CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125319

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA/Serial Number:	125319/0000
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Applicant:	Novartis
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Novartis has proposed that Ilaris is effective in treating symptoms associated with CAPS including Muckle Wells Syndrome (MWS), Familial Cold Autoinflammatory Syndrome (FCAS) [redacted] in patients 4 years and older. Based on my review of the data from the pivotal efficacy study, I conclude that there is sufficient evidence to support the efficacy of Ilaris for the treatment of CAPS associated with MWS in patients at least 9 years old. The Applicant's claims for FCAS, [redacted], and children 4 years and older will be evaluated by other members of review team. b(4)

1.2 Brief Overview of Clinical Studies

Novartis has submitted one primary efficacy study and two open-label trials to evaluate the efficacy and safety of Ilaris in patients diagnosed with CAPS. As CAPS is a rare disease with only a few hundred cases diagnosed, the Applicant applied for and was granted Orphan drug (December 18, 2008) and Fast Track (June 27, 2008) status for the treatment of CAPS. The primary efficacy study CACZ885D2304 (D2304) only evaluated patients diagnosed with MWS, while two open-label studies, CACZ885A2102 (A2102) and CACZ885D2306 (D2306), evaluated patients diagnosed with MWS, FCAS, NOMID, MWS/NOMID.

A2102

This was a two-stage, open-label, Phase 2, dose titration study to assess the clinical efficacy, safety, pharmacokinetics and pharmacodynamics of Ilaris in patients diagnosed with CAPS including MWS, FCAS, NOMID, and NOMID/MWS. The primary objective of this study was to determine the efficacy of Ilaris administered as an intravenous (i.v.) infusion and subcutaneous (s.c.) injection. Secondary objectives were to assess the safety, tolerability, immunogenicity, pharmacokinetics (PK) and pharmacodynamics (PD). Patients who finished participation in A2102 could transition into D2304 or D2306.

D2304

In this three-part, multi-center, Phase 3 study, patients diagnosed with MWS were treated with Ilaris. The primary objective was to assess the efficacy of Ilaris in Part 2 as determined by the Physician's global assessment of autoinflammatory disease activity, assessment of skin disease, and inflammation markers. Secondary objectives were to assess the safety, tolerability and immunogenicity of Ilaris, to assess overall efficacy in Part I and Part III, to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of canakinumab and to assess the effect on disease progression with regards to deafness, kidney function, neurological and ophthalmological symptoms. Upon completion of this study, patients were allowed to enroll in Study D2306.

D2306

This open-label, Phase 3 study was designed to evaluate the safety and efficacy of Ilaris in patients diagnosed with MWS, FCAS, or MWS/NOMID. The primary objective was to assess the long-term safety and tolerability of Ilaris. Secondary objectives were to assess the maintenance of response over time, patients who required a dose adjustment or an administration

frequency adjustment, immunogenicity, PK, the long-term effects of Ilaris on disease progression, and the long term maintenance of Health-Related Quality of Life.

1.3 Statistical Issues and Findings

The Applicant has made claims for treating CAPS associated with MWS, FCAS, ——— in patients 4 years and older. However, the pivotal efficacy study only evaluated patients 9 years and older diagnosed with MWS. In a pre-IND meeting held on Jan 18, 2006, FDA indicated that a controlled study would be required for an indication of FCAS; however, this issue was not addressed in the pre-BLA meeting held on Oct 21, 2008. The Applicant claims the results from the two open-label studies provide sufficient evidence of effectiveness in patients 4 years and older and those diagnosed with FCAS ——— It needs to be noted that these claims are not supported by statistical evidence; the clinical validity of these claims will be assessed by the medical review team. b(4)

2. INTRODUCTION

2.1 Overview

Ilaris, formerly ACZ885, has been in development under IND 100,040 to treat patients diagnosed with Cryopyrin Associated Periodic Syndromes (CAPS). CAPS is a rare hereditary systemic autoinflammatory disease that is made up of the following syndromes; MWS, FCAS, and NOMID. These syndromes often are referred to as phenotypes and can occur singly or overlap (MWS/FCAS, or MWS/NOMID). According to the Applicant, the world-wide incidence of CAPS is unknown and often misdiagnosed but only a few hundred cases are currently diagnosed. The only approved product for the treatment of CAPS is Arcalyst which is labeled for patients 12 years and older. Since the current NDA evaluates patients down to 4 years of age and evaluates, according to the medical review team, much sicker patients than were studied for Arcalyst, Novartis was granted priority review for this submission by the Division of Anesthesia, Analgesia, and Rheumatoid Products (DAARP).

