CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

CROSS DISCIPLINE TEAM LEADER REVIEW

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Addendum to Cross-Discipline Team Leader Memorandum

Date: May 25, 2009

To: File, BLA 125319

From: Jeffrey Siegel, M.D. Jeffrey N. Siegel 5/25/09
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: Appropriate indication for Ilaris: Differing views between Clinical Reviewer and Biostatistics reviewers
BLA 125319
canakinumab (Ilaris)
Novartis Inc.
Proposed indication: Cryopyrin-Associated Periodic Syndromes (CAPS)

In the Biostatistics review of Ilaris (canakinumab) for CAPS, David Petullo concluded that there was sufficient evidence to support the efficacy of canakinumab for CAPS associated with Muckle-Wells syndrome (MWS) patients at least 9 years old. He further stated that the Applicant's claims for the other forms of CAPS - familial cold autoinflammatory syndrome (FCAS) ——— b(4)
——— for children under 9 years old would be evaluated by other members of the review team. The clinical reviewer, Dr. Carolyn Yancey, concluded that canakinumab should be approved for the MWS and the FCAS forms of CAPS. ———
——— that approval should be for children aged 4 years old and older. I agree with Dr. Yancey's conclusions. The three different presentations of CAPS represent syndromes with overlapping signs and symptoms all of which are characterized by a common genetic mutation in the gene for cryopyrin. All three syndromes are characterized by chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonuclear leukocytosis with organ infiltration as well as by increases in the acute phase reactants C-reactive protein (CRP) and serum amyloid A (SAA). Therefore, efficacy data for the syndrome of middle severity, MWS, can be generalized to the milder form, FCAS. In addition, limited data on treatment of FCAS are available for the open-label trials D2306 and A2102. In these trials, 10 patients with FCAS were enrolled and all experienced a complete response.

b(4)

With respect to the age for the indication of canakinumab in CAPS, I agree with Dr. Yancey that the data provided by the Applicant support approval for children aged 4 and older. FCAS and MWS present similarly in children and adults. Therefore efficacy data in adults may be extrapolated to children and only safety and dosing information are necessary. The Applicant submitted data on 15 children aged 4, 5, 6, 6, 7, 8, 9, 13, 14, 14, 15, 16, 16, 17 and 17 years of age. Safety in children was similar to adults. The Clinical Pharmacology review team reviewed the pharmacokinetic data and concluded that the proposed dosing for children was acceptable, including weight-based dosing of 2 mg/kg in children 15-40 kg.

Team Leader Memo

FDA Center for Drug Evaluation and Research
Office of New Drugs
Office of Drug Evaluation 2
Division of Anesthesia, Analgesia and Rheumatology Products

Cross-Discipline Team Leader Memorandum

Date: May 18, 2009

To: File, BLA 125319

From: Jeffrey Siegel, M.D. Jeffrey M. Siegel 5/18/09
Clinical Team Leader
ODE2 - Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)

Re: BLA 125319
canakinumab (Ilaris)
Novartis Inc.
Proposed indication: Cryopyrin-Associated Periodic Syndromes (CAPS)

TABLE OF CONTENTS

1. Introduction to Review

The Applicant, Novartis, is submitting this biologic licensing application for canakinumab (Ilaris) for the orphan disease Cryopyrin-Associated Periodic Syndromes (CAPS). Canakinumab is a recombinant human monoclonal anti-human interleukin-1β antibody of the IgG1κ isotype. It antagonizes the activity of the cytokine IL-1β by binding it and interfering with its interaction with the IL-1 receptor. It differs from another approved IL-1 blocker, rilonacept in several ways. First, canakinumab is a monoclonal antibody while rilonacept is a soluble IL-1 receptor fusion protein. Second, canakinumab selectively blocks the activity of IL-1β while rilonacept blocks the activity of several proteins that bind to the IL-1 receptor, including IL-1β, IL-1α and IL-1ra (IL-1 receptor antagonist). Novartis conducted a single controlled, randomized-withdrawal trial of canakinumab in CAPS in 35 patients with Muckle-Wells syndrome (MWS). In addition, Novartis submitted data from two open-label, uncontrolled trials of canakinumab in patients with various forms of CAPS. Novartis proposes that canakinumab be given every 8 weeks subcutaneously (sc) at a dose of 150 mg in patients with body weight of 40 kg or more and at 2 mg/kg for patients with a body weight of 15-40 kg. Canakinumab has also been studied in rheumatoid arthritis. ——— b(4)
——— In all, a total of approximately 700 patients have received canakinumab. In CAPS, the safety database consists of 78 patients, including 15 pediatric patients, who have received at least one dose, 56 patients who have been treated for at least 6 months and 31 patients who have received treatment for one year or more.

