

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125319

MEDICAL REVIEW(S)



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
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Erratum Memo
BLA 125319
Ilaris (canakinumab)

DATE: June 10, 2009

RE: Errors in the Clinical Review for BLA 125319

DRUG: Ilaris (canakinumab), New Molecular Entity

FROM: Carolyn L. Yancey M.D. *Carolyn L. Yancey MD 6/10/09*
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THROUGH: Jeffrey N. Siegel, M.D. *Jeffrey N. Siegel 6/12/09*
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TO: Action Package File: BLA 125319

This memo addresses three errors in the Clinical Review (May 5, 2009) for BLA 125319 Ilaris (canakinumab) for the proposed indication of treatment of CAPS in adults and children aged 4 years and older including Familial Cold Autoinflammatory syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Summary of Errors:

- Under Section 4.2 Clinical Microbiology: the text under this section should have been deleted up to the final sentence because Section 4.2 applies to anti-infectives, not the microbiology issues of biologics.
- Under Section 4.2 Clinical Microbiology: the last sentence explaining the status of CMC site inspections should be moved up to the last line of Section 4.1 Chemistry Manufacturing and Controls.
- Under Section 7.3.2 Nonfatal Serious Adverse Events: on page 53, under the heading CAPS Disease, in the first sentence, the typo as the number 9 should be the number 7 for the total number of SAEs.

CLINICAL REVIEW

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|------------------------|---|
| Application Type | BLA |
| Application Number(s) | 125319 |
| Priority or Standard | P |
| Submit Date(s) | December 15, 2008 |
| Received Date(s) | December 17, 2008 |
| PDUFA Goal Date | June 17, 2009 |
| Reviewer Name | Carolyn L. Yancey, MD <i>Carolyn L. Yancey</i> |
| Clinical Team Leader | Jeffrey N. Siegel, MD <i>Jeffrey N. Siegel</i> |
| Review Completion Date | May 5, 2009 <i>May 4, 2009</i> <i>5/11/09</i> |
| Established Name | Canakinumab |
| (Proposed) Trade Name | Ilaris |
| Therapeutic Class | Anti-interleukin-1beta (IL- β) monoclonal antibody (MAb) |
| Applicant | Novartis |
| Formulation(s) | 150 mg/ml per single-use vial |
| Dosing Regimen | 150 mg subcutaneous (s.c.) for CAPS patients with body weight > 40 kg and 2 mg/kg for CAPS patients with body weight \geq 15 kg and < 40 kg, every 8 weeks. |
| Indication(s) | Cryopyrin-Associated Periodic Syndrome (CAPS) |
| Intended Population(s) | Adults and children \geq 4 years and older. |

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In consideration of the observed efficacy and safety profile of this NME and IL-1 blocker, canakinumab (Ilaris) should be approved for the treatment of CAPS in adults and children ≥ 4 years of age and older, including FCAS and MWS. Refer to Section 9.2 Labeling Recommendations for revisions to the proposed canakinumab labeling.

1.2 Risk Benefit Assessment

Cryopyrin-associated periodic syndromes (CAPS) represent a spectrum of three rare, serious, autosomal dominant, systemic inflammatory conditions characterized by fever, fatigue, headache/migraine, myalgias, arthralgia and abdominal pain, urticarial skin rash and conjunctivitis. CAPS is characterized by a single point mutation in the NALP3/CIAS1 gene on chromosome 1q44. The genetic defect results in increased production of interleukin 1beta (IL-1 β). The mildest form of CAPS is familial cold autoinflammatory syndrome (FCAS) which does not have neurologic involvement. Muckle-Wells syndrome (MWS) is a more severe form that is associated with neurologic involvement and sensorineural deafness. The most severe form is neonatal-onset multisystemic inflammatory disease (NOMID). NOMID is associated with serious neurologic involvement including mental retardation and chronic aseptic meningitis. CAPS affect only a few hundred patients in the US and only a few thousand world-wide. In consideration of the rarity of this disease, the Agency agreed to accept clinical evidence from a single randomized clinical trial to demonstrate efficacy of canakinumab in CAPS.

Canakinumab demonstrated clinical efficacy in the pivotal Study D2304 in patients with MWS based on Part 2, the randomized, double blind, placebo controlled withdrawal period. In the initial open-label period of Study D2304, Part 1, 31 of 35 patients (97%) met the prespecified efficacy endpoint of complete response, defined by the Physician's global assessment of auto-inflammatory disease activity \leq minimal (using a 5-point scale as absent, minimal, mild, moderate or severe), and assessment of skin disease \leq minimal (using the same 5-point scale described above), and normal serum values of CRP and SAA (< 10 mg/L). In the randomized, withdrawal period of Part 2, a greater proportion of patients randomized to continue canakinumab maintained a complete response as compared to patients randomized to placebo: 100% (15 of 15 patients) versus 19% (3 of 16 patients), respectively.

Supportive evidence of efficacy comes from secondary analyses of the randomized withdrawal period for Study D2304 which showed a significantly longer time to relapse with canakinumab than with placebo. In addition, in the two supportive open label trials of canakinumab in CAPS, e.g., FCAS, MWS, and MWS overlapping with NOMID, the majority of patients had a complete response. Longer term treatment studies include Part 3 of Study D2304 and Study A2102, which

did not report relapses in patients treated for up to 36 months, suggesting maintenance of clinical benefit with the every 8 week dosing regimen.

The clinical development program for canakinumab provides evidence for efficacy in MWS as shown in Study D2304. Canakinumab also appears effective in FCAS based on complete response in all patients treated in the open label Studies A2102 and D2306.

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Canakinumab was well tolerated and reflects a safety profile similar to other IL-1 blocker therapies, rilonacept and anakinra. No deaths were observed in the three CAPS studies. Two types of adverse events (AEs) were noticeable in the safety database for canakinumab, infectious and vertigo. Infectious AEs were observed in patients with CAPS receiving canakinumab consistent with canakinumab's immunosuppressive mechanisms of action. The infectious events observed responded to standard of care treatment and resolved. No opportunistic infections were observed in any patient population exposed to canakinumab. Since vertigo is a recognized symptom of MWS, it is uncertain whether the 10 observed cases of vertigo in these studies are due to canakinumab treatment or to the underlying disease. No malignancies were observed in any CAPS patient.

The proposed route of sc injection was well tolerated and the observed injection reactions were few and mild. In all the canakinumab clinical trials, there were no observed cases of hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, and no evidence of immunogenicity to canakinumab in any of the clinical trials. Notable, a small number of patients experienced laboratory abnormalities, e.g., transient increases in liver enzymes, and a few patients experienced asymptomatic increases in bilirubin, each of which resolved.

The final formulation of canakinumab 150 mg powder for solution for sc injections (150 mg/mL) was used throughout the clinical trials and is the intended formulation for marketing. The lack of sc injection site reactions supports the sc route of administration. The PK established in the dose-finding period of Study A2102 and the clinical efficacy and sustained tolerability observed in the three CAPS studies support the proposed dosing interval of every 8 weeks. Overall, the three clinical trials provide evidence for substantial efficacy of canakinumab in patients with CAPS. The main risk associated with canakinumab treatment is the risk of infection associated with the immunosuppressive mechanism of canakinumab. In view of the seriousness of the underlying condition, CAPS, the substantial efficacy, and the lack of serious toxicities observed in these clinical trials, the risk-benefit relationship is favorable.

Long-term effects of canakinumab on the growth and development of children, particularly small children, are not fully established. Data collected in the CAPS trials with pediatric patients appear to be favorable with respect to growth and development.

1.3 Recommendations for Postmarket Risk Management Activities

Due to the proposed mode of action of known inhibitors of the IL-1 pathway, increased infections were expected with canakinumab treatment. Infections were observed in the CAPS studies and in studies in other diseases. Notable, no difference in the type infections observed in adults compared to children was observed in the CAPS studies in the original BLA or in the additional four-month safety data through 12Jan2009. As the CAPS adult and pediatric study populations are small due to this rare disease, it will be important to monitor for infectious events in a postmarket pharmacovigilance plan.

Laboratory abnormalities cited above as transient increases in liver enzymes and some asymptomatic increases bilirubin should also be included in the pharmacovigilance monitoring. Though no malignancies were observed in the CAPS safety database, the occurrence of malignancies should be monitored based on the known association between immunosuppressive therapy and malignancy. Cases of vertigo should also be monitored.

Pregnancy outcomes should also be monitored. Safety during pregnancy and the health of the fetus and newborn have not been studied during canakinumab treatment. Data, so far, do not suggest concerns, but the risks to women who become pregnant and their babies are still unknown.

Though available safety data support a favorable safety profile for canakinumab, the possibility of new and unexpected events should be monitored according to a risk management plan. Though a Risk Evaluation and Mitigation Strategy (REMS) is not required for this NME, a pharmacovigilance plan should be employed to monitor the safety profile of canakinumab in patients with CAPS (refer to Section 9.2 Labeling Recommendations for the proposed revisions to the labeling including information for the Health Care Professional and patients).

1.4 Recommendations for Postmarket Studies/Clinical Trials

The Safety Risk Management Plan including a Pharmacovigilance Plan as proposed by the applicant appears adequate to monitor for the safety of this NME, IL-1 blocker therapy, canakinumab, in the proposed indication of CAPS in adults and children ≥ 4 years of age. No postmarket studies or clinical trials are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Canakinumab is a recombinant human monoclonal anti-human interleukin-1 β antibody of the IgG1/k isotype developed to selectively bind to and neutralize the activity of IL-1 β . IL-1 β is a pro-inflammatory cytokine produced by mononuclear phagocytes in response to injury and infection. As noted earlier in this review, IL-1 β plays a dominant role in the pathogenesis of

CAPS and is the only disease-mediating cytokine identified in this disease spectrum. The CAPS genetic defects are mutations in the NLRP3/CIAS1 gene on chromosome 1q44. The mutations are associated with uncontrolled caspase 1 activity resulting in increased production of IL-1 β . The clinical response of CAPS patients to IL-1 receptor blockade supports the pathological role of IL-1 in this disease spectrum.

Canakinumab is proposed for the indication of treatment of the signs and symptoms of CAPS in adults and children ≥ 4 years of age. The proposed dose is a fixed dose regimen of 150 mg for CAPS patients with body weight > 40 kg and a weight based dose regimen for patients with body weight ≥ 15 kg and ≤ 40 kg. Canakinumab is proposed to be administered every eight weeks as a single dose via sc administration based on its longer half-life of ~ 26 days.

2.2 Tables of Currently Available Treatments for Proposed Indications

Prior to the advent of IL-1 blocker therapy, there were no effective treatments available to CAPS patients. Antihistamines and non-steroidal anti-inflammatory agents are not effective and high dose corticosteroids are only partially effective at controlling symptoms with the risk of unsatisfactory long term side effects. Anabolic steroids, gold salts, colchicine, cyclophosphamide, azathioprine, thalidomide, disease modifying anti-rheumatic drugs (DMARDs), anti-TNF and chlorambucil have not been shown to be effective therapy and are associated with significant safety risks. The IL-1 receptor antagonist, anakinra (Kineret) is not approved for use in CAPS though it has been used in patients with CAPS. The disadvantage of anakinra is based on its very short half-life requiring daily injections. Rilonacept (IL-1 trap, Arcalyst $\text{\textcircled{R}}$) is approved in the US for the treatment of FCAS and MWS patients over 12 years of age. Rilonacept has a longer half-life than anakinra and is administered by sc injection once weekly.

2.3 Availability of Proposed Active Ingredient in the United States

Canakinumab is not marketed in the US or in any other country.

2.4 Important Safety Issues With Consideration to Related Drugs

In general, the adverse event profile for canakinumab is similar to that observed with other cytokine blockers used off-label to treat CAPS or to the approved biologic, rilonacept (Arcalyst) indicated in CAPS, FCAS and MWS in adults and children ≥ 12 years of age. The major safety risks with administration of IL-1 blocker therapy are increased incidence of infections. Hematologic abnormalities including transient neutropenia has been observed. The impact of treatment with IL-1 blocker therapy on the immune system and the development of malignancies are not known, though treatment with immunosuppressants including an IL-1 blocker may result in an increase in the risk of malignancies. As with other immunosuppressive therapies, IL-1 blockers have a theoretical risk of predisposing patients to malignancies but evidence for such a risk is currently lacking.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This BLA application is Novartis' first submission for the indication of CAPS with the NME canakinumab. A brief summary of the regulatory background for canakinumab in CAPS and other diseases follows:

- The first Pre-IND 100,040 meeting was conducted January 2006.
- It was acknowledged that since CAPS is a rare condition, that large studies would not be possible. The Agency recommended at least 6 months of efficacy data and at least 12 months of safety data to support an indication in CAPS. The sponsor proposed to conduct a randomized trial in MWS
- The second Pre-IND 100,040 meeting was conducted April 2006. Canakinumab clinical trials

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- The IND 100,040 was opened on June 6, 2006
- A Phase 3 MWS clinical study design (Study D2304) was submitted under the IND 100,040 in October 2006. The protocol was generally acceptable; however, comments to the sponsor included recommendation that the primary endpoint, based on the physician's assessment, be expanded to include patient assessments in order to evaluate disease flaring in order to improve the accuracy of the physician's assessment. The three-part study design with Part 2 as the randomized, double blind, placebo controlled withdrawal period was acceptable to the Agency.
- Orphan Designation was granted December 18, 2007 for the treatment of CAPS.
- Fast Track Designation was granted April 24, 2008 for the treatment of CAPS

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- Canakinumab demonstrated clinical effectiveness in Phase 1/2a study with MWS in which ~20 patients were observed with clinical response within 1 to 7 days, e.g. decreased fever, rash, conjunctivitis, arthralgia and myalgia.
- On March 20, 2008, Novartis reported multiple occurrences of vertigo under the canakinumab clinical development programs. The Agency request Novartis to report the total canakinumab exposure and submit a risk-benefit analysis. Electronystagmography was added to the safety monitoring but excluded after further review within the Agency. Additional safety clinical monitoring in open label Study D2306 included serum estradiol levels in children to assess safety and tolerability of IL-1

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The sponsor communicated intent to seek a priority review for the original proposed BLA 125,319.

- On December 15, 2008, Novartis submitted the BLA 125,319 for Llaris (canakinumab) for Llaris (canakinumab, formerly ACZ885) injection for the treatment of CAPS in adults and the pediatric patient population ≥ 4 years of age.
- Filing Meeting was conducted on January 29, 2009 and priority Review was granted. The PDUFA deadline is June 17, 2009.

2.6 Other Relevant Background Information

CAPS is a rare disease affecting only a few hundred patients in the US. It is only possible to study CAPS in a small number of patients. CAPS is a life-long multi-system inflammatory disease which may present at any time from early childhood to adulthood and may present in the neonatal period. There are no spontaneous remissions in CAPS. Patients typically suffer from fever, fatigue, headache/migraine, muscle, joint and abdominal pain, urticarial rash, conjunctivitis and papillaeoedema. Additional signs and symptoms include destructive arthritis, cerebral demyelination, and neurological symptoms. Severe disabilities may include sensorineural deafness, visual loss and amyloidosis-mediated organ dysfunctions including kidney failure.

All other relevant background information is incorporated into the appropriate sections of this clinical review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the data quality and integrity were adequate. The amount of missing data was negligible. The applicant responded promptly to information requests from the Division. Overall, there were no major issues regarding data quality and integrity of each study. At the time of this clinical review, the Division of Scientific Investigations (DSI) is conducting three foreign study site visits. The results of these inspection visits are not available at the time of completion of this review. In addition, consultation from the Division of Drug Marketing, Advertising, and Communications (DDMAC) has not been completed at the time of completion of this review.

3.2 Compliance with Good Clinical Practices

Studies D2304, A2102 and D2036 were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good clinical Practices (GCP). The clinical trials were conducted in compliance with the study protocols submitted to the Agency. The protocols, amendments,

Investigator's Brochures and other required documents received by the Institutional Review Boards and Independent Ethics Committees were approved prior to implementation of these trials.

3.3 Financial Disclosures

Financial disclosure was reviewed and deemed to be complete. No financial interest was reported that would be expected to influence the integrity of these overall study results or influence in any way, the final outcomes.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

During the canakinumab clinical development program, canakinumab drug substance manufacturing changes included two different products.

_____ were contained in the cell culture media used to produce product type A and B. The drug substance process _____

_____ product type C. Study A2102 employed the _____ /Product type A, Study D2034 employed the _____ /Product type B, and Study D2306 employed _____ Product type C. Study D2034 employed a lyophilisate.

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Two bridging studies in marmosets showed lack of significant PK differences between these two drug products. The bioavailability and binding affinity of canakinumab to IL-1 β of the line material were similar to that of the _____ line material (refer to the Chemistry, Manufacturing and Controls review by Ruth Rodriguez, PhD).

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4.2 Clinical Microbiology

Under this BLA for canakinumab in CAPS, there were no clinical microbiology related issues at the time of this clinical review. However, the manufacturing inspection site visits are pending at the time of this clinical review (refer to the CMC review by Ruth Rodriguez, PhD).

4.3 Preclinical Pharmacology/Toxicology

Pharmacology Toxicology did not identify any problems with the Pharmacology Toxicology results that would preclude approval. See the Pharmacology Toxicology review by Kathleen Young, PhD

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Canakinumab is a high-affinity human monoclonal anti-human interleukin-1 β (IL-1 β) antibody of the IgG1/k isotype that was designed to bind selectively to and neutralize the activity of IL-1 β , a pro-inflammatory cytokine, which is produced by mononuclear phagocytes in response to injury and infection. IL-1 β is known to play a dominant role in the pathology of the rare group of autoinflammatory conditions known as Cryopyrin-Associated Periodic Syndromes (CAPS). As noted earlier in this review, CAPS is a rare inherited condition which includes a spectrum of individual disorders attributed to mutations on one gene and all resulting from excessive production of IL-1 β .

4.4.2 Pharmacodynamics

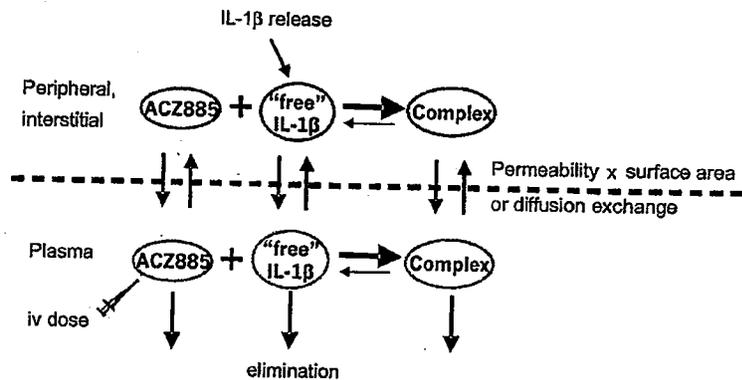
The pharmacodynamic (PD) action of canakinumab is to bind to and inactivate IL-1 β and thus to inhibit the down-stream events of IL-1 signaling, including IL-1 β production, IL-1 β pathway related gene activation, elevation of acute phase proteins such as SAA and CRP, and the mobilization of neutrophils and platelets from bone marrow. Endogenous IL-1 β production rate estimated by the PK-binding model varied with study population, being greatest for CAPS at 9.57 ± 1.34 ng/day. The other populations had lower IL-1 β production rates, up to 50% lower for the healthy populations.

Serum levels of IL-1 β bound to canakinumab were used to monitor the PD action. The ability to bind and capture circulating IL-1 β was assessed in all clinical studies by showing an increase in total IL-1 β levels with canakinumab due to the lower clearance of the larger complex than of the smaller free IL-1 β . An increase in total IL-1 β was observed in healthy subjects and in patient populations including CAPS after canakinumab dosing. Levels of total IL-1 β rose with increasing doses of canakinumab and peak concentrations of total IL-1 β were achieved later than the peak canakinumab concentrations. Using the population-based PK-binding model, the ability of canakinumab to bind IL-1 β is described by the apparent, in vivo dissociation constant, which was estimated at 1.1 ± 0.2 nM in CAPS patients. See the Clinical Pharmacology review by Srikanth Nallani, PhD.

4.4.3 Pharmacokinetics

Serum canakinumab concentrations and total IL-1 β were assessed from all patients in this study and five other canakinumab studies. These data were analyzed using nonlinear mixed-effects modeling to evaluate a population PK/PD model of canakinumab. A schematic of the binding and kinetic model for canakinumab (ACZ885) and IL-1 β is presented in **Figure 1**.

Figure 1.



Sponsor Figure 9-2, p 71 of 3953

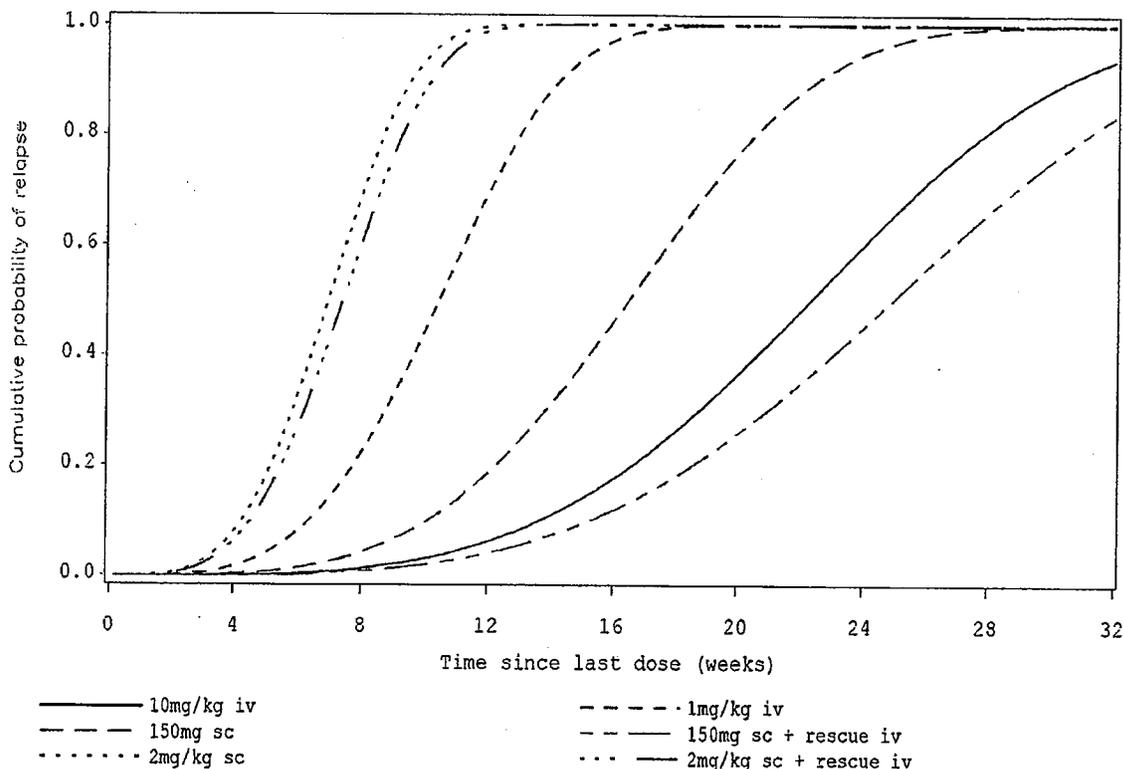
Canakinumab distributed between two compartments, ~55% in the central plasma and ~45% in the peripheral compartment. Canakinumab bound and reduced circulating levels of free IL-1 β by preventing IL-1 β binding at the receptor site. Bioavailability of canakinumab was ~63% to 70%. Canakinumab was absorbed at a rate of ~30% per day. The PK parameters of canakinumab were consistent with expected PK characteristics of a human IgG molecule. The serum clearance (CL) of canakinumab averaged 0.18 L/d with a low total volume of distribution, 5.62 L, via intravenous administration. The bioavailability of canakinumab was ~71% via subcutaneous administration. The half-life of canakinumab is ~26 to 30 days. These results are similar to other monoclonal antibodies.

In children, the peak concentrations of canakinumab occurred between 2 to 7 days following a sc dose of 150 mg or 2 mg/kg dose of canakinumab. T_{1/2} ranged from 23 to 26 days, similar to that in adults. No notable influence of age on canakinumab clearance, volume of distribution, or intercompartmental rate of distribution, after correction for body weight was reported. The metabolism of canakinumab was not studied because IgGs are not metabolized in the liver or excreted in bile or urine, but broken down intracellularly.

