patient (3%) as reported above, in the canakinumab treatment group, was excluded from the per protocol analysis. This exclusion was due to missing primary efficacy endpoint data, as stated above. There were no patients excluded from the placebo treatment group in Part 2. In Part 2, 13 of 15 patients (87%), in the canakinumab treatment group, and 15 of 16 patients (94%), in the placebo group, had protocol deviations which did not cause exclusion from the efficacy analyses. The majority of these protocol deviations were missing laboratory tests and visits outside the pre-specified allowable visit window.

Part 3

In Part 3, 17 patients (55%) had protocol deviations at the time of the interim database lock (12Sept08). No reported protocol deviation led to exclusion from the analysis population.

III. Results

A. Patient Disposition

This study was conducted among 11 centers across 5 countries: France (5), Germany (1), India (1), United Kingdom (1) and the United States (3).

A total of 35 patients enrolled in Part 1. Four (4) patients discontinued Part 1 due to failure to achieve a *complete response* to canakinumab treatment. (See **Table 48)** Subsequently, 31 patients (89%) were randomized into Part 2 in approximately equal ratio into two study arms. All of these patients were included in the ITT and safety population.

One patient was excluded from the per protocol (PP) analysis due to missing primary endpoint assessments. In Part 2, 13 of 16 placebo-treated patients (81%) experienced *disease flare* and were withdrawn from Part 2. No canakinumab-treated patient (0%) of 15 patients experienced *disease flare* in Part 2.

Table 48.

Patient Disposition Study D2304					
	Part 1	Part 2		Total in Part 2	Total
Total # pts studied	ACZ885 N = 35 n (%)	ACZ885 N = 15 n (%)	Placebo N = 16 n (%)	N = 31 n (%)	N = 31 n (%)
Screening failures	6				
Enrolled	35 (100%)				
Not randomized into Part 2	NA				
Randomized		15 (100%)	16 (100%)		31 (100%)
Completed	31 (89%)	15 (100%)	4 (25%)	19 (61%)	31 (100%)
Discontinued	4 (11%)	0/15 (0%)	13/16 (81%)		
Adverse event	0	0	0		
Serious adverse event	0	0	0		
Clinical relapse or early withdrawal	0	0	13 (81%)		
Lack of complete response	4 (11%)				
Other	0	0	0		
Analysis Population					
Safety		15 (100%)	16 (100%)		
ITT		15 (100%)	16 (100%)		31 (100%)
Per Protocol (PP)		14 (92%)	16 (100%)		30 (97%)

Summary of Patients Not Randomized from Part 1 into Part 2

Four (4) patients were not randomized from Part 1 into Part 2:

- Pt # D2304-0010-00002 had a complete response in Part 1, experienced a disease flare based on the investigator's judgment though CRP and SAA < 10 mg/L; she was rolled back into Study A2102.
- Pt # D2304-0010-00003 had complete response in Part 1 but had disease flare per investigator's judgment yet had CRP and SAA < 10 mg/L; she was rolled over to Study A2102.
- Pt # D2304-0501-00003 had complete response in Part 1, had disease flare based on investigator's judgment (by phone). While still enrolled in Study D2304, this patient was administered anakinra from Day 46 to Day 61. She did not fulfill relapse criteria on Day 61. On Day 61, she was withdrawn from Part 1 due to unsatisfactory therapeutic effect.
- Pt # D2304-0502-00003 was withdrawn from Part 1 due to unsatisfactory therapeutic effect. She was reported to have had a very low serum canakinumab concentration possibly attributed to her self-administered canakinumab injection of 150 mg sc. Injections of canakinumab were not self-administered per the protocol. The implication was that possibly this patient received a smaller amount of active canakinumab due to self injection compared to clinician injection.

B. Concomitant Medications

Part 1

The most common concomitant medications received by patients in Part 1 were paracetomol (43%) and non-steroidal anti-inflammatory drugs (20%). (See **Table 49**)

Part 2

The majority of patients in both study arms received concomitant medications. The drug classes were similar to those reported in Part 1. Noteworthy, 3 patients (19%) in the placebo group received corticosteroids compared to 0% in the canakinumab group in Part 2. (See **Table 50**)

Table 49.

Concomitant Medications in ≥ 5% of Patients in Part 1, Study D2304	
Medication Class ***ATC Class*** ***Preferred Term (PT)***	**Part 1** ACZ885, N = 35 n (%)
Any ATC class	**32 (91%)**
Ace inhibitors	4 (11%)
Anilides	16 (46%)
Paracetamol	15 (43%)
Propofan	2 (6%)
Antibiotics	2 (6%)
Anticholinergics	2 (6%)
Antiinfectives	2 (6%)
Anti-inflammatory, NSAIDs	7 (20%)
Ibuprofen	2 (6%)
Naproxen	3 (9%)
Benzodiazepine related drugs	2 (6%)
Anti-inflammatory products for vaginal administration	6 (17%)
Naproxen	3 (9%)
Combination vitamins	2 (6%)
Corticosteroids	5 (14%)
Prednisolone acetate	2 (6%)
Corticosteroids acting locally	2 (6%)
Corticosteroids for local oral tx.	2 (6%)
Corticosteroids, plain	2 (6%)
Corticosteroids, potent	2 (6%)
Diphenylpropylamine derivatives	2 (6%)
Glucocorticoids	5 (14%)
Prednisolone acetate	2 (6%)
Influenza vaccines	5 (14%)
Influenza vaccine	4 (11%)
Non-Drug therapies	6 (17%)
Progestogens and estrogrens in fixed combination	6 (17%)
Propionic acid derivatives	6 (17%)
Proton pump inhibitors	2 (6%)
Selective beta-2-adrenoreceptor agonists	3 (9%)
Selective serotonin reuptake inhibitors	2 (6%)
Thyroid hormones	2 (6%)

Adapted from sponsor Table 14.3-1.9, p350- 367 of 3953
ATC = Anatomical Therapeutic Chemical Classification System used for the classification of drugs. It is controlled by the World Health Organization (WHO) Drug Class Collaborating System.

Table 50.

Concomitant Medications in ≥ 5% of Patients in Part 2, Study D2304			
Medication Class *ATC Class* *Preferred Term (PT)*	Part 2 ACZ885, N = 15 n (%)	 Placebo, N = 16 n (%)	 Total, N = 31 n (%)
Any ATC class	**15 (100%)**	**15 (93%)**	**31 (97%)**
Ace inhibitors, plain	1 (7%)	3 (19%)	4 (13%)
Acetic acid derivatives and related substances	2 (13%)	2 (13%)	4 (13%)
Diclofenac	0	2 (13%)	2 (7%)
Anilides	10 (67%)	9 (56%)	19 (61%)
Paracetamol	9 (60%)	7 (44%)	16 (32%)
Antifect. and antisept. for local oral treatment	1 (7%)	1 (6%)	2 (7%)
anti-inflam. prep, non-steroidal for topical use	4 (27%)	6 (38%)	10 (32%)
Diclofenac	0	2 (13%)	2 (7%)
Ibuprofen	3 (20%)	3 (19%)	6 (19%)
NSAIDs	1 (7%)	2 (13%)	3 (10%)
Diclofenac	0	2 (13%)	2 (7%)
Anti-inflam. products for vaginal administration	4 (27%)	3 (19%)	7 (23%)
Antiseptics	0	1 (6%)	1 (3%)
Antivirals	1 (7%)	0	1 (3%)
Benzodiazepine derivatives	2 (13%)	1 (6%)	3 (10%)
Beta blocking agents	1 (7%)	0	1 (3%)
Cephalosporins and related agents	3 (20%)	0	3 (10%)
Corticosteroids	0	3 (19%)	3 (10%)
Corticosteroids acting locally	0	2 (13%)	2 (7%)
Corticosteroids, plain	1 (7%)	1 (6%)	2 (7%)
Corticosteroids, potent group	1 (7%)	1 (6%)	2 (7%)
Diphenylmethane derivatives	2 (13%)	1 (6%)	3 (10%)
Fluorquinolones	1 (7%)	1 (6%)	2 (6%)
Glucocorticoids	1 (7%)	3 (19%)	4 (13%)
Natural opium alkaloids	2 (13%)	1 (6%)	3 (10%)
Non-drug therapeutics and procedures	7 (47%)	2 (13%)	9 (29%)
Nucleosides and nucleotides excl rev. transcr. Inhibitors	1 (7%)	2 (13%)	3 (10%)
Other centrally acting agents	2 (13%)	2 (13%)	4 (13%)
Other ophthaomologicals	2 (13%)	1 (6%)	3 (10%)
Penicillins with extended spectr.	4 (27%)	3 (19%)	7 (23%)
Progestogens and estrogens, fixed combinations	3 (20%)	2 (13%)	5 (16%)
Propionic acid derivatives	4 (27%)	5 (31%)	9 (29%)
Proton pump inhibitors	1 (7%)	1 (6%)	1 (6%)
Selective beta-2-adrenoreceptor agonists	2 (13%)	1 (6%)	3 (10%)
Selective serotonin reuptake inhibitors	1 (7%)	1 (6%)	2 (7%)

Adapted from sponsor Table 14.3-1.10, p 368-384 of 3953

C. Patient Demographic and Other Baseline Disease Characteristics

Patient demographics were summarized across treatment groups in each Part of Study D2304. In Part 1, the majority of the patient population was ≥ 17 years of age and equally matched for age, race, weight, and previous participation in Study A2102. In Parts 1 and 2, patients were well

balanced across the treatment groups. The majority of the patient population was > 17 years (87%), female (68%), Caucasian (94%) and had a mean weight of 60 kg. The majority of patients (77%) were canakinumab naïve (see **Table 51**). Five MWS pediatric patients < 18 years were enrolled in Study D2304. They were 9, 14, 15, 16, and 17 years of age.

Table 51.

Baseline Demographic Characteristics, Study D2304				
	Part 1	Part 2		
Demographic Variable	ACZ885 N = 35	ACZ885 N = 15	Placebo N = 16	Total N = 31
Baseline age n (%)				
≥ 4 yrs to < 17 years	4 (11%)	2 (13%)	2 (13%)	4 (13%)
≥ 17 yrs to < 75 years	31 (89%)	13 (87%)	14 (87%)	27 (87%)
Sex n (%)				
Female	25 (71%)	14 (93%)	7 (44%)	21 (68%)
Male	10 (29%)	1 (7%)	9 (56%)	10 (32%)
Age (yrs)				
Mean (SD)	34 (15)	34 (14)	33 (16)	34 (15)
Median (min, max)	36 (9, 74)	37 (9, 58)	31 (14, 74)	36 (9, 74)
Cohort n (%)				
Pts from Study A2102	9 (26%)	4 (27%)	3 (19%)	7 (23%)
ACZ885 naïve pts	26 (74%)	11 (73%)	13 (81%)	24 (77%)
Race n (%)				
Caucasian	33 (94%)	15 (100%)	14 (88%)	29 (94%)
Other	1 (3%)	0	1 (6%)	1 (3%)
Weight (kg)				
Mean (SD)	60 (11)	59 (12)	61 (9)	60 (11)

Adapted from sponsor Table 11-2, p 78 of 3953

The baseline characteristics confirmed the overall severity of disease in these MWS patients. CRP and SAA levels were elevated in the majority of patients across each Part and/or treatment group. CRP and SAA values were slightly higher in placebo-treated patients group compared to canakinumab-treated patients (see **Table 52**). The baseline Physician Global assessment of autoinflammatory disease in Part 1 scored the majority of canakinumab-treated patients as *moderate* (63%). Four (4) patients (11%) were assessed by their physician as *severe* at baseline in Part 1. In Part 2, across both treatment groups, the global assessment of autoinflammatory disease characteristics was balanced across study arms (see **Table 52**). The baseline skin disease was generally *moderate* in Part 1 with only one patient reported with *severe* skin disease. The assessments of skin disease were balanced in Part 2 across the two treatment groups (see **Table 52**). The baseline Patient's Global assessment of disease symptoms in Part 1 was scored as *mild* (23%) or *moderate* (26%) in the majority of patients. Part 2 assessments for the Patient's global assessment of disease symptoms were well balanced (see **Table 52**).

Table 52.

Baseline CAPS Disease Characteristics Study D2304 (ITT)				
	Part 1	Per Randomization in Part 2		
	ACZ885	ACZ885	PBO	Total
	N=35	N=15	N=16	N=31
C-Reactive Protein (mg/L)				
Mean (SD)	31 (27)	29 (26)	38 (29)	34 (27)
Median (min, max)	20 (2, 105)	20 (2, 102)	26 (8, 105)	22 (2, 105)
Serum Amyloid A (mg/L)				
Mean (SD)	137 (166)	142 (178)	162 (168)	152 (170)
Median (min, max)	49 (3, 530)	48 (4, 508)	112 (9, 530)	85 (4, 530)
Physician Global assessment of auto-inflammatory disease activity n (%)				
Minimal	2 (6)	1 (7)	0 (0)	1 (3)
Mild	7 (20)	2 (13)	5 (31)	7 (23)
Moderate	22 (63)	10 (67)	9 (56)	19 (61)
Severe	4 (11)	2 (13)	2 (13)	4 (13)
Assessment of skin disease n (%)				
Absent	4 (11)	1 (7)	2 (13)	3 (10)
Minimal	6 (17)	3 (20)	3 (19)	6 (19)
Mild	9 (28)	4 (27)	5 (31)	9 (29)
Moderate	15 (43)	7 (47)	5 (31)	12 (39)
Severe	1 (3)	0 (0.0)	1 (6)	1 (3)
Patient's Global assessment of symptoms n (%)				
Absent	4 (11)	2 (13)	2 (13)	4 (13)
Minimal	6 (17)	2 (13)	2 (13)	4 (13)
Mild	8 (23)	4 (27)	3 (19)	7 (23)
Moderate	9 (26)	5 (33)	3 (19)	8 (26)
Severe	4 (11)	2 (13)	2 (13)	4 (13)
Four (4) placebo pts had missing data in the Patient's Global assessment of disease data.				

Normal levels: CRP < 0.5 mg/L; SAA < 6.5 mg/L. Four placebo-treated patients did not complete the Patient's global assessment of symptoms. Results are reported for 12 rather than 16 patients.

Health-Related Quality of Life Assessments

The baseline health-related quality of life assessments are summarized in **Table 53**. These baseline health-related quality of life assessments, with the exception of the HAQ-DL, demonstrated the severity of disease in this MWS study population. The SF-36 PCS and MCS scores in each treatment group were below 50 at baseline indicating the impact of MWS disease on the health-related quality of life assessments. A SF-36 score of 50 represents the mean of the US population. There were no clinically meaningful differences observed at baseline in the SF-36 (PCS and MCS) scores across treatment groups. These data confirmed the severity of MWS disease at baseline (see **Table 53**). The CHQ-PF28 demonstrated no clinically meaningful difference at baseline across treatment groups. The FACIT-F demonstrated that patients suffered from fatigue at baseline (see **Table 53**). Of note, although physical function as measured by the SF-36 PCS was impacted by disease, HAQ-DI scores were not significantly impacted by disease. HAQ-DI scores were normal at baseline in at least 50% of patients with a median score of 0 (higher values up to a maximum of 3 suggest increased functional disability (see **Table 53**).

Table 53.

Baseline CAPS Disease Characteristics Study D2304 (ITT)				
	Part 1	Per Randomization in Part 2		
	ACZ885 N=35	ACZ885 N=15	PBO N=16	Total N=31
SF-36 Physical Component Summary Score				
Mean (SD)	42 (11)	40 (12)	42 (8)	41 (10)
Median (min, max)	43 (24, 59)	40 (24, 55)	43 (30, 55)	41 (24, 55)
SF-36 Mental Component Summary Score				
Mean (SD)	44 (12)	39 (8)	47 (14)	43 (12)
Median (min, max)	46 (21, 65)	38 (25, 53)	50 (21, 65)	46 (21, 65)
CHQ-PF28 Physical score				
Mean (SD)	43 (13)	46 (5)	39 (24)	43 (13)
Median (min, max)	49 (23, 56)	49 (40, 50)	39 (23, 56)	49 (23, 56)
CHQ-PF28 Psychosocial score				
Mean (SD)	54 (8)	53 (9)	57 (7)	54 (8)
Median (min, max)	55 (43, 61)	55 (43, 61)	57 (52, 61)	55 (47, 61)
FACIT-F score				
Mean (SD)	29 (13)	24 (11)	30 (14)	27 (13)
Median (min, max)	30 (6, 49)	27 (10, 41)	31 (6, 49)	30 (6, 49)
HAQ-DI				
Mean (SD)	0.4 (0.65)	0.6 (0.72)	0.3 (0.52)	0.4 (0.63)
Median (min, max)	0.0 (0, 2.3)	0.4 (0, 2.3)	0 (0, 1.6)	0 (0, 2.3)

HAQ-DI: higher scores up to a maximum of 3 indicate increased functional disability.
SF-36 PCS and MCS: indicate better mental and physical quality of life; a summary score of 50 represents the mean US population with 10 points above/below as one standard deviation difference in either direction.
CHQ-PF28: scoring for this instrument is analogous to the scoring for the SF-36.
FACIT-F: lower values from a maximum of 52 suggest increased fatigue.

Special Assessments

Special assessments were included in Study D2304 based on co-morbidities in patients with CAPS disease. The majority of patients had *clinically significant abnormality* in the audiogram at baseline, as presented in **Table 54**. Audiogram assessments mainly reported sensorineural hearing loss. Neurological and ophthalmological assessments were predominantly either normal or abnormal but with *clinically insignificant abnormalities*.

The majority of patients had normal baseline brain MRI assessments. The *clinically significant abnormalities* at baseline in MRI of the brain included multiple signs of demyelination and multiple white matter abnormalities of the brain.

Table 54.

Baseline CAPS Disease Assessments Study D2304 (ITT)				
	Part 1	Per randomization in Part 2		
	ACZ885 N = 35	ACZ885 N = 15	PBO N = 16	Total N = 31
Audiogram n (%)				
Normal	5 (14%)	3 (20%)	1 (6%)	4 (13%)
Clin. insignificant abn.	8 (23%)	4 (27%)	3 (17%)	7 (23%)
Clin. significant abn.	22 (63%)	8 (53%)	12 (75%)	20 (65%)
Neurological assessment n (%)				
Normal	15 (43%)	5 (33%)	7 (44%)	12 (37%)
Clin. insignificant abn.	12 (34%)	4 (27%)	7 (44%)	11 (36%)
Clin. Significant abn.	8 (23%)	6 (40%)	2 (13%)	8 (26%)
Ophthalmological asssessment n (%)				
Normal	13 (37%)	5 (33%)	8 (50%)	13 (42%)
Clin. insignifcant abn.	16 (46%)	7 (46%)	7 (44%)	14 (45%)
Clin. significant abn.	5 (14%)	2 (13%)	1 (6%)	3 (10%)
Missing	1 (3%)	1 (7%)	0 (0%)	1 (3%)
MRI assessment n (%)				
Normal	24 (69%)	8 (53%)	12 (75%)	20 (65%)
Clin. insignificant abn.	4 (11%)	2 (13%)	2 (13%)	4 (13%)
Clin. significant abn.	2 (6%)	2 (13%)	0 (0.0%)	2 (7%)
Missing	5 (14%)	3 (20%)	2 (13%)	5 (16%)
clin. = clinically; abn. = abnormality				

C. Relevant Patient Medical History and Continuing Medical Conditions

In Part 1, the most common PT for >10% of patient's medical history and ongoing medical conditions were: conjunctivitis (31 patients, 89%); urticaria (29 patients, 83%); headache (25 patients, 71%); myalgias (19 patients, 54%); neurosensory deafness (10 patients, 29%); migraine headache (8 patients, 23%); deafness (7 patients, 20%); iron deficiency anemia, vertigo, mouth ulceration and hypertension in 5 patients each, 14%, respectively; asthenia, arthritis, and eczema in 4 patients each, 11% respectively. Noteworthy, 2 patients each (6%) had renal amyloidosis; papillaedema; and increased liver function tests. One (1) patient each (3%) had pericarditis/ pleurocarditis, and meningitis.

D. Primary Efficacy Results

Part 1

The treatment effect of the initial exposure to canakinumab in open label Part 1 is critical to the interpretation of the outcome of the primary efficacy analysis of the randomized withdrawal in Part 2. In Part 1, 34 of 35 MWS patients (97%) achieved the primary efficacy endpoint, a *complete response* with canakinumab treatment. Twenty-five of 35 patients (71%) demonstrated a *complete response* by Day 8, Week 1 in Part 1. There was one patient, # GBR-0001-00006, a 43-year old female who was not a *complete responder* by Day 15 in Part 1. She experienced a viral infection which the PI considered not to be related to the study medication. By Week 8 (Day 57), this patient was scored as a *complete responder* and was randomized into Part 2. This approach was consistent with the pre-specified criteria for complete response and eligibility for randomization into Part 2.

The analyses of the individual disease assessments in Part 1 all showed clinically meaningful improvement and supported the primary efficacy analysis results as measured in Part 2. **Tables 55, 56** and **57** present the results across each disease assessment in open label Part 1, at baseline and at the last assessment in Part 1, followed by the last assessment, by Part 2 randomization, in open label Part 3.

In Part 1 at baseline, the majority of patients had *moderate* (47%) skin disease. By the last assessment in Part 1, 80% had *absent* skin disease. This positive trend in improvement of skin disease was supportive of the primary efficacy analysis (see **Table 55**).

At baseline, the majority of patients had arthralgia scores of *mild, moderate* or *severe* (60%). Just under half (47%) had myalgias scored as *mild, moderate* or *severe.* Arthralgia and myalgias demonstrated consistent improvement from Part 1 through Part 3 in both treatment groups. The majority (88%) of patients scored arthralgia as *absent* at the last assessment in Part 3. Myalgia demonstrated clinically meaningful improvement with 91% *absent* at the last assessment in Part 1. The improvement was sustained through the last assessment in Part 3 (see **Table 55**).

For the parameters of headache/migraine, conjunctivitis and fatigue/malaise, half or more of the patients had scores of *mild, moderate* or *severe.* Headache/migraine, conjunctivitis, and fatigue/malaise demonstrated a positive trend of improvement in the canakinumab- and placebo-treated patient groups from baseline in Part 1 to the last assessment in Part 3. Each of these disease assessments scored more than 80% *absent* by the last assessment in Part 3 (see **Table 56**).

Other symptoms *related* to autoinflammatory syndrome and other symptoms *not related* to autoinflammatory syndrome consistently demonstrated *absent* symptoms in most patients across both measures from baseline in Part 1 through the last assessment in Part 3 (see **Table 57**).

The Physician's Global assessment of autoinflammatory disease at baseline in Part 1 scored the majority of patients as *moderate* (67%). By the last assessment in Part 1, most patient scored *absent* (49%) and *mild* (40%). This clinically meaningful outcome was sustained through the last assessment in Part 3. See **Table 57.**

Overall, a positive trend of improvement in patients continuously treated with canakinumab was demonstrated in Parts 1 through 3. In addition, there was a positive trend of improvement in patients who experienced placebo treatment for 8 weeks and then resumed canakinumab treatment in Part 3. The later treatment effect supported the sustained effects of canakinumab treatment in MWS disease.

Table 55.

Results from Parts 1, 2 and 3 - SKIN ASSESSMENT (without LOCF)				
	According to Randomization in Part 2			
	ACZ885, N = 35 n / N (%)		ACZ885, N = 15 n / N (%)	Placebo, N = 16 n / N (%)
Catgorical Variable	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	1/15 (7%)	28/35 (80%)	14/15 (93%)	13/16 (81%)
Minimal	3/15 (20%)	7/35 (20%)	1/15 (7%)	3/16 (19%)
Mild	4/16 (27%)	0/15 (0%)	0/15 (0%)	0/16 (0%)
Moderate	7/16 (47%)	0/15 (0%)	0/15 (0%)	0/16 (0%)
Severe	0/16 (0%)	0/15 (0%)	0/15 (0%)	0/16 (0%)
Results from Parts 1, 2 and 3 - ARTHRALGIA (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	3/15 (20%)	31/35 (89%)	12/15 (80%)	14/16 (88%)
Minimal	3/15 (20%)	3/35 (9%)	2/15 (13%)	1/16 (6%)
Mild	3/15 (20%)	1/35 (3%)	1/15 (7%)	0/16 (0%)
Moderate	3/15 (20%)	0/35 (0%)	0/15 (0%)	1/16 (6%)
Severe	3/15 (20%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Results from Parts 1, 2 and 3 - MYALGIA (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	5/15 (33%)	32/35 (91%)	12/15 (80%)	14/16 (88%)
Minimal	3/15 (20%)	3/35 (9%)	2/15 (13%)	1/16 (6%)
Mild	4/15 (27%)	0/35 (0%)	1/15 (7%)	1/16 (6%)
Moderate	3/15 (20%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Severe	0/15 (0%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Adapted from sponsor Tables 14.2-2.62 p 14 of 98; Table 14.2-2.68, p 26 of 98; Table 14.2-2.21 p 232 of 3953.				