The development plan of Ilaris for the treatment of CAPS was previously discussed at several meetings with DAARP from 2006-2008. Key statistical issues from these meetings are summarized below:

1. Pre-IND meeting Jan 18, 2006: DARRP agreed that a randomized withdrawal trial with a sufficient number of naïve patients would be acceptable to evaluate the efficacy of Ilaris and that it would be acceptable to include patients that had previous exposure to Ilaris in phase 2 studies. It was also agreed that since the pivotal study would only evaluate MWS patients, it would be acceptable to evaluate the efficacy ——— in an open-label study and submit concurrently with MWS. However, it was stated that for patients diagnosed with FCAS, a demonstration of efficacy would require at least one adequate and controlled trial. b(4)

2. Pre-BLA Oct 21, 2008: The Division agreed that the Applicant may have sufficient data to get an indication for MWS and FCAS associated CAPS ———

Note, the pre-IND meeting indicated a controlled trial would be required for FCAS. However, the sponsor only conducted a controlled trial in patients confirmed to have MWS. There was not an End of Phase 2 meeting conducted.

2.2 Data Sources

For the pivotal efficacy study D2304, all data was supplied electronically by the Applicant as SAS transport files and can be found at the following location in the CDER electronic data room (EDR):

\\cbsap58\M\eCTD_Submissions\STN125319\0000\m5\datasets\acz885d2304

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Applicant conducted one pivotal Phase 3 study and two open-label studies to evaluate the efficacy of Ilaris. While the main focus of my review will be on Part 2 of Study D2304 (pivotal efficacy study), the two open-label studies (A2102 and D2306) will be summarized and discussed.

3.1.1 Study Design and Endpoints

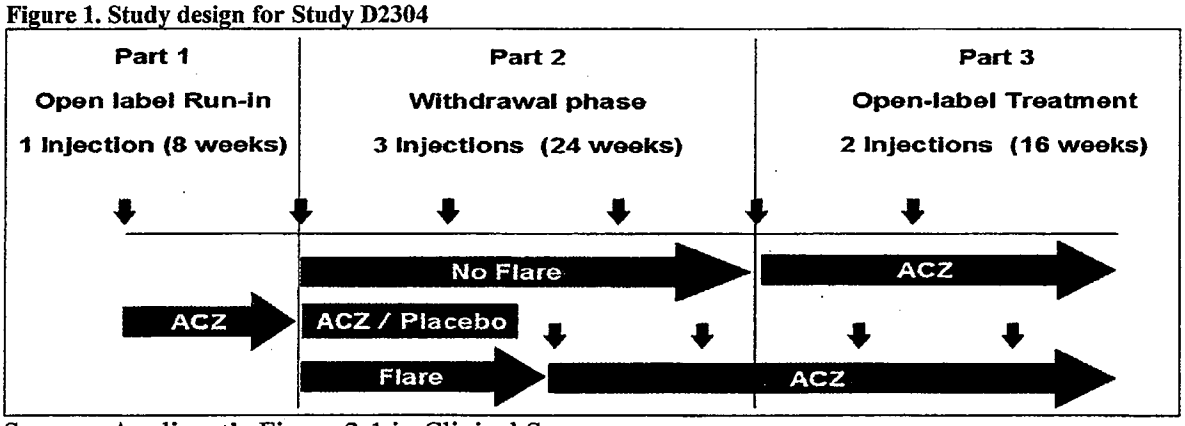
A2102

This study was conducted in two stages. In Stage 1, patients diagnosed with CAPS received three doses of Ilaris. The first dose was administered as 10 mg/kg intravenously (i.v.) followed by an observation period. When a patient started to relapse as defined in the protocol, they received a second dose, 1 mg/kg i.v., and again were observed until relapse. Following the second relapse, a third dose was administered, 150 mg subcutaneously (s.c.). Patients that weighed less than 40 kg received 2 mg/kg. While in Stage 2, patients received an initial s.c. injection of Ilaris and a subsequent dose upon each relapse. Subjects enrolled in Stage 1 were allowed to enter Stage 2 upon relapse. Patients who finished participation in A2102 could transition into D2304 or D2306. Time to relapse after each administration of treatment was defined as the primary efficacy variable.