No formal PK studies in patients with hepatic impairment were performed. In Study A2102, 4 CAPS patients with moderate to end stage renal insufficiency were treated with canakinumab. The clearance and C_{max} of canakinumab in patients with moderate to end stage renal failure was found to be similar to the average adult patients

Specific dose-finding studies were not possible due to the scarcity of patients with CAPS disease. Therefore, modeling was applied to data obtained from patients in Study A2102 whose study design included PK/PD assessments. In Study A2102, dose finding with both routes of administration, iv infusion and sc injection were explored. The population cumulative probability plot of *time to relapse*, by dose group in Study A2102, supported the primary efficacy variable and the treatment effect with canakinumab at the proposed dose of 150 mg sc (see **Figure 2**).

Figure 2 Study A2102



Sponsor figure 11-1, page 86 of 19679, Study A2102

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This BLA clinical review is based on data from the clinical trials conducted by the applicant, Novartis, submitted in the original BLA 125,319 and all related submissions for the period 12 September 2009 through 12 January 2009 (see **Table 1**). This clinical development program with canakinumab was designed to support the proposed indication for the treatment of CAPS in adults and children ≥ 4 years of age and older including: FCAS, MWS. As shown in **Table 1**, there are three completed clinical trials which support the proposed indication. In pivotal Study D2304, Part 1 was 8 weeks, Part 2 was 24 weeks, and Part 3 was ≥ 16 weeks at the time of the BLA submission. All three studies employed canakinumab 150 mg sc administered every 8 weeks. Only Part 2 of Study D2304 included a placebo group. Study D2036 remains open for longer term safety.

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Table 1 Clinical Trials Providing Efficacy Data in CAPS Studies D2304, A2102 and D2306

| Study No. | Efficacy objectives, Population | No. Treated | ACZ Treatment (mg or mg/kg) | Efficacy criteria |
|---|---|--------------|---|--|
| Placebo-controlled, double-blind trial | | | | |
| D2304 | Efficacy / safety in MWS (part I: uncontrolled) | 35 | part I (single dose, 8 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c (15-40kg) | complete response |
| | (part II: placebo-controlled, double-blind, withdrawal) | 31 | part II (multiple doses, up to 24 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c (15-40kg) | primary endpoint: proportion with flare |
| | (part III: uncontrolled) | 31 (cut off) | placebo (part II only) part III (16 wk if finished part II, or longer) 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c. (15-40kg) | complete response |
| Uncontrolled, open-label trials | | | | |
| A2102 | Efficacy / safety in CAPS (MWS, FCAS, MWS/NOMID) | 4 | (dose ranging, 3 doses, rescue for flare) | primary endpoint: time to relapse complete response |
| | | 34 | (selected dose) 150 mg s.c. (age >16yr), 2 mg/kg (age ≤16 yr) | |
| D2306 | Efficacy / safety in CAPS (MWS, FCAS, MWS/NOMID) | 57 (cut-off) | 150 mg s.c. q8wk (>40kg), 2 mg/kg s.c. (15-40kg) | Complete response |

Adapted from Sponsor Table 4-3, page 17 of 49, Clinical Overview. Study D2304 Part 1 and 2 are complete; Part 3 of Study D2034 was open at the time of the BLA submission. Study D2036 is open at this time of the BLA submission.

5.2 Review Strategy

This efficacy and safety review is focused on three clinical trials (Study D2304, A2102 and D2306). Studies A2102 and D2306 serve as two supportive studies to the pivotal study D2034 which explores the efficacy and safety of canakinumab in CAPS in MWS. Studies A2102 and D2036 include patients with FCAS, MWS and MWS overlapping with NOMID. All three studies include adults and children with CAPS. The dose finding explorations were conducted in Study A2102 which was the first study performed among these three studies. The main efficacy conclusions are derived from Part 1, the run-in open label period preceding Part 2, the randomized, double blind, placebo controlled withdrawal period of Study D2304. These two periods in Study D2034 were further supported by the efficacy results characterizing the clinical response from canakinumab treatment in the two open label supportive studies, A2102 and D2036, as well as Part 3 of Study D2304.

The review of safety was based on safety assessments for all exposed patients from all three CAPS studies. The safety data were evaluated for deaths, serious adverse events (SAEs), adverse events (AEs), laboratory parameters, vital signs, and any potential safety signals associated with this class of IL-1 blocker therapies. Safety data was supported by clinical trial safety data in adult patients with other diseases, e.g., rheumatoid arthritis, psoriasis, mild asthma, age-related macular degeneration, as well as healthy adult subjects.

The biostatistics review was conducted by David Petullo.

5.3 Discussion of Individual Studies/Clinical Trials

See Section 9, Appendices, Subsection 9.4 Review of Individual Study Reports for the individual protocol review and results of pivotal Study D2304, open label Study A2102, and open label long term Study D2306.

6 Review of Efficacy

Efficacy Summary

The efficacy of canakinumab in the treatment of the signs and symptoms of CAPS disease was demonstrated by the results from pivotal Study D2304, Part 2, and from two supportive open label trials, Studies A2102 and D2306. These studies utilized a fixed dose of 150 mg sc in patients > 40 kg and a weight based dose of 2 mg/kg sc for pediatric patient population ≥ 15 kg and ≤ 40 kg. In Part 1 of Study D2304 most patients (97%) had a complete response to open label canakinumab as assessed by the physician global assessment of autoinflammatory disease activity \leq minimal using a 5-point scale ranging from *absent* to *severe* and assessment of skin disease \leq minimal using the same 5-point scale and normal serum values of CRP and/or SAA (< 10 mg/L). Efficacy was demonstrated in a controlled manner in Part 2 in which a significantly greater proportion of patients flared when withdrawn to placebo than when continued on canakinumab treatment. In Parts 3 of this same study, the response to open label canakinumab treatment was measured as maintenance of complete response and in patients who received canakinumab in Part 2 and as recovery of complete response in patients randomized to placebo in Part 2 who flared. The data from Part 3 provide supportive evidence of efficacy.

Supportive open label Studies A2102 and D2306 assessed treatment of canakinumab as measured by complete response. In Study A2102, patients received an initial dose of canakinumab followed by repeated doses each of which was administered when patients relapsed following complete response. In Study D2306, patients received canakinumab sc every 8 weeks. Study A2102 and D2306 demonstrated canakinumab treatment effect as measured by complete response in the majority of patients. Study A2102 provided additional supportive evidence of canakinumab based on a longer time to relapse among patients receiving higher doses than patients receiving lower doses. The following conclusions can be drawn from the results in these three studies:

1. In the initial open label 8 week period, Part 1 of Study D2304, the onset of the clinical benefit of canakinumab treatment was observed as early as 1 week of canakinumab treatment. Improvement across all disease assessments of CAPS was observed. The primary endpoint, complete response, was achieved by 97% (34 of 35) of CAPS patients treated with canakinumab in Part 1.
2. The primary efficacy analysis in Part 2, the randomized, double blind, placebo controlled withdrawal period was the proportion of patients with disease relapse/flare over 24 weeks. 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 endpoint, the proportion of patients with disease relapse/flare, demonstrated a statistically significant outcome for canakinumab compared to placebo. The odds ratio in Part 2 was zero with a 95% CI [0, 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 longevity of response was statistically superior in patients treated with canakinumab than in patients treated with placebo.

3. In the open label Studies A2102 and D2306, the majority of patients had a complete response: 93% of adult patients and 86% of pediatric patients in Study A2102, and, in Study D2306, complete response was observed in 61% of canakinumab naïve patients. There was some decline of the CAPS disease assessments' treatment response overtime due to escape from the therapeutic effect of canakinumab in CAPS disease.

4. The response rates to canakinumab were maintained longer term in adult and pediatric patients administered the proposed dose regimens, fixed dose of 150 mg sc for patient weight > 40 kg, and weight based dose, 2 mg/kg sc for the pediatric patient population ≥ 15 kg and ≤ 40 kg, respectively. In Part 3 of Study D2304, 97% of patients were without disease relapse. One patient experienced disease relapse by Day 336 from baseline.

6.1 Indication

The canakinumab development program was designed to support the proposed indication for the treatment of CAPS disease in adults and children aged 4 years and older including FCAS, MWS,

b(4)

6.1.1 Methods

The efficacy data contained in Section 6 of this review were generated from the randomized, withdrawal pivotal Study D2304 and from two supportive open label Studies A2102 and D2306. The analyses of the primary efficacy endpoints across these three clinical trials differed based upon the study design.

1) Study D2304 was a three part, Phase 3 trial starting with open label treatment period (Part 1), followed by a double-blind, placebo controlled, withdrawal period (Part 2), which was then followed by a second open label period (Part 3). Only patients with MWS were included in this trial. The primary efficacy variable in Study D2304 was the number of patients with MWS who experienced *disease flare* in Part 2, defined as those patients who experienced a *clinical relapse*. In Study D2304, only complete responders without *disease relapse* (identified in Part 1) were randomized into Part 2 and, subsequently, enrolled into Part 3. The clinical investigator's clinical assessment of CAPS disease activity was completed with a 5-point scale (*absent, minimal, mild, moderate* and *severe*) for the Physician's Global assessment of autoinflammatory disease activity

including skin disease, arthralgia, myalgias, headaches/migraine, conjunctivitis and fatigue/malaise.

Key secondary endpoints analyzed included:

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

Health related quality of life (HRQoL) patient reported outcomes were assessed using the SF-36, FACIT-F, HAD-QI in adults and the CHQ-CF87 in children.

2) Study A2102 was a non-randomized, open label, uncontrolled, single group, Phase 2 trial with two stages (periods). Patients with all three CAPS diseases were included in this study. The primary efficacy variable in Study A2102 was the *time from each dose administration to relapse* after a patient achieved *complete response* to canakinumab treatment. CAPS disease activity was assessed in Study A2102 with the same 5-point scale (*absent, minimal, mild, moderate* and *severe*) for the Physician's Global assessment of autoinflammatory disease activity as described above in Study D2304.

Secondary endpoints in Study A2102 assessed the impact of covariates on *time to relapse*. The four covariates assessed were: previous canakinumab treatment (yes or no); previous anakinra treatment (yes or no); clinical picture (FCAS, MWS or MWS overlapping with NOMID); and gender. Due to the limited number of dosing periods of data in some of the five different dosing regimen, secondary analyses in Study A2102 were restricted to periods where 150 mg sc was administered without the need for an additional canakinumab dose within a week. Other efficacy analyses included the same HRQoL variables analyzed in Study D2304.

3) Study D2306 was a non-randomized, open label, single treatment group, long term safety, tolerability and efficacy Phase 3 trial of canakinumab in patients with all three CAPS diseases requiring therapeutic intervention. The primary efficacy variable in Study D2306 was the response to treatment expressed as *complete response*. CAPS disease activity assessments were completed in Study D2306 with the same 5-point scale (*absent, minimal, mild, moderate* and *severe*) for the Physician's Global assessment of autoinflammatory disease activity described above in Studies D2304 and A2102.

Study D2306 also assessed canakinumab up-titration which was permitted in patients not achieving *complete response* with the first canakinumab dose, e.g., the proposed fixed dose of 150 mg sc in adults > 40 kg or the weight based dose of 2 mg/kg in pediatric patients ≥ 15 kg and ≤ 40 kg. Key secondary efficacy analyses in Study D2306 included assessment of safety, tolerability, and immunogenicity of canakinumab.

General Description of Endpoints

CAPS disease is a spectrum of three distinct clinical conditions each of which is associated with an uncontrolled caspase 1 activity resulting in increased production of IL-1 β . Patients with CAPS disease experience a life long multisystem inflammatory disease presenting in early childhood. Patients typically suffer from fever, fatigue, headache/migraine, muscle, joint and abdominal pain, urticarial skin rash, conjunctivitis and papillaedema in the more severe forms of CAPS disease. Other symptoms include destructive arthritis, cerebral demyelination and unusual neurological symptoms. Severe disabilities including sensorineural deafness, visual loss, and amyloidosis-mediated organ dysfunctions, such as renal failure, are typical complications of CAPS disease.

CAPS Disease Guidance for Industry

No guidelines for the clinical development in CAPS exist as this condition is rare and most often presents as overlapping syndromes, hence the description as a disease spectrum.

Improvement in Signs and Symptoms of CAPS Disease Spectrum

The induction and maintenance of a *complete* clinical and serological *response*, e.g., with serum markers of inflammation such as C-reactive protein (CRP) and/or Serum Amyloid A (SAA), as well as *time to relapse*, were considered clinically meaningful key efficacy endpoints based on the disease signs and symptoms across all three diagnoses. Patients were permitted to roll over from one study to the next study in this canakinumab development program.

Primary Efficacy Endpoints

Study D2304

Pivotal Study D2304 was the single trial which included a randomized, double-blind study design. In Part1, the primary efficacy endpoint, *complete response* to treatment was defined as:

- Physician global assessment of autoinflammatory disease activity \leq minimal (using a 5-point scale ranging from *absent* to *severe*), AND
- Assessment of skin disease \leq 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 \geq 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*) for the following assessments:

- Skin disease (urticarial skin rash)
- Arthralgia

- Myalgia
- Headache/migraine
- Conjunctivitis
- Fatigue/malaise
- Other symptoms related to autoinflammatory syndrome
- 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 from baseline by at least one category.

Study A2102

The primary efficacy variable in this supportive open label study was *time* (from each dose administration) *to relapse* after a patient achieved a *complete response* to treatment.

The definition of complete response, relapse and partial response were revised based on the experience from the first 4 patients enrolled in Stage 1 in order to allow for a quick re-treatment in the case of *relapse*. The final definition of *complete response* to treatment was:

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

The final definition of *relapse* was:

- 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.

- Physician global assessment of disease activity > minimal

OR

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

The final definition of *partial response* to treatment was:

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

AND

- Physician global assessment improvement over baseline by one step.

Study D2306

The primary efficacy was defined as *complete response* in this open label, long term study. *Complete response* to treatment was defined as above in Study A2102 using normal serum values of CRP and/or SAA (< 10 mg/L).

For patients who had achieved *complete response*, *relapse* was 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 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.

Secondary Efficacy Endpoints

Study D2304, A2102 and D2306

The secondary endpoints unique to the randomized withdrawal Study D2304 were:

- Proportion of canakinumab treatment responders in Part 1; and
- Proportion of patients without *disease relapse* in Part 3;

Secondary endpoints analyzed across all three studies were:

- Safety,
- Tolerability;
- PK and PD assessments of canakinumab including total IL-1 β ;
- Immunogenicity assessments for anti-canakinumab antibodies;
- Change in serum inflammatory markers, CRP and/or SAA;
- Patient's assessment of disease symptoms and assessment of skin disease;
- Special assessments were assessed by the categories of *normal*, *clinically insignificant abnormality* or *clinically significant abnormality based on the physician's judgement*:
 1. Audiogram assessment;
 2. Neurological and ophthalmological assessment; and
 3. MRI of the brain.
- Renal function including creatinine clearance and proteinuria (only in Study A2102);
- HRQoL assessments were analyzed in all three studies:
 1. Medical Outcome Short Form (36) Health Survey (SF-36), physical and mental component summary scores (PCS and MCS);
 2. Functional disability as measured by the Health Assessment Questionnaire (HAQ-DI);

3. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score measures fatigue.
4. Child Health Questionnaire-Parent Form (CHQ-PF28) in children/adolescent patients, 5 years to 17 years. This is a parent administered questionnaire.

6.1.2 Demographics

The baseline demographic characteristics of the participants in three CAPS studies are shown in **Table 2**. In Studies D2304, A2102 and D2306, the patient populations were representative of adult and pediatric patients with clinically active CAPS disease. The only randomized study, D2304, was well balanced across treatment groups. Studies A2102 and D2306 included pediatric patients as young as 4 years and 5 years of age, respectively. The majority of patients in the three CAPS studies were >18 years of age, Caucasian, female, and weighed > 55 kg (see **Table 2**). Most of the patients in Study D2306 were primarily enrolled from a prior study. Patients in Study D2304 and A2102 were primarily were canakinumab naïve patients (see **Table 2**). Overall, the demographic characteristics were similar among these three studies.

Table 2.

| Summary of Baseline Demographics Across Studies D2304, A2102 and D2306 | | | | | |
|--|------------------|------------------|-------------------|------------------|------------------|
| | D2304 Part 1 | D2304 Part 2 | | A2102 | D2306 |
| | ACZ885 N = 36 | ACZ885 N = 15 | Placebo N = 16 | ACZ885 N = 34 | ACZ885 N = 57 |
| Age (years) n | | | | | |
| Mean (SD) | 34 (15) | 34 (14) | 33 (16) | 30 (14) | 33 (15) |
| Median (min, max) | 36 (9, 74) | 37 (9, 58) | 31 (14, 74) | 32 (4, 51) | 35 (5, 61) |
| Age category n (%) | | | | | |
| < 18 years* | 5 (14%) | 3 (20%) | 2 (13%) | 7 (21%) | 9 (16%) |
| ≥ 18 years | 30 (86%) | 12 (80%) | 14 (88%) | 27 (79%) | 48 (84%) |
| Cohort n (%) | | | | | |
| Pts from prior study | 9 (26%) | 4 (27%) | 3 (19%) | 0 | 39 (68%) |
| from Study A2102 | 9 (26%) | 4 (27%) | 3 (19%) | NA | 22 (39%) |
| from Study D2304 | NA | NA | NA | 0 | 17 (30%) |
| ACZ885 Naïve Pts | 26 (74%) | 11 (73%) | 13 (81%) | 34 (100%) | 18 (3%) |
| Race n (%) | | | | | |
| Caucasian | 33 (94%) | 15 (100%) | 14 (88%) | 31 (91%) | 54 (95%) |
| Asian | 1 (3%) | 0 | 1 (7%) | 2 (6%) | 2 (4%) |
| Other | 1 (3%) | 0 | 1 (6%) | 1 (3%) | 1 (2%) |
| Weight (kg) | | | | | |
| Mean (SD) | 60 (11) | 59 (12) | 61 (9) | 55 (15) | 61 (20) |
| Median (min, max) | 61 (26, 81) | 60 (26, 73) | 63 (46, 74) | 57 (17, 77) | 63 (20, 154) |

Adapted from Sponsor Table 1-10, page 19 of 82, Summary of Clinical Safety; NA= not applicable. Pediatric pts in Studies A2102 (7 pts) and D2304 (5 pts) are unique; in Study D2306 unique as well as roll-over pts from A2101 and D2304 were treated, e.g., total number of pediatric pts = 15.

Disease Characteristics

In general, patients in Studies D2034, A2102, and D2306 had clinically active and severe CAPS disease as many patients had significant auditory and neurological deficiencies, pre-existing

ophthalmological abnormalities, and MRI of the brain abnormalities. In pivotal Study D2304, only MWS patients were enrolled, however, one patient was identified as a MWS/NOMID patient.

In Study D2304, baseline disease characteristics demonstrated a high proportion of *clinically significant abnormalities* for audiogram (63%), neurological (23%), and ophthalmological (14%) assessments. In Study D2304, over 65% of patients had *moderate* and over 11% of patients had *severe* disease at baseline (see **Table 3**). In Study D2304, 43% of patients had *moderate* skin disease at baseline compared with Study A2102 in which 53% of patients had *mild to moderate* skin disease (see **Table 3**).

Baseline demographic characteristics of patients treated with canakinumab or placebo in Study D2304, Part 2, demonstrated a higher proportion of placebo-treated patients (44%) compared to ACZ885-treated patients (27%) with a neurological assessment as *clinically insignificant abnormality*. By contrast, ACZ885-treated patients in Part 2 had a higher percentage of *clinically significant abnormality* (40%) compared to placebo-treated patients (13%) at baseline. Overall, the disease characteristics were otherwise similar between ACZ885- and placebo-treated patients in Part 2 of Study D2304.

In Study A2102, baseline audiology assessments showed *clinically significant abnormality* with hearing impairment/bilateral sensorineural hearing loss in 14 patients out of 25 patients (56%). Eight (8) patients showed *normal* audiology. In Study A2102, 44% of patients had *moderate* and over 15% of patients had *severe* clinical disease at baseline (see **Table 3**). The serum markers of inflammation, CRP and/or SAA, were elevated in both Studies D2304 and A2102. By contrast, in Study D2306, serum markers of inflammation were not elevated at baseline (see **Table 3**). This was not unexpected as 68% of patients in Study D2306 had been previously treated with canakinumab. The baseline disease characteristics support the overall CAPS disease severity of enrolled patients.

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Table 3.

| Summary of Baseline CAPS Disease Characteristics - Studies D2304, A2102 and D2306 | | | | | |
|---|------------------|------------------|-------------------|------------------|------------------|
| | D2304 Part 1 | D2304 Part 2 | | A2102 | D2306 |
| | ACZ885 N = 36 | ACZ885 N = 15 | Placebo N = 16 | ACZ885 N = 34 | ACZ885 N = 57 |
| Confirmation of NALP3 mutation | 35 (100%) | 15 (100%) | 16 (100%) | 34 (100%) | 55 (97%) |
| Audiogram assessment* | | | | | |
| Clinically insignificant abnormality | 8 (23%) | 4 (27%) | 3 (19%) | 11/25 (44%) | ND |
| Clinically significant abnormality | 22 (63%) | 8 (53%) | 12 (75%) | 14/25 (56%) | ND |
| Neurological assessment* | | | | | |
| Clinically insignificant abnormality | 12 (34%) | 4 (27%) | 7 (44%) | 10/25 (40%) | ND |
| Clinically significant abnormality | 8 (23%) | 6 (40%) | 2 (13%) | 1/25 (4%) | |
| Ophthalmological assessment* | | | | | |
| Clinically insignificant abnormality | 16 (46%) | 7 (47%) | 7 (44%) | 10/24 (42%) | ND |
| Clinically significant abnormality | 5 (14%) | 2 (13%) | 1 (6%) | 7/24 (29%) | ND |
| MRI assessment* | | | | | |
| Clinically insignificant abnormality | 4 (11%) | 2 (13%) | 2 (13%) | 5/20 (25%) | ND |
| Clinically significant abnormality | 2 (6%) | 2 (13%) | 0 | 1/20 (5%) | ND |
| Physician's global assessment of autoinflammatory disease | | | | | |
| Minimal | 2 (6%) | 1 (7%) | 0 | 4 (12%) | 12 (21%) |
| Mild | 7 (20%) | 2 (13%) | 5 (31%) | 9 (27%) | 16 (28%) |
| Moderate | 22 (63%) | 10 (67%) | 9 (56%) | 15 (44%) | 9 (16%) |
| Severe | 4 (11%) | 2 (13%) | 2 (13%) | 5 (15%) | 1 (2%) |
| Assessment of skin disease | | | | | |
| Minimal | 6 (17%) | 3 (20%) | 3 (19%) | 7 (21%) | 7 (12%) |
| Mild | 9 (26%) | 4 (27%) | 5 (31%) | 10 (29%) | 6 (11%) |
| Moderate | 15 (43%) | 7 (47%) | 5 (31%) | 8 (24%) | 5 (9%) |
| Severe | 1 (3%) | 0 | 1 (6%) | 3 (9%) | 0 |
| Patient's global assessment of symptoms | | | | | |
| Minimal | 6 (17%) | 2 (13%) | 2 (13%) | 3 (9%) | ND |
| Mild | 8 (32%) | 4 (27%) | 3 (19%) | 10 (29%) | ND |
| Moderate | 9 (26%) | 5 (33%) | 3 (19%) | 11 (32%) | ND |
| Severe | 4 (11%) | 2 (13%) | 2 (13%) | 5 (15%) | ND |
| C-reactive protein (mg/L) | | | | | |
| Median (range) | 20 (2 - 105) | 20 (2 - 102) | 26 (8 - 105) | 36 (0.2 - 288) | 3 (0 - 44) |
| Serum amyloid A (mg/L) | | | | | |
| Median (range) | 49 (3 - 530) | 48 (4 - 508) | 112 (9 - 530) | 66 (2 - 908) | 6 (0 - 175) |

Adapted from Sponsor Table 1-11, page 21 of 82, clinical safety; * = categories of normal/absent were not shown, see individual study report results; ND = not done; Study D2306 interim analysis did not include audiogram, neurological, ophthalmological, MRI and patient's global assessments.

Medical Histories

In Study D2304, the medical histories primarily concerned the musculoskeletal and connective tissue system, eye disorders, and skin disorders. Specific conditions included conjunctivitis, arthralgia, urticaria, and headache, all co-morbidities typical of CAPS diseases. Two patients had amyloidosis, 5 vertigo, 5 hypertension and 2 abnormal liver function tests. One patient had demyelination at the baseline assessment. In Study A2102, 7 patients with adult MWS were diagnosed with amyloidosis. Four patients had renal insufficiency and three of whom had amyloidosis at baseline assessment. The patients enrolled in all three studies demonstrated typical disease severity of CAPS across these three studies.