Adapted from sponsor Tables 14.2-2.62, p 14 of 98; Table 14.2-2.68, p 26 of 98; Table 14.2-2.21 p 232 of 3953

Table 56.

Results from Parts 1, 2 and 3 - HEADACHE/ MIGRAINE (without LOCF)				
	According to Randomization in Part 2			
	ACZ885, N = 35 n /N (%)		ACZ885, N = 15 n /N (%)	Placebo, N = 16 n /N (%)
Categorical Variable	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	15/35 (43%)	26/35 (74%)	12/15 (80%)	14/16 (88%)
Minimal	2/35 (6%)	8/35 (23%)	3/15 (20%)	2/16 (13%)
Mild	9/35 (26%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Moderate	3/35 (9%)	1/35 (3%)	0/15 (0%)	0/16 (0%)
Severe	6/35 (17%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Results from Parts 1, 2 and 3 - CONJUNCTIVITIS (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	3/15 (20%)	21/35 (60%)	12/15 (80%)	14/16 (88%)
Minimal	4/15 (27%)	9/35 (26%)	3/15 (20%)	2/16 (13%)
Mild	4/15 (27%)	3/35 (9%)	0/15 (0%)	0/16 (0%)
Moderate	3/15 (20%)	2/35 (6%)	0/15 (0%)	0/16 (0%)
Severe	1/15 (7%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Results from Parts 1, 2 and 3 - FATIGUE/ MALAISE (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	2/15 (13%)	19/35 (54%)	11/15 (73%)	13/16 (81%)
Minimal	2/15 (13%)	11/35 (31%)	3/15 (20%)	2/16 (13%)
Mild	3/15 (20%)	4/35 (11%)	0/15 (0%)	0/16 (0%)
Moderate	5/15 (33%)	1/35 (3%)	1/15 (7%)	1/16 (6%)
Severe	3/15 (20%)	0/35 (0%)	0/15 (0%)	0/16 (0%)

Adapted from sponsor (IR # 10) Table 14.2-2.72 thru 2.77, p 38 of 98; Table 14.2-2.80, p 50 of 98; Table 14.2-2.86, p 62 of 98.

Table 57.

Results from Parts 1, 2 and 3 - OTHER SYMPTOMS RELATED TO AUTOINFLAMMATORY SYNDROME (without LOCF)				
	According to Randomization in Part 2			
	ACZ885, N = 35 n/ N (%)		ACZ885, N = 15 n/ N (%)	Placebo, N = 16 n/ N (%)
Categorical Variable	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	12/15 (80%)	30/35 (86%)	14/15 (93%)	14/16 (88%)
Minimal	1/15 (7%)	4/35 (11%)	0/15 (0%)	2/16 (13%)
Mild	2/15 (13%)	0/35 (0%)	1/15 (7%)	0/16 (0%)
Moderate	0/15 (0%)	1/35 (3%)	0/15 (0%)	0/16 (0%)
Severe	0/15 (0%)	0/35 (0%)	0/15 (0%)	0/16 (0%)
Results from Parts 1, 2 and 3 - OTHER SYMPTOMS *NOT* RELATED TO AUTOINFLAMMATORY SYNDROME (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	13/15 (87%)	26/35 (74%)	11/15 (73%)	12/16 (75%)
Minimal	1/15 (7%)	4/35 (11%)	0/15 (0%)	3/16 (19%)
Mild	0/15 (0%)	4/35 (11%)	1/15 (7%)	0/16 (0%)
Moderate	1/15 (7%)	0/35 (0%)	2/15 (13%)	1/16 (6%)
Severe	0/15 (0%)	1/35 (3%)	1/15 (7%)	0/16 (0%)
Results from Parts 1, 2 and 3 - PHYSICIAN'S GLOBAL ASSESSMENT OF AUTOINFLAMMATORY DISEASE ACTIVITY (without LOCF)				
	Baseline Part 1 (Day 1)	Last Assessment End of Part 1	Last Assessment End of Part 3	Last Assessment End of Part 3
Absent	0/15 (0%)	17/35 (49%)	9/15 (60%)	9/16 (56%)
Minimal	1/15 (7%)	14/35 (40%)	6/15 (40%)	6/16 (38%)
Mild	2/15 (13%)	2/35 (6%)	0/15 (0%)	0/16 (0%)
Moderate	10/15 (67%)	2/35 (6%)	0/15 (0%)	1/16 (6%)
Severe	2/15 (13%)	0/35 0%)	0/15 (0%)	0/16 (0%)

Adapted from sponsor Table 14.2-2.15, p 223 of 3953; Table 14.2-2.90, p 69 of 98; Table 14.2-2.96, p81 of 98.

D. Primary Efficacy Results (Continued)

Part 2

Part 1 assessed the initial exposure to canakinumab in an open label manner over 8 weeks. In contrast, Part 2 assessed the continued treatment effect of canakinumab based on the likelihood of *disease flare* over 24 weeks in patients randomized to remain on canakinumab or in those randomized to placebo. All patients randomized into the canakinumab treatment group sustained *complete response* from Part 1 with no *disease flare* throughout Part 2. This sustained response to canakinumab treatment contrasted with *disease flare* in 81% (13 of 16) of placebo-treated patients. The primary efficacy variable, the *proportion of patients with disease flare*, demonstrated a statistically significant outcome for canakinumab compared to placebo treatment. The odds ratio in Part 2 was zero (0) with a 95% CI [0, 0.09] and p-value < 0.01 indicating that the likelihood of disease flare with canakinumab treatment was significantly less than with placebo treatment. The primary efficacy analysis was repeated for the per protocol (PP) population and remained supportive of the primary efficacy analysis, ITT population. The statistics reviewer, David Petullo, confirmed this conclusion (see **Table 58).**

Table 58.

Primary Efficacy Analyses - Study D2304							
Proportion of Patients with Disease Flare: Comparison between Treatment Groups at the End of Part 2 - (ITT population)							
	ACZ885 N = 15		Placebo N = 16		Differences in Response rates ACZ885 vs Placebo		
	n / N (%)	95% CI	n / N (%)	95% CI	Difference	95% CI	p-value*
Pts with disease flare	0 /15 (0.0)	(0, 0.22)	13/16 (81%)	(0.54, 0.96)	- 0.81	(-1.00, -0.62)	<0.001 **
n = total number of pts having disease flare; N = total number of pts in treatment group; * p-value from Fisher's exact test; ** statistical significance (two sided) at 5% level.							

Additional Analysis: Primary Efficacy

Thirteen (13) of 16 placebo-treated patients discontinued during Part 2: 3 of these 13 patients discontinued without meeting the definition of *relapse* and 10 patients discontinued based on *relapse*, per the protocol. We examined the response for these patients who discontinued during Part 2. As shown in **Tables 59** and **60**, the 13 placebo-treated patients demonstrated a decline in their clinical disease activity based upon the Physician's Global assessment of autoinflammatory disease, skin disease assessment, and the 5-point scale of other clinical CAPS disease features. All assessments trended toward decreased clinical response at the end of Part 2 compared to the last assessment in Part 1, after canakinumab treatment was withdrawn. This additional analysis of patients who discontinued in Part 2 was supportive of the primary efficacy analysis favoring canakinumab treatment compared to placebo.

Table 59.

Results from Patients who Discontinued Study D2304			
Patient # ID	Baseline Part 1 Day 1	Last Assessment End of Part 1	End of Part 2
Physician Global Assessment of Autoinflammatory Disease			
Absent	2/13 (15%)	11/13 (85%)	8/13 (62%)
Minimal	7/13 (54%)	1/13 (8%)	1/13 (8%)
Mild	3/13 (23%)	1/13 (8%)	2/13 (15%)
Moderate	0/13 (0%)	0/13 (0%)	2/13 (31%)
Severe	0/13 (0%)	0/13 (0%)	0/13 (0%)
Skin Assessment			
Absent	6/13 (46%)	6/13 (46%)	7/13 (54%)
Minimal	0/13 (0%)	6/13 (46%)	2/13 (15%)
Mild	0/13 (0%)	1/13 (8%)	2/13 (15%)
Moderate	5/13 (38%)	0/13 (0%)	2/13 (15%)
Severe	2/13 (15%)	0/13 (0%)	0/13 (0%)
Arthralgia			
Absent	3/13 ((23%)	9/13 (69%)	0/13 (0%)
Minimal	4/13 (31%)	4/13 (31%)	3/13 (23%)
Mild	3/13 (23%)	0/13 (0%)	6/13 (46%)
Moderate	2/13 (15%)	0/13 (0%)	3/13 (23%)
Severe	1/13 (8%)	0/13 (0%)	0/13 (0%)
Myalgia			
Absent	0/13 (0%)	9/13 (69%)	5/13 (38%)
Minimal	6/13 (46%)	4/13 (31%)	1/13 (8%)
Mild	3/13 (23%)	0/13 (0%)	3/13 (23%)
Moderate	3/13 (23%)	0/13 (0%)	4/13 (31%)
Severe	1/13 (8%)	0/13 (0%)	0/13 (0%)

Table 60.

Results from Patients who Discontinued Study D2304			
Patient # ID	Baseline Part 1 Day 1	Last Assessment End of Part 1	End of Part 2
Headache/Migraine			
Absent	2/13 (15%)	10/13 (77%)	3/13 (23%)
Minimal	2/13 (15%)	3/13 (23%)	4/13 (31%)
Mild	4/13 (31%)	0/13 (0%)	5/13 (38%)
Moderate	5/13 (38%)	0/13 (0%)	1/13 (8%)
Severe	0/13 (0%)	0/13 (0%)	0/13 (0%)
Conjunctivitis			
Absent	3/13 (23%)	9/13 (69%)	3/13 (23%)
Minimal	1/13 (8%)	2/13 (15%)	4/13 (31%)
Mild	5/13 (38%)	2/13 (15%)	2/13 (15%)
Moderate	3/13 (23%)	0/13 (0%)	4/13 (23%)
Severe	1/13 (8%)	0/13 (0%)	0/13 (23%)
Fatigue/Malaise			
Absent	4/13 (31%)	10/13 (77%)	8/13 (62%)
Minimal	0/13 (0%)	3/13 (23%)	1/13 (8%)
Mild	3/13 (23%)	0/13 (0%)	4/13 (23%)
Moderate	6/13 (46%)	0/13 (0%)	0/13 (0%)
Severe	0/13 (0%)	0/13 (0%)	0/13 (0%)
Other Symptoms Related to Disease			
Absent	6/13 (46%)	9/13 (69%)	4/13 (31%)
Minimal	1/13 (8%)	4/13 (31%)	1/13 (8%)
Mild	4/13 (31%)	0/13 (0%)	5/13 (38%)
Moderate	1/13 (8%)	0/13 (0%)	2/13 (15%)
Severe	1/13 (8%)	0/13 (0%)	1/13 (8%)
Other Symptoms *NOT* Related to Disease			
Absent	7/13 (54%)	10/13 (77%)	3/13 (23%)
Minimal	1/13 (8%)	2/13 (15%)	3/13 (23%)
Mild	4/13 (31%)	1/13 98%)	4/13 (31%)
Moderate	1/13 (8%)	0/13 (0%)	3/13 (23%)
Severe	0/13 (0%)	0/13 (0%)	0/13 (0%)

Additional Analysis: Pediatric Patients

Pediatric patients were assessed for their treatment effect to canakinumab. Patients with body weight $\geq$ 15 kg and $\leq$ 40 kg were administered canakinumab as 2 mg/kg and patients > 40 kg were administered canakinumab 150 mg sc. Five pediatric patients were enrolled in this study and only one patient (9 year old, 26 kg) weighed less than 40 kg. This patient experienced decreased CRP and/or SAA levels from baseline to the end of Week 1 in Part 1 and showed a sustained normal CRP and/or SAA levels through Part 3 (see **Table 61**). Weight-based dosing will be discussed separately in the individual study reports for Studies A2102 and D2306.

Table 61.

Pediatric Patients in Study D2304								
		Part 1		Part 1		Part 2	Part 2	Part 3
Age	Weight (kg), Treatment	Baseline CRP mg/L	Week 1 CRP mg/L	Baseline SAA mg/L	Week 1 SAA mg/L	Flare	Discontinuned	
14 yrs	66 kg, PBO	22	2	168	2	yes	Lack therap. eff.	
9 yrs	26 kg, ACZ	16	1	19	2			AE (UTI, pyrexia)
15 yrs	49 kg, ACZ	47	2	123	0			
16 yrs	56 kg, PBO	72	1	143	0	yes		
17 yrs	71 kg, ACZ	14	2	48	3			

All five (5) pediatric patients in Study D2304 had *complete response* in Part 1.

E. Secondary Efficacy Results

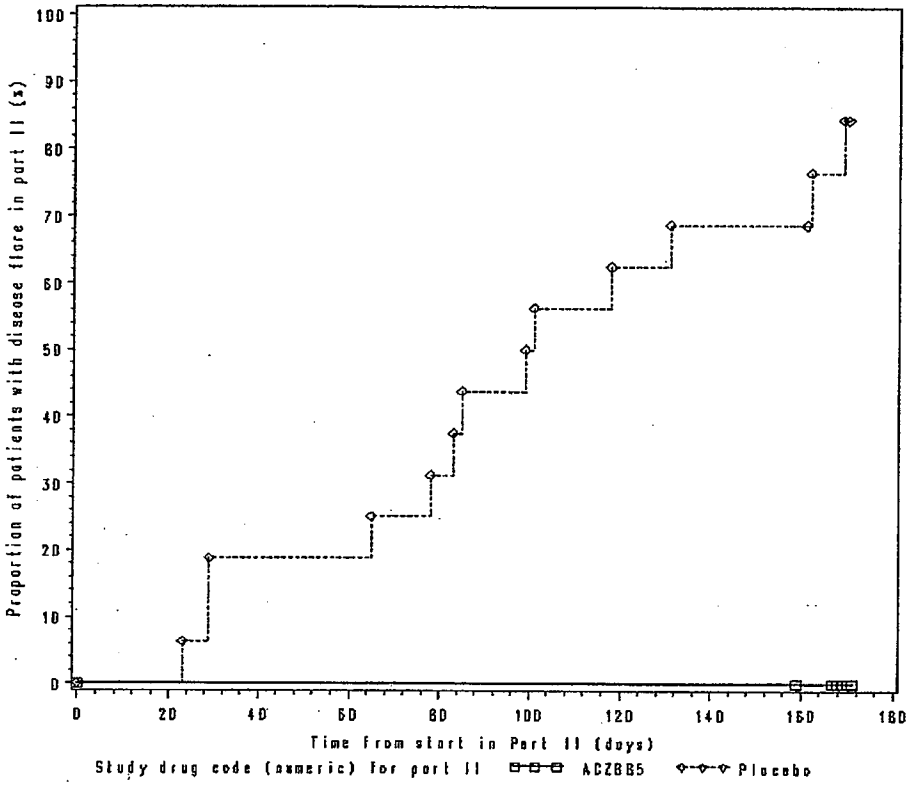
Time to Disease Flare

Part 2

The *time to disease flare* was a secondary efficacy assessment analyzed in Part 2 of this study. The ITT population was employed for this analysis. The Kaplan-Meier estimates plotted against time demonstrated the substantial treatment effect of canakinumab compared to placebo (see **Figure 9**). The median *time to disease flare* in Part 2 was approximately 100 days in placebo-treated patients. Among patients randomized to placebo, three (3) patients experienced disease flare as early as Day 29 in Part 2. The mean *time to disease flare* across subsets of MWS patients was 101 days [22, 168]:

- Rollover from Study A2102: n = 3 patients; mean time to flare 102 days [77, 130]
- Canakinumab naïve patients: n = 10 patients; mean time to flare 85 days [53, 168]
- Pediatric MWS patients: n = 2 patients; mean time to flare 134 days [100, 168]
- Adult MWS patients : n = 11 patients; mean time to flare 81 days [22, 161]

Figure 9. Kaplan-Meier Estimates for the Time to Disease Flare in Part 2 (ITT Population) Source: Figure 11-1, p 85 of 3953



Overall, the analysis of time to flare supported the primary efficacy analysis as measured by the proportion of patients who had disease flare.

F. Subgroup Analyses

To explore the effect of canakinumab treatment in patients with MWS, subgroup analyses were performed. The parameters included: patients rolled-over from Study A2102; canakinumab naïve patients based on the proportion with *complete response* in Part 1; the proportion of patients with *disease flare* in Part 2; and stratification by age and by sex (see **Table 62**). No canakinumab-treated patients experienced *disease flare* in Part 2. There was no difference between subgroup populations indicating maintenance of efficacy based on canakinumab treatment. These subgroup analyses supported the primary efficacy analysis in favor of canakinumab compared to placebo in patients with MWS.

Table 62.

Proportion of Pts with Complete Response, Part 1 Study D2304 by Subgroup (ITT)		Proportion of Pts with Disease Flare, Part 2 Study D2304 by Subgroup (ITT)	
	ACZ885 N = 35 n / N (%)	ACZ885 N = 15 n / N (%)	Placebo N = 16 n / N (%)
All Pts in Part 1	34/ 35 (97%)		
Cohorts			
Pts from Study A2102	9/ 9 (100%)	0/ 4 (0.0%)	3/ 3 (100%)
ACZ885 naïve pts	25/ 26 (96%)	0/ 11 (0.0%)	10/ 13 (77%)
< 16 years	4/ 4 (100%)	0/ 2 (0.0%)	2/ 2 (100%)
> 16 years	30/ 31 (97%)	0/ 13 (0.0%)	11/ 14 (79%)
Male	10/ 10 (100%)	0/ 1 (0.0%)	9/ 9 (100%)
Female	24/ 25 (96%)	0/ 14 (0.0%)	4/ 7 (57%)
n = total # of pts not having disease flare; N = total # of pts in the treatment group.		n = total number of pts having disease flare; N = total # of pts in the treatment group.	

G. Protein Markers of Inflammation

To explore the effect of canakinumab treatment on objective markers of inflammation in patients with MWS, CRP and SAA were assessed in Parts 1 through 3. In open label canakinumab treatment Part 1, CRP and SAA serum levels decreased in all patients by Day 8 and continued low through the last assessment of Part 1 (see **Tables 63** and **64**). These data demonstrated maintenance of response to open label canakinumab treatment and supported the primary efficacy analysis in favor of canakinumab treatment compared to placebo.

Table 63.

CRP (mg/L): Summary of Change from Baseline in Part 1 (without LOCF) by Treatment Group				
		ACZ885		
		All pts starting in Part 1		
Time Point	Statistic	Baseline	Post	Change from Baseline
Baseline	n	35		
	Mean (SD)	31 (27)		
	Median (min, max)	20 (2, 105)		
Part 1, Day 8	n	35	35	35
	Mean (SD)	31 (27)	5 (13)	-25 (29)
	Median (min, max)	20 (2, 105)	2 (0.3, 69)	-16 (-100, 33)
Part 1, Day 15	n	11	11	11
	Mean (SD)	35 (25)	8 (11)	-28 (31)
	Median (min, max)	27 (4, 83)	4 (0.6, 38)	-26 (-79, 27)
Part 1, Day 57, Wk 8	n	35	35	35
	Mean (SD)	31 (27)	6 (8)	-25 (25)
	Median (min, max)	20 (2, 105)	3 (0.3, 31)	-14 (-99, 7)
Last Assessment	n	35	35	35
	Mean (SD)	31 (27)	6 (8)	-25 (25)
	Median (min, max)	20 (2, 105)	3 (0.3, 31)	-14 (-99, 7)

Normal levels: CRP < 0.5 mg/L; SAA < 6.5 mg/L.

Table 64.

SAA (mg/L): Summary of Change from Baseline in Part 1 (without LOCF) by Treatment Group				
		ACZ885		
		All pts starting in Part 1		
Time Point	Statistic	Baseline	Post	Change from Baseline
Baseline	n	35		
	Mean (SD)	137 (166)		
	Median (min, max)	49 (3, 530)		
Part 1, Day 8	n	35	35	35
	Mean (SD)	137 (166)	18 (77)	-119 (181)
	Median (min, max)	49 (3, 530)	3 (0.0, 461)	-45 (-518, 308)
Part 1, Day 15	n	10	10	10
	Mean (SD)	115 (151)	17 (39)	-97 (165)
	Median (min, max)	28 (3, 395)	4 (1, 128)	-22 (-390, 119)
Part 1, Day 57 Week 8	n	35	35	35
	Mean (SD)	137 (166)	15 (27)	-122 (35, 162)
	Median (min, max)	49 (3, 530)	7 (0.0, 152)	-40 (-499, -0.1)
Last Assessment	n	35	35	35
	Mean (SD)	137 (166)	15 (27)	-122 (162)
	Median (min, max)	49 (3, 530)	7 (0.0, 152)	-40 (-499, -0.1)

Normal levels: CRP < 0.5 mg/L; SAA < 6.5 mg/L.

In Part 2, comparison of CRP and SAA levels in the group randomized to continue canakinumab treatment versus the group randomized to placebo was analyzed (see **Table 65**). CRP and SAA levels essentially remained unchanged in the canakinumab treatment group in Part 2. In contrast, CRP and/or SAA levels increased from Week 8 through the last assessment of Part 2 in placebo treated patients.

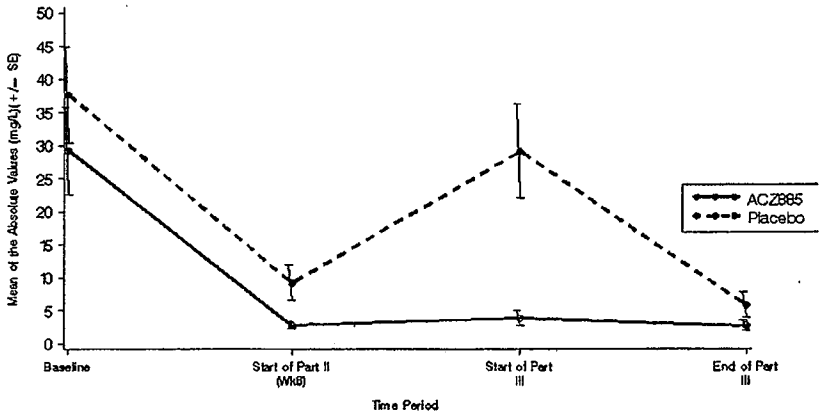
Table 65.

CRP (mg/L) and SAA (mg/L) Comparison between ACZ885 and Placebo-Treatment in Part 2 (using LOCF, ITT Population)							
	ACZ885			Placebo			
Laboratory Tests	Week 8	Last Assessment in Part 2	Change from Week 8	Week 8	Last Assessment in Part 2	Change from Week 8	p-value **
C-Reactive Protein (mg/L)							
n	15	15	15	16	16	16	<0.001 *
Mean (SD)	3 (2)	4 (4)	1 (3)	9 (11)	29 (28)	20 (24)	
Median (min, max)	2 (0.6, 9)	2 (0.2, 15)	0.40 (-2.8, 11)	5 (0.6, 31)	24 (3, 105)	11 (1.3, 95)	
Serum Amyloid A (mg/L)							
n	15	15	15	16	16	16	0.002 *
Mean (SD)	8 (8)	10 (11)	2 (9)	24 (38)	95 (142)	71 (137)	
Median (min, max)	6 (0.0, 35)	6 (0.0, 39)	-0.2 (-5, 31)	9 (2, 152)	44 (3, 560)	14 (-4, 542)	
* statistical significance (two-sided) at the 0.05 level; * * p-value was derived from stratified Wilcoxon rank sum test, startified by cohort for the change from Week 8. Source: Table 11-8, p 87/3953.							

The difference between the treatment effect on CRP and SAA levels in the canakinumab treatment group compared to placebo demonstrated a statistically significant outcome in favor of continued canakinumab treatment compared to placebo (see **Table 65**). These data support the primary efficacy analysis in favor of continued canakinumab treatment compared to placebo.