As of the time of writing of this memorandum, review of this application had not revealed major issues involving CMC issues, pharmacology/toxicology, clinical pharmacology or clinical. However, the CMC review had not been completed and inspections of the clinical studies and the manufacturing facilities had not been completed. No major toxicities had been observed in the clinical trials. However, infections were seen in canakinumab-treated patients and immunosuppression is an expected pharmacologic effect of the product. This memo will review the regulatory background for this application, the evidence supporting efficacy and safety of canakinumab in CAPS and key findings in other disciplines.

2. Background – Regulatory history

CAPS comprises 3 distinct autoinflammatory diseases that are all characterized by mutations in the gene for the protein cryopyrin. Cryopyrin is a protein component of the inflammasome, an intracellular complex of proteins that responds to external dangers (e.g., bacterial infection) by activating caspase 1 and releasing interleukin-1β (IL-1β). CAPS is inherited in an autosomal dominant manner. CAPS is rare, with approximately 200-300 affected patients in the US. Novartis applied for and was granted orphan status for canakinumab for the treatment of CAPS on December 18, 2007. The autoinflammatory disorders comprising CAPS are familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and Neonatal Onset Multisystem Inflammatory Disorder (NOMID). The common features of these 3 conditions are chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and

polymorphonuclear leukocytosis with organ infiltration. NOMID is the most serious, presenting early in life with severe dermatologic, rheumatologic and neurologic manifestations. MWS is associated with sensorineural deafness and an increased risk of amyloidosis. FCAS is characterized by urticaria-like skin lesions, swollen and painful joints, conjunctivitis and fevers following exposure to cold.

The pathogenesis of CAPS is believed to be related to uncontrolled overproduction and release of IL-1 with resultant inflammation. It is not well understood how mutations in the same gene can give rise to different clinical syndromes. Currently there is one other product approved for CAPS, the IL-1 blocker rilonacept. Rilonacept is approved for the treatment of FCAS and MWS patients over 12 years of age. Rilonacept is given by sc injection once weekly. Investigators have also explored use of the IL-1 blocker anakinra with reports in the literature of good responses. Anakinra, which is approved for treatment of rheumatoid arthritis, is widely used off-label for treatment of CAPS.

Novartis approached the Agency at a pre-IND meeting to explore a clinical development program for canakinumab in CAPS. They proposed to conduct a randomized withdrawal trial in patients with MWS [redacted] The Agency told b(4)
the company that in view of the small number of patients with CAPS that a single adequate and well-controlled trial in MWS could, in principle, provide evidence of efficacy for approval. The Agency also told the company that at least 12 months of exposure at the dose recommended for approval would be needed for the safety database. In October, 2006, Novartis submitted the protocol for the MWS clinical trial, which consisted of an initial open-label phase followed by a randomized, placebo-controlled withdrawal phase. This design was acceptable to the Agency. Novartis subsequently applied for and received Fast Track designation for the treatment of CAPS [redacted] b(4)

When the randomized withdrawal portion of the MWS trial was completed, the Applicant held a pre-BLA meeting with the Agency. At that meeting they proposed an indication for [redacted] CAPS based on the results of the Phase 3 trial in MWS and additional data in patients with FCAS and MWS overlapping with NOMID.

b(4)

[redacted] Novartis submitted the BLA on December 15, 2008. They were granted priority review.

3. CMC/Microbiology/Device

3.1. General product quality considerations

At the time of this review the Product review had not been completed. The CMC supervisor, Dr. Chana Fuchs, provided the following summary of the current state of the review. She said that from the current review it appeared that the CMC reviewer, Dr. Ruth Cordoba-Rodriguez, would support approval. They anticipate some product-related

postmarketing commitments (PMC's). They are planning on sending an information request to the Applicant that would explore modification of some of the specifications of drug substance and drug product.