D2304

This was a three-part study where Part 1 was an eight week open-label, active treatment, single dose, run-in phase to identify patients that responded to treatment. Only those patients that responded to treatment in Part 1 and did not relapse by Week 8, entered Part 2, a 24-week, randomized, double-blind, placebo-controlled, withdrawal phase. Randomization to either placebo or Ilaris was stratified by previous exposure (naïve or transferred from Study A2102) and by age ($16 \leq$ or > 16). Upon disease relapse or completion of Part 2, patients entered Part 3, a 16-week, open-label, active treatment phase. The Applicant determined that 20 patients (10 per treatment arm) would have 90% power to detect a difference in flare rates of 15% for the active group and 90% for the placebo group. The design of this study is depicted in Figure 1. Since CAPS is a rare disease, patients were allowed to rollover from the open-label Phase 2 study (A2102) into Part 1 when they experienced a disease relapse.

Figure 1. Study design for Study D2304



Source: Applicant's Figure 2-1 in Clinical Summary

Clinical assessments of efficacy were evaluated at weeks 0, 1, 2, 8, and then every four weeks until the end of the study. These assessments included a physicians global assessment of disease activity (PHY), physicians assessment of skin disease (SKN), arthralgia, myalagia, headache/migraine, conjunctivitis, fatigue/malaise, other symptoms related to CAPS, and other symptoms not related to CAPS. These assessments were measured on a 5-point scale where 1=absent, 2=minimal, 3=mild, 4=moderate, and 5=severe. Serum values (mg/L) of C-reactive protein (CRP) and serum amyloid A (SAA) were also measured at each visit.

To determine which patients responded to treatment in Part 1, a complete response was defined as:

- PHY and SKN ≤ 2
  AND
- CRP and/or SAA < 10 mg/L.

In Part 2, a disease flare was defined as:

- CRP and/or SAA > 30 mg/L
  AND EITHER
- PHY > 2
  OR
- PHY=2 and SKD > 2.

Efficacy in Part 2 was evaluated by comparing the proportion of complete responders that relapsed in each treatment group.

In the open-label studies, A2102 and D2306, relapse was defined as above. In study A2102, there was an additional definition for patients that had low SAA or CRP values but had clinical diagnoses that required re-treatment.

D2306

In this open-label, Phase 3 study, patients received Ilaris as an s.c. injection every 8 weeks for a minimum of 6 months to a maximum of 2 years. The dosing regimen was the same as used for Study D2304. Patients from studies A2102 and D2304 were allowed to enter this study. The primary efficacy variable was defined as the number of patients that did not relapse where relapse was as defined the same as in Study D2304.

3.1.2 Patient Disposition and Demographics

A2102

This multi-center, multi-country, open-label, dose titration study was conducted in France, Germany, India, Spain, and the United Kingdom. Patient demographics are shown in Table 1. The mean age of all patients was 30 years with a range of 4 to 51 years. The ages of the individual pediatric patients were 4, 6, 6, 7, 16, and 17 years old. Of these patients, 25 adults and 6 pediatric patients (91%) completed the study. One pediatric patient discontinued due to an adverse event, one adult discontinued due to unsatisfactory therapeutic effect, and one adult discontinued due to administrative problems.

Table 1. Patient demographics for Study A2102.

Subgroup		Count (%), N=34
Race	Caucasian	31 (91)
	Other	3 (9)
Gender	Male	13 (38)
	Female	21 (62)
Age (years)	< 18	7 (21)
	≥ 18	27 (79)
Phenotype	MWS	27 (79)
	FCAS	2 (6)
	NOMID	1 (3)
	MWS/NOMID	4 (12)

Source: Reviewer

D2304

This pivotal Phase 3 study was conducted at multiple centers in France, Germany, India, United Kingdom, and the United States. This study screened 41 patients of which 35 were enrolled into Part 1. Of these 35 patients, 31 achieved a complete response and were randomized into Part 2. Sixteen patients were randomized to placebo, and 15 patients were randomized to Ilaris. Patient demographics (Table 2) and baseline characteristics measured at the beginning of Part 1 (Table 3) were summarized based on these treatment assignments. The 2 pediatric patients examined in the placebo group were 14 and 16 years old, while the 3 examined in the Ilaris group were 9, 15, and 17 years old. Seven patients rolled over from study A2102 and 24 patients were naïve. Overall, demographics and baseline measurements were balanced across treatment groups. The only noted difference was that there was only one male patient evaluated in the Ilaris treatment group. However, there was still a significant treatment effect for the primary efficacy endpoint when gender was accounted for in the analysis.