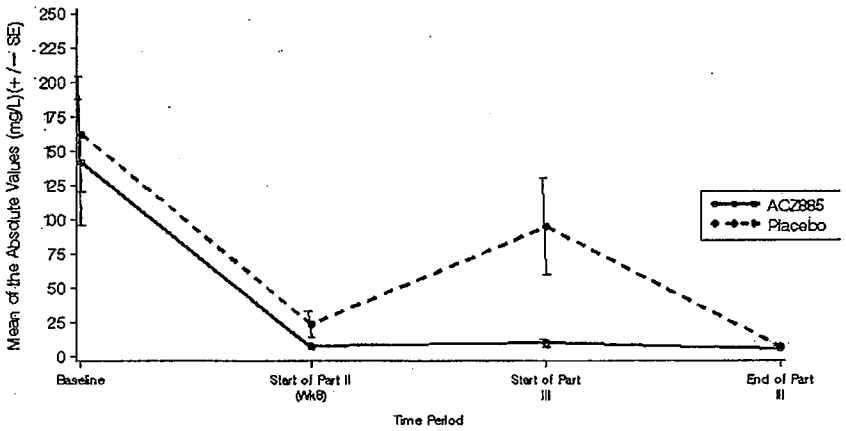
To explore the effect on CRP and SAA levels with continued canakinumab treatment from baseline in Part 1 through Part 3, graphic demonstration of the substantial improvement in CRP and SAA levels with canakinumab treatment is presented in **Figures 10** and **11**. The mean CRP and SAA levels were plotted against time from baseline to the start of Part 2, then through the start of Part 3 and, finally, through the end of Part 3 (see **Figures 10** and **11**).

Figure 10. CRP (mg/L) from Baseline through Part 3, Study D2304 (ITT population)



Source: figure 11-2, p88 of 3953.

Figure 11. SAA (mg/L) from Baseline though Part 3, Study D2304 (ITT population).



Source: Figure 11-3, p 89 of 3953.

Canakinumab treatment resulted in reductions in CRP and SAA levels to the normal range. The CRP and SAA levels increased in Part 2 in patients randomized to placebo but remained unchanged in patients remaining on canakinumab. These data supported the primary efficacy analysis favoring continuous canakinumab compared to placebo in patients with MWS.

H. Assessment of Disease Symptoms

For the randomized withdrawal portion of this study, disease symptoms were assessed from the start of Part 2 to the last assessment of Part 2. Assessments were conducted for the Physician's Global assessment of autoinflammatory disease activity, skin disease, and the Patient's Global assessment of symptoms. At the start of Part 2, over 85% of patients in both the canakinumab and the placebo treatment group scored *absent* or *minimal.* At the last assessment in Part 2, all canakinumab-treated patients maintained clinical response as measured by the Physician Global assessment of disease symptoms. By contrast, placebo-treated patients worsened with zero (0%) *absent*, 25% *minimal* and 50 % *mild* at the last assessment in Part 2.

Skin disease was scored as *absent* in all patients across both treatment groups at the start of Part 2. At the last assessment, clinical improvement was maintained in the canakinumab treated patients. By contrast, among placebo-treated patients only 31% scored as *absent* and half (50%) scored as mild to moderate skin disease at the last assessment in Part 2 (see **Table 66**).

In the Patient's Global assessment of disease symptoms, patients across both treatment groups scored at least 80% *absent* at the start of Part 2. By the last assessment in Part 2, 67% of the canakinumab-treated patients remained as absent or minimal, though 4 patients scored their symptoms as severe (27%). By contrast at the last assessment in Part 2, placebo-treated patient scores worsened with only 31% remaining absent or minimal. The remaining placebo-treated patients (58%) were scored as mild or moderate by the end of Part 2 (see **Table 66**).

In summary, the results for skin assessment, for the Physician's Global assessment of autoinflammatory disease and for the Patient's Global assessment of symptoms, all showed better retention of clinical benefits for the canakinumab group than for the placebo group.

Table 66.

Part 2 - From Week 8 through the Last Assessment of Part 2 Physician's Global Assessment of Autoinflammatory Disease, Skin Disease, and Patient's Global Assessment of Disease Symptoms				
Frequency and Treatment Comparison (LOCF, ITT Population)				
	ACZ885, N = 15		Placebo, N = 16	
	Start of Part 2, Week 8	Last assessment in Part 2	Start of Part 2, Week 8	Last assessment in Part 2
Physician Global Assessment of Autoinflammatory Disease Activity n (%)				
Absent	9 (60%)	8 (53%)	8 (50%)	0
Minimal	4 (27%)	7 (47%)	8 (50%)	4 (25%)
Mild	2 (13%)	0	0	8 (50%)
Moderate	0	0	0	4 (25%)
Severe	0	0	0	
Assessment of Skin Disease n (%)				
Absent	13 (87%)	14 (93%)	13 (81%)	5 (31%)
Minimal	2 (13%)	1 (7%)	3 (19%)	3 (19%)
Mild	0	0	0	5 (31%)
Moderate	0	0	0	3 (19%)
Severe	0	0	0	0
Patient's Global Assessment of Symptoms n (%)				
Absent	9 (60%)	6 (40%)	8 (50%)	0
Minimal	4 (27%)	4 (27%)	5 (31%)	5 (31%)
Mild	0	1 (7%)	2 (13%)	4 (25%)
Moderate	0	0	0	6 (38%)
Severe	1 (7%)	4 (27%)	0	0

I. Other Efficacy Measures

1. Health-Related Quality of Life Assessments

Health-related quality of life assessments completed in Part 2 (from Week 8 of Part 2 to the last assessment of Part 2) are summarized in **Table 67**. Pediatric patients were assessed with the CHQ-PF28 questionnaire and adult patients were assessed with the FACIT-F, the SF-36 (PCS and MCS) and the HAQ-DI. The health related quality of life measurements generally demonstrated sustained benefit in the canakinumab-treated patients except for slight worsening as measured by the HAQ-DI. In placebo-treated patients, scores worsened from the start of Part 2 to the last assessment in Part 2, as measured by the CHQ-PF28 physical summary score, the FACIT-F score and the SF-36 (PCS) [see **Table 67**].

Table 67.

Health-Related Quality of Life Variables in Part 2: Summary Statistics (using LOCF, ITT Population)						
	ACZ885			Placebo		
Variables	Start, Week 8 of Part 2	Last assessment of Part 2	Change from Week 8 to last assessment P2	Start, Week 8 of Part 2	Last assessment of Part 2	Change from Week 8 to last assessment P2
CHQ-PF28 physical summary score (pediatrics)						
n	3	3	3	2	2	2
Mean (SD)	53 (3)	55 (3)	2 (6)	54 (2)	42 (12)	-12 (14)
Median (min, max)	54 (50, 55)	54 (53, 58)	-0.4 (-2, 8)	54 (53, 55)	42 (33, 50)	-12(-22, -2)
CHQ-PF28 psychosocial summary score (pediatrics)						
Mean (SD)	50 (11)	46 (15)	-3 (13)	57 (3)	57 (3)	0.1 (5)
Median (min, max)	44 (43, 62)	54 (29, 55)	-6.8 (-15, 11)	57 (55, 60)	57 (56, 58)	0.1 (-3, 3)
FACIT-F score (adults)						
n	11	11	11	13	13	13
Mean (SD)	41 (11)	38 (13)	-3 (10)	41 (13)	33 (11)	-8 (6)
Median (min, max)	44 (11, 50)	41 (10, 50)	-4 (-19, 9)	46 (14, 52)	35 (16, 48)	-9 (-17, 2)
SF-36 PCS (adults)						
n	11	11	11	12	12	12
Mean (SD)	52 (7)	47 (13)	-5 (9)	50 (9)	43 (7)	-7 (7)
Median (min, max)	54 (39, 64)	48 (25, 65)	-2 (-22, 7)	53 (34, 62)	43 (34, 54)	-3 (-19, 2)
SF-36 MCS (adults)						
Mean (SD)	47 (13)	45 (15)	-2 (11)	47 (13)	46 (13)	-2 (9)
Median (min, max)	51 (19, 59)	50 (16, 64)	-2 (-16, 24)	53 (19, 59)	47 (19, 60)	-2 (-14, 20)
HAQ score (adults)						
n	12	12	12	13	13	13
Mean (SD)	0.2 (0.4)	0.4 (0.6)	0.2 (0.3)	0.1 (0.4)	0.2 (0.4)	0.05 (0.1)
Median (min, max)	0 (0, 1.4)	0 (0, 1.8)	0 (0, 1)	0 (0, 1.4)	0 (0, 1.6)	0 (-0.1, 0.3)

CHQ-PF28 scored from 0 to 100 (increase in score indicates improvement); FACIT-F scored from 0 to 52 (increase in score indicates decreasing fatigue); SF-36 scored from 0 to 100 (increase in score indicates improvement); HAQ scored from 0 to 3 (increase in score indicates worsening disease). Adpated from sponsor Table 11-10, pp 94-95 of 3953; P2= Part 2.

2. Special Assessments

Special assessments including audiogram, neurological and ophthalmological assessments, and MRI of the brain, were completed at baseline in Part 1, at the end of Part 2, and at the end of Part 3. Changes from baseline to the end of Part 2 for audiogram assessments were only observed for one patient (placebo-treated change from normal to clinically insignificant abnormality). Neurological and ophthalmological assessments showed essentially no change over time.

At the end of Part 3 (interim database lock), all clinically significant audiogram results were pre-existing since baseline in Part 1, with two patients having slight improvements at the end of Part 2 compared to baseline in Part 1. Clinically significant neurological assessments were unchanged pre-existing conditions at the end of Part 3, with two patients having an improvement in symptoms. Three patients had clinically significant ophthalmological assessments in Part 3. Two patients had symptoms since Part 1 (glaucoma), one patient had congenital left papillary coloboma and the third patient had symptoms since Part 2 (optic disc drusen). All *clinically significant abnormal* MRI findings in Part 3 were present in Part 1. These special assessment results suggest that canakinumab treatment did not impact some of the major morbidities of MWS disease during the course of the study.

3. Total IL-1β Concentration

Total IL-1β concentrations increased over Part 1, as measured by the mean, median and geometric mean, to peak levels on Day 29. In Part 2, total IL-1β concentrations decreased substantially in patients randomized to placebo treatment from Day 29 through Day 169 when total IL-1β levels were similar to those reported at baseline in Part 1. In Part 2, in patients

randomized to canakinumab treatment, IL-1β levels fluctuated between the level reported at the end of Part 1/start of Part 2 and higher but with no consistent further increase. The increased IL-1β levels do not necessarily translate into increased IL-1β effect since canakinumab blocks IL-1β from binding at receptor sites. Therefore, much of the increased circulating IL-1β may reflect canakinumab bound, inactive IL-1β.

IV. Discussion of Efficacy Findings and Conclusions

Study D2304 was conducted in accordance with the protocol under IND 100,040. No protocol amendments to this protocol were submitted and the study conduct was acceptable.

Of the 35 MWS patients enrolled in Part 1 open label canakinumab treatment, 34 (97%) completed Part 1 and achieved *complete response*, the primary efficacy endpoint in Part 1. *Complete response* to treatment was defined as the 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 CRP and/or SAA, 10 mg/L. Noteworthy, all five pediatric patients in Study D2304, ages 9 years to 17 years, achieved *complete response* in Part 1.

In addition to the assessment of *complete response*, a 5-point scale (categorical variables *absent, minimal, moderate* and *severe*) for the Physician's Global assessment of autoinflammatory disease and CAPS disease parameters, e.g. skin disease; arthralgia, myalgias, headache/ migraine; conjunctivitis; fatigue/malaise; other symptoms *related* to autoinflammatory syndrome; and other symptoms *not related* to autoinflammatory syndrome, were assessed in Part 1. Each parameter demonstrated a positive trend toward improvement in patients continuously treated with canakinumab in Part 1, except for the latter two assessments, other symptoms *related* to autoinflammatory syndrome, and other symptoms *not related* to autoinflammatory syndrome. These two parameters had a high proportion of *absent* scores from the start of Part 1 through the last assessment of Part 1. This observation suggests that the other assessments included the most common symptoms of MWS.

In Part 2, the primary efficacy variable was the *proportion of patients who experienced disease flare* defined as those patients who had a *clinical relapse*. For the primary analysis, patients who discontinued from Part 2 for any reason were imputed as disease flare. Only the *complete responders*, without disease relapse identified in Part 1, were randomized into Part 2, and subsequently enrolled in open label Part 3.

All patients randomized to canakinumab treatment sustained *complete response* from Part 1 without *disease flare* throughout Part 2. This substantial sustained clinical response to canakinumab treatment contrasted with *disease flare* in 81% (13 of 16) placebo-treated patients in Part 2. The primary efficacy variable, the *proportion of patients with disease flare*, demonstrated a statistically significant outcome for canakinumab compared to placebo treatment. The odds ratio in Part 2 was zero (0) with a 95% CI [0, 0.09] and p-value < 0.01 indicating that the likelihood of disease flare with canakinumab treatment was significantly less than with placebo treatment. Though only interim data for Part 3 is available through the database cutoff (12Sep08), only one patient experienced *disease relapse*. This result supported the sustained

effect of continuous canakinumab treatment and supported the primary efficacy analysis in favor of canakinumab treatment compared to placebo.

Time-to-disease flare was a secondary efficacy endpoint assessment in Part 2. The median *time to disease flare* in Part 2 was approximately 100 days in placebo-treated patients and could not be calculated for canakinumab-treated patients since no patients flared in the canakinumab group. The Kaplan-Meier estimates demonstrated the substantial treatment effect of canakinumab compared to placebo. Overall, *time to disease flare* supported the primary efficacy analysis in favor of canakinumab treatment compared to placebo.

In addition, secondary analyses included subgroup analyses. There was no difference between subgroup populations, e.g., age ≤ 16 years, age > 16 years; sex; patients from Study A2102 compared to canakinumab naïve patients, indicating maintenance of clinical effects with canakinumab treatment. Subgroup analyses supported the primary efficacy analysis in favor of canakinumab treatment over placebo.

CRP and SAA serum levels, serum markers of inflammation, were assessed in Part 1 through Part 3. In Part 1, CRP and SAA serum levels decreased in all patients by Day 8 and remained low through the last assessment of Part 1. In Part 2, in patients randomized to continue to receive canakinumab, CRP and SAA levels essentially remained unchanged (low) through the last assessment of Part 2. In contrast, CRP and SAA levels in placebo-treated patients increased from Week 8, the start of Part 2, through the last assessment of Part 2. This difference between the treatment effect on CRP and SAA levels in the canakinumab treatment group compared to placebo treatment group, demonstrated a statistically significant difference in favor of continued canakinumab treatment compared to placebo. In Part 3, CRP/SAA levels remained low (normal) in patients who received continued canakinumab treatment and became low in placebo-treated patients in Part 2 who enrolled in open label Part 3. These data supported the primary efficacy analysis favoring continuous canakinumab treatment compared to placebo in patients with MWS.

In Part 2, the randomized withdrawal portion of this study, the Physician Global assessment of autoinflammatory disease symptoms, skin disease assessment, and the Patient's Global assessment of symptoms demonstrated a sustained response in canakinumab-treated patients. In contrast, placebo-treated patents in Part 2 demonstrated worsening across these assessments from the start of Part 2 to the last assessment of Part 2. This outcome supported the primary efficacy analysis favoring continued canakinumab treatment compared to placebo. In Part 3, 97% of patients were without disease relapse. One patient experienced disease relapse by Day 336 from baseline.

Special assessments, e.g., audiogram, ophthalmological and neurological assessments, and MRI of the brain, were performed as part of the efficacy/disease evaluations at baseline and at the end of each Part. Clinically significant abnormalities reported at baseline in Part 1 remained unchanged at the end of Part 3 (at database lock), in general, in each of these special assessments. These results suggest that canakinumab did not affect some of the major morbidities associated with MWS disease over the course of this clinical trial.

In general, the health-related quality of life assessments demonstrated improvement in Part 1 with open label canakinumab. In Part 2, these improvements were maintained with continued canakinumab treatment in contrast to placebo-treated patients whose measurements slightly worsened over time. The health-related quality of life assessments were secondary endpoints and did not have an adequate statistical analytic plan to address multiplicities. These results should not be included in labeling.

In conclusion, Study D2304 achieved the primary efficacy endpoint, as measured by the *proportion of patients with disease flare,* favoring canakinumab treatment compared to placebo. This effect was demonstrated in adult and in pediatric patients across all Parts of this Phase 3 clinical trial.

V. Safety Analysis and Summary
The safety analyses and conclusions from Study D2304 are reported in Section 7 of this clinical review.

Study A2102

The following description of this Phase 2 protocol for Study A2102 is based upon the original protocol (24Oct2004). Protocol amendments are noted in the section where they apply.

I. Protocol

A. Title
An open-label, Phase 2 dose titration study of ACZ885 (canakinumab, human anti-IL-1β monoclonal antibody) to assess the clinical efficacy, safety, PK and PD in patients with NALP3 mutations

B. Objectives

1. Primary Objective

a. To determine the efficacy of canakinumab administered as iv infusion and sc injection to improve the clinical status of patients with NALP3 (CIAS1, PYPAF1) mutations.

2. Secondary Objectives

a. To assess the safety, tolerability, immunogenicity of canakinumab administered as iv infusion and sc injection in patients with NALP3 mutations,
b. To assess PK/ PD of canakinumab administered as iv infusion and sc injection in patients with NALP3 mutations,
c. To assess PK/PD relationships to derive a dose and dosing regimen for Phase 3 trials,
d. To assess the efficacy of canakinumab to modify disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms,
e. To assess the efficacy of canakinumab to modify health-related quality of life, and

f. To conduct exploratory genomic studies to identify gene expression patterns in blood that would be associated with treatment response to canakinumab, or that would possibly correlate with the severity or progression of autoinflammatory diseases.

C. Study Design

Study A2102 was a non-randomized, open label, uncontrolled, single group, Phase 2 clinical trial with two stages (periods). Due to the severity of CAPS disease, it was decided not to include a placebo control. All enrolled patients were to have been treated with ACZ885 in this open label study.

Treatment with anakinra was to have been discontinued upon enrollment and patients were to have been carefully monitored with clinical and laboratory assessments until relapse would have occurred. After this relapse, treatment with canakinumab was to have been started. The responses to treatment were to have been assessed weekly (Stage 1) or monthly (Stage 2).

Stage 1

In Study A2102, Stage 1 was to have been a Phase 1/ Phase 2a dose titration study in MWS patients in which canakinumab was to have been administered as a single iv infusion of 10 mg/kg followed by an observation period (period # 1). Evaluation of the primary efficacy variable was the time from each dose administration to relapse (after having achieved a *complete response* to treatment). Each canakinumab administration was designated as a "period". Stage 1 was designed to define a dose and dosing regimen for Phase 3 Studies D2304 and D2306. After patients relapsed, they were to receive the second administration of canakinumab as a single iv infusion of 1 mg/kg, followed by observation (period # 2).

Protocol Amendment # 2 (5Sept2005) introduced a third treatment period (period # 3) with administration of canakinumab as a single sc injection of 150 mg.

Protocol Amendment # 3 (21Dec2005) introduced Stage 2 of this Phase 1/2a protocol amended to be a Phase 2 clinical trial. Additional subcutaneous treatment periods were included in the study design to explore the efficacy, safety and tolerability, PK/PD of repeat sc canakinumab in patients with NALP3 mutations as compared to iv administration.

Stage 2

Patients were to have been administered sc injection 150 mg canakinumab upon each relapse. Patients enrolled in Stage 1 had the option to roll-over into Stage 2. Patients would have completed their study participation when they either transitioned to Phase 3 Study D2304, to Phase 3 Study D2306, or discontinued Study A2102.

Protocol Amendment # 4 (21Sept2006) expanded Study A2102 to become a multi-national, multi-center, Phase 2 study. This amendment allowed enrollment of other CAPS diagnoses, FCAS and MWS/NOMID overlap, and included adolescents and children ≥ 4 years of age. Children and adolescents ≤ 16 years of age were to be dosed on a weight basis with canakinumab, 2 mg/kg sc with body weight ≥ 15 kg and ≤ 40 kg.

1. Duration

Stage 1: Three single doses
Stage 2: Re-dosing upon relapse until the Phase 3 study would have been in place (estimated approximate duration – up to one year).

The duration of Study A2102 (Stage 2) was to have been based upon re-dosing with each relapse until patients rolled over into Phase 3 Studies D2304 or D2306 or until discontinuation from Study A2102.

2. Study Population

Selection of Patients, Sample Size and Power Calculations
This study population was to have included CAPS diseases: MWS, Neonatal Onset Multisystem Inflammatory Disease (NOMID) overlapping MWS, and Familial Cold Autoinflammatory Syndrome (FCAS). The planned sample size (original protocol) was to have been 4 to 6 patients in Stage 1. The initial proposed small number, 4 to 6 patients in Stage 1, was based on the rarity of CAPS disease. No formal sample size calculations were performed because only descriptive statistics were planned in this open label study design. No power calculations were planned in this open label study.

Protocol Amendment # 3 (21Dec 2005) changed the planned sample size to enroll up to 14 additional patients in Stage 2.

Protocol Amendment # 4 (21Sept2006) allowed inclusion in Stage 2 of up to 21 additional adult and pediatric patients with MWS, FCAS or NOMID with a clinical picture overlapping with MWS, e.g,. the total enrollment increased to 25 patients.

Protocol Amendment # 7 (24Jul2007), based on increased demand by clinical investigators, increased the total sample size from 25 patients to 50 patients.

3. Inclusion Criteria

The inclusion criteria in Study A2102 are similar to those reported in Study D2304. Only those criteria which are different in Study A2102 will be listed below.

a. Document molecular diagnosis of NALP3 mutations and clinical picture characteristic of MWS, FCAS, or NOMID overlapping MWS, either untreated or insufficiently treated.

Protocol Amendment # 4 (21Sept2006) allowed patients who had either CRP or SAA at baseline ≥ 30 mg/L to be enrolled. Patients with baseline CRP or SAA < 30 mg/L could be enrolled if the clinical picture required adequate treatment. The final decision for enrollment, in the setting of normal CRP and SAA, was to be a joint agreement between the investigator and the sponsor.

b. Patients under anakinra therapy or any other IL-1 blocking therapy, whose clinical symptoms improved with anakinra/ IL-1 blocking therapy, could be enrolled if they were willing to discontinue anakinra/ IL-1 blocking therapy until a clinical picture of the disease (relapse) became evident. Patients with either CRP or SAA at baseline which was ≥ 30 mg/L could be

enrolled. Patients with baseline CRP or SAA < 30 mg/L could be enrolled if the clinical picture required adequate treatment (as according to the final decision as to whether such a patient could be enrolled would have needed joint agreement between the investigator and the sponsor).

Protocol Amendment # 6 (26Apr2007) revised this criterion based on the 4 patients in Stage 1 who showed that reappearance of clinical symptoms were always accompanied by CRP and/or SAA levels > 30 mg/L and that additional testing of CRP/SAA at a later time did not further define relapse, but rather prohibited quick re-treatment. Therefore, the definition of relapse or incomplete remission was revised as follows: at least 2 symptoms required along with CRP and/or SAA > 30 mg/L (on one occasion).

c. Patients with a very severe phenotype requiring oral prednisone could be enrolled if they were on a stable dose (≤ 0.4 mg/kg/day or ≤ 20 mg/day, whichever was lower) for at least one-week prior to the screening visit. Steroid therapy could have been tapered during treatment with canakinumab at the discretion of the investigator.
d. Body weight ≥ 12 kg and < 100 kg.
e. Negative tuberculin skin test reaction (PPD 5 tuberculin units or according to local standard practice), < 5 mm induration at 48 to 72 hours after administration at the screening visit or within 2 months prior to the screening visit, according to national guidelines (e.g., according to patients who had a positive PPD skin test with documentation of Bacillus Calmette-Guérin (BCG) vaccination, who were at low environmental risk for tuberculosis (TB) infection, or reactivation, and had a negative chest X-ray, could be included. A positive PPD test was defined using the criteria for tuberculin positivity by risk group (MMWR 2000 guidance):

- ≥ 15 mm of induration for persons with no risk factors for TB;
- ≥ 10 mm of induration for persons with an increased probability of recent infection or with other clinical conditions that increased the risk for TB;
- ≥ 5 mm of induration for very high risk population (HIV), contact TB cases, immuno-suppression (organ transplantation, steroids > 15 mg/day of prednisone for 1 month or more).

Protocol Amendment # 4 (21Sept2006) included expanded definition for tuberculin positivity by risk group (MMWR 2000 guidance).

4. Exclusion Criteria
a. Live vaccinations within months prior to the start of the trial, during the trial, and up to 3 months following the last dose.

Protocol Amendment # 5 (05March 2007) added the text, "no live vaccinations within months prior to the start of the trail, during the trial, and up to 3 months following the last dose.

b. History of renal transplant.
c. History and/or evidence of lymphoma.

Protocol Amendment # 6 (26Apr2007) added exclusion criteria: history of renal transplant and history and/or evidence of lymphoma.