3.2. Facilities review/inspection

The Investigations and Preapproval Compliance Branch is currently in the process of conducting their facilities inspections.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team is in agreement that the BLA can be approved pending agreement on labeling. The pharmacology/toxicology primary reviewer, Dr. Kathleen Young, and supervisory reviewer, Dr. Adam Wasserman, agree that there are no significant issues raised by the nonclinical data with large safety margins above the clinical exposure expected in humans. In particular, Dr. Wasserman notes that the animal studies also provide adequate safety margins if the label were to recommend higher doses of 4 mg/kg in children under 40 kg and 300 mg in adults in patients who do not respond to the standard dose.

Animal studies of juvenile development did not indicate a significant risk.

4.1. Carcinogenicity

The Agency agreed with the Applicant that standard carcinogenicity assays were not needed. The pharmacology/toxicology review team agreed that carcinogenicity studies are not needed based on Agency precedent, feasibility and scientific rationale.

4.2. Reproductive toxicology

The Applicant conducted reproductive toxicology studies with canakinumab in the marmoset and with a surrogate anti-IL-1β monoclonal antibody in the mouse. These studies showed some variations and skeletal delays, in particular an increased incidence of delayed or incomplete ossification of skull and vertebra in mice and vertebral variations in marmosets. The pharmacology/toxicology review team does not consider these to be a significant adverse finding for two reasons: 1) the delays in ossification in the marmoset were not as pronounced in the mouse studies and 2) the findings in the mouse are likely a "worst case" since monoclonal antibodies pass the placenta early in development when major organ systems are developing in the mouse but they do not pass the placenta in the human until much later in fetal development, when major organ system development is futher advanced. Therefore, they recommend these reproductive toxicology findings be included in the label as a precautionary statement. The reproductive toxicology findings seen in the rilonacept animal studies were not observed in the canakinumab studies. The review team recommends a Pregnancy Category – b(4)

5. Clinical Pharmacology/Biopharmaceutics

5.1. General clinical pharmacology/biopharmaceutics considerations

In studies in adult patients with CAPS receiving 150 mg canakinumab sc peak serum levels were observed by day 7. The apparent half-life was approximately 26 days. Pharmacokinetics were linear in healthy volunteers, patients with CAPS, and patients with rheumatoid arthritis receiving 0.3-10 mg/kg intravenously. Pharmacokinetic parameters increased in a dose-proportional manner in patients receiving 150 mg and 300 mg sc.

The clinical pharmacology review team examined weight-based dosing in detail because the Applicant is recommending canakinumab at a dose of 150 mg for patients over 40 kg and at 2 mg/kg for children weighing between 15 and 40 kg. They conclude that weight-based dosing is acceptable. However, children weighing less than 40 kg had lower exposure (37% less) than adults. Therefore, they recommend that for children who do not respond to 2 mg/kg that the dose should be increased to 3 mg/kg, a dose that would provide similar exposure as the 150 mg sc dose in adults.

Clearance varied according to body weight. There was no indication of accelerated clearance or changes in pharmacokinetic properties of canakinumab with repeated administration.

5.2. Drug-drug interactions

No formal drug-drug interaction studies were performed. The clinical pharmacology review team notes that cytochrome P450 is generally suppressed in inflammatory states so when inflammation is suppressed with canakinumab cytochrome P450 activity is expected to normalize. They recommend wording in the label include monitoring of patients taking drugs with a narrow therapeutic index in patients who initiate treatment with canakinumab.

5.3. Pathway of Elimination

The route of elimination of canakinumab was not formally studied. Hepatic and renal impairment are not expected to affect the protein degradation pathways that are responsible for the elimination of canakinumab.

5.4. Demographic interactions/special populations

Dose adjustment does not appear to be necessary in the elderly based on 1 patient with CAPS and 7 patients with RA over age 65 treated with canakinumab. Pharmacokinetic parameters did not appear to be significantly different in the elderly. Concerning pediatric patients, the proposed dose of 2 mg/kg in children 15-40 kg appears appropriate. Dose adjustment is not needed with respect to gender, race or renal impairment.