Concomitant Medications

The total number of patients taking at least one concomitant medication at Baseline has been summarized in tables in the Individual Study Reports. In Part 1 of pivotal Study D2304, the most common concomitant medications were paracetamol (43% of patients) and topical non-steroidal anti-inflammatory drugs (20% of patients). Corticosteroids were used in 14% of the patients with prednisolone acetate accounting for 6%. In Part 2 of Study D2304, all patients treated with canakinumab and the majority of placebo-treated patients (94%) received concomitant medications. The drug classes in Part 2 were comparable to those described in Part 1. Note-worthy, 20% of patients in Part 2 received antibiotics (cephalosporin or amoxicillin) compared to none in the placebo- treated group.

In Study A2102, all patients took concomitant medications during the study. The most common medications were iron supplements, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), amoxicillin and oral contraceptives. Four (4) patients took systemic corticosteroids and in one NOMID patient, steroids were tapered and discontinued during this study. The majority (71%) of patients in Study A2102 had previously received anakinra prior to enrollment.

In Study D2306, concomitant medications were not analyzed in the interim report.

6.1.3 Patient Disposition

Patient participation in the pivotal Study D2304 and the two supportive open label studies, A2102 and D2306, are summarized in **Table 4**. In Part 1 of Study D2304, all patients were treated with canakinumab and the majority (89%) completed Part 1 with four (4) patients who discontinued due to disease flare defined as lack of *complete response* per the protocol. In Part 2, the randomized, double-blind, withdrawal, multiple-dose period of Study D2304, no patients treated with canakinumab experienced *disease flare* Part 2 compared to 25% in the placebo-treated patients (see **Table 4**). Thirteen (13) placebo-treated patients (81%) discontinued Part 2 due to *clinical response* or early withdrawal.

In the two open label supportive studies, A2102 and D2306, the majority of enrolled patients completed the studies. Though only interim cutoff data for Study D2306 was available at this review the rate of discontinuation in the two open label studies was less than the rate of discontinuation observed in the randomized, withdrawal period, Part 2 of Study D2304.

A very small number of adverse events caused patients to discontinue a CAPS study (see **Table 4**). The adverse event in Study A2102 was an unplanned pregnancy in a 17-year old patient with MWS/NOMID. One patient with MWS/NOMID experienced lack of efficacy and discontinued Study A2102. One patient with FCAS discontinued Study A2102 due inability to comply with the study visit schedule. In Study D2306, a 46-year old patient with MWS experienced worsening of multiple sclerosis like lesions of demyelination and was permanently discontinued.

Table 4.

| Summary of Patient Disposition - Studies D2304, A2102 and D2306 | | | | | | |
|---|------------------------------------|-------------------------------------|---|---|--|--|
| | Study D2304 | | | Study A2102 | Study D2306 | |
| | Part 1 (8 wks) ACZ885 N = 35 | Part 2 (24 wks) ACZ885 N = 15 | Parts 1-3 (48 wks) Placebo N = 16 | Open label (46 wks) ACZ885 N = 34 | Open label (≤ 8 wks) ACZ885 N = 57 | |
| Enrolled | 35 | 15 | 16 | 34 | 58* | |
| Completed n (%) | 31 (89%) | 15 | 4 (25%) | 31 (91%) | NA | |
| Discontinued n (%) | 4 (11%) | 0 | 13 (81%) | 3 (9%) | 1 (2%) | |
| Adverse events | 0 | 0 | 0 | 1 (3%) | 1 (2%) | |
| Clinical relapse or early withdrawal | 0 | 0 | 13 (81%) | 0 | 0 | |
| Lack of complete response | 4 (11%) | | | 5 (14%) | 1 (3%) | |
| Other | 0 | 0 | 0 | 1** (3%) | 0 | |

* One patient was enrolled but was only in screening at the time of the data cutoff (12Sept08). No treatment had yet been received by this patient.
 ** Patient was unable to comply with study visit schedule.

Adapted from Sponsor Table 1-12, page 24 of 82, summary of clinical safety.

Patients Randomized by Country

The CAPS development program was global and included multiple countries in each study.

Study D2304: conducted among 11 centers across 5 countries: France (5), Germany (1), India (1), United Kingdom (1) and the United States (3).

Study A2102: conducted among 8 centers across four countries: France (1), Germany (5), India (1), Spain (1), and the United Kingdom (1).

Study D2306: [interim data cutoff 12Sept2008] conducted among 14 centers: France (3), Germany (5), India (1), Spain (1), United Kingdom (1) and USA (3).

No unethical conduct was reported at any center and no single center appeared to disproportionately represent the primary efficacy results.

6.1.4 Analysis of Primary Endpoint(s)

In this BLA application, only pivotal Study D2304 includes a randomized, controlled assessment of efficacy. The two supportive studies, A2102 and D2306, both utilized open label study designs. Therefore, only Study D2304 will be discussed under this primary efficacy analysis section.

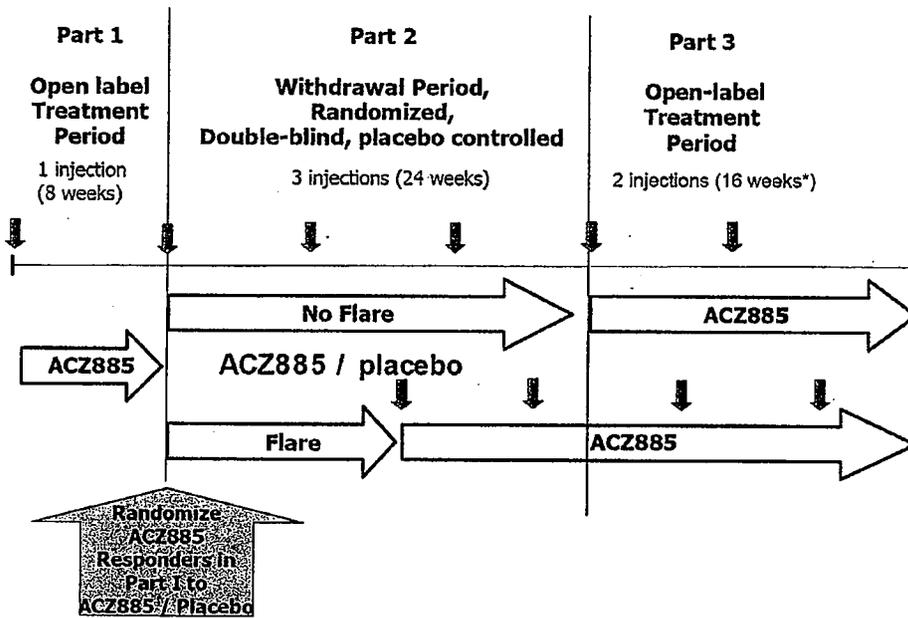
The primary efficacy endpoint analysis is based upon pivotal Study D2304, Part 2, the 24 week, randomized, double blind, placebo controlled withdrawal period. The treatment effect of the initial exposure to canakinumab, as measured by complete response, in the 8-week, open label Part 1 of pivotal Study D2304 is critical to the interpretation of the outcome of the primary efficacy endpoint analysis of the proportion of patients with disease relapse/flare in the randomized, double blind, placebo-controlled withdrawal period in Part 2 of Study D2304. In open label period, Part 1, the treatment effect of canakinumab was based upon complete response defined by a clinically meaningful composite measure consisting of the Physician's Global assessment of autoinflammatory disease and the assessment of skin disease reported as ≤ minimal as well as normal levels of serum biomarkers, CRP and/or SAA values (<10 mg/L). In Part

2, the randomized, double blind, placebo controlled withdrawal period, the primary efficacy endpoint analysis was the proportion of patients with disease relapse/flare defined by a composite measure consisting of the Physician’s Global assessment of disease activity, assessment of skin disease, and the measured levels of serum biomarkers of inflammation, CRP and/or SAA. The Agency agreed upon the primary efficacy endpoint in pivotal Study D2304. See the Individual Study Report reviews for additional details.

Part 1- Complete Response

In Part 1, 34 of 35 MWS patients (97%) achieved the primary endpoint, a *complete response* with canakinumab treatment (see **Figure 3**). 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 *complete response* 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.

Figure 3



Part 2 - Disease Relapse/Flare

Part 1 included the assessment of the initial exposure to canakinumab in the 8 week, open label treatment. In contrast, Part 2 included assessment of the continued treatment effect of canakinumab based on the likelihood of *disease relapse/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 endpoint, the *proportion of patients with disease relapse/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, using the ITT population. The statistics reviewer, David Petullo, confirmed this conclusion (see **Table 5**).

Table 5.

| Primary Efficacy Analyses - Study D2304 | | | | | | | |
|--|--------------|-----------|---------------|--------------|-------------------------------|----------------|-----------|
| Proportion of Patients with Disease Flare: Comparison between Treatment Groups at the End of Part 2 - (ITT population) | | | | | | | |
| | ACZ885 | | Placebo | | Differences in Response rates | | |
| | N = 15 | | N = 16 | | 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, -0.82) | <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.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary analyses completed across all three CAPS clinical trials support the primary efficacy analysis, as measured by the *proportion of patients with disease relapse/flare* demonstrated in Part 2 of Study D2304, as well as the favorable rate of *complete response* demonstrated in the open label Part 1 of Study D2304. Secondary analyses are grouped based upon the nature of the clinical data. Additional data from pivotal Study D2304 is followed by supportive data from open label studies, A2102 and D2306.

Assessments of Specific Disease Manifestations

Study D2304, Part 1 Specific Disease Assessments

In Part 1, the analyses of specific disease manifestations all showed clinically meaningful improvement and supported the primary efficacy endpoint analysis as measured in Part 2. 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, based upon Part 2 randomization, in open label Part 3 are presented in **Tables 6, 7 and 8**.

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 6**). 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. Improvement was sustained through the last assessment in Part 3 (see **Table 6**).

For the parameters of headache/migraine, conjunctivitis, and fatigue/malaise, half or more of the patients had scores of *mild*, *moderate* or *severe* at baseline. Headache/migraine, conjunctivitis, and fatigue/ malaise demonstrated a positive trend of improvement in 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 7**).

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 8**).

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 with canakinumab treatment was sustained through the last assessment in Part 3. See **Table 8**.

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 demonstrated in Part 3 supported the sustained effects of canakinumab treatment in MWS disease.

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Table 6

| Results from Parts 1, 2 and 3 - SKIN ASSESSMENT (without LOCF) | | | | |
|--|--------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Categorical Variable | According to Randomization in Part 2 | | | |
| | ACZ885, N = 35 n / N (%) | | ACZ885, N = 15 n / N (%) | Placebo, N = 16 n / N (%) |
| | 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) | | | | |
| 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 | 3/15 (20%) | 31/35 (89%) | 12/15 (80%) |
| 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) | | | | |
| 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 | 5/15 (33%) | 32/35 (91%) | 12/15 (80%) |
| 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

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Table 7.

| Results from Parts 1, 2 and 3 - HEADACHE/ MIGRAINE (without LOCF) | | | | |
|--|------------------------------------|--|--|--|
| According to Randomization in Part 2 | | | | |
| Categorical Variable | ACZ885, N = 35 n /N (%) | | ACZ885, N = 15 n /N (%) | Placebo, N = 16 n /N (%) |
| | 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) | | | | |
| 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 | 3/15 (20%) | 21/35 (60%) | 12/15 (80%) |
| 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) | | | | |
| 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 | 2/15 (13%) | 19/35 (54%) | 11/15 (73%) |
| 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.

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Table 8

| Results from Parts 1, 2 and 3 - OTHER SYMPTOMS RELATED TO AUTOINFLAMMATORY SYNDROME (without LOCF) | | | | |
|---|----------------------------|----------------------------------|----------------------------------|----------------------------------|
| According to Randomization in Part 2 | | | | |
| Categorical Variable | ACZ885, N = 35 n/ N (%) | | ACZ885, N = 15 n/ N (%) | Placebo, N = 16 n/ N (%) |
| | 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) | | | | |
| 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 | 13/15 (87%) | 26/35 (74%) | 11/15 (73%) |
| 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) | | | | |
| 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 | 0/15 (0%) | 17/35 (49%) | 9/15 (60%) |
| 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.

Study D2304, Part 2 - Specific Disease Manifestations

In Part 2, the randomized, double blind, placebo controlled withdrawal portion of Study D2304, 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 *complete 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 9**).

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 9**).

Table 9.

| 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 |

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

Study A2102 - Specific Disease Manifestations

The analyses of individual disease assessments in open label Study A2102 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 the Individual Study Report for Study A2102). 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 and showed 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 that in the majority of patients, *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.

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 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 the canakinumab treatment effect (see **Table 83** in the Individual Study Report for Study A2102).

Study D2306 – Specific Disease Manifestations

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. Though the assessments of disease activity data were incomplete, these limited data support improved disease assessments in this open label trial with canakinumab treatment in patients with CAPS disease (see **Table 90** in the Individual Study Report for Study D2306).

The 5-point scale of disease parameters used to assess the Physician's Global assessment on autoinflammatory disease activity, e.g., skin disease, arthralgia, myalgias, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms *related* to autoinflammatory syndrome and symptoms *not related* to autoinflammatory syndrome, were accounted for in the summary for the Physician's Global assessment of autoinflammatory disease activity (see **Table 90** in the Individual Study Report for Study D2306). These disease assessment results support the treatment effect of canakinumab in patients with CAPS disease.

Study D2304 - Analysis of Patients Who Discontinued from Part 2

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 met the definition of *relapse*, per the protocol. These thirteen (13) placebo-treated patients demonstrated a decline, during Part 2, in their clinical disease activity based upon the Physical Global assessment of autoinflammatory disease, skin disease assessment, and the 5-point scale of other CAPS disease features (see **Tables 59** and **60** in the Individual Study Report for Study D2304). 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.

Time to Disease Flare

Study D2304 and open label Study A2102 studied as secondary efficacy endpoint, the *time to disease flare*. *Time to disease flare* was not measured in open label Study D2306. Study D2034 studied *time to disease flare* in patients randomized to placebo in the randomized withdrawal phase. Study A2102 measured time to disease flare following individual doses of canakinumab since repeat doses were only given when disease flared after an initial complete response.

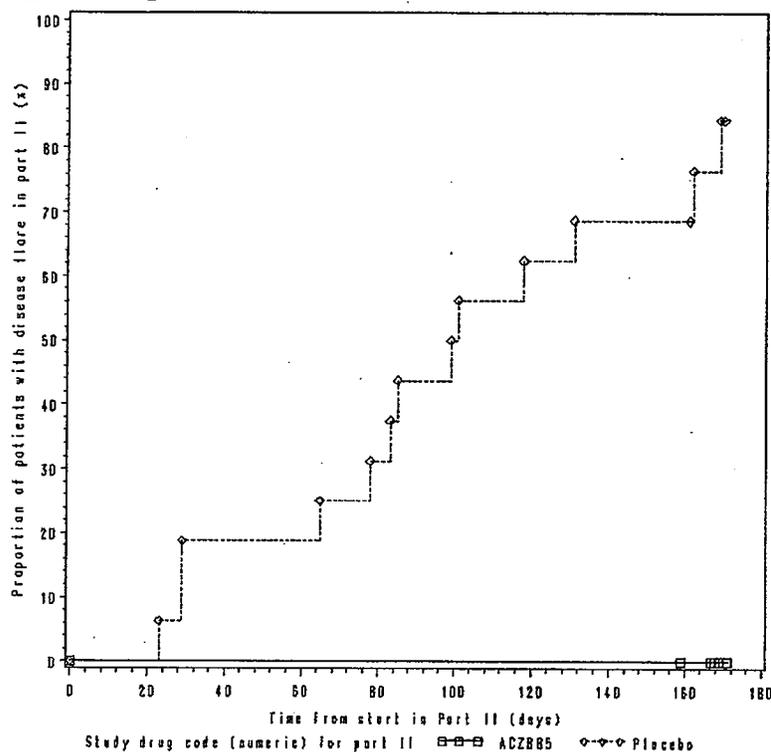
Study D2304 - Time to Disease Flare

In the pivotal Study D2304, *time to disease flare* was a secondary efficacy assessment analyzed in Part 2 using the ITT population. The Kaplan-Meier estimates demonstrated the substantial treatment effect of canakinumab compared to placebo (see **Figure 4**). 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. Mean *time to disease flare* across the 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]

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

Figure 4 Kaplan-Meier Estimate of Time to Disease Flare – Study D2034, Part 2



Sponsor figure 3-1, page 33 of 51, Summary of Clinical Efficacy.

Study A2102 - Complete Response

In open label Study A2102, the primary endpoint was *time (from each dose administration) to relapse and complete response*. In Stage 1, all four (4) patients achieved *complete response* following canakinumab, 10 mg/kg or 1 mg/kg iv, by 2 to 7 days from dosing (see **Table 10**). 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 (see **Table 10**). Twenty-four (24) patients (83%) achieved a *complete response* after every dose of canakinumab 150 mg sc. The results in Study A2102 as measured by *complete response* support efficacy with the proposed fixed dose of canakinumab in patients with CAPS diseases.

Table 10

| 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.

Study A2102 - Complete Response followed by Time to Relapse

To further 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 11**). The results with the proposed dose regimen of canakinumab 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.

Pediatric patients in Study A2102 were analyzed separately to explore the proposed weight based dose regimen, 2 mg/kg sc, in patients 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 which is shorter in duration compared to *time to relapse* observed in adult patients (see **Table 11**). One concern with the proposed weight based dose regimen was the risk of under dosing smaller weight patients and, subsequently, potentially observing less favorable clinical outcomes in smaller

weight patients treated with canakinumab. However, in fact pediatric patients treated with the proposed weight based dose regimen demonstrated *complete response* comparable to adult patients treated with the fixed dose regimen of canakinumab.

Table 11.

| 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

Study D2306 - Complete Response and Relapse

In Study D2306, *complete response* was identical to the definition in Study A2102. Maintenance of *complete response* over time was defined in Study D2306 by the number of patients *without relapse*. No patient treated with canakinumab and for whom *relapse* data was available, experienced *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** in Individual Study Report for Study D2306). Among patients with *relapse* assessment data (19 patients), none had a *relapse*.

Study D2306 - Canakinumab Naïve Patients and Complete Response

In open label Study D2306, *complete response* was observed in 61% of canakinumab naïve patients (see **Table 12**). Out of four (4) canakinumab naïve patients (all MWS) not achieving *complete response* based upon the investigator’s judgment, two (2) patients achieved *complete response* based upon the protocol definition of *complete response* (see **Table 12**).

Despite limited interim report *relapse* and *complete response* data, these outcomes support the primary efficacy analyses based upon *complete response* in all three studies and supported the longer treatment effect of canakinumab therapy at the proposed fixed dose regimen and at the proposed weight based dose regimen every 8 weeks in patients with CAPS disease.

Table 12

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

Study D2306 - Canakinumab Up-Titration and *Complete Response*

Canakinumab dose up-titration was permitted in this open label 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.

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.

Objective Measures of Response to Canakinumab

Study D2304, Parts 1 through 3 - Protein Markers of Inflammation

To explore the effect of canakinumab treatment on serum markers of inflammation in patients with MWS, CRP and/or SAA were assessed in Parts 1 through 3. In open label canakinumab treatment Part 1, CRP and/or SAA serum levels decreased in all patients by Day 8 and continued low through the last assessment of Part 1 (see **Tables 13 and 14**). These data demonstrated maintenance of response to canakinumab treatment and supported the primary efficacy analysis in favor of canakinumab treatment compared to placebo in patients with MWS.

Table 13.

| 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 14.

| 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/or SAA levels in the group randomized to continue canakinumab treatment versus the group randomized to placebo was analyzed. CRP and/or 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 (see Table 15).

Table 15.

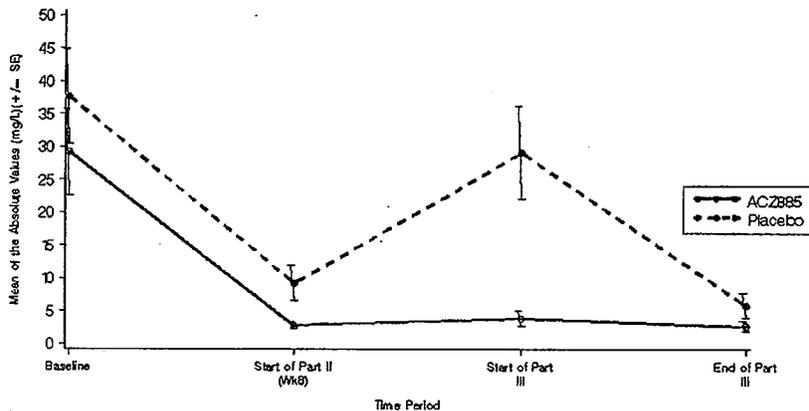
| CRP (mg/L) and SAA (mg/L) Comparison between ACZ885 and Placebo-Treatment in Part 2 (using LOCF, ITT Population) | | | | | | | |
|--|-------------|---------------------------|--------------------|-------------|---------------------------|--------------------|------------|
| Laboratory Tests | ACZ885 | | | Placebo | | | p-value ** |
| | Week 8 | Last Assessment in Part 2 | Change from Week 8 | Week 8 | Last Assessment in Part 2 | Change from Week 8 | |
| 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) | |

Adapted from sponsor Table 3-14, page 34 of 51, Summary of Clinical Efficacy

The difference between the treatment effect on CRP and/or SAA levels in the canakinumab treatment group compared to the placebo group in Part 2 demonstrated a statistically significant outcome in favor of continued canakinumab treatment compared to placebo (see **Table 15**). These data supported the primary efficacy analysis in favor of continued canakinumab treatment compared to placebo.

To illustrate the effect on CRP and/or SAA levels with continued canakinumab treatment from baseline in Part 1 through Part 3, graphic demonstration of the substantial improvement in CRP levels with canakinumab treatment is presented in **Figure 5**. The SAA levels also demonstrate substantial improvement with canakinumab treatment (see **Figure 11** in Individual Study Report D2304). The mean CRP and/or 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. Canakinumab treatment resulted in reductions in CRP and/or SAA levels to the normal range. The CRP and/or SAA levels increased in Part 2 in patients randomized to placebo but remained unchanged in patients remaining on canakinumab (**Figures 5 and 6**). These data supported the primary efficacy analysis favoring continuous canakinumab compared to placebo in patients with MWS.

Figure 5. CRP (mg/L) from Baseline through Part 3, Study D2304 (ITT population)



Source: figure 11-2, p 88 of 3953.

Study A2102- Protein Markers of Inflammation

To explore the effect of canakinumab treatment on objective markers of inflammation in patients with CAPS disease, CRP and SAA were assessed in open label Study A2102. 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/or SAA did not return to peak levels observed at baseline in the majority of dose regimens (see **Tables 80 and 81** in the Individual Study Report for Study A2102). These data support the primary efficacy variable and the duration of the treatment effect of canakinumab at the proposed fixed dose of 150 mg sc.

Study D2306 – Protein Markers of Inflammation

To explore the effect of canakinumab treatment on objective serum markers of inflammation, CRP and/or SAA were assessed for the change from baseline in roll-over and canakinumab naïve patients, by visit. Less than half of rollover patients (40%) and only 22% of canakinumab naïve patients had CRP levels performed by Visit 5, Day 57. Although these are limited data, both treatment groups demonstrated a decrease in CRP and/or SAA levels by Visit 5, Day 57 (see **Table 91** see the Individual Study Report for Study D2306). 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.

Clinical Response to Canakinumab in Children and Adolescents with CAPS Disease

Study D2304 - Pediatric Patients and Complete Response

Pediatric patients were assessed for their response to canakinumab. Patients with body weight \geq 15 kg and \leq 40 kg were administered canakinumab 2 mg/kg sc and patients > 40 kg were administered a fixed dose of canakinumab 150 mg sc. Five (5) pediatric patients were enrolled in Study D2034 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 16**). All five (5) pediatric patients in Study D2304 had *complete response* in Part 1. Weight-based dosing is discussed separately in the Individual Study Report for open label Studies A2102 and D2306.

Table 16.

| Pediatric Patients in Study D2304 | | | | | | | | |
|-----------------------------------|------------------------|-------------------|-----------------|-------------------|-----------------|--------|-------------------|-------------------|
| Age | Weight (kg), Treatment | Part 1 | | Part 1 | | Part 2 | Part 2 | Part 3 |
| | | Baseline CRP mg/L | Week 1 CRP mg/L | Baseline SAA mg/L | Week 1 SAA mg/L | Flare | Discontinued | |
| 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 | | | |

Study A2101 – Pediatric Patients and Complete Response

Pediatric patients were analyzed separately to assess weight based dosing and *complete response*. All 5 pediatric patients receiving 2 mg/kg sc canakinumab treatment achieved *complete response* within 2 to 8 days from first dosing. In Study A2102, the primary efficacy variable, as measured by *complete response*, was achieved in all pediatric patients with the proposed weight based dose regimen of canakinumab.