5. Study Treatments

Canakinumab vials contained 150 mg as a lyophilized cake. Canakinumab was to have been reconstituted with water to obtain solutions for iv injection or sc infusion. Patients were required to remain within reasonable proximity to the study center from the afternoon before dosing until the morning of Day 3, which included clinical visits at Days 1 through 3. Inpatient stay was required only until Day 2.

Canakinumab treatment was to have started with a high dose (10 mg/kg iv) to ensure that unknown levels of IL-1β would have been effectively neutralized. Preclinical data from marmosets with 100 mg/kg iv for 4 weeks without AEs justified the human dose selection in Study A2102. Human healthy volunteers with two doses of 10 mg/kg iv was well tolerated without any AEs. Therefore, if a dose of 10 mg/kg achieved a *complete remission*, a second treatment would be justified if a patient were to relapse again. A second dose was to have been lower than the first dose to evaluate which dose would result in a minimal exposure to achieve remission. Therefore, a second infusion or injection was dependent upon the time when the relapse occurred. Based upon known PK of canakinumab from healthy volunteer data, 5 mg/kg would have been needed if relapse were to have occurred within the first 20 days after the first dosing.

Additional regimens were to include the following:

- 3 mg/kg, if relapse between Days 20 to 55 and
- 1 mg/kg, if relapse later than 55 Days.

A second observation period followed to evaluate the clinical response to canakinumab and *time to relapse*. If the second dose was too low to have met the criteria for *complete remission* within 2 days, rescue treatment was to have been initiated with another canakinumab dose of 2 mg/kg. This dosing regimen would have allowed evaluation of the minimal exposure required for effective neutralization of IL-1β and clinical remission.

The proposed canakinumab formulation was to have been for self-administration of a sc injection. Therefore, in period # 3 of Stage 1 and throughout Stage 2, sc doses of canakinumab 150 mg were administered.

Dosage in Stage 1

- First dose - single administration, 10 mg/kg iv infusion over 120 minutes followed by observation period # 1.
- Second dose - single administration, 1 mg/kg iv, upon relapse, followed by observation period # 2.
- Upon second relapse, the third dose - single administration, 150 mg sc followed by observation period # 3.

Period #1	Period #2	Period #3
10 mg/kg iv	1 mg/kg iv	150 mg sc

Dosage in Stage 2

- Patients were to have been administered a single sc injection of canakinumab 150 mg upon each relapse (children from 4 to 16 years were dosed on a weight basis equivalent to 2 mg/kg sc).
- If patients who were treated with 150 mg sc (or 2 mg/kg) failed to achieve *completed response* within 7 days after dosing, or if disease progressed or worsened within these 7 days, the patient could have been re-dosed with rescue, 5 mg/kg or 10 mg/kg canakinumab, which would have been administered as an iv infusion agreed upon by the investigator and the applicant.

Rescue Therapy

Rescue therapy in Stage 2 was to have applied to patients treated with canakinumab 150 mg s.c. who did not achieve *complete response* within 7 days after dosing, or if disease progressed or worsened within these 7 days. These patients could have been re-dosed with canakinumab between 5 or 10 mg/kg canakinumab as an i.v. infusion over ~120 minutes, as agreed between the investigator and the Sponsor.

Protocol Amendment # 6 (26Apr2007) in Stage 2, based on the first experience in children with MWS, introduced an additional dose level of the rescue therapy (10 mg/kg iv canakinumab). The decision of administering either 5 or 10 mg/kg iv of canakinumab was made on a case-by-case basis between the investigator and the sponsor based on the patient's age, weight and medical conditions.

In case of rescue therapy, a new period would be started (see **Table 68**, Evaluation and Visit Scheduled assessment). Once clinical relapse was established, patients would be treated with further single sc injections of canakinumab. Patients who still would not have achieved *complete response* within 7 days following iv dosing would have been withdrawn from the study. Treatment with anakinra or another therapy to which the patient agrees could have been initiated.

6. Study Schedule of Events

The time points of all evaluations in Stage 1 of Study A2102 are presented in **Table 68** and the time points of all evaluations in Stage 2 of Study A2102 are presented in **Table 69.**

Table 68.
Evaluation and Visit Schedule in Stage 1 (Periods 1, 2 and 3) of Study A2102

Study phase	Screening	Run-In[2]		Periods 1-3								
				Baseline		Treatment						
[1] Visit Numbers, Period 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
Period 2					Visit 104	Visit 105	Visit 106	Visit 107	Visit 108	Visit 109	Visit 110	Visit 111
Period 3					Visit 204	Visit 205	Visit 206	Visit 207	Visit 208	Visit 209	Visit 210	Visit 211
Day	D -15 to -2	D -15 to -2		D -1		D 1	D 2	D 3	D 8	D 15	D 22	D 29[6]
Time												
Inclusion /Exclusion criteria	X			X[3]								
Relevant medical history / Current medical conditions	X			X[3]								
Demography	X											
Physical examination	X				X							
Hepatitis and HIV screen	X											
Pregnancy test	X				X							
Drug administration record						X						
Comments	As required											
Vital signs and body measurements												
Body height	X											
Body weight	X				X							
Body temperature	X	X	X		X	X	X	X	X	X	X	X
Blood pressure / Pulse rate	X[4]	X	X		X[4]	X	X	X	X	X	X	X
ECG evaluation	X				X							
Hematology, Blood chemistry, Urinalysis	X	X	X		X	X	X	X	X	X	X	X[7]
Adverse Events	As required											
Prior/concomitant meds/therapies	X	X	X	X	As required							
Physician's clinical assessment	X	X	X		X	X	X	X	X	X	X	X
Review of Patient's diary	X	X	X		X	X	X	X	X	X	X	X
Local tolerability assessment of injection site						X[8]	X[8]	X[8]	X[8]			
Blood collection for efficacy (CRP, SAA)	X	X	X		X	X	X	X	X	X	X	X
24-h urine collection for creatinine clearance	X											
PK blood collection						X	X	X	X	X	X	X
PK skin biopsy								X[5]				
Immunogenicity blood collection						X			X			
PD blood collection						X	X	X	X	X	X	X
Pharmacogenomics blood collection						X	X	X	X	X	X	X

Sponsor Table 9-2, p 53 in Study A2102 Report

1. Visit structure given for internal programming purpose only.
2. Run-in applies only to patients who discontinued treatment with anakinra.
3. Review of inclusion/exclusion criteria/current medical conditions were required at baseline.
4. Standing/supine BP and pulse measurements were required.
5. Only associated with first dosing (10 mg/kg, iv).
6. And further weekly visits until clear relapse was diagnosed.
7. Hematology only.
8. After sc (period # 3) only.

Protocol Amendment # 1 (30Jun2005), issued 5 months after study start/after the inclusion of all 4 patients in Stage 1, added blood samples for PG at additional later time points (at each clinical visit) to investigate whether the observed early gene expression changes were transient or whether they were stable throughout the remission period.

Table 69.
Evaluation and Visit Schedule in Stage 2 of Study A2102

							Periods 1-x[10]						
Study Phase	Screening	Run-In[2]		Baseline				Treatment					Study Completion[5]
[1]Visit numbers, Period 1	301[3]	302[3]	303[3]	304			305		306	307	308	309[4]	
Period 2					354		355		356		358	359[4]	
[10]Period 3					404		405		406		408	409[4]	777
Day	-15 to -2			-1	-1		1		2	3[12]	8	38[4]	
Time						0h	2h	6h					
Inclusion / exclusion criteria	X			X[6]									
Medical history	X												
Current medical conditions	X			X[6]									
Demography	X												
Physical examination	X			X	X								X
Hepatitis and HIV screen	X												X
Pregnancy test (serum)	X												
Pregnancy test (urine)				X	X								X
PPD tuberculin skin test	X												X
Drug administration record						X					X[13]		
Study completion information													X
Comments							As required						
Vital signs and body measurements:													
Body height	X			X[11]	X[11]								X[11]

Table 69. *(continued).*
Evaluation and Visit Schedule in Stage 2 of Study A2102

							Periods 1-x[10]						
Study Phase	Screening	Run-In[2]		Baseline				Treatment					Study Completion[5]
[1]Visit numbers, Period 1	301[3]	302[3]	303[3]	304			305		306	307	308	309[4]	
Period 2					354		355		356		358	359[4]	
[10]Period 3					404		405		406		408	409[4]	777
Day	-15 to -2			-1	-1		1		2	3[12]	8	38[4]	
Time						0h	2h	6h					
Body weight	X			X	X								X
Body temperature	X	X	X	X	X	X			X	X	X	X	X
Blood pressure, pulse rate	X[7]	X	X	X[7]	X	X			X	X	X	X	X
ECG	X			X									X
Hematology, Blood chemistry, Urinalysis	X	X	X	X	X				X			X	X
ANA screen	X	X	X	X	X								X
Adverse events and infection occurrence									As required				
Local tolerability						X	X	X	X		As required		
Prior / concomitant medications / therapies	X			X[6]					As required				
Investigator's clinical assessment of disease activity	X	X	X	X	X	X			X	X	X	X	X
Review of patient's assessment of symptoms	X	X	X	X	X	X			X	X	X	X	X
Inflammation markers (CRP, SAA)	X	X	X	X	X				X	X	X	X	X
Audiogram[9]				X									
24-h urine collection[8]				X									
SF-36 (adults)				X	X				X		X	X	X
FACIT-F (adults)				X	X				X		X	X	X
HAQ (adults)				X	X				X		X	X	X
CHQ-CH87 (children)				X	X				X		X	X	X
MRI of brain[9]				X									

Table 69. *(Continued)*
Evaluation and Visit Schedule in Stage 2 of Study A2102

								Periods 1-x[10]						
Study Phase	Screening	Run-In[2]		Baseline				Treatment						Study Completion[5]
[1]Visit numbers, Period 1	301[3]	302[3]	303[3]	304				305		306	307	308	309[4]	
Period 2					354			355		356		358	359[4]	
[10]Period 3					404			405		406		408	409[4]	777
Day	-15 to -2			-1	-1			1		2	3[12]	8	38[4]	
Time						0h	2h	6h						
Neurological assessment[9]				X										
Ophthalmological assessment[9]				X										
Immunogenicity blood collection						X							X	
PK blood collection						X	X[12]	X		X	X	X[12]	X	X
PD (IL-1β) blood collection						X	X[12]	X		X	X	X[12]	X	X
Soluble protein markers blood collection						X				X	X	X[12]	X	X
PG blood collection						X		X		X	X	X[12]	X	X

Sponsor Table 9-3, pp 53-56

1. Visit structure given for internal programming purposes only.
2. Run-in applied only to patients who discontinued treatment with anakinra.
3. Visits applied only to newly enrolled patients, not to patients continuing from Stage 1.
4. And further monthly visits (Day 68, 98, etc.) until clear relapse was diagnosed.
5. For pts entering Phase 3 studies, visits were performed in concomitance to the first baseline visit of the Phase 3 protocol Study D2304 or D2306 or the extension phase.
6. Review of inclusion/exclusion criteria and current medical conditions was required at the first baseline evaluation.
7. Standing/ supine BP and pulse was required.
8. Assessment was to have been performed at first baseline and every 4 months, at the closest scheduled visit. Only for pts with FCAS: if baseline audiogram was normal, follow-up assessment was performed at the discretion of the investigator.
9. Assessment was performed at first baseline and once/year, at the closest scheduled visit. Patients with severe renal insufficiency (GFR < 30 mL/min/1.73m^2) or who were planned to have renal transplant would not perform the brain MRI due to the risk of developing nephrogenic systemic fibrosis (NSF) following administration of gadolinium contrast agent. Only for patients with FCAS: if baseline MRI and neurological assessment showed normal results, follow-up assessments could be performed at the discretion of the PI. Ophthalmological assessments were performed per protocol.

Table 69. *(Continued)* Evaluation and Visit Schedule - Stage 2

								Periods 1-x[10]						
Study Phase	Screening	Run-In[2]		Baseline				Treatment						Study Completion[5]
[1]Visit numbers, Period 1	301[3]	302[3]	303[3]	304				305		306	307	308	309[4]	
Period 2					354			355		356		358	359[4]	
[10]Period 3					404			405		406		408	409[4]	777
Day	-15 to -2			-1	-1			1		2	3[12]	8	38[4]	
Time						0h	2h	6h						

[10] Further periods were possible (there were up to 20 Periods in the study).
[11] For children < 16 years.
[12] Period 1 only.
[13] Only applicable for rescue therapy. In case of rescue therapy, a new period had to be started. Baseline evaluations were to be conducted pre-dose.

Sponsor Table 9-3, p 56 in Study A2102 Report

7. Protocol Specification for Study Visits

Study A2102 included screening assessments 2 to 15 days prior to initiation of the study to determine eligibility. The run-in period only applied to patients previously treated with anakinra. The run-in period, in anakinra previously treated patients, was defined as the time period when anakinra was discontinued until these patients experienced clinical and/or laboratory evidence of relapse, as defined in the protocol. This period varied between different patients.

Baseline was defined as assessments made during the patient's visits up to one day (Day -1) prior to each canakinumab administration. Routine clinical chemistry, hematology and urinalysis screens were evaluated in addition to screens for hepatitis B and C, human immunodeficiency virus)HIV), a pregnancy test in female patients and a purified protein derivative (PPD) tuberculin skin test.

- Treatment Period(s):
  Patients were admitted to the study site at least 2 hours prior to dosing and were required to remain close to the study site from dosing until the morning of Day 3 which included Days 1, 2, and 3. Physicians were onsite for at least 4 hours after each dosing. All patients were to fast for at least 3 hours after administration of canakinumab. Study visits and the planned evaluations at each visit are presented in **Tables 68** and **69**.
- Special Assessments:
  a. Only in Stage 1 (Visit 7) was a skin biopsy for PK assessment performed.
  b. In Stage 2, at baseline Day -1, special assessments included audiogram, neurological and ophthalmological assessment, and MRI of the brain. These assessments were repeated at study completion for each patient.
  c. In Stage 2, health-related quality of life assessments, the SF-36 (adults), the FACIT-F (adults), the HAQ-DI (adults) and the CHQ-CH87 (children), were to have been completed at baseline, Day 2, 8 and 38. The scoring for each of these instruments was defined in the individual study report for Study D2304 of this clinical review (see Section # 7, Study D2304 Individual Study Report).
- End of Study Evaluation:
  Once *relapse* after *complete response* had occurred after the last dose of canakinumab, the end of study evaluation was performed. The end of study evaluation was also performed when a patient prematurely withdrew from the study for whatever reason.

8. Removal of Patients from Treatment or Assessment and Replacement

Patients would have been withdrawn from Study A2102 for withdrawal of informed consent, pregnancy, study discontinuation or any medical condition which required discontinuation. Protocol deviations should not have been cause for patient withdrawal unless they were indicated significant risk to the patient's safety. Patients discontinued from Study A2102 for any reason were to have been required to follow-up within 60 days. Treatment with anakinra could have been initiated at the discretion of the investigator. Patients who completed Study A2102 up to 30 days enrollment would be deemed fully evaluable and would not be replaced.

9. Concomitant and Prior Therapy

Patients were to remain on their current medication other than medication for the treatment of signs and symptoms of CAPS disease, whenever possible, for the duration of the study. If additions to chronic medications were required, these medications were discussed with Novartis. Antihypertensive medication, gastric protection, folic acid, NSAIDs and analgesics were considered appropriate therapy for CAPS patients. Anti-inflammatory therapy with colchicine, corticosteroids, chlorambucil, dapsone, azathioprine, and mycophenolate mofetil was not allowed starting 3 weeks prior to dosing and during the study. If patients had been treated with therapeutic antibodies, e.g., anti-TNF alpha blocker, discontinuation ≥ 60 days before dosing was required. Patients whose symptoms had improved with anakinra were to be permitted to enroll in this open label canakinumab study. Anakinra was to be discontinued in these patients until they experienced a clinical and laboratory relapse as defined in the protocol. This period was defined as the run-in time and varied among different patients.

D. Rescue Medication

This protocol is silent on rescue medication. Rescue therapy with canakinumab is reported in the **Study Treatments** section of this individual study review.

E. Outcome Measures

1. Primary Efficacy Endpoint

The primary efficacy variable was to be the *time* (from each dose administration) *to relapse* after a patient would have achieved a *complete response* to treatment.

Complete remission (complete response) was initially defined as,

- After 7 days of canakinumab treatment:

Absence of symptoms of skin rash
- Absence of joint or muscle pain
- Marked improvement of arthralgia
- Normal serum values of CRP and SAA (< 10 mg/L)
- Normal temperature (< 37.5°C)
- Normal leukocyte count

- After 2 days of canakinumab treatment:
  - Absence of symptoms of skin rash
  - CRP and SAA in serum reduced by > 30% as compared to pretreatment
  - Normal temperature (< 37.5°C)

Relapse or *incomplete remission* was initially defined as ≥ 2 of the following symptoms along with CRP and/or SAA values > 30 mg/L on two occasions in 1 week:
- Reappearance of symptoms of skin rash
- Reappearance of joint or muscle pain
- Reappearance of eye discomfort or redness
- Reappearance of fatigue or malaise
- Reappearance of fever or chills

Based on the experience from the first 4 patients enrolled in Stage 1, the definition of relapse or incomplete remission was revised in *Protocol Amendment # 3 (21Dec2005) to require the presence of the above symptoms on one single occasion in Week 1, in order to allow quick re-treatment in the case of a relapse.* A major revision of the definition of *complete response* to treatment, *relapse*, and *partial response* to treatment was introduced with *Protocol Amendment # 4 (21 Sept2006)* based upon preliminary results of the ongoing Study A2102 and on advice from regulatory agencies.

The definition of *complete response* to treatment was *revised* to:

- Physician global assessment of disease activity ≤ minimal (using a 5-point scale ranging from absent to severe)
- Assessment of skin disease ≤ minimal (using a 5-point scale ranging from absent to severe
- Normal serum values of CRP and/or SAA (< 10 mg/L)

The definition of *relapse* was *revised* using the following criteria (to be assessed on the same day):

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

OR, for patients who would have had had low CRP and SAA values (< 30 mg/L) at baseline

Per Protocol Amendment # 6 (26Apr2007): CRP and/or SAA values < 30 mg/L, but a clinical picture which would have required adequate re-treatment (the final decision would have needed a joint agreement between the investigator and the sponsor).

- Physician global assessment of disease activity > minimal

OR

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

The definition of **Partial Response** to treatment was *revised* as:

- Partial response would have been absence of *complete response* but a reduction of CRP and/or SAA over baseline by > 30% but not reached normal values (< 10 mg/L)
  AND
- Physician global assessment improvement over baseline by one step.

Follow up period was defined as a period up to 60 days.

2. Secondary Efficacy Endpoints

The secondary efficacy variables were to have included assessment of

- Safety,
- Tolerability
- PK and PD assessments of canakinumab including total IL-1β and soluble protein markers, and

- Immunogenicity assessments for anti-canakinumab antibodies.

Protocol Amendment # 4 (21Sept2006) added special assessments of monitoring canakinumab potency to modify long-term disease co-morbid outcomes;

- Deafness; renal function including creatinine clearance and proteinuria; neurological and ophthalmological assessments; and MRI of the brain.

Protocol Amendment # 4 (21Sept2006) added health-related quality of life assessments.

Health-Related Quality of Life (HRQoL) Patient Reported Outcome (PRO) instruments employed:

- SF-36, PCS and MCS (adults);
- FACIT-F (adults);
- HAQ-DI (adults);
- CHQ-CF87 (children and adolescents, 10 years to 18 years of age)

F. Statistical Analyses

Three populations were to have been employed in Study A2102 for analysis:

- Safety Population: All patients who received at least one dose of canakinumab. The safety population was used for all efficacy-related analyses. For all safety-related assessments, patients were classified at screening as either "adult" defined as ≥ 18 years of age or "pediatric" defined as ≤ 17 years of age.
- Stage 1 Analysis Set: All patients who received at least one dose of canakinumab in Stage 1, Study A2102.
- Patients who withdrew from Study A2102 to enroll into Study D2304, and then re-entered Study A2102: All these patients were to have been assigned a second Pt # ID for the second part of their participation in Study A2102.
- Efficacy-Related Assessments: For all efficacy-related assessments, with the exception of *time-to-relapse*, patients were grouped by dosing regimen, e.g., 10 mg/kg iv; 1 mg/kg iv; 150 g sc; 2 mg/kg sc; and rescue iv (either 5 mg/kg or 10 mg/kg). Patients who received more than one dosing regimen were included in more than one of these dose groups. For *time-to-relapse*, patients were grouped by combined dosing regimen where the rescue dose was combined with the previous dose regimen. Therefore, groups were 10 mg/kg iv; 1 mg/kg iv; 150 mg sc; 150 mg sc + rescue iv; 2 mg/kg sc; and 2 mg/kg sc + rescue iv.

Demographic and baseline disease characteristics, PK/PD, efficacy and safety data were summarized either by age group or by dose regimen. Due to the multiple periods in this study, two types of analyses were to have been completed.

- In the '*1st period per dose regimen only*' analysis, only data from the first period within the dose regimen was employed.
- In the '*all periods averaged*' analysis, if there were multiple periods for a patient within a dosing regimen, the arithmetic mean of the measurements within the patient was calculated first and then was summarized across patients. The 'end of period' time-point

was the time just prior to re-dosing. This time-point summarized efficacy assessments at the *time of relapse*.

Statistical analyses were to have been performed to assess the time from last dose to relapse for each canakinumab dose regimen and the impact of covariates on time-to-response. For each analysis, a Weibull "gap-time" frailty model was to have been employed. This model accounts for the censored nature of the time to relapse data, e.g. whether or not a patient relapsed, and the potential correlation between time to relapse within each patient.

Primary Efficacy Analysis of Time-To-Relapse

The primary efficacy variable in this open label study was *time from each dose to relapse* after having achieved a *complete response*. The primary analysis included data from all patients in all periods. For patients who required an additional rescue dose of canakinumab after approximately 1 week, the dose regimen was defined as a separate group with both doses combined. The time of the rescue dose was employed as the time of dosing in the calculation of *time-to-relapse*. In the linear predictor of the Weibull model, the dose regimen was fitted as a fixed effect and the patient was fitted as a normally distributed random effect. For each dose regimen, the population estimate of the median time-to-relapse was to have been calculated with its 95% CI.

Secondary Analysis of Time-To-Relapse

The secondary efficacy analyses were to have assessed the impact of covariates on the *time-to-relapse*. Due to the limited number of periods of data in some of the five dosing regimens, the secondary analyses were restricted to those periods where a dose of 150 mg sc was administered without the need for an additional canakinumab dose within a week. Data from all other dosing regimens were excluded.

Univariate models were fitted with the following four (4) covariates:

- Previous canakinumab treatment (Yes or No);
- Previous anakinra treatment (Yes or No);
- Clinical picture (FCAS, MWS or MWS/NOMID); and
- Gender (Male or Female).

[Note: Any patient with a clinical picture of only NOMID was to have been counted as MWS overlap NOMID.]

For each model, the population estimate of the median *time-to-relapse* in each of the categories was to have been calculated along with its 95% CI. The likelihood ratio test was to be used to compare the null model (without the covariate) with the model including the covariate.

Other Efficacy Variables

HRQoL measures were:

- SF-36 (PCS and MCS), adults
- HAQ-DI, adults
- FACIT-F, adults
- CHQ-PR28, pediatric patients

Pharmacokinetic Evaluations

Non-compartmental analysis was used to calculate single dose PK parameters, e.g., AUC, C_{max}, T_{max}, and T ½, based on the following:

- For patients who completed Stage 1 and 2: non-compartmental PK parameters following the initial dose of 10 mg/kg and 150 mg sc were calculated.
- For patients who completed only Stage 2: non-compartmental PK parameters following the initial dose of 150 mg sc or 2 mg/kg sc were calculated.

Descriptive statistics were to have been used to summarize the PK variables. No formal statistical analysis was performed on the PK variables.

Pharmacodynamic Evaluations

The safety analysis set was to have been used for most of the PD evaluations including total IL-1β and the serum protein markers, CRP and SAA. Each of these variables was to have been analyzed by dosing regimen. Due to the multiple periods, two types of summary tables were produced:

- "1st Period per dose regimen only" with only data from the first period within the dose regimen.
- "All periods averaged" , if there were multiple periods for a patient within a dosing regimen then the arithmetic mean of the measurements within the patient was to have been calculated first and then to have been summarized across patients.

Immunogenicity Assessments

Anti-canakinumab antibody concentrations were to have been assessed in the serum.