5.5. Thorough QT study or other QT assessment

The effects of canakinumab on QT were not formally assessed as biologic protein products are generally not expected to interact with cardiac ion channels.

5.6. Notable issues

None.

6. Clinical/Statistical

6.1. General Discussion

Since CAPS is an orphan indication, affecting only 200-300 patients in the US, the review division agreed to consider approval of canakinumab for CAPS based on favorable results from a single adequate and well-controlled trial. The Applicant conducted a single trial with an open-label phase followed by a randomized withdrawal phase in patients with MWS to assess efficacy. Two other open-label trials provide supportive evidence of efficacy and included a broader range of patients with CAPS including FCAS and MWS/NOMID overlap and children with CAPS.

Unlike Regeneron, which chose to study primarily patients with the milder form of CAPS, FCAS, for approval of rilonacept (Arcalyst), Novartis studied patients with a more severe form of CAPS, MWS. Both FCAS and MWS are characterized by chronic inflammation, rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonuclear leukocytosis with organ infiltration. However, patients with MWS additionally have sensorineural deafness and are at risk for amyloidosis. In the clinical trials the Applicant assessed complete response as a measure of clinical effect, which incorporated a composite of the physician global assessment of no more than minimal, assessment of skin manifestations no more than minimal and normalization of acute phase reactants. For the randomized withdrawal phase only patients who had achieved a complete response in the open-label phase were randomized. The primary endpoint for the randomized withdrawal phase was disease flare.

The pivotal trial enrolled 35 patients with MWS. Both the initial open-label phase and the randomized withdrawal phase showed positive results with a large effect size. In the two supportive open-label trials a majority of patients achieved complete response. There were no major issues regarding efficacy.

The safety database for patients with CAPS contains a total of 78 patients, including 15 pediatric patients. A total of 56 patients with CAPS have received canakinumab for 6 months or longer; 31 patients for 1 year or longer. The children who were treated range in age from 5 to 17 years of age. Overall the database consists of approximately 890 patients. The additional patients include patients with RA, psoriasis and a variety of other conditions. There were no major safety issues identified that would preclude approval of canakinumab. The major safety signals identified were infections and vertigo. Vertigo is a known complication of CAPS. Vertigo remitted in patients while canakinumab treatment was continued.

6.2. Efficacy

6.2.1. Dose identification/selection and limitations

The Applicant conducted an initial dose-finding study, Study A2102. In this trial, patients with CAPS were treated with an initial dose of canakinumab either iv or sc and were observed for clinical response. After they achieved a complete response the time was measured until they had relapse of disease (Figure 1; this and other figures and tables in this section copied from the clinical review of Dr. Yancey and the biostatistics review of Dr. Petullo [Table 2]). These data indicated a longer time to relapse with the 10 mg/kg iv dose (median time approximately 22 weeks) than with the 1 mg/kg iv dose (median time approximately 10 weeks). The 150 mg sc dose chosen for further development had a time-to-relapse midway between the 1 mg/kg and the 10 mg/kg iv doses. These data provide adequate rationale for the choice of the 150 mg sc every 8 week dose regimen for further development. Further support for the every 8 week regimen is provided by the long-term data from Study D2304, in which few disease flares were observed.