6.1.6 Other Endpoints

Health Related Quality of Life Assessments

Study D2304- HRQoL

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

Study A2102 and Study D2306 - HRQoL

The HRQoL assessments completed in Study A2102 were prone to bias by the nature of the open label study design and therefore, should not be included in labeling. See the Individual Study Report for Study A2102 for additional details. In open label Study D2306, the HRQoL assessment data were not submitted in the interim report.

Study D2304 - 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 abnormal* 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.

Study A2102 - Special Assessments

The same special assessments included in Study D2304 were included in Study A2102. 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.

Study D2306 – Special Assessments

Special assessments were not included in the interim cutoff data of Study D2306.

Study A2102 – Renal Function Assessments

CAPS disease, particularly, MWS and MWS overlapping with NOMID, may be associated with renal function impairment. Four (4) patients enrolled in Study A2102 with 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.

6.1.7 Subpopulations

Study D2304 - Muckle-Wells Syndrome

To explore the effect of canakinumab treatment in patients with MWS, subgroup analyses were completed. 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 17**). 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 in patients with MWS. These subgroup analyses supported the primary efficacy analysis in favor of canakinumab compared to placebo in patients with MWS.

Table 17.

| | 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. | |

Study A2102 - Time to Relapse/Flare in Subpopulations of CAPS Disease

To explore the effect of canakinumab treatment in CAPS disease, subgroup analyses were performed (see **Table 18**). Noteworthy, patients with FCAS had a longer *time to relapse* than did patients with MWS or MWS overlap with NOMID. Both FCAS patients achieved complete response. FCAS is the mildest form of the CAPS disease spectrum which may, in part, explain the longer duration of *time to relapse* with FCAS patients compared to MWS and MWS overlapping NOMID.

Table 18.

| 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.

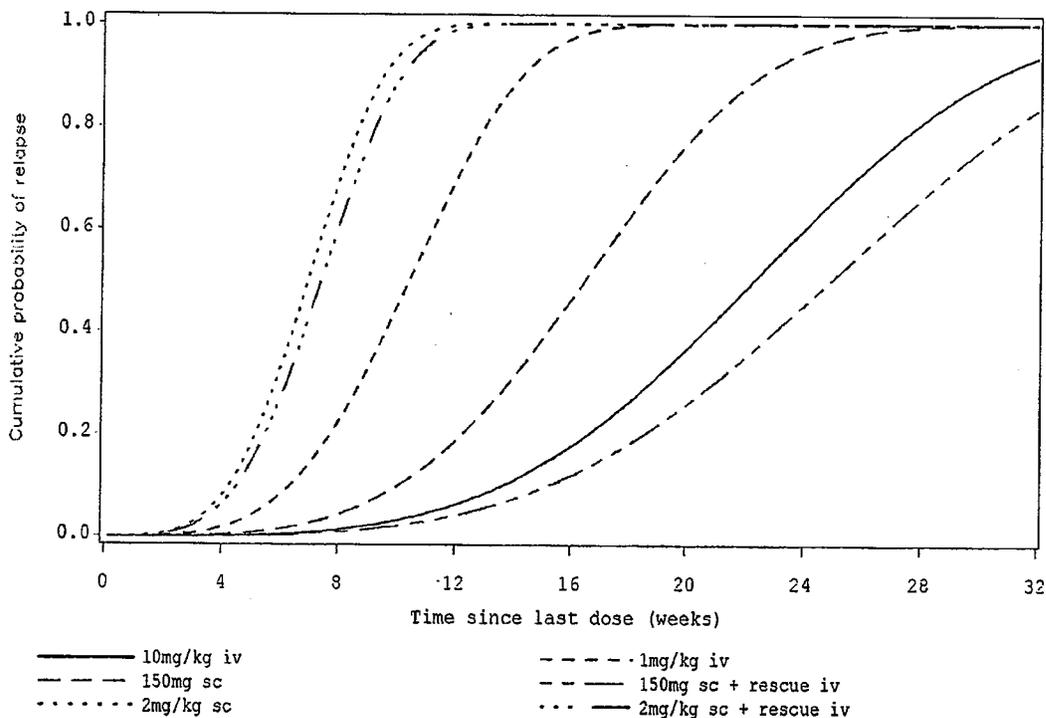
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Specific dose-finding studies were not possible due to the scarcity of patients with CAPS disease. Therefore, modeling was applied to data obtained from patients in Study A2102 whose study design included PK/PD assessments.

Study A2102 - Population Cumulative Probability and Time to Relapse

Study A2102 included dose finding with both routes of administration, iv infusion and sc injection. The population cumulative probability plot of *time to relapse*, by dose group in Study A2102, supported the primary efficacy variable and the treatment effect with canakinumab at the proposed dose of 150 mg sc (see **Figure 7**). 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 7**. The doses with 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 optimal frequency in smaller weight patients administered canakinumab as weight based dosing. The pediatric patient population demonstrated adequate *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. The adequacy of weight based dosing is also explained in Study D2306 results which include longer term extension data with *complete response* and *time to relapse*.

Figure 7.



Sponsor figure 11-1, page 86 of 10679

Both dose regimens, the fixed dose as 150 mg sc for adult patients > 40 kg and the weight based dose as 2 mg/kg sc for pediatric patients ≥ 15 kg and ≤ 40 kg, achieved the primary efficacy endpoint in Part 2 of Study D2034, as measured by the *proportion of patients with disease relapse/flare*, and by the treatment effect outcome in open label period, Part 1 of Study D2304, with 97% of patients achieving a *complete response* with canakinumab treatment. In addition, both open label canakinumab studies, A2012 and D2036, supported the clinical response to canakinumab in patients with active CAPS disease. Therefore, the proposed canakinumab dosage and administration for adults and the pediatric patient population ≥ 4 years of age with CAPS disease is acceptable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Both dose regimens, as described above, achieved the primary efficacy analysis outcome in Part 2 of Study D2034, as measured by the proportion of patients with disease relapse/flare, and by the treatment effect results in open label period, Part 1 of Study D2304, as measured by complete response. In addition, both open label treatment studies, A2012 and D2036, supported the clinical response to canakinumab in patients with CAPS disease. There was no evidence for tolerance effects in any of these three studies because substantial efficacy persisted through the longer term treatment periods. Therefore, the proposed canakinumab dosage and administration for adults and the pediatric patient population ≥ 4 years of age is acceptable.

6.1.10 Additional Efficacy Issues/Analyses

All efficacy analyses are included in the appropriate subsections of Section 6.0 Review of Efficacy.

7 Review of Safety

Safety Summary

The safety profile of canakinumab in CAPS disease is based upon exposure of adult and pediatric patients with active CAPS disease in three clinical trials: pivotal Study D2304 which included a randomized, double blind, placebo controlled withdrawal period, and two open label Studies, A2102 and D2306. The safety database was not pooled due to the different study designs across these three trials, the small number of patients with this rare disease, and the medical need for treatment. In addition, patients rolled over from one trial to another and contributed data to more than one clinical trial.

The safety and tolerability data on canakinumab from CAPS studies (completed or with an interim data cut-off) included 78 patients, including 15 children aged 4, 5, 6, 7, 8, 9, 13, 14, 14, 15, 16, 16, 17 and 17 years of age. Patients were classified as having FCAS, 63 as MWS, five with MWS overlapping with NOMID and one with NOMID. Patients were observed for up to three-and-a-half years with a total exposure of 69 patient-years. As this is a rare disease with less than several hundred patients world-wide, these data are adequate to reach a conclusion about the safety and tolerability of this proposed formulation.

The safety profile of canakinumab treated patients was similar to the safety profile observed in adult and pediatric patients treated with another biologic product in the class of IL-1 blocker therapy in CAPS disease, rilonacept. Infections are expected adverse events in view of the immunosuppressive properties of canakinumab. Infections were a frequent AE in the canakinumab database. However, it is unknown how the rate of infections with canakinumab would compare to untreated patients since all the patients in the clinical trials were exposed to canakinumab. There were no opportunistic or unusual infections, such as mycobacterial infection, observed in any of the canakinumab clinical trials. The observed infections responded to standard treatment. The most common infectious AE was nasopharyngitis in each of the three CAPS trials.

Vertigo was observed in 10 CAPS patients, of which two patients had a past medical history of vertigo. In 7 of 10 observed cases of vertigo, no medical treatment was administered. Two of 10 cases of vertigo were serious AEs and the majority of vertigo cases were mild in severity. Vertigo is a known complication of more severe CAPS disease, specifically, MWS, MWS overlapping with NOMID, and NOMID. The potential relationship of vertigo to canakinumab treatment or to the underlying CAPS disease has not been established. The occurrence of vertigo with canakinumab should be noted in the label if canakinumab is approved. Vertigo should be assessed post approval with standard Pharmacovigilance methods.

The proposed route of administration for canakinumab, as a fixed dose regimen in adult patients with body weight > 40 kg and as a weight based dose regimen in pediatric patient population \geq 15 kg and \leq 40 kg, is by subcutaneous injection. The majority of CAPS patients did not experience sc injection site reactions and a small number of patients had a mild local tolerability reaction. One placebo-treated patient had a mild reaction. This favorable trend of no injection site reaction was also observed with sc canakinumab treatment in other diseases.

There were no adverse events suggestive of anaphylactoid or anaphylactic reactions. None of the CAPS patients or patients with other diseases was observed with a treatment induced immune response to canakinumab. No malignancies or opportunistic or unusual infections were observed and two cases of leukopenia were observed, neither of which was associated with an infection. In conclusion, canakinumab was well tolerated in the CAPS adult and pediatric patient populations studied at the proposed fixed and at the weight based dose regimens proposed to be administered sc every 8 weeks.

7.1 Methods

The safety assessment of canakinumab was based on the datasets which included all subjects who received at least one dose of study drug in any of the three CAPS disease studies as well as studies in other diseases. The safety review for the indication of CAPS includes three datasets from three multiple dose clinical trials, two trials in other diseases (RA and _____ studied in multiple dose early development trials, and three trials including healthy subjects, _____, all single dose trials. Open label Study A2102 was complete and Studies D2304 and D2306 were incomplete at the time of the BLA submission. Safety data from the original BLA application (17December2008) was supplemented by the 120-Day Safety Update (120-DSU) received on 31March2009. The cutoff date for interim safety data submitted in the original BLA application was 12September2008. The cutoff date for the 120-DSU report was 12Jan2009.

b(4)

As described in the Individual Study Reports and in Section 6.0, Study D2304 includes a 24-week, randomized, double blind, placebo controlled, withdrawal period, Part 2, preceded by an 8-week, open label period, Part 1, and followed by a 16-week, longer term extension period, Part 3. The baseline demographic and disease characteristics representative of adults and children with active MWS disease include typical signs and symptoms of this complex condition. Study D2034 provides an adequate safety assessment of canakinumab as it would likely be used in clinical practice. The limitation to the interpretation of the safety data from this study include the following concern: all patients in Part 1 (8weeks) were exposed to canakinumab and those patients randomized to canakinumab in Part 2, the randomized withdrawal period, have exposure which is approximately three times longer than those patients randomized to placebo in Part 2. Adverse events observed in Part 2 may suggest safety risks events which are delayed in onset after extended canakinumab exposure. In addition, for patients who flared in Part 2 and rolled over to the open label period, Part 3, their double-blind period was less than 24 weeks duration.

Study A2102 includes an early dose-finding period, Stage 1, and an open label longer term extension period, Stage 2. Study D2306 is an open label longer term extension trial (see Table

a). Studies A2102 and D2306 include all three phenotypes of CAPS compared to Study D2034 which is limited to MWS. Due to the different study designs, the small number of patients with this rare disease, and the medical need for treatment, patients rolled over from one trial to another and contributed data to more than one clinical trial.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials in CAPS disease, other diseases, and in healthy subjects are presented in **Table 19**.

Table 19.

| Safety Database for Canakinumab - CAPS and Other Diseases in Clinical Trials | | | | | |
|--|-----------------------|--|-----------------|---|-----------------------------|
| Safety Database | Clinical Trial No. | No. Treated | Study Duration | Treatment (mg or mg/kg) | Population |
| Placebo-Controlled, Double-Blind Trial | | | | | |
| CAPS Disease | Study D2304 | | 48 weeks | | MWS |
| | Part 1 (uncontrolled) | 35 | 8 weeks | SD, 8 wks, 150 mg sc or 2 mg/kg sc | MWS |
| | Part 2 | 31 | 24 weeks | MD, 24 wks, same ACZ885 or PBO | MWS |
| | Part 3 (uncontrolled) | 17/31 completed or d/c by 29Aug08; ongoing | 16 weeks | MD, ≥ 16 wks, same as ACZ885 | MWS |
| Uncontrolled, Open Label Trials | | | | | |
| | A2102 | 34 | up to 28 mos | MD, iv or sc ACZ885 | FCAS, MWS, MWS/NOMID, NOMID |
| | D2306 (interim) | 57 | 2 ys planned | MD, ACZ885 150 mg sc or 2 mg/kg sc; Up-titration max 600 mg or 8 mg/kg sc | FCAS, MWS, MWS/NOMID, NOMID |
| | | | Cutoff 12Sept08 | | |
| Placebo-Controlled, Double-Blind Trials | | | | | |
| Other diseases | A2101 | 53 | 17 weeks | ACZ885 iv doses | RA |
| | | 23 | 18 weeks | ACZ885 150 mg sc | |
| Healthy subjects/ | A1101 | 48 | 16 weeks | ACZ885 iv doses | Healthy Subjects |
| Single dose | | 50 | 17 weeks | ACZ885 iv doses | Healthy Subjects |
| | | 26 | 24 weeks | ACZ885 iv doses or Ranibizumab iv | |

Adapted from Sponsor Table 1-1, 1-2, 1-3, pages 11 to 13 of 82, Summary of Clinical Safety; Abbreviations: SD = single dose; MD = multiple dose; ACZ885 = canakinumab.

7.1.2 Categorization of Adverse Events

All safety analyses were performed on all patients who received at least 1 dose of study medication. The primary safety assessments for all trials consisted of all reported adverse events (AEs), rare AEs and unexpected, and serious adverse events (SAEs) with their severity, and laboratory changes, mainly in patients exposed to multiple doses. All adverse events (AEs) were coded using MedDRA. The trials in other diseases included placebo-controlled studies in the early stages of multiple-dose treatment. The healthy subject data included AEs from single or double-dose in short term trials. The serious adverse events (SAEs) were compared to SAEs reported with other IL-1 blockers with similar action (riloncept, pack-age insert) for comparison of the type, frequency, severity, and duration of events observed with canakinumab. A literature search for any unreported safety event with canakinumab (cutoff 12Sept2008) was also included. The main focus of this safety review for canakinumab in the indication of CAPS disease is to characterize the overall safety of canakinumab's potential immunosuppressant effects related to its mechanism of action and immunogenicity of canakinumab:

1. AEs indicating impaired immune response such as infection and malignancy;
2. Injection site reactions such as redness, rash, pain, swelling, induration and itching;

-
3. AEs related to altered immune reactions, e.g., hypersensitivity, autoimmune reactions;
 4. Laboratory signs of impaired immune response including lowered white cell counts and or neutropenia;
 5. Signs of immunogenicity, e.g., development of anti-canakinumab antibodies.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Three multiple dose clinical trials were examined for canakinumab exposure in CAPS disease: Study A2102 (uncontrolled, open label); Study D2304 (pivotal study, uncontrolled open label period, Part 1; randomized, double blind, placebo controlled, withdrawal period, Part 2; and an uncontrolled, open label longer term extension period, Part 3); and Study D2306 (uncontrolled, open label study). As noted previously, some patients were enrolled in more than one study or enrolled twice into one study.

The applicant determined that formal pooled analyses of the safety data were not appropriate as the trials were designed differently, with different comparators, sometimes had sequential phases with different treatment, dosing or routes of administration, and included some patients who had participated in more than one trial. Population groupings were made to optimize these limited safety data. Therefore, safety data from each clinical trial was analyzed independently as the study population, collectively, e.g., CAPS patients, and used to evaluate specific safety concerns listed above in Section 7.1.2.

In the CAPS studies, the time period under placebo treatment in the randomized, double blind, placebo controlled, withdrawal period (Part 2) of Study D2304 was counted as exposure to canakinumab. This approach was employed because canakinumab has a long half-life, ~26 days, and some treatment effect from open label canakinumab treatment in Part 1 of Study D2304 should still be present at randomization into Part 2, of Study D2304. All of the different application forms, different doses and different drug product formulations were considered under the treatment effect of canakinumab, e.g., different doses in Study A2102, Stage 1, the dose-finding period.

For patients still under canakinumab treatment in ongoing studies, the day of the last clinical visit in a trial was used as the treatment end date to calculate the treatment exposure. For completed studies, the date of the end of the study visit was used as the treatment end date.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The total safety database includes a total of 890 subjects including CAPS disease studies and non-CAPS disease studies in which ~700 patients (exact number is not known due to blinding of ongoing studies) received canakinumab treatment. Approximately 470 patients are currently on canakinumab treatment in ongoing clinical trials.

The safety data for the indication of CAPS disease was based upon 78 patients, including 15 pediatric patients, treated with canakinumab for an overall exposure of 69 patient-years (pt-yrs) and a treatment duration of up to three-and-a-half-years, 182 weeks. The number of patients exposed to canakinumab and the duration of the trials of each exposed group are presented in **Table 20**. All of the different application forms, different doses, and different drug products were analyzed, e.g., different doses in Study A2102. The start of treatment was defined as the first canakinumab dose by either sc injection or iv infusion.

Table 20.

| Number of Patients Exposed to Canakinumab | | |
|--|---------------------------------|---------------------------|
| Studies | Duration in weeks of exposure | No. of Unique Pts Treated |
| CAPS | | Total = 78 |
| A2102 | up to 114 weeks (2.3 years) | |
| D2304 | up to 48 weeks (4 years) | |
| D2306 | up to 8 weeks (cutoff 12Sept08) | |
| Other diseases | | Total = 57 |
| A2101 (RA) | 17 weeks | 38 |
| | 18 weeks | 19 |
| Healthy subjects/ single dose | | Total = 95 |
| A1101 (Healthy subjects) | | 36 |
| | | 39 |
| | | 20 |
| Summary | | |
| 152 M/F subjects and trials with interim analysis | | |
| 78 M/F CAPS patients (including 15 pediatric patients) | | |

b(4)

The number of CAPS patients exposed for different periods of observation, including the mean and median values, the range of exposures, and patient-years of exposure are presented in **Table 21**. At the interim data cutoff, several CAPS patients had participated in more than one CAPS trial. In Study A2102 of 34 enrolled patients, 9 rolled over to Study D2304 (2 patients returned to Study A2102 as they did not achieve eligibility for Part 2, Study D2304) and 22 patients rolled over directly. From Study D2304, 10 canakinumab naive patients rolled over to Study D2306. Nine patients participated in all three CAPS studies, e.g., D2304, A2102 and D2306.

Longer Term Exposure

Most of the longer term exposure for CAPS patients is from Study D2304 in which Parts through Part 3 include observations over a 48 week period. In Study A2102, longer term exposure lasted from 4 months to 2 years and 4 months. In Study D2306, the first patient was enrolled 19May08 and the interim data cutoff was 12Sept08, limiting reported exposure to only 4 weeks duration. Overall, 31 patients had been exposed to canakinumab for approximately one year or longer.

Table 21.

| Cumulative Duration of Exposure (CAPS) Studies D2304, A2102 and D2306 Combined* | |
|---|------------------------------|
| Duration of Exposure (weeks) | ACZ885 N = 78 Pts |
| ≥ 1 day | 78 |
| ≥ 12 weeks | 59 |
| ≥ 24 weeks | 56 |
| ≥ 36 weeks | 54 |
| ≥ 48 weeks | 31 |
| ≥ 96 weeks | 6 |
| ≥ 144 weeks | 4 |
| Cumulative Exposure | |
| Mean duration (days) | 323 |
| Median duration (min, max) days | 316 (1, 1269) |
| Patient-years | 69 pt-ys |
| * Study D2304 up to 48 weeks; Study A2102 up to 28 months; Study D2306 up to 8 weeks, database cut-off (12Sept08). | |

Pediatric Patients

As noted in the proposed indication for CAPS disease, the pediatric patient population included children ≥ 4 years of age in Studies A2102 and D2304, and children ≥ 9 years of age in Study D2304 (see Table 22). Notably, Study D2304 only includes patients with MWS.

Table 22.

| Pediatric Patients in CAPS Studies D2304, A2102 and D2306 | | |
|--|-----------------------|------------------|
| Pt Age (yrs) | CAPS Diagnosis | Treatment |
| Study D2304 | | |
| 9-yrs | MWS | ACZ885 |
| 15-yrs | MWS | ACZ885 |
| 16-yrs | MWS | ACZ885 |
| 17-yr | MWS | ACZ885 |
| 14-yr | MWS | Placebo |
| Study A2102 | | |
| 16-yrs | MWS/NOMID | ACZ885 |
| 17-yrs | MWS/NOMID | ACZ885 |
| Study A2102 roll-over into Study D2306 | | |
| 4-yrs | MWS | ACZ885 |
| 6-yrs | MWS | ACZ885 |
| 13-yrs | MWS | ACZ885 |
| 7-yrs | MWS | ACZ885 |
| 6-yrs | MWS | ACZ885 |
| Study D2304 roll-over into Study D2306 | | |
| 14-yrs* | MWS | ACZ885 |
| Study D2306 | | |
| 14-yrs* | MWS | ACZ885 |
| 8-yrs | MWS/NOMID | ACZ885 |
| 5-yrs | FCAS | ACZ885 |
| * Same patient. | | |

Injections

The number of injections received by patients in each of three CAPS studies is summarized in **Table 23**. Canakinumab sc injections were administered every 8 weeks in Study D2304 and Study D2306. In Stage 1 of Study A2102, all of the 4 initial patients received 3 doses of canakinumab as 10 mg/kg iv, 1 mg/kg iv, and 150 mg sc. In Stage 2 of Study A2102, all patients received at least one sc canakinumab injection. The number of canakinumab doses varied for each patient dependent on the patient’s response to treatment, e.g., *time to relapse* and need for re-treatment. The number of total doses ranged from 1 to 20, the median number of doses was 4 s.c. injections per patient. In Study D2306, 57 patients received at least one dose, and 22 patients received > 1 sc injection of canakinumab: 5 patients received 3 sc injections; 17 patients received 2 sc injections; and 35 patients received one sc injection of canakinumab.

Table 23.

| | Number of sc Injections / iv Infusions in CAPS Patients | | | | | |
|-------------------|---|------------------|-------------------|------------------|------------------|------------------|
| | Study D2304 | | | Study A2102 | Study D2306 | |
| | Part 1 (8 wks) | Part 2 (24 wks) | | 46 wks | ≤ 8 wks | |
| | ACZ885 N = 35 | ACZ885 N = 15 | Placebo N = 16 | ACZ885 N = 31 | ACZ885 N = 34 | ACZ885 N = 57 |
| # of injections | | | | | | |
| Median (min, max) | 1 (1, 1) | 3 (3, 3) | 2 (1, 3) | 2 (1, 5) | 4 (1, 20) | 1 (1, 3) |

There was prolongation of Part 3 for patients who discontinued Part 2 prematurely.

Adapted from sponsor Table 1-9, page 18 of 82, Summary of Clinical Safety

7.2.2 Explorations for Dose Response

Studies D2034, A2102 and D2304 assessed the efficacy of canakinumab in the two proposed dose regimens, a fixed dose as 150 mg sc for patients > 40 kg and a weight based dose as 2 mg/kg sc for the pediatric population ≥ 15 kg and ≤ 40 kg in patients with CAPS disease. Both of proposed dose regimens achieved the primary efficacy analysis outcome in Part 2/Study D2034, as measured by the *proportion of patients with disease relapse/flare* and in the open label treatment period, Part 1, with 97% of patients achieving *complete response* with canakinumab treatment.

The optimal dose and frequency of canakinumab administration for CAPS was explored in Study A2102 by examining different doses and routes of administration. All the doses explored in adults – 10 mg/kg iv, 1 mg/kg iv, and 150 mg sc – induced complete response in the majority of patients. For the 10 mg/kg iv dose, the median time to relapse following complete response was longer, e.g., median time in days, than with the 1 mg/kg iv dose.

The proposed canakinumab dose of 150 mg sc demonstrated a median time to relapse which was in between the two iv doses, 10 mg/kg and 1 mg/kg. See Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations and **Figure 7**, the population cumulative probability plot of the time to relapse by dose group. Pediatric patients treated with weight based canakinumab dosing demonstrated *complete response* which was comparable to adult patients treated with a fixed dose of canakinumab.

7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology Toxicology review by Kathleen Young, PhD.

7.2.4 Routine Clinical Testing

Routine hematology, biochemistry, special anti-canakinumab antibody tests and tests for serum biomarkers were assessed in these clinical trials with patients who have active CAPS disease.