Table 2. Patient demographics for Study D2304.

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)	Mean	33	34
	[Range]	[14, 74]	[9, 58]
n (%)	< 18 years	2 (13)	3 (20)
	≥ 18 years	14 (87)	12 (80)

Source: Reviewer

Table 3. Baseline characteristics based on treatment assignment

Measurement		Placebo, N=16	Ilaris, N=15
PHY (5-point scale)	Mean	3.9	4.0
	[Range]	[3, 5]	[2, 5]
SKD (5-point scale)	Mean	3.1	3.1
	[Range]	[1, 6]	[1, 4]
SAA (mg/L)	Mean	162	142
	[Range]	[9, 530]	[4, 508]
CRP (mg/L)	Mean	38	29
	[Range]	[8, 105]	[2, 102]

Source: Reviewer

There were 4 patients in Part 1 and 12 placebo patients in Part 2 that withdrew due to an unsatisfactory therapeutic effect. In Part 3, there was one patient that withdrew due to an adverse event and one patient that withdrew due to an unsatisfactory therapeutic effect.

D2306

This currently ongoing study is an open-label, multi-center study that is being conducted at 14 different centers throughout France, Germany, India, Spain United Kingdom and USA. Fifty seven patients had received treatment at the time of interim data cut-off on September 12th, 2008. The age of patients ranged from 4 to 57 years with a mean age of 33 years. Patient demographics are shown in Table 4. These patients included 22 rollover patients from A2102, 17 rollover patients from study D2304, and 18 naïve patients. One patient discontinued due to an adverse event. While it appears there were nine pediatric patients evaluated (ages 5, 5*, 7, 7, 8*, 9, 14, 14*, 15) only three of them were new patients (indicated by asterisk). Of the other six patients, five were from study A2102 and one was from study D2304.

Table 4. Patient demographics for study D2306

Subgroup	Count (%), N=57	
Race	Caucasian	54 (95)
	Other	3 (5)
Gender	Male (%)	26 (46)
	Female (%)	31 (54)
Age	< 18 years	9 (16)
	≥ 18 years	48 (84)
Phenotype	MWS	46 (81)
	FCAS	8 (14)
	NOMID	-
	MWS/NOMID	3 (5)

Source: Reviewer

3.1.3 Statistical Methodologies

A2102

While the Applicant defined the primary efficacy variable as the time to relapse from each dose administration, the medical review team was focused on the proportion of patients that achieved complete response as defined in the pivotal efficacy study and whether or not they returned to complete response status following multiple relapses. Data was reported for all patients that received at least one dose of study drug.

D2304

In the withdrawal period of the pivotal efficacy study, D2304, the primary efficacy endpoint was the proportion of patients that had a disease flare. A flare was defined as either a disease relapse or discontinued prior to completing Part 2. The Applicant defined disease relapse as:

- CRP and/or SAA > 30 mg/L
  AND EITHER
- PHY > 2
  OR
- PHY=2 and SKD > 2.

Any patient that discontinued regardless of reason was considered as having a disease flare in Part 2. The intent-to-treat (ITT) population in Part 2 consisted of all patients randomized that received at least one dose of study drug. The proportion of patients with a disease flare in each treatment group was compared using an exact test about the odds ratio, adjusting for previous exposure to Ilaris. To examine the robustness of this analysis, the proportions were also compared using a Fisher's exact test. An exact 95% CI was reported for the proportion of flares in each treatment group.

Secondary endpoints evaluated in Part 2 were time to flare and weekly CRP, SAA, PHY, and SKD. Time to flare was reported as mean, median, min, and max and CRP, SAA, PHY, and SKD values were averaged and reported for each weekly visit.