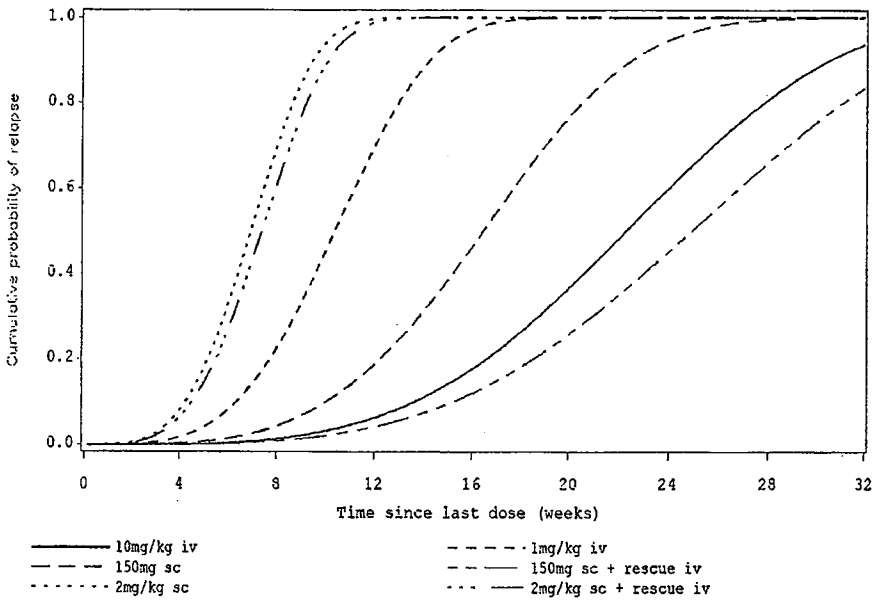

Figure 1: Cumulative Probability Plot of time-to-relapse, Study A2102

The time-to-relapse data from Study A2102 also show the shortest time to relapse in the children receiving weight-based dosing with 2 mg/kg sc (median time approximately 7 weeks). This finding is consistent with the observation of the Clinical Pharmacology team that children receiving weight-based dosing have lower exposure than adults and suggests that higher doses may be needed in children who fail to respond to the 2 mg/kg dose.

6.2.2. Phase 3/ clinical studies essential to regulatory decision

The Applicant submitted results from a single Phase 3 clinical trial in patients with CAPS, Study D2304, that included an initial open-label phase followed by a randomized withdrawal period (Figure 2). The trial enrolled patients age 4-75 with a molecular diagnosis of NALP3 mutation diagnostic of CAPS and compatible signs and symptoms for CAPS. In the initial open-label phase patients received a single dose of canakinumab 150 mg sc or, for children 15-40 kg, 2 mg/kg sc. Patients who achieved a complete response were randomized into Part 2. Complete response was defined as no more than minimal score (2 on a 5-point scale where 1=absent, 2=minimal, 3=mild, 4=moderate, 5=severe) on the physician global, no more than minimal on physician assessment of skin manifestations of CAPS and normalization (<10 mg/L) of C-reactive protein (CRP) or serum amyloid A (SAA). The primary endpoint for the randomized withdrawal phase was disease relapse, defined as CRP and/or SAA above 30 mg/L and either a physician global of greater than minimal or a physician global of minimal plus a score for skin disease of greater than minimal. The protocol specified the primary efficacy analysis as the odds ratio for disease relapse in Part 2 using the ITT population using an exact test about the odds ratio.

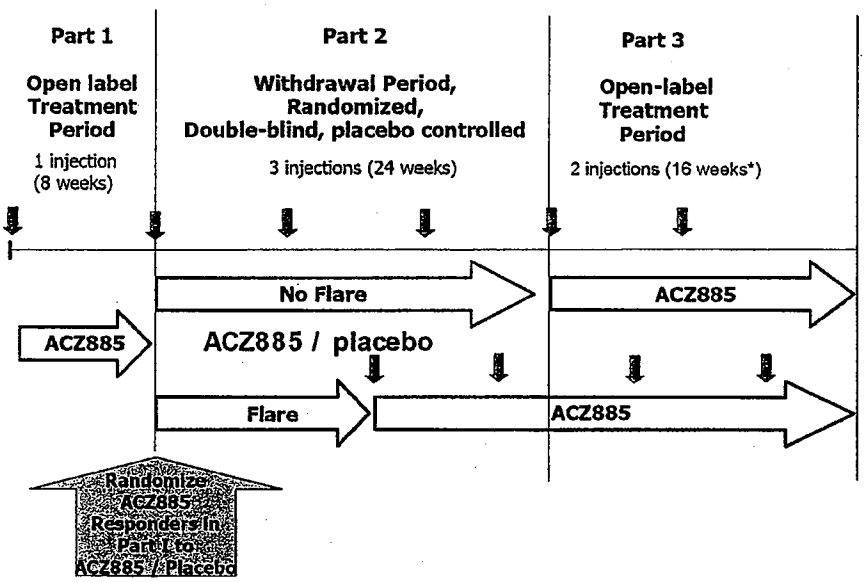

Figure 2: Study Design, Study D2304

The conduct of the trial was acceptable. There were no amendments during the course of the trial. Protocol deviations were minimal. Compliance was 100% as patients received their canakinumab dosing at study visits and no visits were missed. Of 35 enrolled subjects 89% completed Part 1 (Table 1). A total of 34 responded but 3 withdrew prior to Week 8 due to unsatisfactory therapeutic effect. All 15 patients randomized to canakinumab in Part 2 completed that part of the study. In contrast, 13 of 16 patients

randomized to placebo discontinued Part 2 early, all due to clinical relapse or early withdrawal. There were no dropouts due to toxicity.