7.2.5 Metabolic, Clearance, and Interaction Workup

The clinical pharmacology assessments of human pharmacology, bioavailability, and bioequivalence parameters were adequate in this CAPS disease clinical development program. See the clinical Pharmacology review by Srikanth Nallani, PhD and Hao Zhu, PhD.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Additional data were used to evaluate the overall safety and adverse events of canakinumab including a review of published data with biologic formulations with a similar action, e.g., Arcalyst (rilonacept, IL-1 blocker; package labeling) for comparison of the type, frequency, severity and duration of events to canakinumab. Rilonacept is the only approved IL-1 blocker indicated for the signs and symptoms of CAPS disease, FCAS and MWS in adults and children \geq 12 years of age. The serious adverse events (SAEs) such as infection, malignancy and potentially vertigo, were compared to SAEs reported for rilonacept and Kineret (anakinra, IL-1 blocker) in patients with CAPS disease. Anakinra is not approved in CAPS disease but has been investigated in this patient population.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in the three CAPS studies reported through the cutoff 12Sept2008. There were no deaths in the 2 controlled trials in _____ and in RA, respectively.

b(4)

Two (2) deaths were reported in two different studies in other diseases, e.g., _____ and COPD. Examination of the narratives showed the deaths to be of a type that can be expected in these patient populations and are not clearly related to canakinumab treatment.

Individual Death Narratives

_____: an 88-year old female diagnosed with _____ had pre-existing cardiovascular disease including history of angina, CVA, left ventricular failure and hypertension. She died 5 months after receiving a single iv dose of 10 mg/kg canakinumab.

b(4)

She experienced a fall at home, sprained her knee and was hospitalized. Her condition deteriorated and she died. Death was attributed to cardiac failure.

Study B2204: a 75-year old male with COPD received one dose of blinded study medication, e.g. 1 mg/kg canakinumab or placebo. He presented with dyspnea and pulmonary congestion, and was hospitalized due to worsening dyspnea, productive cough and pneumonia. Despite treatment with antibiotics, tracheotomy and assisted ventilation, he died of respiratory failure. Causality for death was attributed to pneumonia and underlying COPD.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were assessed by reviewing the CRFs, narratives, and databases in this BLA submission. All SAEs were reported within 24 hours of occurrence and were reported by individual study. An SAE was defined as any event that met the following criteria: death; life-threatening; hospitalization/prolonged hospitalization; persistent or significant disability/incapacity; important medical event requiring medical or surgical intervention to prevent a serious outcome; and or pregnancy/spontaneous abortion/elective abortion.

CAPS Disease

A total of 9 SAEs occurred across the three CAPS trials at the data cutoff (see **Table 24**). All SAEs were single events and resolved during the individual study. Three of 9 events may have a causal relationship to canakinumab: two (2) cases of vertigo, one each in Study D2304 and A2102, and 1 case of a respiratory tract infection in Study A2102. Notably, there was one case of pyrexia in a patient with MWS.

Vertigo as is a well known symptom of the more severe forms of CAPS disease, MWS and the most severe phenotype in this disease spectrum, NOMID. It has not been established if canakinumab may be associated with vertigo unrelated to the underlying disease. There is no clear mechanism by which vertigo would be expected to occur as an adverse reaction to canakinumab.

Infection is an expected risk of canakinumab treatment due to the immune modulating and suppressive effects of this biologic therapy. In Study A2102, a 35-year old/F with MWS overlapping with NOMID presented on Day 359 with cough, vomiting and malaise, and was diagnosed with a severe lower respiratory tract infection. She was hospitalized on Day 366 on which her chest x-ray revealed consolidation in the left lung base. The etiology of the lower respiratory tract infection remains unknown; however, a community acquired pneumonia due to gram-positive bacteria was the most likely etiology. She was treated with amoxicillin and completely recovered on Day 372. Study treatment was not discontinued.

Pyrexia is less marked in the CAPS disease spectrum compared to the episodic fever syndromes. One 9-year old/F MWS patient (Study D2304, Part 3) experienced high fever which prompted hospitalization. She experienced three separate urinary tract infections of mild to moderate severity (organism - *E. coli*) and completed multiple courses of antibiotics. Urine test revealed 200,000 leukocytes/mL, gram negative bacillus, and gram positive cocci. She was treated with

cefixime, cefotaxime sodium and netilmicin sulfate for urinary tract infection. No treatment was given for pyrexia. Pyrexia resolved 6 days after the last dose of canakinumab. A relationship between the urinary tract infection, with secondary pyrexia, and the study drug cannot be excluded.

These serious adverse events observed in patients with CAPS disease are consistent with known effects of canakinumab treatment and/or the more severe forms of this disease spectrum. Infections and vertigo are the most common serious adverse events associated with canakinumab treatment in these CAPS studies. CAP disease flares are expected in this disease spectrum characterized by episodic and recurrent systemic inflammation. Vertigo is a known complication of CAPS disease. A potential mechanism of action for vertigo related to this study product formulation is not unknown.

Table 24

| SAEs in CAPS Studies D2304, A2102 and D2306 | | |
|--|---|--|
| Study D2304 - 4 SAEs | | |
| Pt # | Treatment | Brief Summary |
| 0007-00001 19-yr old/F/ MWS | ACZ885 Part 3 150 mg sc, 3 injections | Vertigo (SAE); resolved. Blindness unilateral (SAE); resolved. Increased intraocular pressure (SAE); resolved. She was hospitalized with rotatory vertigo, headache and vomiting. She experienced right visual loss with acute right angle glaucoma and papillitis. |
| 0002-00001 9-yr old/F/ MWS | ACZ885 Part 2 2 mg/kg sc | Pyrexia (SAE); resolved. Pyrexia was due to urinary tract infection (non-serious AE) recurrent and resistant to multiple antibiotics. |
| Study A2102 - 3 SAEs | | |
| 0002-05108 7-yr old/M/ MWS | ACZ885 50 mg sc; 125 mg iv rescue | Vertigo (SAE); resolved. Pt had acute vertigo attacks with nausea; audio-vestibular exams showed normal hearing/equilibrium w/o nystagmus. Pt. tx'ed with dimenhydrinate for vertigo; event resolved. |
| 0001-05106 35-yr old/F/ MWS Overallp NOMID | ACZ885 150 mg sc | Lower respiratory tract infection (SAE); resolved Pt hospitalized due to cough, vomiting, malaise; found to have positive CXR with consolidation in left lung base. Tx w/antibiotics. |
| 0006-05118 20-yr old/F/ NOMID | ACZ885 150 mg sc | Whole body pain/ fibromyalgia/ Pain (SAE); resolved. Developed fibromyalgia on Day 104; Pt. hospitalized on Day 303 with worsening chronic pain due to fibromyalgia. |
| Study D2306 - 2 SAEs | | |
| 0003-00001 51-yr old/F/ MWS | ACZ885 150 mg sc | Worsening synovial cyst in lumbar spine (SAE); resolved. Pt had moderate paresthesia; MRI showed worsening synovial cyst with nerve root compression; ablation of lumbar cyst was completed; paresthesia ongoing at hospital discharge. |
| 0002-00001 41-yr old/F/ MWS | ACZ885 150 mg sc; up-titrated to 300 mg sc | Flare of MWS (SAE); ongoing, at last report. After MWS flare, dose was up-titrated, headaches worsened. Pt hospitalized due to flare of MWS. Pt continued in study. |

Study — No SAEs were reported in this trial. **b(4)**

RA

Study A2101: Seven (7) non-fatal SAEs were reported in Study A2101 (RA), two (2) of which were in the placebo group. Three (3) of 7 SAEs were infectious in nature and occurred in patients treated with canakinumab. The infectious SAEs were erysipelas, pneumonitis and tracheobronchitis. No pathogens were identified in any of these three infections. The SAEs in Study A2102 are summarized in **Table 25**.

Table 25.

| 7 SAEs in Study A2101 - Rheumatoid Arthritis | | |
|--|---------------------|--|
| Pt # | Treatment | Brief Summary |
| 0002-00008 63-yr old/F/ RA | ACZ885 1 mg/kg | Infection/ erysipelas (SAE); Resolved. Second episode of erysipelas post 2nd infusion. Pt had recurrent edema of the lower extremities and obesity. Pt was treated with ciprofloxacin and sulfamycin. Signs and symptoms resolved. |
| 0021-00001 57-yr old/F/ RA | ACZ885 1 mg/kg | Infection/ probable pneumonitis (SAE); Resolved. Pt. was hospitalized with fever, cough, hypoxia. Bacterial and bronchoalveolar cultures were negative. Treated with antibiotics and prednisolone. Patient recovered. |
| 0001-00007 47-yr old/F/ RA | ACZ885 10 mg/kg | Infection/ tracheobronchitis (SAE); Improving. Hospitalized with severe dyspnea and cough one week after 2nd infusion. Pt taking concomitant MTX, tramadol, indomethacin and prednisolone (5 mg). Treated with cefuroxime; Pt. recovered. |
| 0002-00003 55-yr old/F/ RA | ACZ885 0.3 mg/kg | Recurrent angina pectoris of unknown origin (SAE); Resolved. <i>Helicobacter pylori</i> gastritis (significant AE); Resolved. Hospitalized; myocardial scintigraphy was normal. |
| 0001-00004 65-yr old/F/ RA | ACZ885 10 mg/kg | Femur fracture/pelvic ring fracture due to fall from bike (SAE) Pt was taking MTX, tocopherol and estradiol for osteoporosis. Pt was hospitalized and recovered. |
| 0008-00002 35-yr old/F/ RA | Placebo | Arthrodesis left wrist, arthralgia (SAE); Resolved. Hospitalized for surgical procedure 2.5 months post PBO. |
| 0012-00003 47-yr old/F/ RA | Placebo | Worsening RA (SAE); Resolved. Hospitalized for worsening RA of left knee. Tx'ed with intra-articular methylprednisolone, 80 mg; MTX ↑ from 15 mg/wk to 20 mg/wk sc. |
| No SAEs were reported in _____ | | |

b(4)

Healthy Volunteer/Single-Dose Studies

Study A1101 (Healthy Japanese Subjects): No SAEs were reported in healthy volunteers.

_____ : Two SAEs were reported in this study: one fatal SAE was reported in an 88-year old/F who experienced cardiac failure, and a second SAE was reported in an 84-year old/F who experienced a recurrence of breast cancer.

b(4)

_____ One patient (_____-0001-5110) experienced a spontaneous abortion (SAE).

b(4)

10 Ongoing Studies

Studies A2210, A2201E1, A2204 (RA studies)

Studies A2207, A2211, A2206 (RA studies)

Study A2203 (Systemic Juvenile Idiopathic Arthritis)

Study A2212 (Acute Gout)

Study A2213 (Type 2 Diabetes Mellitus)

Study B2204 (COPD)

Out of 612 patients in 10 ongoing studies, 58 SAEs were reported by the data cutoff (12Sept08). Sixteen cases of confirmed infections were identified, e.g., urosepsis, lower respiratory tract infection, hand abscess, acute appendicitis, diverticulitis, soft tissue injury with infection, pharyngitis, acute adenitis, diarrhea, pneumonia, sinusitis (2 events), and exacerbation of COPD (4 events). The majority of non-infectious events consisted of random events and did not trend with any new or unexpected events beyond those observed in the reported studies.

7.3.3 Drop-outs and/ or Discontinuations

According to the CAPS study protocols, patients were to be withdrawn from a study if any of the following occurred: clinically significant deterioration in a patients medical status; clinically significant abnormal laboratory or other test result as determined by the investigator/ sponsor; investigator believed it was in the best interest of the patient; parent or legal guardian requested withdrawal of a patient from a study; or eligibility protocol violation was identified after patient had been enrolled into a study.

The total number of dropouts for the three CAPS studies is shown in **Table 26**. In Study D2304, all patients in Part 1 were treated with canakinumab and 89% completed this period. Four patients withdrew due to lack of complete response (refer to Section 6.1.3 Patient Disposition, Study D2304). In Part 2, the randomized withdrawal period, 13 placebo-treated patients (81%) discontinued due either to clinical relapse or to early withdrawal. In Part 2, two AEs prompted withdrawal from this study for two different patients: one urinary tract infection in a canakinumab-treated patient and one event of pharyngitis in a placebo-treated patient. Study treatment was temporarily stopped for both patients and then resumed after the event resolved.

In Study A2102, three patients discontinued (refer to Section 6.1.3 Patient Disposition, Studies A2102). Only one of these three patients experienced an AE as the reason for discontinuation, an unplanned pregnancy. In the longer term extension Study D2306, one patient discontinued due to worsening of pre-existing multiple sclerosis demyelination lesions reported on MRI of the brain. The latter AE was an expected complication in patients with active CAPS disease and was pre-existing finding in this patient.

Table 26.

| Summary of Dropouts and/or Discontinuations in CAPS Studies | | | | | | |
|---|---------------------------|---------------------------|----------------------------|---------------------------|---------------------------|---------------------------|
| | Study D2304 | | | Study A2102 | Study D2306 | |
| | Part 1 (8 wks) | Part 2 (24 wks) | | 46 wks | ≤ 8 wks | |
| | ACZ885 N = 35 n (%) | ACZ885 N = 15 n (%) | Placebo N = 16 n (%) | ACZ885 N = 31 n (%) | ACZ885 N = 34 n (%) | ACZ885 N = 57 n (%) |
| Completed | 31 (89%) | 15 (100%) | 4 (25%) | 21 (20%) | 31 (91%) | N/A |
| Discontinued | 4 (11%) | 0 | 13 (81%) | 6 (17%) | 3 (9%) | 1 (2%) |
| Adverse event | 0 | 1 (6%, UTI) | 1 (6%, pharyngitis) | 2 (6%) | 1 (3%) pregnancy | 1 (2%) |
| Clinical relapse or early withdrawal | 0 | 0 | 13 (81%) | 0 | 0 | 0 |
| Lack of complete response | 4 (11%) | 0 | 0 | 0 | 1 (3%) | 0 |
| Administrative/other | 0 | 0 | 0 | 0 | 1 (3%) | 0 |

In Study A2102, Administrative/other event: patient did not comply with scheduled study visits.

Examination of the discontinuations due to adverse events for the clinical trials in the other indications under development showed that discontinuations were infrequent and did not reveal any pattern of adverse events associated with discontinuation.

All of the AEs prompting dropout or discontinuation across Studies D2304, A2102 and D2306 were expected for patients with active CAPS disease. One upper respiratory tract infection, pharyngitis, and one UTI, were reported as the AE prompting study discontinuation. Though the CAPS patient numbers are small, these two infectious AEs are consistent with the known risks of the immune suppression mechanism of action related to IL-1 blocker therapy and, specifically, canakinumab treatment.

7.3.4 Significant Adverse Events

Due to the different study designs and durations of exposure, significant AEs in each of the three CAPS studies are reviewed separately. In general, the AEs in the CAPS trials were mild to moderate with very few severe events. There were no trends in a specific organ class or in the type of AE observed across these data.

In Study D2034, Part 1, AEs were mainly mild (29%) to moderate (43%) in severity. Four patients (11%) experienced severe AEs in Part 1: one patient each experienced severe palpitations and rhinitis; joint crepitation; enuresis; and dizziness and hot flush. A 9-year old boy with MWS experienced severe enuresis.

In Part 2, all AEs were mild to moderate except one severe AE of complex regional pain syndrome in one patient randomized to canakinumab.

In Part 3 though the data cutoff, AEs were all mild to moderate in severity. In the patients randomized to receive canakinumab in Part 2, 5 (14%) of 35 AEs were severe. In patients randomized to receive placebo treatment, 7 (16%) of 42 AEs were severe. The one severe event occurring more than once was unilateral blindness, vertigo, acute glaucoma and papillitis in a 19-year old/F patient (# D2304-0007-00001) with a severe form of MWS. Her past medical history included non-infective meningitis related to MWS, goiter with thyroidectomy and papillitis, and ongoing chronic headache, fatigue and vomiting related to MWS, urticaria, arthralgia, bilateral deafness,

decreased bone density, secondary renal and thyroid amyloidosis, hypertension and conjunctivitis. The ophthalmological severe events were reported by this patient on two occasions 125 days and 132 days after the first canakinumab dose, respectively. Both resolved within 2 days.

In Study A2102, the majority of AEs were also mild to moderate in severity. One pediatric patient experienced vertigo and weight increase. The vertigo resolved with dimenhydrinate treatment.

Longer Term Extension Studies with Severe AEs

In Study D2304, the majority of AEs reported through the data cutoff were mild to moderate in severity with 20% of patients reporting one severe AE. Severe AEs each as a single event were: palpitations, vertigo, tinnitus, angle closure glaucoma, diarrhea, papillitis, pyrexia, rhinitis, procedural pain, increased intraocular pressure, joint crepitation, musculoskeletal stiffness, complex regional pain syndrome, dizziness, sciatica, enuresis, epistaxis, unilateral blindness and hot flush. No additional severe AEs were reported in Study A2102. In the longer term extension Study D2306, 33 AEs were reported through the data cutoff, all of mild severity except one case of vertigo assessed as moderate in severity. Many of these severe AEs appear consistent with the underlying disease.

Severe AEs in Other Diseases Study A2102 (RA)

There were 325 AEs with canakinumab treatment: 228 were mild, 92 moderate and 5 severe. The 5 severe AEs were: flaring of RA, worsening of pain in left knee joint, bicycle accident fall, increase of pain and stiffness in hands, and increase in pain and stiffness in knee and neck. In the placebo group, 98 AEs reported with 80, 36, 36 and 2 as mild, moderate and severe, respectively. The two severe events were arthritis and flaring of RA.

b(4)

No severe AEs were reported. Twenty-three (23) AEs were reported with canakinumab treatment, 11 AEs were reported in the canakinumab 150 mg sc single dose group, 4 were mild and 7 were moderate in severity. In the multiple dose groups, canakinumab 150 mg sc, 12 AEs were reported, 7 were mild and 5 were moderate in severity. Both of the AEs reported in patients who received placebo were moderate in severity.

Severe AEs in Healthy Subjects or Single Dose Patients Study A1101 (Healthy Japanese Subjects)

No severe AEs were reported in the single ascending iv or sc dose in healthy Japanese subjects receiving placebo or canakinumab.

b(4)

Most AEs were mild in severity and four AEs were graded as severe in Study B2101. In Part 2 of this study (canakinumab 1, 3 and 10 mg/kg iv dose escalation), two patients, one each from the canakinumab 10 mg/kg cohort and from the placebo treatment cohort had a severe Infectious AE, influenza. In Part 3 of this study (canakinumab 10 mg/kg iv), two severe AEs were reported as pneumothorax and abdominal pain. Causality attributed to study drug is

suspected with the two infectious AEs, influenza. Infections were the most common AE observed across the three CAPS studies and across the other studies, though the safety data is limited in the latter group of studies.

Two severe AEs were reported as SAEs: one death (refer to Section 7.3.1 Deaths) and one case of recurrent breast cancer (refer to Section 7.3.2 Nonfatal Serious Adverse Events).

b(4)

In conclusion, the severe AEs reported in the CAPS studies are consistent with the known safety risks of infection associated with the immune suppression of IL-1 blocker therapy, e. g., canakinumab treatment, and many well known complications of CAPS disease. Notably, no unusual or opportunistic severe infections were reported with canakinumab in the CAPS studies or in other diseases through the data cutoff.

7.3.5 Submission Specific Primary Safety Concerns

Potentially clinically significant adverse events known to be associated with active CAPS disease and or the biologic class of IL-1 blockers are reported separately as specific safety risks in this review of canakinumab.

Clinically Significant MRIs

The more severe forms of CAPS disease are known to be associated with cerebral demyelination and neurologic signs and symptoms including papilloedema, sensorineural deafness, visual loss, amyloidosis-mediated organ dysfunctions and unusual neurological symptoms. Special assessments including MRI of the brain were completed in Studies D2304 and A2102. The assessment of *normal*, *clinically insignificant abnormality* or *clinically significant abnormality* was based upon clinical assessments by the specialist who was administering the assessment.

Two cases of *clinically significant* MRIs demonstrated change from baseline:

- Pt # D2304-0002-00003: a 46-year old/F/MWS entered Study D2304 with multiple signs of demyelination, amygdalotomy, ankle edema, vertigo, exertion dyspnea and memory disorder. In Part 3, her MRI demonstrated mild worsening of multiple sclerosis-like lesions (AE). Her neurological assessment was significant for decrease in severity and frequency of pre-existing headaches. She completed Study D2304 and rolled over to open label Study D2306, after which time she experienced mild left hypoesthesia. Repeat MRI was reported to show new multiple sclerosis-like lesions (AE). Study medication was discontinued due to event of demyelination.
- Pt # D2304-0007-00002: a 23-year old/F/ MWS with a past medical history of “multiple white substance abnormalities” in the frontal, parietal and subtentorial regions of her MRI, headache, insomnia, vertigo, neck tenderness, and non-infectious chronic meningitis related to severe MWS. She completed Part 1 and was randomized in Part 2 to receive canakinumab. In Part 2, her MRI demonstrated additional hyper-opaque signals in the hippocampal and periventricular areas of the brain. No relevant clinical symptoms were reported during the study. She continues in Study D2306.

These abnormal findings in MRI of the brain are expected based on the pre-existing lesions and the known complication of cerebral demyelination which may be observed in patients with a more severe form of CAPS disease.

Malignancy

No malignancies were reported in any of the CAPS studies through the data cutoff.

Two cases of recurrent breast cancer were reported in two studies in other diseases: One case occurred in Study _____ in an 84-year old/F treated with ranibizumab and one case occurred in Study A1101 (healthy Japanese subjects) in a healthy subject. It appears unlikely that either of these two cases were causally related to the study drug. b(4)

Infections and Infestations

Study D2304

The most frequently reported AEs (74%) in Study D2304 were in the primary SOC, Infections and Infestations (see **Table 27**). The preferred terms (PTs) most frequently reported in canakinumab treated patients were: nasopharyngitis, 34%; influenza and rhinitis, 17%, respectively; gastroenteritis, 9%; and urinary tract infection and viral infection, 6%, respectively. Nasopharyngitis, influenza, and rhinitis were observed in Part 1 through 3 in canakinumab-treated patients. In general, the pattern of AEs in Part 1 was similar to that seen in Parts 2 and 3. The proportion of patients with infectious AEs in Parts 1, 2 and 3 was, in general, proportionate to the duration of the different parts of the study.

Eighty-eight percent (88%) of patients in Study A2102 had an infectious AE. In adult CAPS patients, the most commonly reported AEs were infectious: upper respiratory tract infection, 38%; nasopharyngitis, 29%; pharyngitis, 12%; and gastroenteritis and rhinitis, 9%, respectively. In pediatric patients, the most commonly reported infectious AEs by PT were: upper respiratory tract infection, 71%; nasopharyngitis, 43%; pharyngitis, 43%; and rhinitis, 29% (see **Table 27**). b(4)

Study D2306

Eleven percent (11%) of patients in Study D2306 had infections of mild severity: influenza, diarrhea, gastritis, bronchitis, oral herpes, and vaginal infection. Fewer AEs were reported as moderate severity: kidney infection, laryngitis, and cellulitis of right forearm. These data were limited to 8 weeks of exposure at the data cutoff for this ongoing.

In conclusion, there was no evidence that the type or rate of infections in the three CAPS studies increased with longer term exposure. The most common infectious AEs occurring with canakinumab treatment were upper respiratory tract and lower respiratory tract infections predominantly of viral etiology. No serious or unusual infections, e.g., opportunistic infections or systemic herpes or fungal infections, toxoplasma, mycobacteria, aspergillus, Pneumocystis, Cryptococcus or cytomegalovirus, were reported in canakinumab-treated CAPS patients by the data cutoff.