D2306
The primary efficacy variable was defined by the Applicant as the proportion of patients that did not relapse as determined by PHY, SKD, SAA, and CRP. The criteria used to define a disease flare were the same as those used in the pivotal efficacy study D2304.

3.1.4 Results

A2102
According to the Applicant, in Stage 1, the four patients evaluated achieved a complete response after each i.v. dose. In Stage 2, 28 out of 29 patients achieved a complete response. In the subsequent dose-relapse periods, 83% of patients (24 patients) achieved a complete response after every dose. In 96 dose-relapse periods, rescue treatment was administered on 5 occasions to 4 patients.

The five pediatrics patients evaluated achieved a complete clinical response after the first dose. However, two patients experienced a rapid relapse and required rescue treatment to return to complete response status. In the following dose-relapse periods, three pediatric patients achieved a complete response after every dose. However, rescue treatment was required on 11 occasions for the other 2 patients.

D2304
Of the 35 patients that entered Part 1, 34 (97%) achieved a complete response as defined in the protocol. Of these, 25 patients were in complete response by week 1, 8 were in complete response by week 2 and 1 patient by week 8. While 34 patients responded to treatment as defined by complete response, 3 discontinued due to unsatisfactory therapeutic effect prior to Week 8, therefore only 31 patients were randomized into Part 2. According to the data provided, there were no patients that experienced a relapse during Part 1.

Primary Efficacy Endpoint: Of those 31 patients randomized into Part 2, there were no disease flares in the Ilaris treatment group. However, there were 13 (81%) patients in the placebo group that met the definition of disease flare. Of these, ten met the criteria of relapse and three discontinued prior to completing Part 2. I was able to duplicate the Applicant's analysis of the primary efficacy variable. The results are shown in Table 5. The null hypothesis of a flare being equally likely in both groups, i.e. an odds ratio equal to one, was rejected with a p-value < 0.01. Note, while the 95% CI that I reported is slightly different than that reported by the Applicant, my conclusion is not different from the Applicant's. The proportion of flares for each treatment group was also compared using a Fisher's exact test used; p-value < 0.05, results not shown.

Table 5. Results from the primary efficacy analysis, proportion of disease flares.

	Placebo, N=16	Ilaris, N=15		Odds Ratio (Ilaris/Placebo)
Proportion of Flares (%)	13 (81)	0 (0)		0
95% CI	[0.54, 0.96]	[0, 0.22]		[0, 0.09]
p-value	-	-		< 0.01

Source: Reviewer

Secondary Efficacy Endpoints: While the Applicant included the 3 patients that discontinued when estimating the time to flare in Part 2, I only included the patients that meet the definition of disease relapse. The mean time to relapse for the 10 placebo patients that met the definition of a relapse ranged from 28 days to 168 days with a mean 95 days and a median of 91 days.

The mean weekly CRP and SAA values for all patients are shown in Table 6 and mean weekly PHY and SKD scores are shown in Table 7. At baseline or week zero, the mean scores for all patients were elevated but were much lower by week one as all patients were complete responders. By the end of Part 2, the scores for patients that were no longer on Ilaris had increased while the scores for those patients that remained on Ilaris did not substantially increase. However, once the placebo patients returned to treatment in Part 3, scores again decreased.

Table 6 Mean weekly values for CRP and SAA.

Assessment		Mean values (mg/mL) by week										
		Part 1			Part 2						Part 3**	
		0	1	8	12	16	20	24	28	32	40	48
CRP	Placebo	37.6	2.5	9.2	12.0	15.1	19.7	28.4	29.7	29.2	8.1	5.8
	Ilaris	29.2	6.9	2.8	4.8	4.8	6.7	3.3	4.2	3.9	7.1	2.9
SAA	placebo	162.2	4.4	23.8	26.3	41.3	54.2	100.8	97.2	94.9	12.9	11.7
	Ilaris	141.9	34.9*	7.6	14.3	15.1	14.9	7.9	10.8	9.9	12.8	6.4

Note: Missing values were imputed using the LOCF method.
*Pt 0002-00004 had a SAA value of 461, when excluded mean was 4.
**Missing values imputed were not imputed in Part 3.

Source: Reviewer

Table 7. Mean weekly scores for PHY and SKD.