Table 1

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

The demographics of the patients in Study D2304 are shown in Table 2. The majority were adults but 5 of 35 enrolled patients were pediatric patients aged 9-17. There was a female preponderance and an imbalance between randomized study arms in Part 2 with respect to sex in that all but one of the patients randomized to canakinumab were female while 7 of 16 of the patients in the placebo arm were female. Baseline disease characteristics (Table 3) showed a population with moderately active disease based on CRP and/or SAA as well as the physician global, assessment of skin disease and patient assessment.

Table 2: Patient Demographics for Study D2304 by Randomized Study Arm

Subgroup		Placebo, N=16	Ilaris, N=15
Race n (%)	Caucasian	14 (87)	15 (100)
	Other	2 (13)	0 (0)
Gender n (%)	Male	9 (56)	1 (7)
	Female	7 (44)	14 (93)
Age (years) n (%)	Mean	33	34
	[Range]	[14, 74]	[9, 58]
	< 18 years	2 (13)	3 (20)
	≥ 18 years	14 (87)	12 (80)

Source: Reviewer

Table 3

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

Of 35 patients enrolled in the study, 31 or 89% met criteria for a complete response in Part 1 and were randomized into Part 2. All 5 pediatric patients experienced a complete response. In addition to improvement in the physician global, skin disease and CRP and/or SAA, patients also had improvement in arthralgias, myalgias, conjunctivitis, fatigue/malaise (see tables 55 and 56 in Dr. Yancey's review). In Part 2, a significantly greater proportion of patients randomized to placebo (81%) had a disease relapse than did patients who continued on canakinumab (0%, Table 4). The efficacy seen with the primary endpoint of disease flare is supported by objective laboratory measures, including the CRP (Figure 3), which fell during Part 1, remained low in Part 2 in patients remaining on canakinumab but rose in Part 2 in patients randomized to placebo and subsequently fell again in the subsequent open-label extension part when patients were switched from placebo back to canakinumab. David Petullo, the biostatistics reviewer, confirmed the primary efficacy analysis. These data indicate that canakinumab is highly efficacious in patients with CAPS.

Table 4

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, -0.62)	<0.001 **
n = total number of pts having disease flare; N = total number of pts in treatment group; * p-value from Fisher's exact test; ** statistical significance (two sided) at 5% level.							

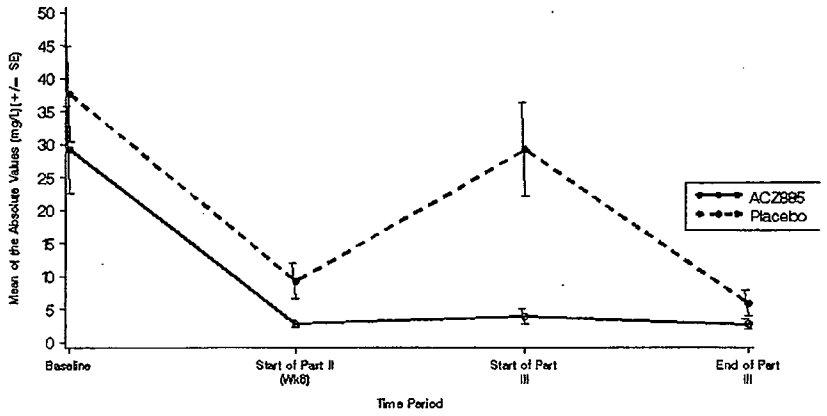

Figure 3: CRP levels in Study D2304

6.2.3. Other efficacy studies

The clinical development program also included two additional trials: Study A2102 and D2306. Although these were open-label trials they provide useful information in that they assessed clinical responses in patients with other forms of CAPS and in younger children. With respect to FCAS, 2 patients were enrolled in Study A2102 and 8 were enrolled in Study D2306. All enrolled patients with FCAS experienced a complete response. Study A2102 enrolled 5 children who received weight-based dosing of 2 mg/kg because their weight was between 15 and 40 kg. All these children experienced a complete response.