Table 27

| AEs for Infections and Infestations by PT in All CAPS Studies | | | | | | |
|---|---------------------------|---------------------------|----------------------------|---------------------------|---------------------------|---------------------------|
| SOC PT | D2304 | | | A2102 | D2306 | |
| | Part 1 | Part 2 | | Parts 1 to 3 | | |
| | 8 weeks | 24 weeks | | 46 weeks | 46 weeks | |
| | ACZ885 N = 35 n (%) | ACZ885 N = 15 n (%) | Placebo N = 16 n (%) | ACZ885 N = 35 n (%) | ACZ885 N = 34 n (%) | ACZ885 N = 57 n (%) |
| Infections and Infestations | 12 (34%) | 12 (80%) | 9 (56%) | 26 (74%) | 30 (88%) | 6 (11%) |
| Acute tonsillitis | 0 | 0 | 0 | 0 | 2 (6%) | 0 |
| Bronchitis | 3 (9%) | 1 (7%) | 1 (6%) | 4 (11%) | 1 (3%) | 1 (2%) |
| Cellulitis | 0 | 0 | 0 | 0 | 0 | 1 (2%) |
| Conjunctivitis viral | 1 (3%) | 0 | 0 | 1 (3%) | 0 | 0 |
| Ear infection | 1 (3%) | 0 | 0 | 1 (3%) | 2 (6%) | 0 |
| Gastroenteritis | 0 | 2 (13%) | 1 (6%) | 3 (9%) | 3 (9%) | 0 |
| Gastroenteritis viral | 0 | 0 | 0 | 1 (3%) | 0 | 0 |
| Herpes simplex | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Infection | 0 | 0 | 0 | 0 | 2 (6%) | 0 |
| Influenza | 1 (3%) | 2 (13%) | 3 (18%) | 6 (17%) | 1 (3%) | 1 (2%) |
| Kidney infection | 0 | 0 | 0 | 0 | 0 | 1 (2%) |
| Laryngitis | 1 (3%) | 0 | 0 | 1 (3%) | 0 | 1 (2%) |
| Localized infection | 0 | 0 | 0 | 0 | 2 (6%) | 0 |
| Lower resp. tract inf. | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Lymphadenitis | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Nasopharyngitis | 4 (11%) | 4 (27%) | 2 (13%) | 12 (34%) | 10 (29%) | 0 |
| Oral herpes | 1 (3%) | 0 | 2 (13%) | 3 (9%) | 2 (6%) | 1 (2%) |
| Otitis media | 1 (3%) | 0 | 0 | 1 (3%) | 0 | 0 |
| Paronychia | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Pharyngitis | 0 | 1 (7%) | 1 (6%) | 4 (11%) | 4 (12%) | 0 |
| Respir. tract infect. | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Rhinitis | 4 (11%) | 1 (7%) | 2 (13%) | 6 (17%) | 3 (9%) | 0 |
| Sinusitis | 1 (3%) | 0 | 0 | 1 (3%) | 2 (6%) | 0 |
| Tinea pedis | 0 | 0 | 1 (7%) | 1 (3%) | 0 | 0 |
| Tonsillitis | 0 | 0 | 0 | 0 | 2 (6%) | 1 (2%) |
| Tooth abscess | 0 | 1 (7%) | 0 | 1 (3%) | 0 | 0 |
| Tooth infection | 0 | 1 (7%) | 0 | 1 (3%) | 1 (3%) | 0 |
| Upper resp. tract inf. | 0 | 1 (7%) | 1 (6%) | 3 (9%) | 13 (38%) | 0 |
| Urinary tract infect. | 0 | 2 (13%) | 0 | 2 (6%) | 0 | 0 |
| Vaginal infection | 0 | 0 | 0 | 0 | 0 | 1 (2%) |
| Viral infection | 0 | 2 (13%) | 0 | 2 (6%) | 2 (6%) | 0 |
| Viral rhinitis | 0 | 0 | 0 | 0 | 1 (3%) | 0 |
| Viral upper respirat. tract infection | 1 (3%) | 0 | 0 | 1 (3%) | 0 | 0 |
| Vulvovaginal mycotic infection | 1 (3%) | 0 | 0 | 1 (3%) | 0 | 0 |

Adapted sponsor Table 2-12, page 41 of 82, safety report

Study

In controlled Study —, nasopharyngitis was the most commonly reported infectious AE in the single-dose canakinumab treatment group. Bronchitis, gastroenteritis and nasopharyngitis occurred in one patient each in the multiple-dose canakinumab treatment group (see Table 28).

b(4)

Study A2101: RA

In controlled Study A2101, nasopharyngitis and urinary tract infection were the most commonly reported infectious AEs. No patients discontinued due to an AE (see Table 28).

Table 28.

| AEs for Infections and Infestations by PT in > 10% of Pts with Other Diseases | | | | | |
|---|--|---|---------------------------|---------------------------|----------------------------|
| SOC PT | 4 weeks | | | A2101 RA 12 weeks | |
| | ACZ885 single dose N = 10 n (%) | ACZ885 multiple dose N = 9 n (%) | Placebo N = 4 n (%) | ACZ885 N = 38 n (%) | Placebo N = 15 n (%) |
| | Pts with any infection AE | 3 (30%) | 3 (33%) | 0 | 26 (68%) |
| Infections and infestations | | | | | |
| Bronchitis | 0 | 1 (11%) | 0 | 2 (5%) | 1 (7%) |
| Gastroenteritis | 0 | 1 (11%) | 0 | 0 | 0 |
| Nasopharyngitis | 2 (20%) | 1 (11%) | 0 | 12 (32%) | 6 (40%) |
| Tooth infection | 1 (10%) | 0 | 0 | 0 | 0 |
| Urinary tract infection | 0 | 0 | 0 | 8 (21%) | 1 (7%) |

b(4)

Adapted from sponsor Table 2-13, p 43 of 82

In conclusion, in the CAPS studies and in the other disease trials were infectious in nature. There were 2 SAEs in 78 CAPS patients treated with canakinumab, chest infection and pyrexia, and neither was reported as an opportunistic infection. The most common infectious AEs were upper respiratory tract infections. This outcome is consistent with the class of IL-1 blocker therapy and the mechanism of action of canakinumab.

Infections in Children with CAPS Disease

There were 15 pediatric patients (<18 years of age) in the three CAPS studies (see Table 29). All children in Studies D2304, A2102 and D2306 had at least one infection. No severe or serious infections were observed in children. One SAE of pyrexia was reported without confirmed infection though a UTI was suspected.

Table 29.

| Comparison of Frequency & Severity of Infections between Adults and Children - CAPS | | |
|---|--------------------------|-----------------------------|
| Study | Patients with Infections | Severe / Serious Infections |
| Study D2304 | | |
| Adults ≥ 18 years | 21/30 (70%) | 1 severe; 0 serious |
| Children < 18 years | 5/5 (100%) | 0 |
| Study A2102 | | |
| Adults ≥ 18 years | 23/27 (85%) | 2 severe / 1 serious |
| Children < 18 years | 7/7 (100%) | 0 |
| Study D2306* | | |
| Adults ≥ 18 years | 6/48 (13%) | 0 |
| Children < 18 years | 0/9 | 0 |

* Study D2306 data reported through interim cutoff 12Sept2008.

Adapted from Sponsor Table 2-6, page 35 of 82, Summary of Clinical Safety.

Leukopenia

Laboratory signs of lowered white cell counts and/or neutropenia, are reported with this class of biologic agent. No leukopenia and/or neutropenia were reported in the CAPS studies or in other disease studies with canakinumab. Leukopenia has been reported with another IL-1 β blocker agent. Leukopenia was reported in one patient receiving rilonacept (package labeling). The neutropenia (absolute neutrophil count < 1 x 10⁹/L) after a large dose of rilonacept (2000 mg iv) was transient in nature and was not associated with any concurrent infection.

Vertigo

CAPS Studies

Vertigo is a known complication of the more severe forms of CAPS disease and was reported as in the pre-existing medical history by ~16% of MWS patients in Study D2034. It is unclear whether there is a causal relationship between canakinumab treatment and the AEs of vertigo..

Vertigo was reported in 10 of 78 patients (13%) with CAPS disease: 5 patients in Study D2304, 3 patients in Study A2102, and 2 patients in Study D2306 (see **Table 30**). Two cases were reported as SAEs, one each in Study D2304 and A2102. The majority of the cases of vertigo were reported as mild in severity. Prior to receiving canakinumab, two CAPS patients reported vertigo and dizziness as significant signs and symptoms of their CAPS medical history. In 7 of 10 patients, no treatment was administered for vertigo and no patient discontinued study medication due to vertigo. One patient with vertigo discontinued the study for other reasons (refer to Section 7.3.2 Nonfatal Serious Adverse Events). The onset of vertigo in the majority of affected patients occurred in < 30 days from initiation of canakinumab treatment.

Table 30.

| Vertigo in CAPS Disease Studies | | | | |
|---------------------------------|-----------|--|---------|------------------------------------|
| Pt # /age / gender | Treatment | Outcome | Serious | Time to onset post 1st dose (days) |
| Study D2304 / MWS | | | | |
| # 0004-00001/ 44-yr/ F | ACZ885 | Positional vertigo; resolved same day. | no | 10 |
| # 0004-00003/ 41-yr/ F | ACZ885 | Vertiginous sensation; resolved 3 days after onset. | no | 1 |
| # 0007-00001/ 19-yr/ F | ACZ885 | Prior history of vertigo; resolved same day. Treated with isoleucine and metopimazine. | yes | 124 |
| # 0010-00004/ 74-yr/ F | ACZ885 | Vertigo onset; resolved same day. | no | 104/ 110 |
| # 0502-00001/ 22-yr/ F | ACZ885 | Vertigo, resolved same day. | no | 204/ 248 |
| Study A2102 / CAPS | | | | |
| # 0002-5108/ 7-yr/ M | ACZ885 | Vertigo, dizziness, nausea, prolonged occurrence; complete recovery. Treated with vomex. | yes | 9/ 122/ 371 |
| # 0002-5109/ 47-yr/ F | ACZ885 | Vertigo; resolved same day. | no | |
| # 0002-5128/ 44-yr/ M | ACZ885 | History of tinnitus, vertigo; resolved after 12 days | no | 2 |
| Study D2306 / CAPS | | | | |
| # 0501-0002/ 26-yr/ F | ACZ885 | Vertigo; resolved same day. | no | 5 / 23 |
| # 0004-0008/ 14-yr/ F | ACZ885 | Vertigo, continuing | no | 25 |

Adapted from sponsor Table 2-14, p 44 of 82

Vertigo in Other Studies

Study A2101 (RA): 3 cases of vertigo were reported as AEs in this trial.

- Pt # A2102-0002-00009 and # A2102-0002-00014 treated with canakinumab 3 mg/kg and 10 mg/kg. Both these cases were mild in severity and treatment was not required for resolution. A causal relationship to canakinumab could not be excluded in these cases of vertigo.
- One patient treated with placebo experienced vertigo twice with mild and moderate severity. No treatment was required for resolution.

No cases of vertigo were reported as an AE in the healthy subject/single dose studies. Exposure to canakinumab could not be excluded as contributing to the vertigo observed in the two cases in Study A2101. A potential mechanism of action to explain vertigo associated with canakinumab treatment is unknown.

Injection Site Reactions

CAPS Studies

The proposed route of administration of canakinumab is sc and these data are summarized across Studies D2304, A2102 and D2306 in **Table 31**. A total of 7% of patients in Parts 1 and 2, experienced an injection site reaction with canakinumab administration (see **Table 31**). In Study A2102, 24% of patients experienced a mild injection site reaction which included pain, redness, swelling and hemorrhage at the site. There was no tendency for an increased incidence of injection site reactions as the number of injections increased. In Study D2306, two patients had injection site pain and one patient experienced local redness and swelling. All events in this longer term extension study through the data cutoff have been mild and resolved within one day.

Other Diseases

In patients with _____, approximately one-quarter of patients treated with canakinumab had an injection site reaction (see **Table 32**). In Studies A1101. _____ injection site reactions were not analyzed. In general, the proposed sc route of canakinumab administration was well tolerated in CAPS patients, including in longer term extension, and in patients with other diseases.

b(4)

Table 31.

| | Injection Site Reactions in CAPS Studies | | | | |
|------------------|--|---------------------------|----------------------------|--------------------------|---------------------------|
| | Study D2304 | Study D2304 | | Study A2102 | Study D2306 |
| | Part 1 | Part 2 | | | |
| | ACZ885 N = 35 n (%) | ACZ885 N = 15 n (%) | Placebo N = 16 n (%) | ACZ885 N = 3 n (%) | ACZ885 N = 57 n (%) |
| Clinical Outcome | | | | | |
| No reaction | 32 (91%) | 13 (87%) | 15 (94%) | 25 (74%) | na |
| Mild | 3 (7%) | 1 (7%) | 1 (6%) | 8 (24%) | 3 (5%) |
| Moderate | 0 | 1 (7%) | 0 | 1 (3%) | 0 |
| Severe | 0 | 0 | 0 | 0 | 0 |

Adapted from Sponsor Table 4-1, page 61 of 82, Summary of Clinical Safety and Table 14.3-4.8 of Study D2304.

Table 32

| Injection Site Reactions - Study | | |
|----------------------------------|----------|---------|
| | ACZ885 | Placebo |
| Category | N = 19 | N = 4 |
| None | 14 (75%) | 3 (75%) |
| Mild | 5 (26%) | 1 (25%) |
| Moderate | 0 | 0 |
| Severe | 0 | 0 |

b(4)

Adapted from Sponsor Table 4-2, page 61 of 82, Summary of Clinical Safety.

Autoimmune Reactions

Some immunomodulatory therapies (e.g., TNF blockers, Type 1 interferon) trigger autoimmunity in some patients. In general, no AEs suggestive of autoimmune disorders or increased auto-antibodies were reported in the CAPS studies or in studies in other diseases.

Immunogenicity Assessments

Thus far, no events of anaphylactoid or anaphylactic reactions have been reported in the three CAPS studies or in studies in other diseases. In Study D2304 and A2102, all patients were assessed for immunogenicity during their study participation and none of the patients demonstrated a treatment induced antibody response to canakinumab regardless of the dose regimen. Immunogenicity analyses were not performed in the interim analysis of the longer term extension Study D2306.

Tuberculin Skin Tests

CAPS Studies

Systematic screening for tuberculosis (TB) was included in all canakinumab studies eligibility criteria. In Study D2034, 11 patients, and in Study A2012, 4 patients had positive PPD test results at screening. Per the protocol(s), chest x-ray was performed to rule out latent or active TB infection. None of these 15 patients had a positive chest x-ray. Six (6) of 44 patients developed a positive PPD skin reaction at the end of Study A2102 or Study D2034. One of these patients was previously treated with anakinra. All of these patients had a negative PPD skin test at screening. Quantiferon blood test was confirmatory in one of 6 patients and negative in three of 6 patients; all four of these patients were treated with prophylactic INH therapy for 6 months. Two of six patients had negative chest x-rays and negative whole body CT and sputum results and were treated with prophylactic INH. No further information was available in one patient.

Tuberculin Skin Tests

Other Diseases

In studies in other diseases, 4 of 48 RA patients developed a positive tuberculin skin test during the study after having a negative result at baseline. None of these patients had a prior history of TB and none had any signs or symptoms of TB during the study. Further testing to exclude latent or active TB, including chest x-ray, Quantiferon and sputum were negative. Among these 4 patients, 2 were on placebo treatment, 1 is still blinded, and 1 was treated with canakinumab.

The observed conversion of PPD skin test from negative to positive in some patients treated with canakinumab without evidence of an acute or latent TB infection is consistent with a primary effect of the initial screening for TB per the usual CDC guidelines for patients receiving

immunosuppressive therapy. Overall, the clinical trials data have not demonstrated an increased risk for reactivation of latent TB infection with canakinumab treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

An adverse event was defined as any untoward medical occurrence including abnormal laboratory finding, symptom, or disease temporally associated with the use of canakinumab, whether or not the adverse event was considered causally related to the use of canakinumab. Treatment-emergent AEs were defined as events beginning on or after administration of canakinumab or pre-existing conditions that worsened on or after study drug administration.

The AE profile of canakinumab in CAPS was significant for infections and vertigo. All observed infections responded to standard of care treatment. No opportunistic or unusual infections were reported. Vertigo was observed across the CAPS studies in canakinumab treated patients. A causal relationship between canakinumab and vertigo remains unclear as vertigo is a known complication of severe CAPS disease and was a pre-existing condition in some CAPS patients enrolled in these studies. In general, the adverse event profile for canakinumab is similar to that observed in another anti-cytokine, rilonacept (Anakinra), approved to treat CAPS disease.

Most patients (>80%) experienced at least one AE in Parts 1 and 2. The proportion of patients experiencing AEs in particular system organ classes (SOCs) is generally higher in Part 2 than Part 1, likely related to the longer duration of exposure in Part 2. The proportions of patients experiencing AEs in the placebo arm in Part 2 cannot be compared directly to the proportions in the canakinumab arm because of the longer duration of exposure in the canakinumab arm.

The most common AEs in Study D2034, Parts 1 through 3, were in the SOC Infections and infestations. In Part 1, the most common AEs were infectious (35%), followed by General disorders and administration site conditions (20%), and Gastrointestinal disorders and Respiratory, thoracic and mediastinal disorders, both (14%). In Part 2, the most common category of AEs was infectious (80%) in patients continuing canakinumab treatment, followed by Gastrointestinal disorders (40%), Respiratory, thoracic, and mediastinal disorders (33%), and Injury, poisoning and procedural complications (27%). In Parts 1 through 3 considered together, the most frequent AEs were consistent with those observed in Part 2. As expected, based on CAPS disease signs and symptoms, AEs in the Musculoskeletal and connective tissue disorders were 17%, 20%, and 37% in Parts 1, 2 and 3, respectively (see **Table 33**). In interpreting data in **Table 33**, it is important to keep that Part 2 was a randomized withdrawal period in which all the patients in the placebo group had previously received study drug. Furthermore, most patients in the placebo group were exposed for a shorter time because they met the endpoint of flare. Therefore, the AE rates in the placebo group cannot be directly compared to those in the canakinumab group **Table 33**.

Table 33.

| Common AEs by SOC n (%) in Study D2304 CAPS | | | | |
|---|---------------------------|---------------------------|----------------------------|---------------------------|
| Primary SOC | Part 1 | Part 2 | | Part 1 to 3 |
| | ACZ885 N = 35 n (%) | ACZ885 N = 15 n (%) | Placebo N = 16 n (%) | ACZ885 N = 35 n (%) |
| n (%) of pts with AEs | 29 (83%) | 15 (100%) | 14 (86%) | 35 (100%) |
| Blood and lymphatic system disorders | 1 (3%) | 0 | 1 (6%) | 2 (6%) |
| Cardiac disorders | 1 (3%) | 0 | 0 | 1 (3%) |
| Ear and labyrinth disorders | 2 (6%) | 1 (7%) | 0 | 8 (23%) |
| Eye disorders | 1 (3%) | 1 (7%) | 1 (6%) | 7 (20%) |
| Gastrointestinal disorders | 6 (17%) | 6 (40%) | 5 (31%) | 17 (49%) |
| General disorders and administration site condit. | 7 (20%) | 3 (20%) | 3 (19%) | 14 (40%) |
| Immune system disorders | 1 (3%) | 2 (13%) | 0 | 3 (9%) |
| Infections and infestations | 12 (34%) | 12 (80%) | 9 (56%) | 26 (74%) |
| Injury, poisoning and proced. complications | 1 (3%) | 4 (27%) | 2 (13%) | 9 (26%) |
| Investigations | 3 (9%) | 0 | 1 (6%) | 5 (14%) |
| Metabolism and nutrition dis. | 2 (6%) | 0 | 1 (6%) | 3 (9%) |
| Musculoskeletal and connect. tissue disorders | 6 (17%) | 3 (20%) | 2 (13%) | 13 (37%) |
| Nervous system disorders | 4 (11%) | 3 (20%) | 0 | 1 (3%) |
| Psychiatric disorders | 1 (3%) | 3 (20%) | 1 (6%) | 6 (17%) |
| Renal and urinary disorders | 1 (3%) | 0 | 0 | 1 (3%) |
| Reproductive system and breast disorders | 1 (3%) | 0 | 0 | 2 (6%) |
| Respiratory, thoracic and mediastinal disorders | 5 (14%) | 5 (33%) | 1 (6%) | 12 (34%) |
| Skin and subcutaneous tissue disorders | 4 (11%) | 1 (7%) | 0 | 9 (26%) |
| Vascular disorders | 2 (6%) | 1 (7%) | 1 (6%) | 4 (11%) |

The common AEs reported by preferred term (PT) are summarized in **Table 34**. Infectious AEs by PT most commonly observed were nasopharyngitis, diarrhea, and influenza like illness in Studies D2304 and A2102 (see **Table 34**). In Study D2306, these limited data available at the interim cutoff do not show findings significantly different from what was observed in the other studies.

Table 34.

| Common AEs by PT in > 1 patient CAPS Studies D2304, A2102 and D2306 | | | |
|---|-------------------------|-------------------------|-------------------------|
| Preferred Term (PT) | D2304 | A2102 | D2306 |
| | Parts 1-3 (48 wks) | (48 wks) | (≤ 8 wks) |
| | ACZ885, N = 35 n (%) | ACZ885, N = 34 n (%) | ACZ885, N = 57 n (%) |
| n (%) of pts with any AE | 35 (100%) | 34 (100%) | 22 (39%) |
| Nasopharyngitis | 12 (34%) | 10 (29%) | 0 |
| Diarrhea | 6 (17%) | 3 (9%) | 1 (2%) |
| Influenza like illness | 6 (17%) | 1 (3%) | 1 (2%) |
| Rhinitis | 6 (17%) | 3 (9%) | 0 |
| Mouth ulceration | 5 (14%) | 4 (12%) | 1 (2%) |
| Nausea | 5 (14%) | 4 (12%) | 1 (2%) |
| Joint sprain | 5 (14%) | 3 (9%) | 0 |
| Vertigo | 4 (11%) | 3 (9%) | 2 (4%) |
| Bronchitis | 4 (11%) | 1 (3%) | 1 (2%) |
| Pharyngitis | 4 (11%) | 4 (12%) | 0 |
| Musculoskeletal pain | 4 (11%) | 1 (3%) | 0 |
| Headache | 4 (11%) | 5 (15%) | 2 (4%) |
| Weight increased | 3 (9%) | 1 (3%) | 0 |
| Pain in extremity | 3 (9%) | 2 (6%) | 0 |
| Epistaxis | 3 (9%) | 1 (3%) | 0 |
| Pharyngolaryngeal pain | 3 (9%) | 6 (18%) | 0 |
| Erythema | 3 (9%) | 0 | 0 |
| Aphthous stomatitis | 3 (9%) | 1 (3%) | 0 |
| Gastroenteritis | 3 (9%) | 3 (9%) | 0 |
| Oral herpes | 3 (9%) | 2 (6%) | 1 (2%) |
| Upper resp. tract infection | 3 (9%) | 13 (38%) | 0 |
| Tinnitus | 2 (6%) | 0 | 0 |
| Abdominal pain | 2 (6%) | 3 (9%) | 0 |
| Abdominal pain upper | 2 (6%) | 2 (6%) | 0 |
| Stomach discomfort | 2 (6%) | 2 (6%) | 0 |
| Asthemia | 2 (6%) | 1 (3%) | 0 |
| Influenza like illness | 2 (6%) | 1 (3%) | 0 |
| Urinary tract infection | 2 (6%) | 0 | 0 |
| Viral infection | 2 (6%) | 2 (6%) | 0 |
| Muscal spasms | 2 (6%) | 4 (12%) | 0 |

Table 34. (Continued)

| Common AEs by PT in > 1 patient CAPS Studies D2304, A2102 and D2306 | | | |
|---|--------------------|------------------|------------------|
| Preferred Term (PT) | D2304 | A2102 | D2306 |
| | Parts 1-3 (48 wks) | (48 wks) | (≤ 8 wks) |
| | ACZ885 N = 35 | ACZ885 N = 34 | ACZ885 N = 57 |
| Memory impairment | 2 (6%) | 0 | 0 |
| Nystagmus | 2 (6%) | 0 | 0 |
| Tension headache | 2 (6%) | 0 | 0 |
| Anxiety | 2 (6%) | 0 | 0 |
| Depression | 2 (6%) | 1 (3%) | 0 |
| Cough | 2 (6%) | 3 (9%) | 0 |
| Respiratory tract congest. | 2 (6%) | 0 | 0 |
| Acne | 2 (6%) | 2 (6%) | 0 |
| Hyperhidrosis | 2 (6%) | 2 (6%) | 0 |
| Pruritus | 2 (6%) | 2 (6%) | 0 |
| Hematoma | 2 (6%) | 4 (12%) | 1 (2%) |
| Hot flush | 2 (6%) | 0 | 0 |
| Procedural pain | 2 (6%) | 0 | 0 |
| Back pain | 2 (6%) | 2 (6%) | 0 |
| Muscle contracture | 2 (6%) | 0 | 0 |
| Arthralgia | 1 (3%) | 2 (6%) | 0 |
| Rash | 1 (3%) | 5 (15%) | 1 (2%) |
| Vomiting | 1 (3%) | 4 (12%) | 0 |
| Ear infection | 1 (3%) | 2 (6%) | 0 |
| Sinusitis | 1 (3%) | 2 (6%) | 0 |

Common AEs - Other Studies

The most common AEs in patients with _____ are shown in Tables 35 and 36, by SOC and PT, respectively. Consistent with the AEs observed in the CAPS studies, infectious AEs, notably nasopharyngitis, were the most common and occurred more often in patients treated with canakinumab compared to placebo.

b(4)

Table 35

| AEs by SOC n (%) of Patients in Study | | | |
|---|--|---|---------------------------|
| | ACZ885 single dose N = 10 n (%) | ACZ885 multiple dose N = 9 n (%) | Placebo N = 4 n (%) |
| Pts with any AEs | 5 (50%) | 6 (67%) | 1 (25%) |
| SOC | | | |
| Gastrointestinal disorders | 2 (20%) | 3 (33%) | 1 (25%) |
| Infections and infestations | 3 (30%) | 3 (33%) | 0 |
| Skin and subcutaneous tissue disorders | 2 (20%) | 1 (11%) | 0 |
| Injury, poisoning and procedural complications | 0 | 2 (22%) | 0 |
| Eye disorders | 0 | 1 (11%) | 0 |
| General disorders and admin. site conditions | 1 (10%) | 0 | 0 |
| Musculoskeletal and connective tiss. disorders | 1 (10%) | 0 | 0 |
| Nervous system disorders | 0 | 1 (11%) | 0 |
| Psychiatric disorders | 1 (10%) | 0 | 0 |
| Reproductive system and breast disorders | 0 | 1 (11%) | 0 |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (25%) |

b(4)

Adapted from sponsor Table 2-1, p 27 of 82

Table 36.

| PT | Common AEs in > 2% of Patients with | | |
|------------------------|--|---|---------------------------|
| | ACZ885 single dose N = 10 n (%) | ACZ885 multiple dose N = 9 n (%) | Placebo N = 4 n (%) |
| n (%) pts with any AEs | 5 (50%) | 6 (67%) | 1 (25%) |
| Nasopharyngitis | 2 (20%) | 1 (11%) | 0 |
| [REDACTED] | 2 (20%) | 1 (11%) | 0 |

b(4)

Adapted from sponsor Table 2-2, p 29 of 82

The most common AEs observed in patients with RA (Study A2101) that occurred more frequently in canakinumab treated patients compared to placebo treated patients: RA flare, pyrexia, UTI, fatigue, sleep disorder, and arthralgia (see Table 37).