Assessment		Mean scores by week										
		Part 1			Part 2						Part 3*	
		0	1	8	12	16	20	24	28	32	40	48
Global	Placebo	3.9	1.6	1.5	1.9	1.9	2.3	2.5	2.8	3.0	1.6	1.7
	Ilaris	4.0	1.5	1.5	1.5	1.6	1.3	1.7	1.5	1.5	1.4	1.2
Skin	placebo	3.1	1.2	1.2	1.4	1.5	1.8	1.9	2.3	2.4	1.2	1.2
	Ilaris	3.1	1.5	1.1	1.1	1.3	1.1	1.3	1.1	1.1	1.1	1.0
Note: Missing values were imputed using the LOCF method. *Missing values imputed were not imputed in Part 3.												

Source: Reviewer

In Part 3, only one patient was reported by the Applicant as having a disease flare. This was a 9-year old male patient that was randomized to the placebo group in Part 2.

D2306: According to the Applicant, at the time of data cutoff, there were no patients that experienced a disease flare. However, 31 patients had not yet been evaluated for a disease flare. Of the 11 naïve patients enrolled, 4 were complete responders, 4 had not yet achieved a complete response, and 3 had not yet been evaluated. All nine pediatric patients enrolled were classified as complete responders, three were reported as not having a disease flare, and six had not yet been evaluated for the disease flare criteria. Of the 57 patients enrolled at the time of BLA submission, 46 were diagnosed as MWS, 8 as FCAS, and 3 as MWS/NOMID, Table 4. When examining only the MWS patients, there were no disease flares reported. However, of the 46 MWS patients, 29 had not yet been evaluated for a disease flare and 2 naïve patients had not yet achieved a complete response. Of the eight FCAS patients, one was classified as not having a disease flare, one naïve patient had not yet achieved a complete response, and seven had not yet been evaluated. With the three MWS/NOMID patients, one was reported as not having a flare and two had not yet been evaluated.

3.2 Evaluation of Safety

The primary medical officer, Dr. Carolyn Yancey, reviewed the safety data for this NDA.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The proportion of flares was examined in males and females, pediatrics and adults, and Caucasian and non Caucasian. Since there were relatively few numbers of patients in each subgroup and there were no flares in Ilaris treated group, these data are simply summarized and reported in Table 8.

Table 8. Subgroup analysis for gender, age, and race

Subgroup		Proportion of flares- n/N (%)	
		Placebo	Ilaris
Gender	Male	9/9 (100)	0/1 (0)
	Female	4/7 (57)	0/14 (0)
Age	< 18 years	2/2 (100)	0/3 (0)
	≥ 18 years	11/14 (79)	0/12 (0)
Race	Caucasian	11/14 (79)	0/15 (0)
	Non-Caucasian	2/2 (100)	0/0 (0)

Source: Reviewer

For the 10 patients in the placebo group that met the definition of a disease relapse, the time to disease relapse was examined for each of the above subgroups, Table 9.

Table 9. Subgroup analysis for time to flare.

Subgroup		Days to flare in patients that met the definition of disease flare, n=10			
		n	mean	min	max
Gender	Male	8	96	28	168
	Female	2	91	64	117
Age	< 18 years	2	134	100	168
	≥ 18 years	8	85	28	130
Race	Caucasian	8	96	28	168
	Non-Caucasian	2	91	64	117

Source: Reviewer

Overall, for the subgroups examined, there were no notable differences in the proportion of disease flares and time to flare.

Note, since there were only five pediatric patients evaluated (2 placebo, 3 Ilaris) no statistical comparisons were conducted; however, there were no disease relapses in the Ilaris treated pediatric patients. There were 10 additional pediatric patients evaluated in the 2 open-label studies that achieved a complete response after treatment with Ilaris. All pediatric patients that were treated with Ilaris are listed in Table 10. There was one placebo patient that dropped out Part 2 of Study D2304 due to lack of efficacy. However, when this patient rolled over to Study D2306 he returned to complete response status.