G. Safety Evaluations

Safety assessments were to have been summarized by age group, adult and pediatric. Safety assessments were to consist of all AEs and SAEs with their severity and relationship to canakinumab. Particular focus was given to the occurrence of infections. Regular monitoring of clinical laboratory tests (including screening for anti-nuclear antibodies and PPD skin test reactivity), vital signs, body weight and height, e.g., only for children < 16 years, physical examination, and ECG was included per protocol. Tolerability assessments of sc injections were to have been completed. Evaluation of the immunogenicity potential of canakinumab was to have been completed.

H. Interim Analyses

Three (3) interim analyses were to have been completed. No statistical analyses were performed in these analyses.

- First Interim analysis: Completed at the end of Stage 1 and evaluated the preliminary efficacy, safety, tolerability, PK, PD and pharmacogenomic results related to iv infusion.
- Second Interim Analysis: Conducted when patients were recruited into Stage 2. This interim analysis supported End-of-Phase 2 discussions with the Division.
- Third Interim Analysis: Provided updated results from 20 patients in Study A2102 (November 2007).

II. Study Conduct

This protocol involved a non-randomized, open-label, Phase 2 clinical trial designed to investigate the clinical efficacy, safety, PK/PD of different doses of canakinumab administered iv and sc in patients with NALP3 mutations and the clinical picture of MWS, FCAS and MWS overlapping with NOMID.

The study design included two stages. In Stage 1, canakinumab was to have been administered as a single iv infusion of 10 mg/kg followed by an observation period in which the *response to treatment* and *time-to-relapse* were assessed. As soon as a patient would have started to clinically relapse, the patient would have received a second dose of canakinumab iv infusion of 1 mg/kg followed by a second observation period. A third treatment period was to have occurred in Stage 1.

In Stage 2, adult patients were to have been administered one sc injection of canakinumab 150 mg sc upon each relapse. Children, aged 4 years or older, were to have been dosed on a weight basis (2 mg/kg, sc). When a patient completed Study A2102 participation, they were to have either transitioned into Phase 3 Study D2304 or D2306, or they would have discontinued Study A2102. New CAPS patients, e.g., canakinumab naïve, would have been allowed to enroll in Stage 2 of Study A2102.

A. Key Changes in the Study Conduct

Study conduct changes which were to have occurred were:

- Immunogenicity was not included in the original protocol and was added with *Protocol Amendment # 3 (21Dec2005).* Therefore, samples for immunogenicity analysis were not collected in Stage 1 (iv administration). In order to collect immunogenicity data related to iv treatment, additional immunogenicity measurements were conducted in the available PK serum samples remaining from Stage 1.
- A priority list was developed for pediatric patients allowing, e.g., the investigator to skip collection of back-up samples *(File Note dated 03Apr2007).*
- Visits and sample numbering changed several times during Study A2102 due to amendments *(File Note 07Jul2008).*
- The following assessments were not performed by Centre # 1 (United Kingdom) due to logistical reasons *(by the time Protocol Amendment # 4 would have been implemented, the study would have almost been completed at this site)*: PPD tuberculin skin test, audiogram, MRI of the brain, neurological and ophthalmological assessment and HRQoL questionnaires.

B. Changes in the Planned Analysis

The sample size was to have been small in the original protocol. Planned analyses were to have consisted of listing data and calculation of descriptive statistics for selected amendments. As the sample size and complexity of Study A2102 increased, the main changes to the planned analyses were:

- Primary and secondary analyses of *time-to-relapse* were added;
- Calculation of descriptive statistics for the majority of disease assessments were added;

- Separate summary tables were completed based on the *1st period* and on *all periods averaged;*
- Statistical analyses which explored the correlation between exposure values (AUC and C_{max}) and pharmacodynamic parameters (e.g., IL-1β and TNF) were not performed, although the correlation between the PK concentrations and IL-1β was explored in the PK/PD population model.
- Data from HRQoL questionnaires were listed and summarized by dose regimen. No statistical analysis of HRQoL questionnaires was performed.

After the database lock, the following changes were to have been made:

- Assessment of each patient against a second partial response criterion, not requiring levels of CRP and/or SAA > 10 mg/L, was to have been performed. Summary tables for the number of responders were to have been completed based upon the revised criterion.
- Because of the known morbidity of renal disease in CAPS patients, kidney function parameters, e.g. creatinine clearance and estimated glomerular filtration rate were to have been summarized in patients with and without renal insufficiency.

C. Protocol Amendments

Study A2102 was amended 8 times. *Protocol amendments (italicized)* are noted in the section where they apply.

D. Treatment Compliance

All patients received the pre-specified iv infusions or sc injections of canakinumab during the scheduled visits. Compliance was assured by the patient attendance. In addition, compliance was verified by determinations of canakinumab levels in the serum.

E. Protocol Deviations

The majority of patients in Study A2102 had at least one protocol deviation. Most of the protocol deviations were minor and would not be expected to have a major impact on clinical response or time to relapse. Minor protocol deviations were predominantly missing laboratory values, visits outside the scheduled window, and mistakes in samples labeling.

Violated Inclusion/Exclusion Criteria

1. Patient # 5118 was diagnosed as MWS/NOMID overlap, however, the CRF reflects that the patient's study presentation was more consistent with NOMID. This patient was reclassified as NOMID.

Protocol File Note (14August2008) clarified that if a patient were to have meningitis, increased cerebrospinal fluid pressure, mental retardation and typical arthritis changes with swollen articulations and/or joint and bone deformities, then the patient should be classified as a case of NOMID.

The severity of NOMID signs and symptoms should have precluded Pt # 5118 from enrollment in Study A2102. This study design is not optimum for inclusion of NOMID patients in regard to

the mandated disease assessments and the dosing regimen on disease flare which may not be safe for NOMID patients.

2. Pt. # 5110 discontinued treatment with colchicine 1 week, instead of 3 weeks, prior to canakinumab dosing.

3. Pt. # 5104 did not have HIV testing at screening. This test was performed at Visit 15 and was negative.

4. Pt. # 5101 had increased urine red blood cells (RBC) and white blood cells (WBC) at screening and a positive urinary culture, b*eta-hemolytic streptococcus group B*. No treatment was recorded in the CRF. The patient was reported to have no clinical symptoms. It could not be excluded that the positive urine culture was due to contamination, repeat urine tests were negative.

Treatment/Dose Deviations
1. Pt # 5131 received the first dose of canakinumab at age 16 years as a fixed dose (150 mg sc) and should have received a weight-based dose (2 mg/kg), per the protocol. The patient turned 17 years within 1 week of the administered dose.

2. Pt. # 5127, period 2, canakinumab was reconstituted by mistake with 1 mL of vehicle instead of water for injection (WFI). The vehicle contains the same excipients as placebo, therefore, by using the vehicle instead of WFI, the concentration of the excipients was increased. The canakinumab concentration and dose injected was not affected. No tolerability issues at the site of injection or other adverse events were reported following the injection.

3. Pt. #5119 traveled from India to the USA and received the second injection of canakinumab prematurely on Day 73. He did not relapse and did not attend Day 2 or Day 8 visits of the second period.

4. Pts. # 5108, # 5117, and # 5123 at Center # 2, received a rescue canakinumab dose slightly higher than 5 mg/kg, range between 5.6 and 5.7 mg/kg. This deviation was not considered major.

Prohibited Co-Medication
1. Pt # 5121 (FCAS) self-injected anakinra 290 days after the first canakinumab injection due to moderate articular pain. This deviation was not accounted for in the *time-to-relapse* analyses. Because this anakinra injection was close to the end of follow-up, it was concluded that the statistical analysis was not likely to be significantly impacted.

Assessments
1. End of this study, PPD skin tests were not performed in Pts # 5120 and 5131. Both patients had discontinued the study.

2. CH-CF87 for children 10 to 18 years of age was completed by 3 children below age 10 years.

III. Results

A. Patient Disposition

This study was conducted among 8 centers across four countries: France (1), Germany (5), India (1), Spain (1), and the United Kingdom (1).

Thirty-four (34) patients enrolled in Study A2102. Twenty-five (25, 93%) of 27 adult patients and 6 pediatric patients (86%) of 7 pediatric patients completed this study (see **Table 70**).

Patient Discontinuations

Three (3) patients discontinued Study A2102, two adults and one pediatric patient:

- One adult patient (MWS/NOMID) discontinued due to lack of efficacy;
- One adult patient (FCAS) discontinued due to inability to comply with patient visits; and
- One pediatric patient (17 years of age, MWS/NOMID) discontinued due to an unplanned pregnancy.

Thirty-one patients (31, 91%) completed this study. Patient attrition in this study was small and did not interfere with interpretation of these open label patient data.

Table 70.

Summary of Patient Disposition Study A2102			
Total # pts studied	**Adult pts N = 27** n (%)	**Pediatric pts N= 7** n (%)	**Total N = 34** n (%)
Screening failures	0	0	0
Enrolled	27	7	34
Completed	25 (93%)	6 (86%)	31 (91%)
Discontinued	2 (6%)	1 (14%)	3 (9%)
Adverse events	0	1	1 (3%)
Lack of efficacy	1	0	1 (3%)
Other*	1		1 (3%)
Analysis Population			
Safety	27	7	34
ITT	27	7	34
Other * = administrative problems/unable to comply with scheduled visits.			

Pediatrics defined as < 18 years of age in Study A2102.

Prior Medications

Over 70% of patients received anakinra prior to enrollment in this study. There were more pediatric than adult patients exposed to anakinra prior to enrollment (see **Table 71**).

Table 71.

Concomitant Medications			
	Adult Pts N = 27	**Pediatric Pts** N = 7	**Total** N = 34
Previous anakinra use			
Yes	18 (67%)	6 (86%)	24 (71%)
No	9 (33%)	1 (14%)	10 (29%)

Five (5) patients had prior exposure to TNF blockers: Adalimumab (1 patient); Etanercept (3 patients); and Infliximab (1 patient). Other prior medication exposure included:

- An investigational caspase-1 inhibitor (3 patients),
- Gold therapy (2 patients),
- Azathioprine (3 patients),
- Cyclosporine A (2 patients),
- Cyclophosphamide (1 patient),
- Mycophenolate mofetil (1 patient),
- Thalidomide (1 patient),
- Methotrexate (1 patient),
- Chloroquine (1 patient),
- Immunoglobulin therapy (1 patient),
- Skin UVA radiation (2 patients),
- Systemic glucocorticosteroids (10 patients), and
- Colchicine (8 patients).

B. Concomitant Medications

All patients took some concomitant medication during this study. The most common concomitant medications were: iron supplements, paracetamol, NSAIDs, amoxicillin, and oral contraceptives. Four patients (Pt # 5118, # 5131, # 5134, and # 5135) were receiving systemic glucocorticosteroids. Steroids were tapered and discontinued during this study in one patient (# 5118, NOMID).

Prohibited Concomitant Medications

Two patients were reported to have taken prohibited concomitant medication:

- Pt # 5121 (FCAS) self-injected one dose of anakinra 290 days after the first canakinumab injection due to moderate arthritis pain secondary to her FCAS disease.
- Pt # 5120 (FCAS) received anakinra after discontinuation from Study A2102, during the follow-up period.

B. Patient Demographic and Other Baseline Disease Characteristics

Patient demographics for Study A2102 were summarized in **Table 72**. The mean adult age was 36 years and mean pediatric age was 10 years. The majority of patients were female, Caucasian, with a mean weight of 61 kg and 32 kg, adult and pediatric patients, respectively. There were 7 pediatric patients enrolled in this study with baseline ages 4, 6, 6, 7, 13, 16, and 17 years.

Table 72.

Baseline Demographic Characteristics, Study A2102			
	Adults Pts. N = 27	Pediatric Pts N = 7	Total N = 34
Age (years)			
Mean (SD)	36 (11)	10 (5)	30 (14)
Range	(18-51)	(4-17)	(4-51)
Gender n (%)			
Female	17 (63%)	4 (57%)	21 (62%)
Male	10 (37%)	3 (43%)	13 (38%)
Race n (%)			
Caucasian	25 (93%)	6 (86%)	31 (91%)
Asian	2 (7%)	0	2 (6%)
Native American	0	1 (14%)	1 (3%)
Body Mass Index (kg per meter squared)			
Mean (SD)	24 (3)	18 (4)	22 (4)
Weight (kg)			
Mean (SD)	61 (8)	32 (14)	55 (15)

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Baseline CAPS disease, by diagnosis, is summarized in **Table 73.** The majority of patients had MWS and all patients had a molecular diagnosis of NALP3 mutation. Twenty-six (26) patients had a family history of CAPS disease with affected relatives in at least one generation and three (3) patients reported no family history of CAPS disease.

Table 73.

Baseline CAPS Disease Diagnoses Study A2102			
	Adult pts N = 27 n (%)	Pediatric pts N= 7 n (%)	Total N = 34 n (%)
CAPS Diagnosis			
FCAS	2 (7%)	0	2 (6%)
MWS	22 (81%)	5 (71%)	27 (79%)
NOMID	1 (4%)	0	1 (3%)
MWS/NOMID	2 (7%)	2 (29%)	4 (12%)

Pediatrics defined as < 18 years of age in Study A2102.

Baseline disease characteristics confirmed the overall disease severity. There were 5 patients (19%), 3 patients (11%), and 4 patients (15%) scored as *severe* by the Physician's Global assessment of autoinflammatory disease, skin assessment, and the Patient's Global assessment of disease symptoms, respectively. The majority of patients scored *mild* or *minimal* disease activity by the Physician's Global assessment of autoinflammatory disease, skin assessment, and the Patient's global assessment of disease symptoms (see **Table 74**).

Table 74.

Baseline CAPS Disease Characteristics Study A2102 (ITT)			
	Adult pts N = 27 n (%)	Pediatric pts N = 7 n (%)	Total N = 34 n (%)
Previous anakinra therapy n (%)			
Yes	18 (67%)	6 (86%)	
No	9 (33%)	1 (14%)	
Physican Global assessment of autoinflammatory disease activity n (%)			
Absent	0	0	0
Minimal	4 (15%)	0	4 (12%)
Mild	9 (33%)	0	9 (26%)
Moderate	8 (30%)	7 (100%)	15 (44%)
Severe	5 (19%)	0	5 (15%)
Assessment of skin disease n (%)			
Absent	3 (11%)	2 (29%)	5 (15%)
Minimal	5 (19%)	2 (29%)	7 (21%)
Mild	8 (30%)	2 (29%)	10 (29%)
Moderate	7 (26%)	1 (14%)	8 (24%)
Severe	3 (11%)	0	3 (9%)
Patient's Global assessment of disease symptoms n (%)			
Absent	2 (7%)	0	2 (6%)
Minimal	3 (11%)	0	3 (9%)
Mild	7 (26%)	3 (43%)	10 (29%)
Moderate	9 (33%)	2 (29%)	11 (32%)
Severe	4 (15%)	1 (14%)	5 (15%)

Pediatrics defined as < 18 years of age in Study A2102.

The average baseline CRP/SAA levels were elevated in all patients and are consistent with the diagnosis of CAPS disease and active signs and symptoms as indicated by the baseline disease assessment scores (see **Table 75**).

Table 75.

Baseline Serum Protein Markers Study A2102 (All pts, N = 34)			
CRP (mg/l)			
Time Point	n = # Pts	Mean (SD)	Median (min, max)
1st Baseline	34	47 (57)	36 (0.2, 288)
SAA (mg/L)			
1st Baseline	34	177 (225)	66 (1.8, 908)

Normal levels: CRP < 0.5 mg/L; SAA < 6.5 mg/L

Special assessments were included in Study A2102 based on co-morbidities in CAPS disease patients (see **Table 76**). The majority of patients had *normal* or *clinically insignificant abnormalities* by neurological and ophthalmological assessments, and by MRI of the brain. Audiogram had the highest baseline incidence of *clinically significant abnormality* (14 out of 25 patients, 56%). The majority of these patients had hearing impairment consistent with bilateral sensorineural hearing loss.

Seven patients (21%), one patient (3%) had *clinically significant abnormality* by ophthalmological, neurological, and MRI of the brain assessment, respectively. Pseudotumor cerebri was

diagnosed in one pediatric patient with a *clinically significant abnormal* MRI. Enlarged fluid spot, subcapsular posterior cataract, corneal opacity, prominent papillae, severe corneal band degeneration, and likely active uveitis were the *clinically significant abnormal* ophthalmological findings across 7 patients. Missing data was highest for MRI (41%) followed by 29%, 27%, and 26% for ophthalmological, neurological, and audiogram assessments, respectively.

Table 76.

Baseline CAPS Disease Special Assessments Study A2102			
	Adult pts N = 27 n (%)	Pediatric pts N = 7 n (%)	Total N = 34 n (%)
Audiogram n (%)			
Normal	5 (19%)	3 (43%)	8 (24%)
Clin. insignificant abn.	1 (4%)	2 (29%)	3 (9%)
Clin. significant abn.	13 (48%)	1 (14%)	14 (41%)
Not available/not done	8 (30%)	1 (14%)	9 (26%)
Neurological assessment n (%)			
Normal	11 (41%)	3 (43%)	14 (41%)
Clin. insignificant abn.	7 (26%)	3 (43%)	10 (29%)
Clin. significant abn.	1 (4%)	0	1 (3%)
Not available/not done	8 (30%)	1 (14%)	9 (27%)
Ophthalmological assessment n (%)			
Normal	6 (22%)	1 (14%)	7 (21%)
Clin. insignificant abn.	8 (30%)	2 (29%)	10 (29%)
Clin. significant abn.	5 (19%)	2 (29%)	7 (21%)
Not available/not done	8 (30%)	2 (29%)	10 (29%)
MRI assessment n (%)			
Normal	12 (44%)	2 (29%)	14 (42%)
Clin. insignificant abn.	4 (15%)	1 (14%)	5 (15%)
Clin. significant abn.	0	1 (14%)	1 (3%)
Not available/not done	11 (41%)	3 (43%)	14 (41%)

C. Relevant Medical History and Continuing Medical Conditions

The most common preferred terms (PT) for > 10% of patients' medical history and ongoing medical conditions, by diagnosis, were:

MWS

- Conjunctivitis or episcleritis (24 patients, 89%); urticarial rash or exathema (23 patients, 85%), fatigue/malaise/lethargy (23 patients, 85%); joint arthropathies (arthritis or arthralgia) and/or joint swelling (23 patients, 85%); myalgia (18 patients, 67%); fever/ pyrexia and/or shivers/rigors (17 patients, 63%); recurring headaches or attacks of migraine (15 patients, 56%); mouth ulcers/aphthous ulcers (9 patients, 33%); amyloidosis (7 adult patients, 26%) and renal amyloidosis (5 patients, 19%) of which 3 of these 5 (60%) presented with renal insufficiency; abdominal pain (4 patients, 15%); and corneal opacity and/or papilla alterations (4 patients, 15%).
- Noteworthy, one patient each, (4%), had chronic meningitis, glaucoma, depression, and delayed puberty.

FCAS

- Urticarial rash (2 patients, 100%); arthralgia (2 patients, 100%); myalgia (1 patient, 50%).

MWS/NOMID

- Overlap patients, in addition to the above noted MWS signs and symptoms, reported papillaedema (4 patients, 100%); visual loss (3 patients, 75%); increased intraocular pressure or glaucoma (2 patients, 50%); and increased intracranial pressure (1 patient, 25%).
- Noteworthy, one patient each, (25%), had learning difficulties, schizoaffective disorders, sterile meningitis, pseudotumor cerebri, and growth retardation.

NOMID

- Only one adult NOMID patient (#5118) was enrolled Study A2102. This patient had suffered depression, patella hypertrophy and exostosis (requiring knee surgery), uveitis, severe corneal band degeneration and cataracta incipiens, as well as renal insufficiency, e.g., necrotizing glomerulonephritis.

Other Baseline Disease Characteristics of Interest

- The majority of patients (24 patients, 71%) in this study had sensorineural hearing loss. The majority of these patients (94%) had the diagnosis of MWS or MWS overlap NOMID.
- At baseline, 5 patients (15%) had hypertension.
- The total WBC count, neutrophils and platelets counts were increased in 38%, 50% and 24% of all patients at baseline. These data are consistent with active signs and symptoms of CAPS disease.
- Renal function at baseline was noteworthy for four (4) patients (# 5118, adult NOMID; # 5132, adult MWS; # 5135, adult MWS; and # 5136, adult MWS) with moderate to end-stage renal insufficiency. Patient # 5136 (MWS) had hemodialysis.
- Abnormal liver function test results were reported in two patients at screening and enrollment.
  - Pt # 5105 had SGOT 2 x the upper limit of normal (ULN), SGPT 1 x ULN and normal total bilirubin and GGT.
  - Pt # 5111 had SGOT 4 x ULN, SGPT 7 x ULN, elevated total cholesterol and normal total bilirubin and GGT.

D. Primary Efficacy Results

The primary efficacy variable in open label canakinumab Study A2102 was the *time (from each dose administration) to relapse.* The primary efficacy response included, if no relapse, time to the end of the period (days from treatment), *relapse* (yes or no) and *complete response*, and two definitions of *partial response* (yes or no). In Stage 1, all four (4) patients achieved *complete response* following canakinumab 10 mg/kg iv or 1 mg/kg iv by 2 to 7 days from dosing. None of these patients required rescue treatment.

Following the first sc dose of 150 mg canakinumab, 28 of 29 patients (97%) achieved a *complete response* assessed within 2 to 9 days from dosing. One adult patient with MWS only achieved a *partial response* and required rescue canakinumab with 5 mg/kg iv canakinumab.

In subsequent long term periods, the clinical response to treatment remained comparable to the first period. Twenty-four (24) patients (83%) achieved a *complete response* after every dose of canakinumab 150 mg sc. Out of 96 periods of canakinumab 150 mg sc, rescue treatment was administered in 5 occasions in 4 patients (see **Table 77**).

The pediatric patients were analyzed separately to assess the weight based dosing and complete response. All 5 pediatric patients (receiving 2 mg/kg canakinumab treatment) achieved *complete response* within 2 to 8 days from first dosing. Two (2) patients (ages 7 years and 4 years, both with the same mutation V198M), who responded at Day 2, experienced a rapid loss of response within one week from dosing and required rescue treatment, after which they achieved *complete response*. In the subsequent long term periods, 3 pediatric patients achieved *complete response* after every injection of 2 mg/kg sc canakinumab, although in isolated instances *complete response* was achieved after Day 8. Out of 22 long term periods (2 mg/kg sc canakinumab), rescue treatment was administered in 11 occasions (2 patients). Patient # 5108 (MWS) needed regular rescue treatment after each injection. Patient # 5123 (MWS) needed a rescue i.v. treatment three times during the study.

Table 77.

Summary of Partial (revised definition) **and Complete Response** (1st period)				
Dose Regimen	**N**	**No Response n (%)**	**Partial but not Complete Response**	**Complete Response**
10 mg/kg iv	4	0	0	4 (100%)
1 mg/kg iv	4	0	0	4 (100%)
150 mg sc	29	0	1 (3%)	28 (97%)
2 mg/kg sc	5	0	0	5 (100%)
Rescue iv *	6	0	1 (17%)	4 (67%)
Summary of Partial (revised definition) **and Complete Response** (all periods)				
10 mg/kg iv	4	0	0	4 (100%)
1 mg/kg iv	4	0	0	4 (100%)
150 mg sc	29	3 (10%)	2 (7%)	24 (83%)
2 mg/kg sc	5	3 (60%)	1 (20%)	1 (20%)
Rescue iv *	6	3 (50%)	0	3 (50%)
* Canakinumab rescue medication at doses of either 5 mg/kg or 10 mg/kg.				

D. Primary Efficacy Results (Continued)

Time to Relapse

To explore *complete response* to canakinumab, *time to relapse* in the *1st period* and *all periods,* i.e., longer term data, were analyzed. The proposed canakinumab dose of 150 mg sc demonstrated a median *time to relapse* of 115 days. The canakinumab dose 10 mg/kg iv demonstrated a longer median *time to relapse* (168 days) than canakinumab 1 mg/kg iv (82 days, median *time to relapse*). The proposed canakinumab dose of 150 mg sc demonstrated median *time to relapse* in between these two iv dose regimen. Similar median *times to relapse* were observed in the 150 mg sc and in the 150 mg + rescue iv dose regimens (see **Table 78**). The results with canakinumab 150 mg sc suggest that the proposed dosing interval of every 8 weeks is adequate to maintain disease response in adult patients.