Some limited information is available on up-titration of canakinumab dose in patients who did not respond adequately to the initial standard dose. Five patients in Study D2306 received up-titration of 300 mg or 4 mg/kg. All experienced complete response. These cases involved only one or two doses of the higher dose.

6.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical reviewer, Dr. Carolyn Yancey, concluded that the clinical development program for canakinumab had demonstrated efficacy in CAPS based on the

positive results in the controlled trial D2304 as well as the supportive studies A2102 and D2306. The statistical reviewer, Dr. David Petullo, concluded that there was sufficient evidence to conclude that canakinumab was efficacious in the treatment of MWS in adults and children aged 9 and older since this was the population enrolled in the controlled study D2304. I agree with their conclusions.

6.2.5. Pediatric use/PREA waivers/deferrals

Since CAPS is an orphan disease, there is no requirement under PREA to conduct studies in the pediatric population. Therefore, canakinumab should receive a pediatric waiver. Nonetheless the Applicant has chosen to enroll children into the canakinumab clinical development program. Overall, a total of 15 children aged 4, 5, 6, 6, 7, 8, 9, 13, 14, 14, 15, 16, 16, 17 and 17 years of age were enrolled in the canakinumab development program. The pediatric subjects have demonstrated favorable responses similar to adult subjects. The reported adverse reactions were comparable to adult subjects.

6.2.6. Discussion of notable efficacy issues

There are no notable efficacy issues.

6.3. Safety

6.3.1. General safety considerations

The total safety database consists of approximately 700 patients who have received canakinumab for CAPS, RA, psoriasis and other conditions. In CAPS the database consists of 78 patients who have received at least one dose of canakinumab (Table 5). Of these, 56 have been treated for at least 6 months and 31 for a year or longer. While this size safety database does not meet the criteria in the ICH E1A guidance document the E1A guidance has an exception for orphan indications. Given that the total number of patients in the US with CAPS is approximately 200-300, a database of 78 patients is acceptable.

Table 5

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).	

Due to the fact that all patients in the controlled trial received canakinumab there are no randomized controlled safety data to identify adverse events. The major safety signals identified in the canakinumab safety database are infections and vertigo. Infections are an expected adverse event based on the mechanism of action of canakinumab, which is to inhibit the function of IL-1β, an important cytokine in host defenses against microorganisms. The CAPS safety database had no death and contained just two serious adverse events that were infectious or potentially infectious in nature: a case of pneumonia and a case of pyrexia associated with a urinary tract infection. Vertigo is a common complication of CAPS disease and the cases of vertigo during canakinumab treatment resolved despite continuing the drug so it is unresolved whether the cases of vertigo are due to canakinumab treatment or to the underlying disease.

6.3.2. Safety findings from submitted clinical trials

There were no deaths in the CAPS safety database. Two deaths were reported in other canakinumab clinical trials: one in a patient with RA; one in a patient with macular degeneration. Both deaths were of a type expected in the patient population and were not clearly related to canakinumab.

A total of 7 serious adverse events (SAE's) were observed in patients with CAPS who received canakinumab. There were 2 cases of vertigo, 1 case of lower respiratory infection that resolved, 1 case of pyrexia related to a recurrent urinary tract infection, 1 case of MWS flare, one case of fibromyalgia and a synovial cyst. The SAE's reported in the RA trial were typical of events seen in the patient population. ——— b(4)

——— Review of dropouts revealed no pattern of dropout due to toxicity.

Regarding other adverse events, the most common adverse event in the CAPS trials was infections, which were seen in approximately three-quarters of all patients in the three parts of Study D2304. The infections were typical of the general population. Injection site reactions were observed in 7% of patients, most of which were mild.