Table 37.

| PT | Common AEs in > 10% Patients with RA | |
|--------------------------|--------------------------------------|----------------------------|
| | A2101 RA | |
| | ACZ885 N = 38 n (%) | Placebo N = 15 n (%) |
| n (%) of pts with any AE | 38 (100%) | 14 (93%) |
| Nasopharyngitis | 12 (32%) | 6 (40%) |
| Rheumatoid arth. flare | 10 (26%) | 2 (13%) |
| Headache | 11 (29%) | 7 (47%) |
| Urinary tract infection | 8 (21%) | 1 (7%) |
| Nausea | 9 (24%) | 5 (33%) |
| Fatigue | 8 (21%) | 2 (13%) |
| Sleep disorder | 8 (21%) | 1 (7%) |
| Arthralgia | 5 (13%) | 1 (7%) |
| Pyrexia | 4 (11%) | 1 (7%) |
| Diarrhea | 4 (11%) | 2 (13%) |
| Vomiting | 4 (11%) | 2 (13%) |

Adapted from sponsor Table 2-3, p 30 of 82

In the three early development studies in healthy subjects, the most common AEs were essentially the same as reported above in the multiple dose studies in patients with disease. The total number of AEs observed did not increase with rising single doses from 1 to 600 mg in Study A1101 (healthy Japanese subjects), with increasing single doses from 1 to 10 mg/kg in _____, or with increasing single doses from 0.3 mg to 10 mg/kg in Study A2101 (RA). There did not appear to be any dose dependency though cohort sizes were small.

b(4)

In healthy subjects, Study A1101, the most common AEs, by SOC, were elevations in laboratory test, specifically, liver enzymes, creatine phosphokinase, CRP and WBC count. In Study _____ the most common AEs were nasopharyngitis, influenza, headache, hypersensitivity and dyspnea. In patients with _____, the most common AEs, by SOC, were general disorders and administration site conditions (10%, one death and one of fatigue) and infections and infestations (10%, lower respiratory tract infection and nasopharyngitis in one patient each) in the canakinumab treatment group.

b(4)

Adverse Events with Arcalyst (rilonacept) in CAPS

In general, the safety profile of canakinumab is similar to that observed with rilonacept, an IL-1 blocker approved 27Feb2008 for CAPS in adults and children ≥ 12 years of age with FCAS and MWS.

7.4.2 Laboratory Findings

No integrated analysis of laboratory data was performed. Laboratory parameters were summarized by descriptive statistics for the absolute value, change from baseline, and by change from Week 8, by treatment group, in Part 2 of Study D2304. Normal ranges for adult laboratory parameters were defined by a central laboratory. For pediatric patients, the normal ranges for laboratory parameters were obtained from standard medicine texts for pediatrics and the laboratory values outside the criteria were defined by the canakinumab clinical team prior to the start of the canakinumab Phase 3 program and were considered to be notable laboratory values.

Analyses focused on hematology and clinical chemistry laboratory values. Changes from baseline in all laboratory parameters were summarized with the mean and standard deviations (SD). Analyses of shifts from normal to abnormal were also completed. Changes in liver function tests, creatinine, and hematology parameters are reported separately.

Hematology in CAPS

Laboratory results at baseline in patients with active CAPS disease showed increased serum markers of inflammation, CRP and SAA, and elevated erythrocyte sedimentation rate (ESR). Low hemoglobin, elevated WBCs with high neutrophil and platelet counts were also observed. No notable changes in the hemoglobin values from baseline were observed in Part 1 through 3 of Study D2034. Mean hemoglobin increased by 7.8 g/L from baseline to the end of the study visit in Part 1. In patients who were randomized to continue to receive canakinumab, no shift from normal baseline to abnormal post-baseline hemoglobin was observed.

In Study A2102, iron deficiency anemia was present at baseline in 6 patients or newly observed during the study, all improved in all patients with hemoglobin and hematocrit levels returning to normal. In CAPS Study D2036, no notable abnormal hemoglobin values were observed.

Platelet Counts in CAPS

In Study D2304, no notable abnormal platelet count changes from baseline were observed across Parts 1 through 3. In Part1, mean platelet counts decreased by $53 \times 10^9/L$ from baseline to the end of the study visit. In the randomized withdrawal period, Part 2, no patients experienced a shift from a normal baseline to an abnormal post-baseline value.

In Study A2102, platelet counts were observed to slightly decrease from baseline to the end of the treatment periods for both adult and pediatric patients. In Study D2036, no notable abnormal platelet count changes were observed. Since elevated platelet counts are seen in certain proinflammatory states, the decreases in platelet counts that nonetheless remain within normal limits may reflect a lessening of the proinflammatory state in CAPS patients with canakinumab.

Clinical Review

Carolyn L. Yancey, MD

BLA 125319 Llaris (canakinumab) in Cryopyrin-Associated Periodic Syndromes (CAPS)

Sponsor: Novartis

Leukocytes in CAPS

In general, abnormalities in WBC, neutrophil and lymphocyte counts were not seen in CAPS patients treated with canakinumab from baseline in Part 1 and in canakinumab treatment in Part 2 in Study D2304. No patients in the canakinumab arm experienced a shift from a normal baseline to an abnormal post-baseline value, whereas one patient in placebo group shifted from normal to high and one patient shifted from high to normal from baseline to end of study visits

In Study A2102, during the first period of each treatment, counts were high at baseline, decreased rapidly at Day 8 to Week 5 and trended with an increase toward the end of the period. A similar pattern was observed in subsequent periods of Study A2102. This pattern of early response and subsequent loss of some of the early treatment effect is consistent with the CRP and SAA values (refer to the Individual Study Reports results of serum markers of inflammation) which decreased in the early period and trended with increase in levels toward the end of a treatment cycle. In Study A2102, the mean lymphocyte levels did not change over time. In Study D2036, no notable abnormal leukocyte levels were observed in the interim data.

Eosinophil Counts in CAPS

In Study D2304 in Part 1, a total of 2 patients (6%) developed newly occurring high eosinophil counts $\geq 1.1 \times$ upper limit of normal (ULN). This abnormality was also observed in one patient in the canakinumab treatment group in Part 2. The basophil and eosinophil count showed minor changes over the treatment periods in Study D2304. It is unclear if this is related to canakinumab treatment or to the inflammatory response of the underlying CAPS disease.

In CAPS Study A2102, the mean absolute basophil counts did not change over time and eosinophil counts increased slightly in pediatric patients. In CAPS Study D2306, eosinophil counts showed no notable abnormalities.

Hematology in Other Diseases

In Study _____, and Study _____ there were no significant changes in hemoglobin, WBC or other hematologic parameters. No notable changes in hematologic parameters were observed in healthy subjects/ _____) or in _____. Patients treated with canakinumab (Study _____)

b(4)

In conclusion, no clinically meaningful changes in the hemoglobin, hematocrit, WBC count, neutrophil, lymphocyte, or eosinophil counts were observed across the CAPS studies or in studies in other diseases and healthy subjects. There appears to be a small lowering of the elevated platelet count in patients with CAPS disease treated with canakinumab. This trend supports the favorable treatment effect of canakinumab also observed with improved levels of serum markers of inflammation, CRP and SAA, in patients treated with canakinumab.

Chemistry Laboratories

Liver Function Tests

In Part 1 of Study D2304, two patients had an increase in AST level $3 \times$ ULN and one patient had an increase in ALT $3 \times$ ULN (see Table 38). In Part 2, no patient in the canakinumab treatment group had an elevation in AST or ALT.

Clinical Review

Carolyn L. Yancey, MD

BLA 125319 Llaris (canakinumab) in Cryopyrin-Associated Periodic Syndromes (CAPS)

Sponsor: Novartis

In Study A2102, there was no meaningful change within the first period as well as within all periods averaged of mean and median biochemistry parameters. Two patients with a history of mildly elevated liver enzymes continued to have mildly elevated liver enzymes during the study:

Pt. #A2102-5105 entered the trial with AST 2x ULN at baseline and stayed in the range of 1.5 to 2 x ULN during the 505 days of canakinumab exposure. There was never any worsening of these laboratory tests;

Pt. # A2102-5111 entered the trial with SGOT were 3.8 x ULN at baseline increased following canakinumab 150 mg sc to 9.5 x ULN until day 78 post dose and decreased to 4-6.7 x ULN towards the end of study (130 post dose). SGPT were 7.3 times ULN of normal at baseline, increased following canakinumab injection to 20 times ULN at day 78 post dose and decreased thereafter to 15 times ULN. Other labs were normal including total bilirubin. Total cholesterol was high during this study (5.2 to 7.6 mmol/L);

In one other patient (Pt. # A2102-5118), there was a transient reversible increase of her AST and LDH assessed by the clinical investigator as toxic hepatitis. Hepatitis B and C were negative. She was concurrently taking oral contraceptive mediation. Her AST and ALT values on Day 127 (Part 2) were 58 U/L and 141 U/L for AST and ALT, respectively and normalized (15 U/L and 17 U/L for AST and ALT, respectively) on Day 169 while on treatment. Her liver function tests remained normal throughout the rest of Study D2304. The patient is currently continuing in study D2306.

In Study D2306, one patient (# D2306-0503-00001) with a history of elevated liver enzymes had ALT and AST ≥ 5 x ULN on Day 8 of this study. This patient entered Study D2306 with similar high levels of both ALT and AST levels. Canakinumab treatment was not discontinued.

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Table 38

| Clinical Chemistry Notable Abnormalities - Parts 1 and 2 in Study D2304 | | | | |
|---|--|------------------------|------------------|-------------------|
| Laboratory Test | Criterion | Part 1 | Part 2 | |
| | | ACZ885 Total, n (%) | ACZ885 n = 15 | Placebo n = 16 |
| ALT (SGPT) | ≥ 3 x ULN | 35, 1 (3%) | 0 | 0 |
| | ≥ 5 x ULN | 35, 1 (3%) | 0 | 0 |
| | ≥ 10 x ULN | 35, 0 | 0 | 0 |
| AST (SGOT) | ≥ 3 x ULN | 35, 2 (6%) | 0 | 0 |
| | ≥ 5 x ULN | 35, 1 (3%) | 0 | 0 |
| | ≥ 10 x ULN | 35, 0 | 0 | 0 |
| Total Bilirubin | > ULN | 35, 0 | 13, 1 (7%) | 0 |
| | ≥ 1.5 x ULN | | 0 | 0 |
| | ≥ 2 x ULN | | 0 | 0 |
| | ≥ 1.5 x ULN if ALT and/or AST ≥ 3 x ULN | | 0 | 0 |
| Albumin | < LLN | 35, 0 | 0 | 0 |
| Alkaline Phosphatase | > 1.5 x ULN | 35, 1 (3%) | 0 | 16, 1 (7%) |
| GGT | > 3 x ULN | 35, 0 | 0 | 0 |
| Creatinine, serum | ≥ 1.5 x ULN | 35, 0 | 0 | 0 |
| Creatinine clearance | 25% decrease from baseline (if ≥ 16 yrs) | 32, 1 (3%) | 13, 1 (8%) | 15, 1 (7%) |
| Potassium | ≤ 3 mmol/L (if ≥ 16 yrs), or ≤ 3.5 mmol/L (if < 16 yrs) | 35, 0 | 0 | 0 |
| | ≥ 5.5 mmol/L | 35, 0 | 0 | 0 |
| Sodium | ≤ 130 mmol/L | 35, 0 | 0 | 0 |
| | ≥ 150 mmol/L | 35, 0 | 0 | 16, 1 (6%) |
| Calcium | < LLN (if ≥ 16 yrs) | 32, 0 | 13, 1 (8%) | 15, 1 (7%) |
| | ≥ 1.2 x ULN (if ≥ 16 yrs) | 32, 0 | 0 | 0 |
| Protein urine dipstix | ≥ ++ (if ≥ 16 yrs); ≥ + or trace (if, 16 yrs) | 27, 0 | 12, 1 (8%) | 14, 0 |

Overall, there were three CAPS patients with notable changes in their ALT and AST values (Studies D2304, A2102 and D2306). Two patients already had abnormal ALT/AST values at baseline and one patient had potential underlying viral hepatitis. In each of these three patients, the increase in ALT/AST was asymptomatic and transient and was not associated with concurrent increases in serum bilirubin. The liver function tests normalized in all three patients despite continuous canakinumab treatment. Brief narratives of the three patients with relevant changes in their ALT and AST values follow:

Pt # A2102-0001-05111: a 19-year old/F/MWS entered Study A2102 with elevated baseline LFT (AST 70 U/L [3.8 x ULN]) and ALT 256 U/L [7.3 x ULN]) and medical history of hepatosplenomegaly, hypercholesterolemia, anemia and depression. Hepatitis B and Hepatitis C antibodies tests were negative. Concomitant medications included iron supplement for anemia and contraceptive medication. Her AST/SGOT increased following canakinumab 150 mg sc injection to 9.5 x ULN until Day 78 post dose and decreased to 4 to 6.7 x ULN towards the end of study (130 Days post dose). SGPT increased following canakinumab injection to 20 X ULN at Day 78 post dose and decreased thereafter to 15 x ULN. GGT, total and direct bilirubin, direct CK, triglycerides were normal. After completion of Study A2102, she rolled over first to Study D2304 where she continued to receive canakinumab. Her AST and ALT values on Day 127, Part 2, were 58 U/L and 141 U/L for AST and ALT, respectively, and normalized as 15 U/L and 17 U/L for AST and ALT, respectively, on Day 169 while on canakinumab treatment. Her liver function tests remained normal throughout the rest of Study D2304. This patient is currently in Study D2306.

Pt. # A2102-0001-05105: a 29-year old/M/MWS entered Study A2102 with past medical history of abnormal liver function tests (AST 73 U/L [2 x ULN] and ALT 47 U/L [> 1 x ULN] at baseline), asthma, amyloidosis and hypertension. Concomitant medications included pulmicort/budesonide for asthma and perindopril. Hepatitis B and Hepatitis C antibodies tests were negative. His AST remained ~ 1.5 to 2 x ULN during the 505 Days of canakinumab exposure. ALT levels remained above ~ 1 to 1.7 x ULN until the end of the study. GGT, total and direct bilirubin, triglycerides, and total cholesterol were normal. After completion, the patient was rolled over to Study D2304 and was randomized to placebo in Part 2. The ALT and AST levels remained elevated at ~ 1 to 1.7 x ULN. At the end of Study D2304, ALT and AST levels were > 5 x ULN (ALT 159 U/L, AST 154 U/L). He subsequently rolled over to open label study D2306 where his ALT and AST levels were observed to decrease, ALT 29 U/L and AST 47 U/L at his while he continued canakinumab treatment. His GGT, total and direct bilirubin were normal.

Pt. # D2304-0030-00002: a 49-year/F/MWS had normal labs at baseline in Study D2304. On day 58, after the first canakinumab dose in Part 1 and prior to entering Part 2, the patient had newly elevated ALT of 197mU/mL (> 5 x ULN) and AST of 121mU/mL (> 5 x ULN) and normal bilirubin values. On Day 91, AST and ALT decreased to 26 U/L and 32 U/L, respectively, and continued to decrease by Day 175 after being randomized to placebo treatment in Part 2. No subsequent increases in LFTs were observed after she was later treated with canakinumab in Part 3. She had marginally increased eosinophil levels. Ultrasound of her abdomen showed minimal fatty liver changes. LFTs returned to normal. Serology tests showed elevated IgG-titers for CMV antibody: 19.20 IU/mL (ref. range: < 0.80 IU/mL) and EBV: 14.27 U/mL (reference range: < 8.00 U/mL). No baseline serology tests were reported for CMV or EBV. CMV IgM antibody, EBV IgM, and Hep A IgM antibodies were reported as normal. She remained asymptomatic, with continued canakinumab treatment.

Bilirubin

Across the three CAPS studies, no bilirubin elevations of clinical significance were observed. One patient had an isolated bilirubin elevation which appeared to be random and was not sustained: Pt. # D2304-0004-00003, a 41-year old/F/MWS patient without any relevant past medical history and negative hepatitis B and C antibody tests at screening. She was observed to have a new occurrence of bilirubin elevation \geq ULN but not greater than 1.5 x ULN by end of Part 2 where she was randomized to canakinumab treatment. During Part 2 and 3, she had isolated mild total bilirubin elevations $>$ ULN but less than ≥ 1.5 x ULN. No relevant concomitant medications were taken during these study periods. AST and ALT and other chemistry values were within normal ranges. She completed Study D2304 and rolled over to Study D2306.

In Study A2102, 5 patients were observed with isolated total bilirubin elevations as < 1.5 ULN. Each of these cases appeared to be an isolated event and all were transient.

One patient in Study D2306 was observed with a bilirubin above the ULN with an increase of ~ 0.9 umol/L from baseline. This patient had a borderline elevated total bilirubin at the beginning of Study D2306. The AST and ALT values were observed to be normal.

In general, there were no clinically significant elevations in total or direct bilirubin. Patients should be monitored for changes in liver function tests during treatment with canakinumab.

Chemistry Laboratories

Liver Function Tests in Other Disease

In Study A2101 (RA), no clinically significant changes in chemistry laboratory results were observed. Three (3) patients treated with canakinumab experienced ALT elevations > 3 ULN after the second canakinumab dose (1 patient had both AST and ALT elevations > 3 x ULN). One patient had elevated AST (27 U/L) and ALT (34 U/L) values at baseline and on Day 22 experienced increased ALT and AST to 121U/L and 86 U/L respectively, 12 days after the second dose. Values had normalized at the end of study visit. Two other patients experienced elevations after the second dose on Day 114 and 28, respectively. In one, ALT and AST values peaked at 110 U/L and 63 U/L, respectively, and decreased towards the end of study visit while in the other patient experienced single peak ALT and AST at the last study visit of 97 U/L and 63 U/L, respectively. Other liver function parameters, including bilirubin, were normal in these patients. These liver function test elevations generally involved only individual elevated values or, in other cases, were observed to return toward normal at subsequent study while the patients continued in the study on continued canakinumab treatment.

In Studies — and A1101 (healthy subjects Japanese), no clinically significant changes in the laboratory test results were observed. Notable in Study —, newly occurring bilirubin elevations without concomitant jaundice were seen in 13 patients: 4 patients in Part 1; 2 in canakinumab 3 mg/kg and 2 in canakinumab 10 mg/kg, 6 patients in Part 2; 4 in canakinumab 10 mg/kg, and 2 in placebo, and 3 patients in Part 3; canakinumab 10 mg/kg. One patient had associated elevations of ALT and AST > 3x ULN. In Study —, three (3) patients had ALT and AST elevations. In Part 1, one patient treated with canakinumab 1 mg/kg had AST and ALT > 3x ULN; in Part 2, one patient treated with canakinumab 10 mg/kg had ALT > 3x ULN; and, in Part 3, one patient treated with canakinumab 10 mg/kg had ALT elevations > 3x ULN. The etiology of these elevated liver function tests remains unclear. Patients should be monitored for changes in liver function tests during treatment with canakinumab.

b(4)

b(4)

Other Chemistry Assessments

No new occurring notable chemistry changes in other parameters in Part 3 of Study D2304 were observed. Although there were some shifts from normal to high in total cholesterol values among canakinumab-treated patients, there were similar numbers of shifts from high to normal. Therefore, there was no signal increases in cholesterol values.

In Study A2102, no meaningful change was observed in chemistry values within the first period as well as within all periods averaged for adult and pediatric patients. In Study D2036, no notable changes were observed in other biochemical parameters.

Creatinine

Renal disease secondary to amyloidosis is a complication of the more severe forms of CAPS disease, MWS and NOMID. Two patients in Study D2304 with a medical history of renal amyloidosis experienced no change in their creatinine values at the end of the study compared

to baseline. Three (3) patients with baseline creatinine clearance ≤ 80 ml/min, including one patient with renal amyloidosis, had unchanged creatinine values throughout the study.

In Study A2102, no changes in serum creatinine were observed for adult and pediatric patients. In four (4) patients with renal insufficiency at baseline, two (2) patients with severe renal involvement experienced no change in renal functions and two patients experienced decline in the calculated glomerular filtration rate (GFR) of 16.5% and 17.0%, respectively, from baseline to the end of the study. For all others, no meaningful changes were observed in renal function. In Study D2306, no notable changes in creatinine and creatinine clearance were observed at the interim cutoff.

Urinalysis

As reported above, renal involvement may be observed in the more severe forms of CAPS disease, MWS and NOMID. In Study D2304, two (2) patients were observed with positive protein dipstick defined as $\geq ++$ for adults and $\geq +$ for pediatric patients. In Part 3, two patients had notable proteinuria, one of which had a urinary tract infection. No relevant medical history was observed with either patient. In Study A2102, no clinically significant changes in the urinalysis were observed. In Study D2036, there were two instances of proteinuria: a 5-year old/MWS on Day 14 and a 34-year old/ MWS on Day 8. The latter patient has proteinuria at baseline. No clinically significant changes in the urinalysis were observed in the remaining studies: A2101, — A1101, —

b(4)

7.4.3 Vital Signs

Weight, blood pressure, body temperature and radial pulse were measured at baseline and at each study visit. In adult patients, height was measured at the pre-treatment visit only. In the pediatric patient population ≥ 4 to < 18 years of age, height was assessed at each study visit. Predefined notable abnormal vital signs definitions were used for analysis only for Studies D2304 and D2306. In Study A2102, no notable abnormal values were predefined in the protocol.

In Study D2304, one notable decrease in supine systolic blood pressure (sBP) was reported in 1 patient (3%) and diastolic blood pressure (dBP) in 2 patients (6%). An increase of sBP was reported in 3 patients (9%) and diastolic pressure in 11 patients (31%). The majority of the increases of sBP or dBP appeared to be isolated observations. No sustained elevations were seen in these patients. Three of these patients had a past medical history of hypertension. None of the elevations were reported as AEs, and no patient started antihypertensive treatment. In addition, no clinically significant change for dBP and sBP from baseline to the end of Part 2 were observed.

In Study D2306, no clinically significant changes in BP were observed. In Study D2036, 14 patients (25%) presented with abnormalities, the majority of whom presented on Day 1. Two patients experienced slightly elevated increase in sBP (~140-144 mmHg) and dBP (~90 mmHg) during the study and one of these two patients, a 46-year old/F/MWS entered the study with notably high supine DBP (~90 to 100mm Hg). One pediatric patient, 9-year old/M/MWS experienced notably abnormal low supine pulse (54 bpm) on Day 7 of the study. In Studies

A1101, there were no clinically significant trends during the courses of observations. In general, hypertension was not a clinically significant event in patients with CAPS disease or in other diseases. These results are consistent with other IL-1 blocker therapy.

b(4)

7.4.4 Electrocardiograms (ECGs)

Since there was no preclinical evidence of a relevant effect of canakinumab on ECG intervals, no specific rationale was determined for analysis of any ECG changes that might occur during canakinumab treatment. No integrated analysis of ECG data was performed. In Study D2304, no shifts were observed in the clinical evaluation of ECG results. In Study A2102, all ECGs were normal or with clinically insignificant abnormalities. No evidence of drug related changes in ventricular rate, PQ/PR interval, QRS duration, QT uncorrected, or corrected, using the Bazett and Fridericia formula, were observed in Study A2102. In Study D2306, analysis of clinically relevant effects in ECG recordings will be reported in the final clinical study report.