Pediatric patients were analyzed separately to explore the proposed weight based dosing with body weight ≥ 15 kg to < 40 kg. The estimated *time to relapse* following canakinumab (2 mg/kg sc) in 5 pediatric patients was 49 days. *Time to relapse* was a shorter duration in pediatric patients compared to adult patients (see **Table 78**). One concern with the proposed weight based dosing was the risk of under dosing smaller weight patients and, subsequently, potentially observing less favorable clinical outcomes in smaller weight patients treated with canakinumab. Pediatric patients treated with weight based dosing demonstrated *complete response* comparable to adult patients treated with a fixed dose of canakinumab. Longer term follow up data in Study D2306 supported the longer term treatment effect of canakinumab in pediatric patients, treated with a weight based canakinumab dose regimen, compared to adult patients treated with a fixed dose canakinumab regimen.

Table 78.

Primary Analysis - Median Time to Relapse by Dose Regimen - Study A2102 (Weibull Analysis, Safety Population)				
Dose Regimen	# Pts who received dose regimen	# Periods	Median Time-to-Relapse (days)	95% CI
10 mg/kg iv	4	4	156	(103, 210)
1 mg/kg iv	4	4	73	(48, 98)
150 mg sc	29	96	115	(94, 136)
150 mg sc + rescue iv	4	5	175	(91, 259)
2 mg/kg sc	4	22	49	(29, 68)
2 mg/kg sc + rescue iv	2	11	52	(27, 77)

Adapted from Sponsor Table 11-3, page 86 of 10679

E. Secondary Efficacy Results

1. Time-to-Relapse in Subpopulations

To explore the effect of canakinumab treatment in CAPS disease, subgroup analyses were performed (see **Table 79**). Noteworthy, patients with FCAS had a longer *time-to-relapse* than did patients with MWS or MWS overlap with NOMID. FCAS is the mildest form of the CAPS disease spectrum which may, in part, explain the longer duration of *time to relapse* with FCAS compared to MWS and MWS overlap NOMID.

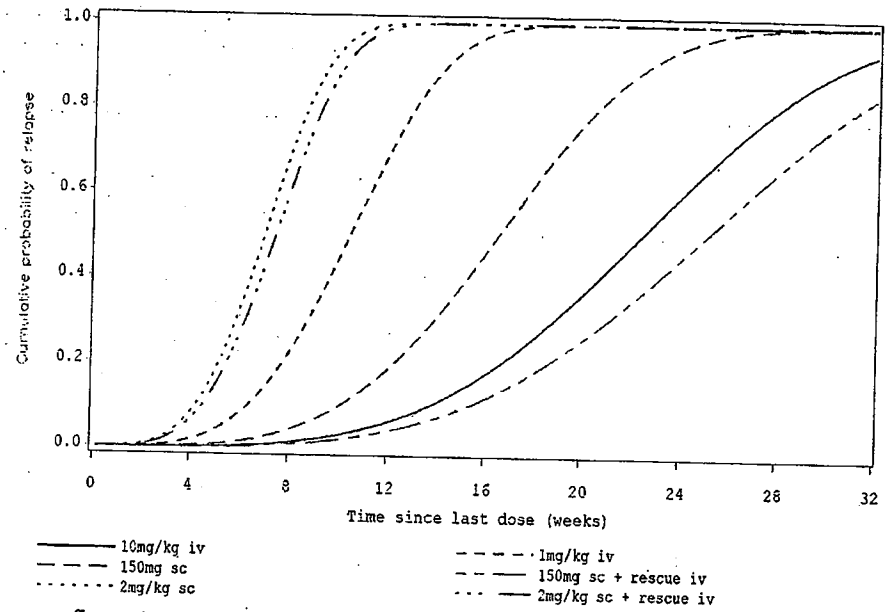
Table 79.

Secondary Analysis - Time to Relapse Study A2102 (Weibull Analysis, Safety Population)						
Variable	Category	# Pts	# Periods	Median Time-to-Relapse (days)	95% CI	p-value (vs null)
None		29	96	119	(95, 142)	
Previous ACZ885?	Yes	25	73	118	(92, 143)	0.82
	No	23	23		(93, 148)	
Previous Anakinra?	Yes	20	69	108	(83, 133)	0.17
	No	9	27	142	(95, 189)	
Clinical Picture	MWS	22	76	120	(94, 146)	0.29
	FCAS	2	2	189	(32, 346)	
	MWS/NOMID	5	18	95	(56, 134)	
Gender	Female	19	64	120	(90, 149)	0.918
	Male	10	32	118	(79, 156)	
Estimates represent the median time-to-relapse for a typical patient. These secondary analyses are based on patients who received the proposed dose of ACZ885 150 mg sc.						

2. Population Cumulative Probability Results

The population cumulative probability plot of *time to relapse,* by dose group, supported the primary efficacy variable and the treatment effect with canakinumab at the proposed dose of 150 mg sc (see **Figure 12**). The shortest time since the last dose (*time to relapse*) was observed with canakinumab 2 mg/kg sc and 2 mg/kg sc + rescue iv, the two farthest dotted lines to the left in **Figure 12**. The doses wit the most prolonged responses (longest time to relapse) were the 10 mg/kg iv and the 150 mg sc + rescue iv groups, followed by the 150 mg sc, the dose proposed for marketing. The shorter *time to relapse* with 2 mg/kg sc and 2 mg/kg sc + rescue iv raises concerns about the optimum frequency in smaller weight patients administered canakinumab as weight based dosing. The pediatric patient population demonstrated similar rates of *complete response* with weight based dosing compared to adult patients' *complete response* with a fixed dose regimen. The dosing interval of canakinumab every 8 weeks appears to be adequate with the weight based dose and the fixed dose regimen based on the results from Study D2306, which include longer term extension data with *complete response* and *time to relapse.*

Figure 12.



Sponsor figure 11-1, page 86 of 10679

3. Serum Protein Markers of Inflammation, CRP and SAA

To explore the effect of canakinumab treatment on objective markers of inflammation in patients with CAPS disease, CRP and SAA were assessed in this open label trial. Across all treatment groups, iv and or sc administration, CRP and or SAA levels decreased to normal levels (< 10 mg/L) within one week after canakinumab administration and remained within normal limits for the duration of this trial. CRP and SAA levels slowly increased towards the end of the treatment period regardless of the route of administration, however, CRP and SAA did not return to peak levels observed at baseline in the majority of dose regimens (see **Tables 80** and **81**). These data

support the primary efficacy variable and the duration of the treatment effect of canakinumab at the proposed dose of 150 mg sc.

Table 80.

CRP Concentration (mg/L) by Dose Regimen - Study A2102							
Time Point		N = 34	10 mg/kg iv N = 4	1 mg/kg iv N = 4	150 mg sc N = 29	2 mg/kg sc N = 5	Rescue iv N = 6
	1st baseline	22					
1st period only	1 Day Post-Dose		47	13	21	4	1
	1 Week Post-Dose		3	4	2	1	1
	5 Weeks Post-dose		2	7	3	1	1
	End of Period		26	27	11	5	3
All periods averaged	1 Day Post-Dose		47	13	14	3	1
	1 Week Post-Dose		3	4	3	1	2
	5 Weeks Post-dose		2	7	4	1	3
	End of Period		26	27	10	3	1

Adapted from sponsor Table 1-15, page 88 of 10679; geometric mean (CV) presented. Rescue iv dosing regimen is a dose of either 5 mg/kg or 10 mg/kg. Source Tables 14.2-2.1.1 and 14.2-2.1.2

Table 81.

SAA Concentration (mg/L) by Dose Regimen - Study A2102							
Time Point		N = 34	10 mg/kg iv N = 4	1 mg/kg iv N = 4	150 mg sc N = 29	2 mg/kg sc N = 5	Rescue iv N = 6
	1st baseline	53					
1st period only	1 Day Post-Dose		175	39	54	10	3
	1 Week Post-Dose		3	10	4	1	3
	5 Weeks Post-dose		4	11	7	2	4
	End of Period		103	92	25	14	4
All periods averaged	1 Day Post-Dose		175	39	33	12	4
	1 Week Post-Dose		3	10	5	3	4
	5 Weeks Post-dose		4	11	7	2	9
	End of Period		103	92	22	10	5

Adapted from sponsor Table 1-15, page 88 of 10679; geometric mean (CV) presented. Rescue iv dosing regimen is a dose of either 5 mg/kg or 10 mg/kg. Source Tables 14.2-2.1.1 and 14.2-2.1.2

4. Assessment of Disease Symptoms

The analyses of individual disease assessments in this open label study all showed clinically meaningful improvement and supported the primary efficacy analysis as measured by *complete response* and *time to relapse*. In Stage 1, the Physician's Global assessment of disease activity was scored predominantly (83% of patients) as *moderate* or *severe* at baseline. This assessment demonstrated rapid improvement with scores from *minimal* to *absent* at 1 Day after dosing and *absent* in all 4 patients at 1 Week after dosing in the 10 mg/kg and 1 mg/kg group. After the first dose of 150 mg canakinumab sc, the Physician's Global assessment of disease activity was scored as *absent* or *minimal* in 27 of 29 patients after 1 week (see **Table 82**). In one patient on Day 8, this assessment was missing, however, the Physician's Global assessment of disease activity for this patient was scored as *absent* on Day 3 and Day 15.

Pediatric patients received weight based dosing with canakinumab (2 mg/kg sc). All pediatric patients had a Physician's Global assessment of disease activity scored as *moderate* at baseline

with improvement to *absent* or *minimal* within Day 1 post the first dose. In subsequent periods, the Physician's Global assessment of disease activity was comparable to the *1st period* demonstrating *complete response* was achieved within 1 week after a dose of canakinumab at the proposed dose of 150 mg sc or 2 mg/kg sc in the majority of patients.

Table 82.

Summary of Physician's Global Assessmentof Disese Activity (*1st dose period per dosing regimen only*) Study A2102							
			n (%)				
	N	Time-Point	Absent	Minimal	Mild	Moderate	Severe
All Patients	34	First baseline	0	4 (11,76%)	9 (26, 47%)	15 (44, 12%)	5 (14, 71%)
10 mg/kg iv	4	1 Day Post-dose	3 (75%)	1 (25%)	0	0	0
	4	1 Week Post-Dose	4 (100%)	0	0	0	0
	4	5 Weeks Post-Dose	3 (75%)	1 (25%)	0	0	0
	4	End of Period	0	0	0	2 (50%)	0
1 mg/kg iv	4	1 Day Post-dose	1 (25%)	3 (75%)	0	0	0
	4	1 Week Post-Dose	4 (100%)	0	0	0	0
	4	5 Weeks Post-Dose	2 (50%)	0	0	0	0
	4	End of Period	1 (25%)	0	2 (50%)	1 (25%)	0
150 mg sc	29	1 Day Post-dose	9 (31%)	14 (48%)	6 (21%)	0	0
	29	1 Week Post-Dose	21 (72%)	6 (21%)	0	1 (3%)	0
	29	5 Weeks Post-Dose	16 (55%)	8 (28%)	1 (3%)	0	0
	29	End of Period	1 (3%)	0	4 (13%)	21 (72%)	1 (3%)
2 mg/kg sc	5	1 Day Post-dose	4 (80%)	1 (20%)	0	0	0
	5	1 Week Post-Dose	2 (40%)	1 (20%)	1 (20%)	1 (20%)	0
	5	5 Weeks Post-Dose	3 (60%)	0	0	0	0
	5	End of Period	0	1 (20%)	0	3 (60%)	0
Recue iv	6	1 Day Post-dose	1 (17%)	3 (50%)	1 (17%)	0	0
	6	1 Week Post-Dose	4 (67%)	0	1 (17%)	1 (17%)	0
	6	5 Weeks Post-Dose	2 (33%)	2 (33%)	2 (33%)	0	0
	6	End of Period	0	0	3 (50%)	2 (33%)	0

Adapted from Sponsor Table 14.2-3.1, page 156 of 10679

Study A2102 also assessed the response of skin disease to canakinumab. At baseline, the majority of patients had active skin disease scored as *mild, moderate* or *severe.* With the proposed canakinumab dose regimen, 150 mg sc and or 2 mg/kg sc, all subsets scored *absent* for skin disease at one week. These data supported the primary efficacy analysis and the canakinumab treatment effect in patients with CAPS disease. At the end of the period, scores for skin disease worsened with assessments of *mild, moderate* and *severe* consistent with a loss of canakinumab treatment effect (see **Table 83**).

Table 83.

Summary of Skin Disease (*1st dose period per dosing regimen only*) Study A2102							
			n (%)				
	N	Time-Point	Absent	Minimal	Mild	Moderate	Severe
All Patients	34	First baseline	5 (15%)	7 (21%)	10 (29%)	8 (24%)	3 (9%)
10 mg/kg iv	4	1 Day Post-dose	3 (75%)	1 (25%)	0	0	0
	4	1 Week Post-Dose	4 (100%)	0	0	0	0
	4	5 Weeks Post-Dose	3 (75%)	1 (25%)	0	0	0
	4	End of Period	0	0	2 (50%)	2 (50%)	0
1 mg/kg iv	4	1 Day Post-dose	2 (50%)	2 (50%)	0	0	0
	4	1 Week Post-Dose	4 (100%)	0	0	0	0
	4	5 Weeks Post-Dose	2 (50%)	0	0	0	0
	4	End of Period	1 (25%)	1 (25%)	1 (25%)	1 (25%)	0
150 mg sc	29	1 Day Post-dose	21 (72%)	6 (21%)	2 (7%)	0	0
	29	1 Week Post-Dose	25 (86%)	3 (10%)	0	0	0
	29	5 Weeks Post-Dose	22 (76%)	3 (10%)	0	0	0
	29	End of Period	8 (28%)	6 (21%)	6 (21%)	5 (17%)	2 (7%)
2 mg/kg sc	5	1 Day Post-dose	4 (80%)	1 (20%)	0	0	0
	5	1 Week Post-Dose	4 (80%)	1 (20%)	0	0	0
	5	5 Weeks Post-Dose	3 (60%)	0	0	0	0
	5	End of Period	3 (60%)	1 (20%)	0	0	0
Recue iv	6	1 Day Post-dose	4 (67%)	1 (17%)	0	0	0
	6	1 Week Post-Dose	6 (100%)	0	0	0	0
	6	5 Weeks Post-Dose	6 (100%)	0	0	0	0
	6	End of Period	3 (50%)	1 (17%)	0	0	0

Adapted from Sponsor Table 14.2-3.1, page 157 of 10679

5. Special Assessments

Special assessments including audiogram, neurological and ophthalmological assessments, and MRI of the brain, were completed in this open label trial. The 12-month follow up audiogram data were incomplete and too small to reach any definitive conclusions. Five of 17 patients diagnosed with abnormal baseline audiogram assessment, shifted from *clinically significant abnormal* to *clinically insignificant abnormality* at 12-months follow-up. Nine patients (9) demonstrated no change. One adult MWS patient worsened from *clinically insignificant abnormality* to *clinically significant abnormality*, specifically, worsening bilateral high frequency sensorineural hearing loss. The follow up data for neurological, ophthalmological and MRI assessments were too small to reach any meaningful conclusions.

6. Renal Function Assessments

CAPS disease, particularly, MWS and MWS which overlaps with NOMID, may be associated with renal function impairment. Four (4) patients enrolled in Study A2102 had baseline renal insufficiency: Patients # 5118, # 5132, # 5135, had moderate renal insufficiency; and Patient # 5136 had severe renal insufficiency. Renal function remained unchanged in two patients and minimally decreased in the other two patients. Two other patients (Patients # 5122 and # 5199) had renal amyloidosis without abnormal glomerular filtration rate at baseline. No meaningful changes of improvement or worsening in renal function were observed by the end of this trial.

7. Quality of Life Assessments

Health-related quality of life assessments (HRQoL) were completed in this trial. Nineteen (19) of 27 adult patients (70%) completed the HAQ-DI, FACIT-F and SF-36 assessments, and 6 of 7 pediatric patients (86%) completed the CHQ-CH87 questionnaire. Ten of 19 (53%) adult patients

reported HAQ-DI scores from 0.125 to 2.5 (maximum score of 3 indicates severe loss of function). A positive trend toward improvement was demonstrated in the *1st period* and in *all periods averaged* with the proposed canakinumab dose 150 mg sc dose regimen in the first 5 weeks post-dose. A worsening trend was observed toward the end of the treatment period. A trend of improvement followed by later worsening was demonstrated with FACIT-F and SF-36 (PCS and MCS). In general, the HRQoL assessments trend with some early improvement in adult patients.

Low CHQ-CH87 scores in pediatric patients were demonstrated in bodily pain and general health perceptions. Due to different canakinumab doses administered to 6 pediatric patients, the database for CHQ-CH87 was too small to reach a meaningful interpretation.

F. Other Assessments

1. Immunogenicity Results
No patients demonstrated a treatment induced immune response to canakinumab regardless of the dose regimen. Serum samples were analyzed from 34 patients (383 samples). One-hundred and twenty-two (122) serum samples from 19 patients were above the negative cutoff point. Based on the confirmatory assay, no sample demonstrated ≥ 30% decreased signal when incubated with canakinumab. These results supported the lack of induced immune response observed in pivotal Study D2304.

2. Drug Concentration and PK /Clinical Response in Study A2102, Phase 1/2a
Study A2102 included the dose-finding phase 1/2a for canakinumab in CAPS disease. Following the initial sc injection of 150 mg canakinumab in adult patients, peak serum levels were reached at ~7 days (median) with maximum serum concentrations were ~15.9 (± 3.52) μg/mL. The apparent half-life following a single 150 mg sc dose was 26.1 (±7.31) days which was consistent with the PK properties of a typical IgG molecule. Inter-subject variability with a coefficient of variation of ~22% and 29% was observed in C_{max} and AUC_∞ values. Correcting for bio-availability of ~67%, the PK of canakinumab was consistent with the expected PK characteristics of a human IgG molecule. See the Clinical Pharmacology review by Srikanth Nallani, PhD and Hao Zhu, PhD.

3. Pediatric Patients and PK Assessments in Study A2102, Phase 1/2a
Pediatric patients were only enrolled in Stage 2 of Study A2102. PK inference using non-compartmental analysis could not be drawn from 2 patients (# 5108, # 5123) as the duration of PK assessment from their first sc dose was very short (≤ 10 days). Peak concentrations of canakinumab were between 2 to 7 days following sc 150 mg or 2 mg/kg sc. The apparent half-lives ranged from 23 to 26 days, consistent with the PK properties observed 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. For the only two pediatric patients administered the 2 mg/kg sc dose, the clearance was consistent with the smaller body weight of pediatric patients. See the Clinical Pharmacology review by Srikanth Nallani, PhD and Hao Zhu, PhD.

4. Serum Soluble Biomarkers

The effect of canakinumab administration at 10 mg/kg iv and 1 mg/kg iv on serum TNF-α, IL-6, IL-1Ra, sIL-1R and sCTX, as measured by ELISA, was assessed in this open label trial. Only partial data were reported. A rapid decrease in the geometric mean IL-6 level was reported from 27 pg/mL, pre-dose, to 6.5 pg/mL at 24 hours, post 10 mg/kg dose, and to 5.6 pg/mL, post 1 mg/kg dose, respectively, with maintenance of this lower level through the response period. Geometric mean levels of serum IL-1Ra decreased from 639.5 pg/mL, pre-dose to 452.0 pg/mL at 24 hours, post 10 mg/kg dose, with maintenance of this lower level through the response period. A comparable decrease was observed following the 1 mg/kg dose. Serum levels of TNF-α, sIL-1R and sCTX were not affected following canakinumab treatment. Total IL-1β data was not reported in this trial due to lack of sensitivity and reproducibility between batches in the multiplex panel assay.

IV. Discussion of Efficacy Findings and Conclusions

Study A2102 was conducted in accordance with the protocol under IND 100,040. There were 8 protocol amendments as noted in the sections where they apply.

All CAPS diseases were represented in this study population. The majority of patients had co-morbidities typical of active CAPS diseases and had received anakinra or other therapies with unsatisfactory improvement in their disease.

Among 34 patients enrolled, over 85% of patients completed this study and three (3) patients discontinued this study. Only one patient was discontinued due to an AE, unplanned pregnancy. The primary efficacy variable was the *time (from each dose administered) to relapse*. Following the first canakinumab dose of 150 mg sc, 28 of 29 patients (97%) achieved *complete response* assessed within 2 to 9 days from dosing. In subsequent longer term periods, 24 patients (83%) achieved *complete response* after every canakinumab 150 mg sc dose. The results in longer term treatment periods with canakinumab remained comparable to those observed in the one week, 1st period. The rate that the pediatric patient population demonstrated *complete response* was comparable to adult patients treated with the fixed dose regimen. The results from the proposed weight based dose regimen (2 mg/kg sc) and the fixed dose regimen (150 mg sc) suggest that the proposed dosing interval of every 8 weeks is adequate to maintain disease response in adult and pediatric patients with CAPS disease.

The analyses of individual disease assessments in this trial all showed clinically meaningful improvement and supported the primary efficacy analysis. In Stage 1, the Physician Global assessment of disease activity was scored predominantly (83%) of patients) as *moderate* or *severe* at baseline. This assessment demonstrated rapid improvement with scores from *minimal* to *absent* at 1 Day after dosing and absent in all 4 patients at 1 week after dosing in the 10 mg/kg and 1 mg/kg group. After the first dose of canakinumab 150 mg sc, the Physician's Global assessment of disease activity was scored as *absent* or *minimal* in 27 of 29 patients after 1 week. Therefore, after the first canakinumab dose, improvement in this same measure at 1 week was consistent with the fixed dose (150 mg sc) and the weight based dose (2 mg/kg sc) groups. In subsequent treatment periods, improvement in the Physician's Global assessment of disease activity was comparable to that observed in the *1st period* with a *complete response* achieved by

the majority of patients within 1 week after receiving either 150 mg sc or 2 mg/kg sc canakinumab dose.

Study A2102 also assessed the response of skin disease to canakinumab. With the proposed canakinumab dose regimens, 150 mg sc and 2 mg/kg sc, all subsets demonstrated improvement in skin disease at the 1 week time point. By the end of the treatment period, scores worsened as a result of the loss of canakinumab treatment effect. Overall, the analyses of individual disease assessments supported the primary efficacy analyses and the treatment effect of canakinumab.

Additional support for clinical evidence of canakinumab efficacy in CAPS comes from data collected for special assessments. Some improvement in patient's hearing was observed at the 12-month follow up compared to baseline audiogram; however, no trends were observed in neurological and ophthalmological assessments, or in MRI of the brain assessments as these data were limited. There were limited numbers of completed assessments.

To explore the effect of canakinumab treatment on objective markers of inflammation in patients with CAPS disease, CRP and/or SAA were assessed in this trial. Across all treatment groups and routes of administration, CRP and/or SAA levels decreased to normal levels (< 10 mg/L) within one week post canakinumab administration and remained within normal limits for the duration of this trial. CRP and/or SAA levels slowly increased towards the end of the treatment period and did not return to peak levels observed at baseline in the majority of patients. These data supported the primary efficacy variable and the duration of the treatment effect of canakinumab at the proposed dose regimen.

In general, the HRQoL trended with some improvement in adult patients and worsening toward the end of the treatment period. Due to different canakinumab doses administered to 6 pediatric patients, the database for the CHQ-CH87 was too small to reach conclusions. The adult data for HRQoL supported the primary efficacy variable and the treatment effect with canakinumab. Since these HRQoL assessments are open label and prone to bias, they should not be included in labeling.

In conclusion, the treatment with the proposed canakinumab fixed dose regimen and weight-based dose regimen every 8 weeks achieved *complete response* in adult and pediatric CAPS patients in Study A2102 and supported the treatment effect of canakinumab in patients with CAPS diseases.

V. Safety Analysis and Summary
The safety analyses and conclusions from Study A2102 are reported in Section 7 of this clinical review.

Study D2306

The following description of this Phase 3 protocol for ongoing Study D2306 is based upon the original protocolACZ885D2306 (04Jan2008). The interim analysis data cut-off was 12Sep2008

and the study report was 29October2008. Study D2306 was amended once and is noted in the section where this amendment applies.

I. Protocol

A. Title

An open-label, long-term safety and efficacy study of ACZ885 (anti-interleukin-1β monoclonal antibody) administered for at least 6 months in patients with Cryopyrin Associated Periodic Syndromes: Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or Muckle-Wells Syndrome with overlapping symptoms of Neonatal Onset Multisystem Inflammatory Disease

B. Objectives

1. Primary Objective

a. To assess the long-term safety and tolerability of canakinumab in patients who participated in Study A2102 or D2304 or in canakinumab naïve patients with CAPS diseases: FCAS, MWS or MWS with overlap NOMID.