Table 10. Pediatric patients exposed to Ilaris

Subject ID(s)	Study	Age	Sex	Discontinued – yes/no (reason)	Phenotype
0002_05108 0001_00014	A2102 D2306	7	M	No	MWS
0002_05113 0001_00009	A2102 D2306	13	M	No	MWS
0002_05116 0001_00007	A2102 D2306	6	F	No	MWS
0002_05123 0001_00005	A2102 D2306	4	F	No	MWS
0003_05131	A2102	16	F	Yes (pregnancy)	MWS/NOMID
0006_05130	A2102	17	F	No	MWS/NOMID
0022_05127 0031_00001	A2102 D2306	6	M	No	MWS
0001_00008 0041_00010	D2304 D2306	14	M	Yes (lack of efficacy in Part 2)*	MWS
0002_00001	D2304	9	F	Yes (adverse event in Part 3)	MWS
0008_00002	D2304	15	M	No	MWS
0008_00006	D2304	16	M	No	MWS
0502_00002	D2304	17	F	No	MWS
0004_00008	D2306	14	F	No	MWS
0501_00003	D2306	8	M	No	MWS/NOMID
0504_00001	D2306	5	F	No	FCAS
* This patient was randomized to the placebo group in Part 2 of D2304.					

Source: Reviewer

4.2 Other Special/Subgroup Populations

Since patients that had previous exposure to Ilaris were allowed to enroll in the pivotal efficacy trial, the proportion of flares was examined in patients with and without previous exposure (naïve), Table 11.

Table 11. Subgroup analysis of flares based on prior exposure status.

Previous Exposure to Ilaris	Proportion of flares- n/N (%)	
	Placebo	Ilaris
No	10/13 (77)	0/11(0)
Yes	3/3 (100)	0/4 (0)

Source: Reviewer

For the 10 patients in the placebo group that met the definition of a disease relapse, the time to relapse was examined based on exposure to Ilaris, Table 12.

Table 12. Subgroup analysis of time to relapse based on prior exposure status.

Prior Exposure to Ilaris	Time (hrs) to relapse in patients that met the definition of disease relapse, n=10			
	n	mean	min	max
No	7	92	28	168
Yes	3	102	77	130

Source: Reviewer

Overall, there were not any notable differences based on a patient having prior exposure to Ilaris.

While the applicant only examined patients diagnosed with MWS in the pivotal efficacy trial, other phenotypes were examined in the two open-label trials. A summary of the phenotypes studied is shown in Table 13.

Table 13. Summary of phenotypes examined.

Study	Phenotype - n			
	MWS	FCAS	NOMID	MWS/NOMID
A2102	27	2	1	4
D2304*	24	-	-	-
D2306*	10	8	-	1
* Only includes naïve patients				

Source: Reviewer

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The pivotal efficacy study only included MWS patients 9 years and older. The Applicant's claim for pediatric patients 4 years and older is based on one patient in an open-label study, A2102. The claim for FCAS is based on 10 patients from the 2 open-label studies —— b(4)

—— While there does seem to be sufficient evidence to support a claim for MWS in patients 9 years and older, the claims for patients 4 years and older and patients diagnosed with FCAS —— is not supported by statistical evidence.

5.2 Conclusions and Recommendations

Novartis claims that Ilaris is effective in treating symptoms associated with CAPS including MWS, FCAS, —— in patients 4 years and older. Based on my review of the pivotal efficacy study (D2304) and the results of the two open-label studies, I conclude that Ilaris is effective at treating symptoms associated with MWS in patients 9 years and older. While there are data from the two open-label studies that indicate Ilaris may be effective in treating patients diagnosed with FCAS, there were no adequate and well controlled studies conducted to support this claim. b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Signature:

David Petullo, M.S. — Date: 5/8/09

Concurred by:

Dionne Price, Ph.D. Team Leader — Date: 5/8/09

Thomas Permutt, Ph.D. Division Director — Date: 5/8/09

STATISTICS FILING CHECKLIST FOR BLA 125319

BLA Number: 125319 | **Applicant: Novartis** | **Stamp Date:**

Drug Name: ILARIS™ (Canakinumab) | **NDA/BLA Type: Priority** | **December 17, 2008**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Comments:

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.		X		See comment below
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

Comments: The Applicant needs to provide total exposure data for all patients, particularly for patients that were enrolled in multiple studies.

STATISTICS FILING CHECKLIST FOR BLA 125319

Reviewing Statistician — Date: 2/6/09

Supervisor/Team Leader — Date: 2/6/09