There was no clear pattern of abnormal laboratory parameters in patients receiving canakinumab. There were a few patients with elevated liver enzymes but these were transient, did not involve high elevations and mainly occurred in patients with elevated liver enzymes at baseline.

6.3.3. Safety update

The 120-day safety update showed no new safety signals.

6.3.4. Immunogenicity

In the CAPS clinical development program no patients were observed to develop antibodies to canakinumab.

6.3.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Yancey, concluded that the size of the safety database was adequate to assess safety of canakinumab in CAPS in view of the rarity of this disorder. She concluded that the safety profile was similar to that seen with the other IL-1 blocker approved for CAPS, namely rilonacept. She concluded that the major safety signals were infections and vertigo.

6.3.6. Discussion of notable safety issues

The most notable safety issues with canakinumab in CAPS are infections and vertigo. With respect to infections this is an expected adverse event with an immunosuppressive product such as canakinumab. I agree with Dr. Yancey that the evidence suggests that the safety profile is similar to that of the other IL-1 blocker approved for CAPS, rilonacept. There were few infections that were serious. In view of the seriousness of the underlying condition the benefits of canakinumab in CAPS outweigh the risk of infection.

With respect to the adverse events of vertigo, vertigo is a known complication of MWS. In most patients who experienced vertigo it resolved despite continued treatment with canakinumab.

7. Advisory Committee Meeting

No advisory committee meeting was convened to discuss this application. It was judged that the data submitted were adequate to determine whether the risk/benefit relationship was favorable for canakinumab in the treatment of CAPS. Furthermore there were no serious issues in dispute with respect to efficacy or safety and canakinumab is third in class overall and second in class for CAPS.

8. Financial Disclosure

Based on the information submitted by the Applicant there were no financial conflicts of interest that would have the potential to bias the data.

9. Labeling

9.1. Proprietary name

DMETS determined that the proposed proprietary name, Ilaris, was acceptable.

9.2. Physician labeling

b(4)

10. DSI audits

The clinical site inspections undertaken by DSI are still underway at the time of writing of this memo.

11. Conclusions and recommendations

11.1. Regulatory action

Data from the randomized withdrawal trial provide substantial evidence of efficacy for canakinumab in the treatment of cryopyrin-associated periodic syndromes (CAPS). In Study D2304, 89% of patients with MWS enrolled in the open-label part of the trial, Part 1, achieved a complete response. In the randomized withdrawal phase there was a statistically significant difference in the proportion of patients who flared in the two study arms with no patient randomized to continue canakinumab experiencing a flare, while 81% of patients randomized to placebo experienced a flare. Improvements were seen in all aspects of disease activity, including skin disease, patient global and acute phase reactants.

The data from the clinical trials suggest that treatment with canakinumab is associated with a risk of infection. However, serious infections were uncommon in this clinical development program. Treatment with canakinumab is also associated with vertigo and infrequent injection site reactions, the latter of which are generally mild in severity.

At the time of writing of this memo some parts of the review have not been completed, including the CMC review, inspection review and study site inspections. If no issues arise in these areas that would preclude an approval then this BLA should be approved with appropriate modifications to the proposed package insert.

11.2. Safety concerns to be followed postmarketing

There should be appropriate pharmacovigilance with particular attention to monitoring for reports of serious infection.

11.3. Postmarketing studies

11.3.1. Required studies

The Applicant should conduct a study, or trial, investigating the safety of higher doses of canakinumab in patients who do not respond to the recommended doses. The Applicant recommends a dose of 150 mg sc in adults and children over 40 kg and a dose of 2 mg/kg in children 15-40 kg. There is some limited evidence from the clinical trials that increasing the dose in patients with an inadequate response is beneficial; however, the evidence derives from only 5 patients, most given only 1 or 2 doses at the higher dose level. If Ilaris is approved it is likely that some patients will be given the higher doses but the safety of these higher doses used chronically is not adequately characterized. There is adequate information regarding the proposed doses for approval now, but the Applicant should obtain additional information on higher doses postmarketing.

Further studies in children are not required. PREA does not apply for this BLA since CAPS is an orphan indication.

11.3.2. Commitments (PMCs)

No PMC's are necessary.

11.3.3. Other agreements with Sponsor

The Applicant should commit to pharmacovigilance in regard to serious infections.