2. Secondary Objectives

a. To assess the maintenance of response over time defined by the number of patients who did not relapse as determined by the Physician's Global assessment of auto-inflammatory disease activity, assessment of skin disease and serum inflammatory markers, CRP and/or SAA,
b. To assess the number of patients who required a dose adjustment or an administration frequency adjustment with subsequent maintenance of response over-time determined by the Physician's Global assessment of autoinflammatory disease activity, assessment of skin disease, and CRP and/or SAA,
c. To assess the immunogenicity of canakinumab,
d. To assess PK of canakinumab, particularly, comparison of the new without human serum albumin (HAS) drug formulation with the previously used HAS+ formulation.
e. To assess long-term effects of canakinumab on disease progression with regards to deafness, kidney function, neurological and ophthalmological signs and symptoms, and
f. To assess long term maintenance of health-related quality of life of canakinumab by using the HAQ, SF-36, FACIT-F, and CHQ-PF28.

C. Study Design

Study D2306 was a non-randomized, open label, single treatment group, long-term safety, tolerability and efficacy Phase 3 clinical trial of canakinumab in patients with FCAS, MWS and MWS overlap with NOMID requiring therapeutic intervention. The study design of this open label trial is presented in **Table 84.** New patients and patients who rolled over from Study A2102 or D2304 were to have received canakinumab sc injections every 8 weeks. Patients not experiencing sufficient symptomatic relief from this canakinumab dosing regimen were to have been offered an alternative canakinumab dose regimen based upon the clinical investigator's

judgment and prior consultation with the applicant. An end of study visit would occur at 8 weeks, +/- 1 week, after the last sc canakinumab injection.

Table 84. Study Design

Study Period	Screening		Open-label treatment period															End of Study[2]
Visit	1	1.1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16[2]	777*
Week			0	1	4	8	16	24	32	40	48	56	64	72	80	88	96	104
Day (The visit window was +/- 7 days for all visits after screening except Visit 3 which was +/- 1 day)	-15 to -2		1	8	29	57	113	169	225	281	337	393	449	505	561	617	673	729
Administration of medication[1]			X			X	X	X	X	X	X	X	X	X	X	X	X	

Treatment: one s.c. injection of canakinumab every 8 weeks (please see the Section 4 and Section 6 of the Protocol (Appendix 16.1.1).

[1] Dosing was to occur in the morning in order to coordinate sample collection times for pharmacokinetics (PK) and pharmacodynamics (PD). All PK and PD samples were to be collected prior to dosing. Please also note that dosing according to the visit schedule above is every 8 weeks, however, some patients required an up-titration in dosing. For these patients, an unscheduled visit was necessary to determine if the patient was responding to treatment and to provide rescue medication (please refer to Section 4 and Section 6.5.7 of the Protocol, Appendix 16.1.1). Even for patients who were up-titrated, the visit schedule was to be according to when the patients received their first dose of study medication. Once the patient was administered rescue medication, telephone contact with the patient was necessary to determine if the patient was responding to treatment.

[2] Depending on when patients enter this study, additional visits (past Visit 16) may be required to ensure that the patient continues receiving treatment until the study is closed. Therefore, the End of Study Visit may not occur at Week 104 for all patients.

* End of Study (EOS) or in the event of premature termination. This visit was to occur 8 weeks (±1 week) after the last injection.

Sponsor Figure 9-1, page 29 of 1247, Study D2306.

1. Duration

The duration of Study D2306 was to have been a minimum of 6 months and a maximum of 2 years.

2. Study Population

Selection of Patients, Sample Size and Power Calculations

This study was to have included CAPS diseases: FCAS, MWS, or MWS overlap NOMID. The number of planned patients was to have been approximately 80 patients. The final number of patients was to have depended on the number of patients from Study A2102 and D2304, and the number of canakinumab naïve patients who would have enrolled in this study. No formal sample size calculations were to have been performed because only descriptive statistics were planned in this non-controlled study design. No power calculations were planned in this open label study.

Canakinumab Naïve Patients

Patients not previously enrolled in Study A2102 or D2304 were to have had their response to treatment determined at Day 8 to identify canakinumab responders. *Complete response* to treatment was to have been assessed at Day 8 and, subsequently:

a. Patients who were *complete responders* at Day 8 would have continued in this study;
b. Patients who did not achieve *complete response* by Day 8 could have received a canakinumab dose adjustment on Day 8 or earlier, if needed on Day 3 at an unscheduled visit. This canakinumab treatment approach was completed by up-titration.
c. Patients who were *complete responders* on Day 15 (unscheduled visit) following their dose adjustment were continued in this study with the adjusted dose, and

d. Very few patients might not have achieved *complete response* by Day 15, following their initial dose adjustment. These patients would have received a second up-titration regimen if they had not experienced adequate symptomatic relief by Day 15.
e. Study sites were to have contacted the applicant for any patient who had not clinically responded after the second up-titration.

3. Inclusion Criteria
The inclusion and Exclusion Criteria in Study D2306 are similar to those previously reported in Study A2102. Only those eligibility criteria which are different in Study D2036 will be listed below:

Patients eligible to have entered Study D2306 would fulfill the following criteria:
a. Male/female, age ≥ 4 years at screening; and body weight ≥ 15 kg.
b. Patients with a diagnosis of FCAS, MWS, or MWS with overlapping symptoms of NOMID. Severe MWS patients, including central nervous system (CNS) symptoms, could have been included only with prior agreement from the applicant.
c. Patients from Study A2102 could enter this study upon signing informed consent irrespective of whether they were in remission or flaring. However, dosing at Visit 2 (baseline Visit) could only occur if either

1) The patient was experiencing disease flare or
2) at least two months had elapsed from their last canakinumab injection even in the absence of flare, whichever was earlier.

d. Patients who completed Study D2304 could have entered this study, if he/she would have completed the Study D2304 follow-up to and including Visit 15 (End of Study Visit).
e. Patients who discontinued from the Studies A2102 or D2304 and for whom continued treatment with canakinumab was considered appropriate.

4. Exclusion Criteria
Patients who met the following criteria were excluded from this study:
a. Participation in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation with the exception of trials with anakinra, other investigational IL-1 blocking therapies, and/or canakinumab.
b. History of being immunocompromised, including a positive HIV at screening (ELISA and Western blot) test result.
c. Positive HBsAg or Hepatitis C antibody test result.
d. Live vaccinations within 3 months prior to start of this trial, during the trial, and up to 3 months following the last dose.
e. Positive tuberculin skin test reaction – purified protein derivative (PPD) 5 tuberculin units or according to local standard practice (≥ 5 mm induration) at 48 to 72 hours after administration at the screening visit or within 2 months prior to the screening visit, according to national guidelines. Patients with a positive PPD skin test with documentation of Bacillus Calmette-Guérin (BCG) vaccination, who were at low environmental risk for TB infection or reactivation, and had a negative chest x-ray could be included. A positive PPD test was defined by the MMWR 2000 guidance / summarized as criteria for tuberculin positivity by risk group:

1. ≥ 15 mm of induration for persons with no risk factors for TB

2. ≥ 10 mm of induration for persons with an increased probability of recent infection or with other clinical conditions that increased the risk for TB
3. ≥ 5 mm of induration for very high risk population (HIV), contact TB cases, immune-suppression (organ transplantation, steroids > 15 mg/day of prednisone for ≥1 month).

5. Study Treatments

This is an open label, single canakinumab treatment arm study. The canakinumab dosing regimen used in Study D2304 was to be used for Study D2306. Patients with body weight > 40 kg were to have received 150 mg sc of canakinumab per each injection. Patients with body weight ≥ 15 kg and ≤ 40 kg were to have received an equivalent of 2 mg/kg sc of canakinumab per each injection.

Formulation in Study D2306

This study was to have employed a new formulation of canakinumab which was to have been produced with the same cell line as in the pivotal Phase 3 Study D2304; however, with human serum albumin and transferrin removed from the medium (referred to as "HAS-").

Canakinumab Dose Adjustments Including Up-Titration

When the applicant expanded enrollment from different countries, it was observed that not all patients fully responded to a fixed dose of 150 mg sc canakinumab but some patients appeared to respond to higher doses of canakinumab (up-titration). Plasma samples were analyzed for canakinumab concentration and were fitted with the PK model. Some patients required higher canakinumab concentrations than 1μg/mL to maintain sufficient clinical response to avoid relapse.

For patients who would have entered from Study D2304 study who had a shortened dosing frequency or for patients who entered from Study A2102 for whom it was known that additional study medication would be required on Day 1, these patients could be administered canakinumab 300 mg s.c. (or 4 mg/kg for patients with a body weight ≥ 15 kg and ≤ 40 kg) on Day 1. All other patients, including canakinumab naïve patients, would have received canakinumab 150 mg sc (or 2 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg) on Day 1. *Complete responders* at Day 8 would continue with the same dosing regimen.

Patients who did not achieve *complete response* by Day 8 could receive a dose adjustment regimen of canakinumab 300 mg s.c. (or 4 mg/kg for patients with a body weight of ≥ 15 kg and ≤ 40 kg) on Day 8 (or earlier if needed on Day 3). Patients who achieved *complete response* on Day 15 following their dose adjustment would have continued in this study with this adjusted dose (canakinumab 300 mg or 4 mg/kg for patients with a body weight ≥ 15 kg and ≤ 40 kg).

Patients who did not achieve *complete response* by Day 15 following their initial dose adjustment could then have received a second up-titration regimen of canakinumab 300 mg sc (or 4 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg) if they did not experience sufficient symptomatic relief by Day 15. Patients who were *complete responders* on Day 15 following their dose adjustment would have continued in this study with this adjusted dose (canakinumab 600 mg or 8 mg/kg for patients with body weight ≥ 15 kg and ≤ 40 kg).

6. Schedule of Events

See **Table 84** in Section C, Study Design, of this Individual Study Report.

7. Protocol Specification for Study Visits

Study D2306 included Screening assessments at Visit 1 with the first administration of sc canakinumab at Visit 2. Subsequent doses would have been administered at Visits 5 through 16, and, potentially, to the end of the maximum study duration, Visit 777/Week 104 (see **Table 84**). The clinical and laboratory safety monitoring was to have been the same as described in Study A2102. As stated earlier, very few patients would not have achieved *complete response* by Day 15 following their initial canakinumab dose adjustment which could have included up-titration. Patients were allowed to remain in this ongoing study up to a maximum of 2 years enrollment per patient.

8. Removal of Patients from Treatment or Assessment

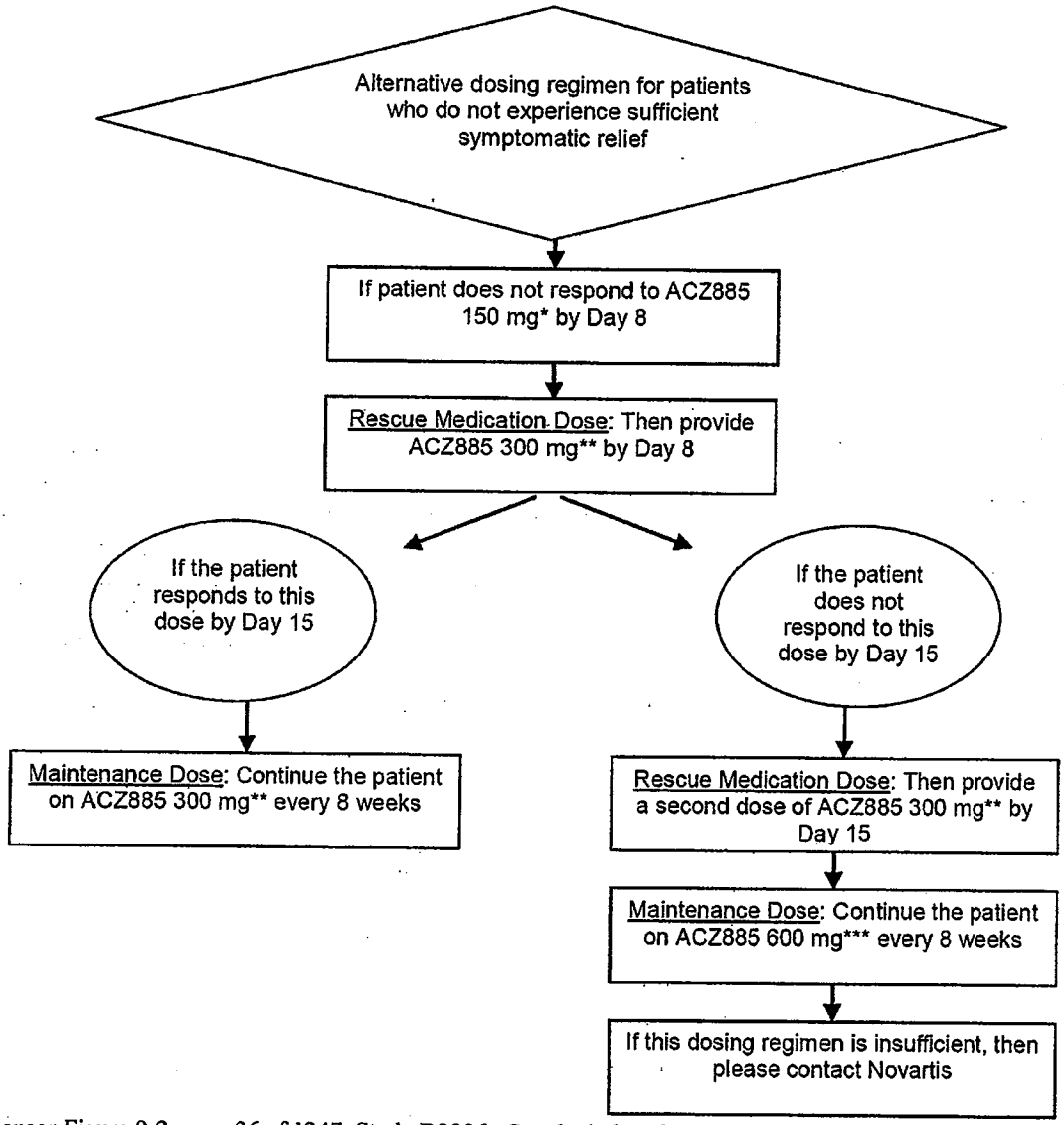
Canakinumab was discontinued for any CAPS patient if the investigator determined that continuing in this study included significant safety risk to the patient. Patients could have been withdrawn from Study D2306 for the following reasons: withdrawal of informed consent; in the case of any severe or serious AE that was not compatible with canakinumab administration, including AEs that required treatment with an unacceptable co-medication, in the case of onset of malignancy; in the case of an uncontrolled life-threatening infection and or pregnancy, and or use of prohibited concomitant medications. If premature withdrawal were to have occurred, the investigator was to have determined the primary reason for withdrawal and have recorded this information in the study eCRF. Due diligence on the part of the investigator was to have been demonstrated for any patient "lost to follow-up".

9. Prior and Concomitant Therapy

Rescue Medication

In order to avoid relapse, rescue canakinumab was to have been allowed during this study. Notification was required with Novartis prior to administering rescue canakinumab treatment to a patient. Telephone contact with the patient was made to determine if the patient was responding to treatment. **Figure 13** outlines the algorithm for the most common dose adjustments derived from modeling and simulation analyses. Other individual canakinumab dose adjustments, e.g., such as increased dosing frequency, required prior consultation with Novartis.

Figure 13. Rescue Medication and alternative Dosing Regimen for Patients who did not experience sufficient symptomatic relief.



Sponsor Figure 9-2, page 36 of 1247, Study D2306. See the below footnotes for Figure x.

For patients entering from the A2102 or D2304 studies on a different dosing regimen other than canakinumab (ACZ885) 150 mg s.c. every 8 weeks, these patients should be administered canakinumab 300 mg s.c. (or 4 mg/kg for patients with a body weight of ≥ 15 kg and ≤ 40 kg) on Day 1. Please consult with Novartis prior to dosing the patient in this study.

The rescue medication scheme above should also be applied to those who previously responded to an every 8 week dosing regimen and who flare in this study prior their next scheduled dose.

* canakinumab 150 mg s.c. for patients whose body weight is > 40 kg (or 2 mg/kg for patients with a body weight of ≥ 15 kg and ≤ 40 kg)

** canakinumab 300 mg s.c. (or 4 mg/kg for patients with a body weight of ≥ 15 kg and ≤ 40 kg)

*** canakinumab 600 mg s.c. (or 8 mg/kg for patients with a body weight of ≥ 15 kg and ≤ 40 kg)

Other Concomitant Medications

Patients were to have remained on their current medications whenever possible for the duration of this trial. All concomitant medications taken during the month prior to Visit 1 and throughout this trial (including physical therapy, blood transfusions, over-the-counter drugs, calcium, vitamins, and DMARDs) were to have been recorded on the Concomitant Medications/Significant Non-Drug Therapy eCRF. The following treatments were not allowed prior to baseline and during this trial:

- Etanercept in the 4 weeks prior to the baseline visit (Day 1) and thereafter;
- Adalimumab in the 8 weeks prior to the baseline visit (Day 1) and thereafter;
- Infliximab in the 12 weeks prior to the baseline visit (Day 1) and thereafter;
- Rituximab in the 26 weeks prior to the baseline visit (Day 1) and thereafter;
- Any other investigational biologics in the 8 weeks prior to the baseline visit (Day 1) and thereafter (with the exception of anakinra therapy – see below);
- Kineret (anakinra therapy) 1 day prior to the baseline visit (Day 1) and thereafter;
- Leflunomide in the 4 weeks prior to the baseline visit (Day 1) and thereafter. After the completion of leflunomide treatment a cholestiramine in dose 8 g 3 times per day for 14 days is recommended;
- Thalidomide in the 4 weeks prior to the baseline visit (Day 1) and thereafter;
- Cyclosporine in the 4 weeks prior to the baseline visit (Day 1) and thereafter;
- i.v. immunoglobulin (i.v. Ig) in the 8 weeks prior to the baseline visit (Day 1) and thereafter;
- 6-Mercaptopurine, azathioprine, cyclophosphamide, or chlorambucil in the 12 weeks prior to the baseline visit (Day 1) and thereafter;
- Dapsone, mycophenolate mofetil in the 3 weeks prior to the baseline visit (Day 1) and thereafter;
- Corticosteroids ≥20mg/day or >0.4 mg/kg, whichever applies, in the 1 week prior to the baseline visit (Day 1) and thereafter;
- Live vaccinations within 3 months prior to the start of the trial, during, and up to 3 months following the last dose; and
- Use of other investigational non-biological drugs at the time of enrollment, within 30 days or 5 half-lives of enrollment, whichever would be longer.

E. Outcome Measures

1. Primary Efficacy Endpoint

Response to Treatment Criteria

The primary objective of this open label trial was to assess the long-term safety and tolerability of canakinumab. The investigator's clinical assessment of disease activity was to have been collected at Visits 2, 5 through Visit 777 (end of the study). Response to treatment (maintained or initial) and evidence of improvement was to have been collected through the investigator's clinical assessment of autoinflammatory disease activity during the clinical observations and laboratory monitoring.

A 5-point scale was used to assess disease activity (ranging from *absent* to *severe*):

- Physician's Global assessment on autoinflammatory disease activity based on the following parameters:
    1. Assessment of skin disease (urticarial skin rash);
    2. Assessment of arthralgia;
    3. Assessment of myalgias;
    4. Assessment of headache/migraine;
    5. Assessment of conjunctivitis;
    6. Assessment of fatigue/malaise;
    7. Assessment of other symptoms related to autoinflammatory syndrome; and
    8. Assessment of symptoms not related to autoinflammatory syndrome.

Response to treatment was to have been defined as follows:

Complete response to treatment was defined as:

- Physician's 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 CRP and/or SAA) (< 10 mg/L).

For *complete responders, relapse* was to have been defined by the following criteria (to be assessed on the same day):

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

AND

- Physician global assessment of autoinflammatory disease activity > *minimal*

OR

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

Partial response to treatment was to have been defined as:

- Absence of *complete response* but a reduction of CRP and/or SAA from baseline by > 30% but not reaching normal values (< 10 mg/L)

AND

- Physician global assessment of autoinflammatory disease activity improvement from baseline by at least one category.

2. Secondary Efficacy Endpoints

The key secondary efficacy variables were to have been included in the assessment of safety, tolerability and immunogenicity of canakinumab. The following secondary efficacy endpoints were to have been analyzed:

- HRQoL

1. SF-36 (PCS and MCS)
2. FACIT-F
3. HAQ-DI
4. CHQ-PF28

F. Statistical Analyses

Populations for Analysis and Sample Size

The safety and efficacy population were to have consisted of all patients who received at least one dose of canakinumab under enrollment in this open label study protocol. Demographic and baseline characteristics were to have been summarized descriptively for the safety population. Continuous variables were to have been summarized by mean, standard deviation, median, minimum, maximum, and the number of patients with non-missing data. Categorical variables were to have been summarized by absolute frequencies and percentages.

There was to have been no minimum requirement in terms of sample size. Study D2306 was to have included eligible patients who would have completed canakinumab Studies A2102 and D2304) or would have been newly identified patients with FCAS, MWS, and MWS with overlapping symptoms of NOMID. Due to the extremely low prevalence (with less than 1 in 1,000,000) in these indications, it was to have been expected that enrollment would have been 60 to 80 patients.

Patient Demographics and Other Baseline Characteristics

Relevant medical history and current medical conditions were to have been listed and summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Previous treatment duration with canakinumab was to have been listed in this open label trial.

Treatments (Canakinumab, Rescue Medication, other Concomitant Therapies)

Exposure to canakinumab (number of injections) and the duration of exposure (in days) was to have been summarized and listed. The number and percentage of patients taking concomitant medication and non-drug therapies was to have been summarized by PT according to the WHO Drug Reference.

Statistical Hypothesis and Method of Analysis

Study D2306 is an open-label single-arm safety trial for patients who were already treated with canakinumab in previous clinical trials (Study A2102 and or D2304) or newly identified patients with FCAS, MWS, or MWS with overlapping symptoms of NOMID. These data were to have been presented in a descriptive manner.

Handling Missing Data/Censoring/Discontinuations

No missing value imputation technique was to have been applied in this open-label, single-arm trial.

Statistical Analysis of Secondary Objectives

A frequency table with number of patients and percentages was to have been presented for patients who would not have relapsed determined by the Physician's Global assessment of

autoinflammatory disease activity, assessment of skin disease and inflammation markers CRP and/or SAA. Kaplan-Meier estimates of the proportion of patients with disease flare, along with the 95% CI intervals using Greenwood's formula was to have been provided. In addition, Kaplan-Meier estimates were to have been plotted against time.

A frequency table with number of patients and percentages was to have been presented for the Physician's Global assessment of autoinflammatory disease activity by time point(s). Frequency tables for the Physician's clinical assessment were to have been presented by visit and to have included the following:

1. Skin disease (urticarial skin rash)
2. Arthralgia
3. Myalgia
4. Headache/migraine
5. Conjunctivitis
6. Fatigue/malaise
7. Other symptoms related to autoinflammatory syndrome
8. Symptoms not related to autoinflammatory syndrome

Summary statistics were to have been provided for CRP and SAA presenting absolute values and change from baseline.

Dose Adjustment
A frequency table was to have been for the number of patients who would have required a dose adjustment or an administration frequency adjustment, with subsequent maintenance of response over time.

Immunogenicity
A frequency table was to have been presented for the number of patients who would have developed immunogenicity.

Long-Term Effect on Disease Progression
For the special assessments, e.g., audiogram, neurological and ophthalmological assessment, the interpretation (*normal, clinically insignificant abnormality, clinically significant abnormality*) were to have been summarized descriptively by shift tables from baseline to each visit. Further specified clinically significant abnormalities were to have been included in the listed data. Data collected from the MRI of the brain were also to have been listed.

Health-Related Quality of Life
Changes in HRQoL were to have been measured using the SF-36, FACIT-F, HAQ-DI and CHQ-PF28. Descriptive analyses were to have been provided.

Interim Analysis
An interim analysis was to have been planned for Study D2306 to have provided supportive data for this submission, particularly, the PK profile of HSA-canakinumab formulation. The interim data cutoff was to have been 12Sept2008.

G. Safety Evaluation

Safety assessments consisted of all AEs and serious AEs with their severity and relationship to canakinumab. To ensure patient safety, every serious AE, regardless of suspected causality, occurring after the patient would have provided informed consent and until 4 weeks after the patient would have stopped this study participation, must have been reported to Novartis within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of an initial SAE must have been reported as follow-up to the original event, regardless of when the event occurred. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported event was to have been reported separately as a new event.