In Study —, no clinically relevant effects were seen in ECG, ECG intervals, QTc intervals (Bazett and Fridericia formulas) or change in QTc intervals from baseline Study —. In Study A1101, no clinical significant abnormality in ECG was observed in this study. In Study —, all ECG evaluations were either normal or showed clinically insignificant abnormalities. In Study —, there were no changes in ECG parameters during the study that were not observed at baseline. Based on the non-clinical data and these clinical data, canakinumab does not appear to have an adverse effect on ECGs in CAPS and in other diseases.

b(4)

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted and none were considered warranted.

7.4.6 Immunogenicity

Studies with canakinumab were assessed for the potential to trigger development of anti-canakinumab antibodies in CAPS patients and in other diseases. No AEs of anaphylactoid or anaphylactic reactions were observed in the CAPS studies or in other diseases. All patients in Studies D2304 and A2102 were assessed for immunogenicity during each study. No patient was observed to show a treatment induced antibody response to canakinumab. Immunogenicity analyses were not performed at the interim cutoff date for Study D2306. These data will be reported in the clinical study final report.

These data suggest that canakinumab appears to be non-immunogenic in adults and in children and adolescents as observed across these studies in CAPS and in other diseases. As there were no anti-canakinumab antibodies detected by an ELISA assay in these CAPS patients, no comparison of the effect on efficacy or safety was completed. These negative data with no evidence of anti-canakinumab antibody formation are dependent on factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. Labeling should include these observed negative results with a

cautionary statement because immunogenicity is a known risk in some patients with exposure to IL-1 blocker therapy. See the Clinical Pharmacology review by Srikanth Nallani, PhD.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Studies A1101 (healthy Japanese subjects), _____ and _____, explored varying single doses of canakinumab. The total number of AEs did not increase with rising single doses of canakinumab from 1 to 600 mg. b(4)

There were no trends of increased AEs with increasing single doses in either Study _____, 1 to 10 mg/kg, or in Study A2101, 0.3 to 10 mg/kg. Overall, though the cohorts are small across these studies, no canakinumab dose-dependency was observed with doses ranging from 0.3 mg to 10 mg/kg. b(4)

7.5.2 Time Dependency for Adverse Events

There were no trends to increasing rates of any adverse events with increasing duration of exposure in Study D2304 or A2102 (refer to **Table 27**, Common AEs by PT)

7.5.3 Drug-Demographic Interactions

No interactions were found between demographics and either efficacy or safety data.

7.5.4 Drug-Disease Interactions

Clinical development for canakinumab is only extensive in one disease thus far, CAPS. No formal PK studies in patients with hepatic impairment were performed. In Study A2102, 4 CAPS patients with moderate to end stage renal insufficiency were treated with canakinumab. The clearance and C_{max} of canakinumab in patients with moderate to end stage renal failure were found to be similar to the average adult patients.

7.5.5 Drug-Drug Interactions

Drug interactions between canakinumab and other medical products have not been investigated in formal studies. Canakinumab is not expected to exhibit the same potential for drug-drug interactions as a small molecule agent. The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1 β) during chronic inflammation. It is expected that for a molecule which binds to IL-1, such as canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted, e.g., warfarin. Therefore, initiation of canakinumab treatment in patients receiving treatment with these types of products, e.g., warfarin, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of

the medicine product may require adjustment as needed. Labeling should reflect this precaution and unknown product interaction.

The incidence of increased serious infections has been associated with administration of another IL-1 blocker in combination with TNF inhibitors. The labeling should include comment that canakinumab is not recommended with concomitant TNF inhibitors because this combination may increase the risk of serious infection observed with both classes of biologic product.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No cases of malignancy were reported in the CAPS studies and two case of recurrent breast cancer were reported in two patients from trials in other conditions (refer to Section 7.3.2 Non-fatal Serious Adverse Events, under Study A1101 in healthy Japanese subjects and _____). No long-term animal studies have been performed to establish the carcinogenic potential of canakinumab as these studies were not considered warranted. See the Pharmacology Toxicology review by Kathleen Young, PhD.

b(4)

7.6.2 Human Reproduction and Pregnancy Data

Although patients were instructed not to become pregnant during the clinical trials with canakinumab, two pregnancies in patients receiving canakinumab were observed.

- One patient in Study _____ became pregnant and had a spontaneous abortion ~ 11 weeks after the last dose of 3 mg/kg canakinumab. She had a past medical history of spontaneous abortions.
- A patient in Study A2102 (CAPS) became pregnant two months after entering this study, discontinued canakinumab for this reason, and had a normal pregnancy with normal delivery of a healthy baby.
- In addition, the wife of a patient in Study A2102 (CAPS) became pregnant. This pregnancy was carried to full term with delivery of a normal baby.

b(4)

There are no adequate and well-controlled studies of canakinumab in pregnant women. As reported in the Pharmacology Toxicology review, canakinumab appeared to have no effect on male fertility parameters in marmoset study. A murine anti-murine IL-1 β antibody was reported to not have any undesirable effects on fertility in male or female mice. In general, the animal studies do not appear to indicate a direct or indirect harmful effect with respect to reproductive toxicity. The risk for the fetus and the mother is unknown. These findings differ from findings with riloncept, in which fetal abnormalities were observed at low exposure in the Cynomolgous monkeys and there was a three-fold increase in the rate of stillbirths in mice treated with murine analogue (refer to the Arcalyst labeling and refer to the Pharmacology Toxicology review by Kathleen Young, PhD).

In addition, it is not known whether canakinumab is excreted in human milk. Animal studies have shown that a murine anti-murine IL-1 β antibody had no undesirable effects on the development in nursing mouse pups and that the antibody was transferred to the pups. The labeling should include this information as it applies to humans.

7.6.3 Pediatrics and Assessment of Effects on Growth

Height and weight were assessed in all three CAPS studies. Due to the inclusion of children and adolescents in the CAPS studies as well as the unknown effects of IL-1 blocker therapy on growth and development, development and sexual maturation, e.g. Tanner Stage assessment, were added to the study visit assessments in the open label longer term extension Study D2306. In general, weight gain as a favorable effect of canakinumab treatment was expected in pediatric patients during the course of these CAPS studies.

Study D2304

Six (6) pediatric patients gained a cumulative weight of 6 kg during this study. Weight gain was not associated with increases in BP, total cholesterol, or triglycerides in the pediatric patients. Two (2) pediatric patients, Pt # D2304-0002-00001, a 9-year old/F, and Pt. # D2304-0001-00008, a 14-year old/M, experienced increases in height of 6 cm and 5 cm, respectively from baseline.

Study A2102

Weight gain was observed in 5 of 7 (71%) pediatric patients in Study A2102. The pediatric patients on average gained 3.5 kg over approximately one year. Height was measured throughout this study in children and adolescents < 16 years of age. All pediatric patients gained from 4 to 7 cm in height over approximately one year. One pediatric patient, Pt. # A2102-0002-5113, a 13-year old/MWS, experienced increased appetite reported as an AE.

Study D2306

The results will be available in the final clinical study report.

In conclusion, though these data are limited due to the small numbers of pediatric patients with this rare disease, there appears to be a favorable trend for growth and development with canakinumab treatment in pediatric patients with CAPS disease.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No case of overdose has been reported with canakinumab. There is no reason to suspect a pharmacological action that could result in drug abuse with this formulation. No such reports have been reported to the Agency.

7.7 Additional Submissions

The four-month (120-day) safety update to this original BLA was submitted on 31Mar2009 and contained additional safety data for the period between the original BLA interim data cutoff date of 12Sept2008 and the new interim data cutoff date of 12Jan2009. These data include:

- Additional safety data from CAPS patients: 1) interim data for Study D2304 in the original BLA is replaced by final data (recruited patients finished treatment) with a full Clinical Study Report; and 2) interim data for open label longer term extension Study D2306 in the original BLA is extended to a new cut-off (more patients recruited) with a second interim report as of 12Jan2009 (see **Table 39**).
- Preliminary safety data of deaths and serious AEs in other disease, e.g., two studies in RA, A2201 and A2207 (see **Table 40**); and
- Deaths and serious AE from ongoing studies in all indications (see **Table 41**).

Table 39 Summary of Clinical Trials with New Clinical Safety Data in CAPS Patients

| Study No. | Efficacy objectives, Population | No. Treated | ACZ Treatment (mg or mg/kg) |
|---|--|---|--|
| Placebo-controlled, double-blind trial | | | |
| D2304 | Efficacy / safety in MWS (part I: uncontrolled) | 35 | part I (single dose, 8 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg (15-40kg) |
| | (part II: placebo-controlled, 31 double-blind, withdrawal) | | part II (multiple doses, up to 24 wks) 150 mg s.c. q8wk (>40kg), 2 mg/kg (15-40kg) placebo (part II only) |
| | (part III: uncontrolled) | 31 (now complete) (final CSR) | part III (16 wk if finished part II, or longer) 150 mg s.c. q8wk (>40kg), 2 mg/kg (15-40kg) |
| Uncontrolled, open-label trial | | | |
| D2306 | Efficacy / safety in CAPS (MWS, FCAS, MWS/NOMID) | 98 (ongoing) (new interim DBL, draft CSR) | 150 mg s.c. q8wk (>40kg), 2 mg/kg (15-40kg) |

update to SCS Table 1-1 (new data is bold and underlined), CSR = clinical study report, DBL = database lock
 Sponsor Table 1-1, page 7 of 41, Summary Clinical Safety, 120-DSU.

Table 40 Summary of Clinical Trials Recently Completed in Rheumatoid Arthritis

| Study No. | Efficacy objectives, Population | No. Treated | ACZ Treatment (mg or mg/kg) |
|---|------------------------------------|-------------|--|
| Placebo-controlled, double-blind trial | | | |
| A2201 | Dose finding in RA (12 weeks) | 274 | ACZ885: 600 mg i.v. then 300 mg s.c. q2wk, n = 71 ACZ885 no loading dose, 300 mg s.c. q2wk, n = 64 ACZ885 no loading dose, 150 mg s.c. q2wk, n = 69 placebo, n = 70 |
| A2207 | Efficacy / safety in RA (12 weeks) | 60 | ACZ885 600 mg i.v. on day 1, day 15, day 43, n=50 placebo, n=10 |

update to SCS Table 1-2
 Sponsor Table 1-2, page 8 of 41, Summary of Clinical Safety, 120-DSU.

Table 41 Summary of Ongoing Clinical Trials in Other Diseases

| Study, disease, duration | planned | recruited (12-Jan-09) | FPFV | Randomization scheme (ACZ:comparator) |
|--------------------------|---------|--------------------------|----------|--|
| A2201-E1 (RA), 76 weeks | 227 | 224 | April-07 | (no comparator) |
| A2201-E2 (RA), 104 weeks | 180 | 4 | Oct-08 | (no comparator) |
| A2204 (RA), 26 weeks | 78 | 78 | March-07 | 2:1 (methotrexate) |
| A2206 (RA), 6 weeks | 32 | 9 | Aug-07 | (no comparator) |
| A2211 (RA), 54 weeks | >179 | 114 | Oct-07 | (no comparator) |
| A2213 (T2DM), 28 weeks | 105 | 104 | Dec-07 | 2:1 (placebo), cohort 1 (n=15) 1:1 (placebo), cohort 2 (n=90) |
| A2203 (sJIA), open ended | 26 | 23 | Dec-06 | (no comparator) |
| A2212 (gout), 16 weeks | 44 | 2 | July-08 | 1:1 (dexamethasone) |
| H2251 (gout), 24 weeks | 440 | 7 | Dec-08 | 6:2 (colchicine) |
| H2255 (gout), 8 weeks | 200 | 28 | Nov-08 | 5:2 (triamcinolone acetonide) |
| B2204 (COPD), 57 weeks | 130 | 128 | Jan-07 | 1:1 (placebo) |

FPFV = First patient first visit, RA = Rheumatoid Arthritis, HV's = healthy volunteers, T2DM = type-2 diabetes mellitus, sJIA = systemic juvenile idiopathic arthritis, COPD = chronic obstructive pulmonary disease

Sponsor Table 1-3, page 8 of 41, Summary Clinical Safety, 120-DSU.

These new clinical safety data are summarized by individual study and grouped by disease, e.g., CAPS and other diseases, as in the original BLA. Deaths and serious AEs are reported by study without any data pooling as in the original BLA.

Exposure

The new clinical safety data in CAPS patients, including the range of exposures and patient-years, is summarized in Table 42. The extent of canakinumab exposure increased from 69 pt-yrs in 78 CAPS patients in the original BLA to 96 pt-yrs in 104 CAPS patients as of 12Jan2009. Based on inclusion of the new clinical safety data in other diseases, RA patients exposed to canakinumab increased from 415 patients in the original BLA to 438 patients as of 12Jan2009.

Table 42.

| Cumulative Extent and Duration of Exposure in CAPS | | |
|--|----------------------------------|------------------------------|
| | Original BLA ACZ885 N = 78 | 120-DSU ACZ885 N = 104 |
| Duration of Exposure | | |
| ≥ 1 day | 78 | 104 |
| ≥ 12 weeks | 59 | 81 |
| ≥ 24 weeks | 56 | 62 |
| ≥ 36 weeks | 54 | 57 |
| ≥ 48 weeks | 31 | 56 |
| ≥ 96 weeks | 6 | 6 |
| ≥ 144 weeks | 4 | 4 |
| Mean duration (days) | 323 | 336 |
| Median duration (days) | 316 | 392 |
| Min, max (days) | 1, 1269 | 9, 1429 |
| Patient-years | 69 | 96 |

Adapted from Sponsor Table 1-4, page 9 of 41, Summary of Clinical Safety, 120-DSU.

Patient Demographics

The patient demographics including the 120-DSU data are consistent with the observations reported in the original BLA. The number of pediatric patients increased from 15 in the original BLA to 23 as of 12Jan2009 (see Table 43). Across adult and pediatric CAPS study populations based on the 120-DSU data, patients with FCAS have increased from 9 to 20; MWS has increased from 63 to 72; MWS/NOMID has increased from 5 to 10; and NOMID remains as 1.

Table 43

| CAPS Disease Diagnosis by Age Group | | | | | | | | |
|-------------------------------------|------------------------------------|---------|--------------------|---------|--------------------|---------|------------|---------|
| Type (total in 120 DSU) | Children and Adolescents n = 23 | | | | Adults n = 81 | | | |
| | ≥ 4 to ≤ 12 years | | ≥ 12 to < 18 years | | ≥ 18 to ≤ 59 years | | > 60 years | |
| | BLA | 120-DSU | BLA | 120-DSU | BLA | 120-DSU | BLA | 120-DSU |
| FCAS (n = 20) | 1 | 2 | na | na | 8 | 15 | na | 3 |
| MWS (n = 72) | 5 | 7 | 6 | 8 | 50 | 53 | 2 | 4 |
| MWS/NOMID (n = 10) | 1 | 2 | 2 | 3 | 2 | 5 | na | na |
| NOMID (n = 1) | na | na | na | na | 1 | 1 | na | na |
| unspecified (n = 1) | na | 1 | na | na | 1 | na | na | na |

Adapted from Sponsor Table 1-5, page 10 of 41, Summary of Clinical Safety 120-DSU

Deaths

Deaths in all patients exposed to canakinumab increased from two (2) in the original BLA to three (3) in the 120-DSU. The new death is briefly described:

Study A2211 (RA)

Pt. # 0051-00024/RA was a 58-year old/M with past medical history of rheumatoid arthritis, chronic gastritis, chronic pancreatitis, atherosclerosis of the aorta, chronic bronchitis, anemia and premature beats. Eighty-five (85) days after starting treatment (blinded), he was hospitalized due to a right hip fracture following a fall and died 6 days later from complications of alcoholic psychosis, liver failure and acute alcohol intoxication. There did not appear to be a causal relationship between his death and the blinded study medication.

Non-Fatal Serious Adverse Events

There were two (2) CAPS patients who experienced a SAE, one of whom had an earlier SAE in an earlier study. In conclusion, number of patients in the 120-DSU with SAEs were 9 CAPS patients out of 104 patients (9%) or 0.094 per patient year of exposure at the data cutoff (12Jan2009). This outcome is not increased compared to the original BLA in which 7 CAPS patients out of 78 patients (9%) or 0.101 per patient year of exposure were reported with non-fatal SAEs.

CAPS Studies

Pt. # D2304-0002-00001: a 9-year old/F/MWS, treated with ACZ885 2 mg/kg sc, experienced initial pyrexia (SAE) and urinary tract infection, the latter event was later associated with sepsis (SAE) reported in the 120-DSU. She had complete recovery.

Pt. # D2306-0005-00001: a 20-year old/F/NOMID treated with ACZ885 150 mg sc, experienced depression and self injury (SAE) with prior history of both. She had complete recovery.

Pt. # D2306-0031-0001: a 6-year old/M/MWS treated with ACZ885 2 mg/kg sc, experienced an intra-abdominal abscess post appendectomy (SAE). He had complete recovery.

Pt. # D2306-0041-0009: an 18-year old/F/MWS treated with ACZ885 150 mg sc, experienced elective abortion without complications. She had complete recovery.

Other Diseases

Studies SA2201 and A2207 (RA)

Both these RA studies are in the reporting phase and now unblinded. The new SAEs reported are: Pt. # 0001-0004: a 65-year old/F/RA (ACZ885), experienced tracheobronchitis with dyspnea and cough and completely recovered; Pt. # 0011-00009, 54-year old/F/RA (ACZ885) experienced gastritis, nausea and vomiting (SAE) and completely recovered; P t# 0050-00001, a 29-year old/F/RA (ACZ885) and Pt. # 0054-00003, a 34-year old/F/RA (placebo), were both hospitalized due to worsening RA (SAE); Pt. # 0054-00006, a 42-year old/F/RA (ACZ885) experienced an acute appendicitis, and later an ovarian cyst (SAE), clostridium colitis (SAE) hospitalized with abdominal pain (SAE). She completely recovered. Pt. # 0056-00022, a 51-year old/F/RA (placebo) experienced peptic ulcer/duodenal (SAE) and complete recovered; Pt. # 0056-00048, a 72-year old/F/RA (ACZ885) experienced sigmoid diverticulitis (SAE) treated with antibiotics and improved; Pt. # 0012-00021, a 56-year old/F/RA (ACZ885) experienced acute sinusitis (SAE) and, separately, experienced rupture of a Baker's cyst (SAE) with leg vein thrombosis (SAE); she completely recovered from both events.

In conclusion, in two unblinded, placebo-controlled RA studies, the number of patients who experienced non-fatal SAEs while receiving canakinumab at 15 out of 292 canakinumab treated patients (5%) is no greater than that on placebo at 7 of 95 placebo-treated patients (7%) at the 120-DSU cutoff. Infections remain the most common SAE and are consistent with the SAEs reported in the original BLA.

Discontinuations

The profile of discontinuations for tolerability or safety is essentially unchanged compared to those reported in the BLA (refer to Section 7.3.3 Dropouts and/or Discontinuations). The discontinuations due to AEs were infrequent and the type and severity of AEs which led to discontinuations was not unexpected and did not introduce new safety concerns. The rate of discontinuations in ongoing studies in other diseases has not yet been submitted to the Agency.

Specific Primary Safety Concerns

There were no new clinically significant MRI findings of the brain in patients with CAPS. Adverse events associated with this biologic class of IL-1 blocker therapy are malignancy, infections and infestations, leukopenia, vertigo, and autoimmune-like reactions. No cases of malignancy in CAPS patients were observed and 1 new case initially reported as a malignancy was later found to be a benign retroperitoneal tumor (Pt. # A2201E1-0077-00002/RA). The tumor was large (30 x 15 cm), considered life-threatening, and was surgically removed. This patient received placebo in the prior core study and then received 6 months of canakinumab treatment prior to recognition of the tumor. Causality appears unlikely to be related to canakinumab treatment.

No increase in the rate of infections, the severity, or the type of infection was observed in comparison to infections reported in the original BLA. No new cases of leukopenia, vertigo or development of an ANA or clinical evidence of any autoimmune reaction were observed in the 120-DSU. Notable, no change in the assessment of tuberculin tests, e.g., no active or latent tuberculosis cases, was reported in the 120-DSU.

In CAPS patients, no change in assessments of injection site reaction were observed in the 120-DSU compared to the original BLA. The majority of CAPS patients did not experience any reactions and those few reactions observed were mild in severity. There were no cases observed with evidence of immunogenicity, e.g., development of human anti-human antibody to canakinumab, and no cases of anaphylactoid or anaphylactic reactions.

The 120-DSU did not present any meaningful change in the rate, type, or severity of SAEs, AE discontinuations, AEs or in the specific safety concerns with this biologic class, e.g., malignancy, infections and infestations, leukopenia, vertigo and auto-immune-like reactions. No change was observed in the rates of severe or serious infectious events in comparison between adults and children observed in the original BLA.

Common Adverse Events

The most common AEs observed in the 120-DSU remain in the same SOC observed in the original BLA. In Study D2304, Parts 1 through 3, with the extended duration of 48-weeks, the SOC of infectious AEs was (77%); the SOC of Gastrointestinal disorders was (51%); and the SOC of Skin and subcutaneous tissue disorders was (29%). Nasopharyngitis remained the most common AEs infectious PT (12 patients, 34%).

In review of the safety data from Study D2306 in the 120-DSU, exposure up to 32 weeks showed no new safety signals. The most common AE PT Headaches occurred at a rate of (10%) in the 120-DSU. As reported in Section 7.4.1 Common Adverse Events of this review, Study A2102 was completed and no new data was submitted in the 120-DSU. No new data in the 120-DSU was submitted for Studies A2201 and A2207 (RA).

Based on review of the common AEs observed in the 120-DSU, no changes in the SOC most often affected, Infections and Infestations, and no relevant change in the type of AE, infectious in nature, was observed compared to the original BLA. Infections remain the most common AE associated with canakinumab treatment CAPS disease. No laboratory test result, e. g., hematology, clinical chemistry, particularly, liver function test, or creatinine, were observed with changes not reported in the original BLA.

120-DSU Conclusions

Based on review of four months additional safety data (120-DSU), no new findings beyond those presented in the safety review of the original BLA were identified. The type, frequency and severity of AEs, serious AEs and events of potential clinical safety concern did not change with increasing the extent and duration of patient exposure to canakinumab treatment. Thus far, no death has occurred in a CAPS patient and the three deaths reported in other diseases do not appear to have a causal relationship to canakinumab treatment. Therefore, there is no change in

the overall assessment of tolerability, safety or risk with respect to the safety profile of canakinumab in CAPS patients or in other diseases.

8 Postmarket Experience

Canakinumab is not marketed in any country and all known recipients of canakinumab are involved in a clinical trial.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 Literature Review/References

Arcalyst™ (rilonacept) Prescribing Information, Regeneron, 2008

9.2 Labeling Recommendations

The first labeling meeting is scheduled for May 11, 2009 which is the same day as the required signature date for this NME BLA clinical review. In brief overview, the Ilaris (canakinumab) labeling should reflect the following information based on this submission:

1. The INDICATIONS AND USAGE Section should include Ilaris indicated for the treatment of CAPS in adults and children age 4 years and older revised to include only FCAS and MWS

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2. The risk of infections with canakinumab treatment;
3. The risk of vertigo with canakinumab treatment though vertigo is a recognized symptom of the more severe forms of CAPS.
4. The lack of evidence for the development of anti-canakinumab antibody in these data.
5. The lack of evidence for the development of malignancy in these data though the risk of development of a malignancy is present based on the immunosuppressive mechanism of action of canakinumab.
6. The recommendation to monitor liver function enzymes and bilirubin.
7. The lack of hypersensitivity reactions, including anaphylactic or anaphylactoid reactions, in these data.

b(4)

9.3 Advisory Committee Meeting

No Advisory Committee was requested for BLA 125319 Ilaris (canakinumab) with the proposed indication for the treatment of patients with CAPS disease because the submitted data appeared to be adequate to conduct a review and reach an action on this Orphan Designation biologic formulation. Currently, only rilonacept is approved for CAPS diseases, FCAS and MWS in adults and children ≥ 12 years of age and older. There were no efficacy or safety issues identified that would necessitate an advisory committee meeting.

9.4 Other Relevant Materials

Consultations with the Division of Scientific Investigations (DSI), Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Division of Medication Error Prevention