Safety monitoring was to have included the following assessments:

- Physical examination, Hepatitis screen, HIV screen;
- Local tolerability (sc injection);
- Infections;
- Vital signs and body measurements;
- Electrocardiogram (ECG) evaluations;
- PPD skin test;
- Chest X-ray;
- Laboratory evaluations: hematology/blood chemistry/ urinalysis
- Pregnancy and assessment of fertility
- Anti-nuclear antibodies; anti-double-stranded DNA antibodies
- Monitoring of sexual maturation (Tanner Stages)
- Special assessments:
  1. Neurological assessment;
  2. Ophthalmological symptoms;
  3. Audiogram: monitor bilateral sensorineural deafness; and
  4. MRI of the brain: assess meningitis and cellular infiltrates

H. PK and PD Assessments

Serum samples for the PK profile were to have included serum samples for canakinumab concentration. Serum samples for the PD profile were to have also been collected for total IL-1β by means of a competitive ELISA assay.

I. Immunogenicity Assessments

Anti-canakinumab antibodies concentrations were to have been assessed in the serum.

II. Study Conduct

This protocol involved an open-label, single treatment arm, long term safety, tolerability, and efficacy study of canakinumab in patients with FCAS, MWS, or MWS with overlapping NOMID who required therapeutic treatment. This was to have been a multinational study in CAPS diseases. The number of planned patients to be enrolled was estimated to be approximately 80 patients. Noteworthy, recruitment in this study is currently ongoing and the final number of patients will depend on the number of patients entered from Study A2102 and

D2304 and how many new patients are identified. Any new patient and any patient who was rolled over from Study A2102 or D2304 would have received canakinumab as an injection every 8 weeks. For patients who did not experience sufficient symptomatic relief from this dosing regimen, an alternative dosing regimen could be offered to the patient based upon the investigator's judgment and prior consultation with the applicant. This alternative dosing was explained in the Study Treatment section of this individual study report.

The investigator's clinical assessment of disease activity was to have been collected at Visits 2, 5 through Visit 777 (end of the study, see **Table 84** under Study Design). The investigator's clinical assessment of disease activity was to be collected at Visit 3 for canakinumab naïve patients only (e.g., patients who were not enrolled in Studies A2102 or D2304) to identify canakinumab responders. The first patient was enrolled in Study D2306 on 19May2008 and the data cutoff for the interim analysis reported in BLA 125319 was 12September2008.

A. Protocol Amendments
Study D2306 protocol was amended as follows:

Protocol Amendment # 1 (14-Feb-2008) was to have ensured that patients with severe renal insufficiency (GFR < 30 mL/min/1.73 m2) or planned liver transplantation would not have undergone administration of a gadolinium contrast agent for the performance of MRI evaluation. Gadolinium is contraindicated in patients with renal disease due to the risk of developing nephrogenic systemic fibrosis (NSF), a serious adverse reaction that may occur after exposure to the extracellular nonionic low osmolar gadolinium-based contrast agent gadodiamide.

B. Treatment Compliance
Patients in Study D2306 received canakinumab injections during the scheduled visits. Compliance was assured by patient and physician attendance.

C. Protocol Deviations
Protocol deviations were to have been recorded but not analyzed for the interim analysis report (12Sept2008). Protocol deviations will be included in the final analysis report.

III. Results

A. Patient Disposition in Study D2306
At the interim data cutoff (12Sept2008), Study D2306 included 14 centers: France (3), Germany (5), India (1), Spain (1), United Kingdom (1) and USA (3).

A total of 57 patients enrolled in this open label study. One more patient (# ID D2306-0504-00006, 46 year old female) was enrolled but was only in screening at the time of the data cutoff. Among 57 enrolled patients, 46 patients had MWS, 8 patients had FCAS and 3 patients had MWS overlapping NOMID (see **Table 85**).

Patient Discontinuations

One year old female patient with MWS was permanently discontinued from this study due an adverse event of worsening of multiple sclerosis (MS) like lesions, e.g. demyelination considered as a pre-existing condition (see **Table 85**).

Summary of Patient Enrollment in Study D2306 from Study D2304 and A2102
Three (3) patients who discontinued Part 1 of Study D2304, due to unsatisfactory therapeutic effect enrolled in Study D2306 at the time of data cutoff:

- Pt # D2306-0001-00010
- Pt # D2306-0001-00011
- Pt # D2306-0501-00002 (Noteworthy, this patient discontinued Part 1 (Study D2304) on 11November2007 and entered Study D2306 after a substantial time period of 9 months, 12August2008.)

After discontinuation in Part 1 (Study D2304), two (2) patients returned to canakinumab treatment in Study A2102 and then entered Study D2306:

- Pt # D2306-0001-00010
- Pt # D2306-0001-00011

Table 85.

Patient Disposition Study D2306	
n (%) of patients (safety population)	
	ACZ885
	N = 57
Total # Patients Studied	**n (%)**
Enrolled	58*
Exposed	57
Completed at data cutoff	57
Discontinued	1
Adverse Event	1
Analysis Data Sets	
Safety Population	57 (100%)
MWS	46 (81%)
FCAS	8 (14%)
MWS with overlap NOMID	3 (5%)
One patient was enrolled but was only in screening at the time of the data cutoff. No treatment had yet been received.	

The efficacy and safety datasets were identical in Study D2306.

Protocol Deviations in Study D2306
Protocol deviations were recorded but not analyzed for this interim analysis (12Sept2008). Protocol deviations will be submitted in the final analysis report.

B. Concomitant Medications
Concomitant medications were recorded but were not analyzed in the interim report (cut off 12Sept2008). Concomitant medications will be submitted in the final analysis report.

C. Patient Demographics and Other Baseline Disease Characteristics

Patient baseline demographics were summarized in this open label study to assess the CAPS disease characteristics and the level of disease activity. The majority of the patient population was > 18 years of age (78%), female (54%), Caucasian (95%), with a mean weight of 61 kg, and a molecular diagnosis of NALP3 (97%) [see **Table 86**]. Two patients (Pt # D2306-0002-00004 and # D2306-0504-00004) did not have a molecular diagnosis with NALP3 mutations. The enrolled patients in Study D2306 were included patients enrolled from previous studies and canakinumab naïve patients: 22 patients (39%) enrolled from Study A2102; 17 patients (30%) enrolled from Study D2304; and 18 new patients (31%) were canakinumab naïve (see **Table 86**).

Table 86.

Baseline Demographic Characteristics, Study D2306	
Demographic Variable	ACZ885 N = 57
Age (years)	
≥ 4 years to < 18 years	9 (16%)
≥ 18 years to < 41	27 (47%)
≥ 41 years to ≤ 75 years	21 (37%)
Gender n (%)	
Female	31 (54%)
Male	26 (46%)
Race n (%)	
Caucasian	54 (95%)
Black	0
Asian	2 (4%)
Other	1 (2%)
Weight (kg)	
Mean (SD)	61 (20)
Cohort n (%)	
Pts from Study A2102	22 (39%)
Pts from Study D2034	17 (30%)
ACZ885 naïve patients	18 (32%)

Adapted from Sponsor table 11-1, page 57 of 1247, Study D2306

The baseline background and disease characteristic exploration included analysis of the levels of serum biomarkers of inflammation, CRP and SAA. Both these serum biomarkers of inflammation were observed to be higher in canakinumab naïve patients compared to roll-over patients previously treated with canakinumab in Study A2102 or D2304 (see **Table 87**). The observed higher values at baseline in canakinumab naïve patients confirmed the expected higher level of disease activity in canakinumab naïve patients compared to previously treated CAPS patients.

At baseline, the Physician's Global assessment of autoinflammatory disease activity was scored as *absent* to *minimal* in the majority of canakinumab roll-over patients (62%) [see **Table 87**]. By contrast, the Physician's global assessment of autoinflammatory disease activity in canakinumab naïve patients was scored as *mild* to *moderate* in the majority of these patients (62%). One roll-over patient (# D2306-0001-00014) was scored as *severe* for the Physician's Global assessment

of autoinflammatory disease activity on Day 1 due to severe abdominal pain and severe aphthous ulcers. The higher CRP and SAA values and the Physician's global assessment of autoinflammatory disease activity in canakinumab naïve patients were consistent with more clinically active CAPS disease not yet treated with canakinumab.

The baseline skin disease assessment was scored as *absent* in over 80% of roll-over patients compared to 61%, as either *mild or moderate,* in canakinumab naïve patients. This contrasting baseline data likely represents carryover of the treatment effect of canakinumab in roll-over patients from Study A2102 and D2304 (see **Table 87**).

Eight (8) FCAS patients were enrolled in this study: 3 females and 5 males; 1 pediatric patient (5 years of age), and 7 adults (between 18 to 55 years of age). One FCAS patient rolled-over from Study A2102 and the other 7 FCAS patients were canakinumab naïve. Noteworthy, the baseline disease assessments for the mildest form of CAPS disease, FCAS, in general, were less severe on the 5-point scale of assessments than with other CAPS diagnoses. The majority of patients with FCAS had baseline disease assessments scored as *minimal* to *moderate* for skin disease, arthralgia, myalgias, headache/migraine, conjunctivitis and fatigue/malaise. The baseline assessment was *minimal* in 1 patient, *mild* in 2 patients and *moderate* in 4 patients.

Table 87.

Background and Disease Characteristics at Baseline (safety data set)			
	ACZ885 Roll-over patients N = 39	ACZ885 Naïve patients N = 18	ACZ885 Total N = 57
CRP (mg/L)			
Mean (SD)	5 (7)	13 (13)	8 (10)
Median (min, max)	2 (0, 28)	7 (0, 44)	3 (0, 444)
SAA (mg/L)			
Mean (SD)	9 (17)	32 (47)	17 (32)
Median (min, max)	5 (0, 94)	12 (0, 175)	6 (0, 175)
Physician's Global assessment of autoinflammatory disease activity n (%)			
Absent	15 (39%)	4 (22%)	19 (33%)
Minimal	9 (23%)	3 (17%)	12 (21%)
Mild	10 (26%)	6 (33%)	16 (28%)
Moderate	4 (10%)	5 (28%)	9 (16%)
Severe	1 (3%)	0	1 (2%)
Assessment of Skin Disease n (%)			
Absent	33 (85%)	6 (33%)	39 (68%)
Minimal	3 (8%)	4 (22%)	7 (12%)
Mild	3 (8%)	3 (17%)	6 (11%)
Moderate	0	5 (28%)	5 (9%)
Severe	0	0	0

Adapted from Sponsor Table 11-2, page 59 of 1247, Study D2306

C. Relevant Patient Medical History and Continuing Medical Conditions

The special assessments to monitor long-term effects on CAPS disease progression, e.g. audiogram, neurological and ophthalmological assessments, and MRI, were not submitted by the

applicant. In addition, monitoring of sexual maturation, e.g. Tanner Stage, was not submitted in the interim analysis.

D. Primary Efficacy Results

The primary objectives of this open label study were to assess safety and tolerability of canakinumab. Key secondary objectives included maintenance of *complete response*. The maintenance of *complete response* over time was defined by the number of patients *without relapse* in this open label trial. *Relapse* was based upon the Physician's Global assessment of auto-inflammatory disease activity, assessment of skin disease, and the level of inflammatory markers, CRP and/or SAA; and the number of patients who required a dose adjustment or an administration frequency adjustment, with subsequent maintenance of *response* over time based on the Physician's Global assessment of autoinflammatory disease activity, assessment of skin disease, and the level of inflammatory markers, CRP and/or SAA.

The data from Study D2306 are by nature, incomplete because the study is ongoing. Nonetheless, these data provide some information of the maintenance of response with longer term canakinumab treatment. No patient treated with canakinumab, and for whom *relapse* data was available, experienced a *relapse,* regardless of whether they had been previously treated with canakinumab or were canakinumab naïve patients. Noteworthy, the majority of patients (31 patients, 54%) had missing *relapse* data at the interim report cutoff (see **Table 88**). Among patients with *relapse* assessment data (19 patients), none had a relapse.

Table 88.

Number (%) of Patients with Relapse and Response Assessment - Study D2306 (safety set)	
	ACZ885 N = 57 n (%)
All Patients (roll-over and naïve patients)	
Pts (with data) without *relapse*	19 (33%)
Pts with *relapse*	0
Pts with missing relapse data (12Sept08)	31 (54%)
ACZ885 Naïve Patients	
ACZ885 naïve pts. - not achieving complete response	4* (7%)
ACZ885 naïve pts. - missing response data (12Sept08)	3 (5%)
* Per investigator, per protocol defined criteria, only 2 pts did not achieve *complete response*.	

Adapted from Sponsor Table 11-3 and 11-4 on page 62 of 1247, Study D2306

Canakinumab Naïve Patients and *Complete Response*

Additional analysis of *complete response* to canakinumab treatment was explored in canakinumab naïve patients. *Complete response* was observed in 61% of canakinumab naïve patients (see **Table 89**). Out of the four (4) canakinumab naive patients (all MWS) not achieving *complete response* based on the investigator's judgment (Pt. # D2306-0001-00004; Pt. # D2306-0002-00001; Pt. # D2306-0002-00002; and Pt. # D2306-0002-00003), two patients (Pt. # D2306-0002-00001 and Pt # D2306-0002-00002) achieved *complete response* based upon the protocol definition of *complete response* (see **Table 89**).

Complete response data for patients in the roll-over group is not reviewed here because *responses* for these patients are reviewed in the study report in which they were originally exposed. Despite limited *relapse* and *complete response* data in this interim report, the outcome supports the primary efficacy analyses, based on *complete response* in Study A2102, D2304 and D2306, and supported the longer treatment effect of canakinumab therapy in patients with CAPS disease.

Table 89.

Response to Treatment - n (%) Canakinumab Naïve Patients - Study D2306 (safety set)	
ACZ885 naïve patients	**ACZ885 N = 18**
ACZ885 naïve pts achieving *complete response*	11 (61%)
Patients without *relapse*	4 (36%)
Patients with *relapse*	0
Patients with missing *relapse* data at cutoff (12Sept08)	7 (64%)
ACZ885 naïve pts NOT achieving *complete response*	4* (22%)
e.g., non-responders	
ACZ885 naïve pts with missing *response* data (12Sept08)	3 (17%)
* Per investigator, per protocol defined criteria, only 2 pts did not achieve *complete response*.	

Canakinumab Up-Titration and *Complete Response*

Canakinumab dose up-titration was permitted in this study for patients not achieving *complete response* with the first canakinumab dose at the proposed fixed dose of 150 mg sc in adults > 40 kg and at the weight based dose, 2 mg/kg, for the pediatric patient population ≥ 15 kg and ≤ 40 kg. Five (5) patients were up-titrated and received twice the dose of their first canakinumab dose. Four (4) patients with MWS (Pt #0001-00014, 9-year old/M; Pt # 0001-00004, 35-year old/F; Pt # 0001-00005, 5-year old/F; Pt # 0501-00002, 26-year old/F) received a single up-titration canakinumab dose; and one patient with MWS/NOMID (Pt # 0005-00001, 21-year old/F) received a 1 mL dose, then received two 2 ml doses. She flared once with a 2 mL and responded to the second 2 mL dose.

One other patient with MWS (Pt # 0002-00001/41 year old/F) experienced *relapse* twice and received 1 mL of canakinumab twice without up-titration of the dose. All FCAS patients received one sc injection of canakinumab except for the pediatric patient # D2306-0504-00001, 5 year old/F/FCAS who received 3 injections of the same dose. All of the MWS/NOMID patients received one injection except for Patient # D2306-0005-00001 who had predominantly NOMID phenotype. This patient received three (3) injections: the second dose was up-titrated and the third dose as the same as the second dose.

All 5 patients who received up-titration doses of canakinumab experienced *complete response* with the higher canakinumab dose. Though these data are limited, these results of up-titration suggest that some patients with MWS or MWS overlapping with NOMID may require higher canakinumab doses than those proposed in order to achieve clinical benefit.

E. Secondary Efficacy Results

Assessment of Disease Symptoms

Assessment of disease symptoms typical of CAPS disease demonstrated decline in the severity of autoinflammatory disease activity from baseline to Visit 5 (Day 57) as measured by the Physician's Global assessment of disease activity and by the assessment of skin disease. No patient scored worse than *minimal* for skin disease and worse than *mild* for the Physician's global assessment of autoinflammatory disease activity at the 1 week or 2 month visits. Though the assessments of disease activity data were incomplete, the limited data supported improved disease assessments in this open label trial with canakinumab treatment in patients with CAPS disease (see **Table 90**).

Table 90.

Summary - Asssessments of Disease Activity by Visit Study D2306 (safety set)		
Categorical Variable	ACZ885 N = 57	
Physician's Global assessment of autoinflammatory disease activity n (%)		
	Visit 3, Day 8	Visit 5, Day 57
Absent	8/16 (50%)	11/19 (58%)
Minimal	7/16 (44%)	4/19 (21%)
Mild	1/16 (6%)	4/19 (21%)
Moderate	0	0
Severe	0	0
Assessment of Skin Disease n (%)		
Absent	13/16 (81%)	17/19 (86%)
Minimal	3/16 (19%)	2/19 (11%)
Mild	0	0
Moderate	0	0
Severe	0	0

F. Assessment of Protein Markers of Inflammation

To explore the effect of canakinumab treatment on objective serum markers of inflammation, CRP and SAA were assessed for the change from baseline in roll-over and canakinumab naïve patients, by visit. Less than half of roll-over patients (40%) and only 22% of canakinumab naïve patients had CRP levels performed by Visit 5, Day 57. Despite these limited data, both treatment groups demonstrated a decrease in CRP and/or SAA levels by Visit 5, Day 57 (see **Table 91**). As expected, the decreasing trend was larger in canakinumab naïve patients than in roll-over patients previously exposed to canakinumab. These data, though limited, supported the maintenance of response to canakinumab treatment in CAPS disease. These data were consistent with the serum markers of inflammation outcomes in pivotal Study D2034 and open label Study A2102.

Table 91.

Summary of Change from Baseline in CRP and SAA (mg/L) Roll-Over Patients and ACZ885 Naïve Patients by Visit inStudy D2306			
CRP (mg/L)			
Roll-over Patients			
	ACZ885 N = 39		
	Baseline	**Post-baseline**	**Change from baseline**
Baseline, Day 1 (n)	37		
Mean (SD)	5 (7)		
Median (min, max)	2 (0, 28)		
Visit 5, Day 57 (n)	15	15	15
Mean (SD)	4 (5)	3 (3)	- 1 (4)
Median (min, max)	3 (0, 16)	2 (0, 10)	10.3 (-12, 7)
ACZ885 Naïve Patients			
Baseline, Day 1 (n)	18		
Mean (SD)	14 (13)		
Median (min, max)	7 (0, 44)		
Visit 5, Day 57 (n)	4	4	4
Mean (SD)	11 (10)	2 (1)	-10 (9)
Median (min, max)	9 (2, 25)	1 (1, 3)	-8 (-22, -2)
SAA (mg/L)			
Roll-Over Patients			
Baseline, Day 1 (n)	37		
Mean (SD)	9 (17)		
Median (min, max)	5 (0, 94)		
Visit 5, Day 57	15	15	15
Mean (SD)	7 (5)	8 (13)	1 (15)
Median (min, max)	6 (0, 20)	6 (1, 54)	-1 (-15, 52)
ACZ885 Naïve Patients			
Baseline, Day 1 (n)	18		
Mean (SD)	32 (47)		
Median (min, max)	12 (0, 175)		
Visit 5, Day 57 (n)	4	4	4
Mean (SD)	17 (14)	2 (0)	-15 (14)
Median (min, max)	13 (5, 36)	2 (1, 2)	-12 (-34, -3)
n = # pts with evaluable measurements at both baseline and post-baseline visit.			

G. Efficacy by Phenotype

No planned subgroup analyses by phenotype were conducted in Study D2306.

H. Quality of Life Assessments

Health-related quality of life data were not submitted in the interim report data.

I. Special Assessments

Special assessments including audiogram, neurological and ophthalmological assessments, and MRI of the brain were not included in these interim data.

IV. Discussion of Efficacy Findings and Conclusions

Study D2306 was conducted in accordance with the Phase 3 protocol submitted under IND 100,040. An interim study report (data cutoff 12Sept2008) was submitted as Study D2306 is currently an ongoing clinical trial.

All CAPS diseases were included in this study population: 46, 8, and 3 patients had MWS, FCAS and MWS overlapping with NOMID, respectively. At the interim data cutoff, 22 patients (39%) were rolled over from Study A2102, 17 patients (30%) were from Study D2034 and 18 patients (32%) were canakinumab naïve patients. The majority of these patients had signs and symptoms typical of CAPS diseases.

Among 57 patients enrolled, adults and children ≥ 4 years to < 18 years of age were included. No canakinumab treated patient for whom *relapse* data was available experienced *relapse*, regardless of whether they had been previously treated with canakinumab or were canakinumab naïve. However, the majority of patients (31 patients, 54%) had missing *relapse* assessment data at the interim report cutoff. *Complete response* was observed in 61% of canakinumab naïve patients. Noteworthy, out of four canakinumab naïve patients not achieving *complete response* based on the investigator's judgment, two patients achieved *complete response* based on the protocol definition of *complete response*.

Although data on relapses were incomplete, the available information on *complete responses* and *relapses* data in this interim report support the primary efficacy analyses based on *complete response* in Study D2306 and support *complete response* results in Study A2102 and pivotal Study D2304. The lack of reported relapses suggests that responses are maintained over time with CAPS disease.

Canakinumab dose up-titration was permitted in this study for patients not achieving *complete response* with the first canakinumab dose at the fixed dose of 150 mg sc in adults > 40 kg and at the weight based dose, 2 mg/kg for the pediatric patient population ≥ 15 kg and ≤ 40 kg. Five patients (4 MWS and 1 MWS/NOMID) received up-titrated canakinumab doses and experienced *complete response* with the higher canakinumab dose. Though these data are limited, the results of up-titration suggest that some patients with MWS or MWS overlapping with NOMID may require higher canakinumab doses than those proposed in order to achieve clinical benefit.

Serum protein markers of inflammation, CRP and SAA, supported the sustained clinical outcomes with canakinumab treatment by reaching normal values which were sustained through Visit 5 (Day 57) in this interim report. As expected, the decreasing values were larger in canakinumab naïve patients than in roll-over patients previously exposed to canakinumab. These continuous responses in rollover patients, though limited, support maintenance of response to canakinumab treatment in CAPS disease and were consistent with the outcomes of serum markers of inflammation in pivotal Study D2034 and open label Study A2102.

Assessment the Physician's Global assessment of disease activity and assessment of skin disease of disease symptoms demonstrated decline in the severity of autoinflammatory disease activity from baseline to Visit 5 (Day 57). No patient scored worse than *minimal* for skin disease and worse than *mild* for the Physician's global assessment of autoinflammatory disease activity. Though the assessments of disease activity data were incomplete, the limited data that were available support improved disease assessments in this open label trial with canakinumab treatment in patients with CAPS disease.

Special assessments of neurological and ophthalmological assessment, MRI of the brain and audiogram assessment were not included in the interim data.

In conclusion, though based on limited interim data, open label Study D2306 provides some useful supportive information based on the data its key secondary efficacy variables, *complete response* and *relapse*, support the sustained longer term treatment effect of canakinumab in adults and children ≥ 4 years to < 18 years of age with CAPS diseases, FCAS, MWS and MWS overlap NOMID. The overall results of this interim report support the primary efficacy results of pivotal Study D2034 and supportive open label Study A2102. The limited canakinumab up-titration data suggest that some patients with CAPS disease may require higher dose of canakinumab than those proposed in this submission.

V. Safety Analysis and summary

The safety analysis and conclusions are reported in Section 7 of this clinical review.

CLINICAL FILING CHECKLIST FOR BLA 125319 Ilaris (canakinumab)

BLA: 125319 **Applicant:** Novartis **Stamp Date:** 15Dec2008

Drug Name: Ilaris (canakinumab) **BLA Type:** New Molecular Entity (NME)

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	✓			
5.	Are all documents submitted in English, or are English translations provided when necessary?	✓			
6.	Is the clinical section legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	✓			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	✓			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study # D2304, Part 2. Indication: Proposed for the treatment of CAPS in adults and children ≥ 4 years and older including: FCAS, MWS,	✓			Given the orphan status, the division has determined that a single adequate and controlled study is sufficient.

b(4)

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2: Not applicable. Indication: Not applicable.				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	✓			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✓	Biologic products are generally not expected to interact w/cardiac ion chanels.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✓			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	✓			Ilaris is an Orphan Designation product for the treatment of CAPS. Patient numbers are expected to be small.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			✓	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	✓			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			
25.	Have narrative summaries been submitted for all deaths and	✓			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	✓			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
34.	Are all datasets to support the critical safety analyses available and complete?	✓			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	✓			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	✓			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	✓			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR BLA 125319 Ilaris (canakinumab)

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Carolyn L. Yancey — February 13, 2009
Reviewing Medical Officer — Date

Jeffrey K. Siegel — 2/13/09
Clinical Team Leader — Date