

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BL 125249/0**

**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  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**BLA Number:** STN 125249

**Drug Name:** Riloncept (IL1-Trap)

**Indication(s):** Cryopyrin-associated periodic syndromes (CAPS)

**Applicant:** Regeneron Pharmaceuticals, Inc.

**Date(s):** Stamp date: May 29, 2007  
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**Review Priority:** Priority

**Biometrics Division:** Division of Biometrics II

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**Keywords:**

NDA, clinical studies, ANCOVA, subgroup analyses

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

Study IL1T-AI-0505 adequately demonstrates that IL-1 Trap produced a statistically significant reduction in signs and symptoms (as measured by the mean Key Symptom Score) relative to the placebo group. In addition, Study IL1T-AI-0505 demonstrates that IL-1 Trap produced statistically significant better maintenance of the reduced signs and symptoms (as measured by the mean KSS) relative to the placebo group. These conclusions are robust against the choice of the statistical methods, are consistent within each component of the KSS, and do not appear to differ within any of the subgroups examined.

## 1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of one phase 3 pivotal study to support the regulatory approval of IL-1 Trap for treatment of cryopyrin-associated periodic syndromes (CAPS).

The pivotal study referred to as IL1T-AI-0505 is titled, "A multi-center, double-blind, placebo-controlled study of the safety, tolerability, and efficacy of riloncept in subjects with cryopyrin-associated periodic syndromes using both parallel group and randomized withdrawal designs". This study involved two parts. Part A was a double-blind, placebo-controlled, six-week phase with the primary objective of evaluation of the efficacy of IL-1 Trap in terms of reduction in signs and symptoms of CAPS in patients not currently receiving IL-1 Trap. Part B was a nine week single blind phase (that followed part A and a six week period where all subjects received IL-1 Trap) with the primary objective of evaluation of the maintenance of the reduced signs and symptoms of CAPS by randomizing subjects who were already receiving IL-1 Trap to either continue with IL-1 Trap or be switched to placebo. The primary endpoint in both parts was the change from baseline in the mean key symptom score (DHAF score) measured on a scale from 0 to 10.

## 1.3 Statistical Issues and Findings

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Analysis of baseline and demographic factors indicate that the treatment groups were adequately balanced to allow attributing differences between the groups to the effect of treatment assignment. (Section 3.1.2)
- Using the full analysis set and the as-randomized treatment assignment, the main conclusions of the primary efficacy analyses are as follows.
  - The results for part A demonstrate that IL-1 Trap produced a statistically significant reduction in signs and symptoms (as measured by the mean KSS) relative to the placebo group.
  - The results for part B demonstrate that IL-1 Trap produced statistically significant better maintenance of the reduced signs and symptoms (as measured by the mean KSS) relative to the placebo group.

These results were found to be robust to the choice of the statistical model. In addition, by-treatment group comparisons of each of the individual components of the KSS were consistent with the results for the mean KSS. Finally, the primary efficacy results were found to be reliable despite a small number of missing daily symptom scores. (Section 3.1.2)

- Eleven subjects were provided the wrong study medication for at least a portion of the first three weeks of the randomized withdrawal period of part B. Discussion is provided indicating why the conclusions of the primary efficacy analyses for part B remain reliable. (Section 3.1.2)
- Although possible due to the unique study design employed for this trial, the efficacy observed in the randomized withdrawal period of part B does not appear to have been affected by the treatment assignment for part A. (Section 3.1.2)
- A descriptive summary of the primary efficacy variable, mean KSS, by gender and age for both parts A and B did not reveal any differing effects in those subgroups. Subgroup analyses by race were not possible as all subjects in this study were white. (Section 4.1)
- A disparity between treatment groups in the use of concomitant medications, specifically anti-inflammatory and antipyretic use was noted by the medical reviewer. Analyses of the primary efficacy variable, mean KSS, using the protocol specified primary efficacy analysis methods sub-grouped by baseline concomitant anti-inflammatory and/or antipyretics use are provided and do not reveal differing treatment effects for these subgroups. (Section 4.2)
- Concern was raised by the medical reviewer that by experiencing an injection site reaction, a subject may have been unblinded to treatment assignment which may have affected the subject's rating of the symptom scores. A subgroup analysis using the protocol specified primary efficacy analysis methods for the primary efficacy endpoint, mean KSS, while excluding subjects with injection site reactions is provided. The results in this subgroup are consistent with those of the overall group.

## 2. INTRODUCTION

### 2.1 Overview

The sponsor has submitted the results of one phase 3 pivotal study to support the regulatory approval of IL-1 Trap for treatment of cryopyrin-associated periodic syndromes (CAPS).

The pivotal study referred to as IL1T-AI-0505 is titled, "A multi-center, double-blind, placebo-controlled study of the safety, tolerability, and efficacy of rilonacept in subjects with cryopyrin-associated periodic syndromes using both parallel group and randomized withdrawal designs". This study involved two parts. Part A was a double-blind, placebo-controlled, six-week phase with the primary objective of evaluation of the efficacy of IL-1 Trap in terms of reduction in signs and symptoms of CAPS in patients not currently receiving IL-1 Trap. Part B was a nine week single blind phase (that followed part A and a six week period where all subjects received IL-1 Trap) with the primary objective of evaluation of the maintenance of the reduced signs and symptoms of CAPS by randomizing subjects who were already receiving IL-1 Trap to either continue with IL-1 Trap or be switched to placebo. The primary endpoint in both parts was the change from baseline in the mean key symptom score (DHAF score).

Communication with the sponsor regarding this study is documented under BB-IND 11781. Pertinent parts of the statistical portion of those communications are summarized herein. The Division responded to the sponsor's request for a special protocol assessment on November 18, 2005. Although the special protocol assessment was denied due to outstanding CMC development plans, responses to the sponsor's specific questions in the special protocol assessment request were provided. The Division agreed that the two parts of the pivotal study are "statistically independent events in the sense that there are two randomizations" and that no multiple comparison correction is needed to account for the two efficacy analyses resulting from part A and part B.

## 2.2 Data Sources

The following data sets were submitted electronically and utilized in the review of this study.

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\\Cbsap58\M\CTD\_Submissions\STN125249\0003\m5\datasets\study-il1t-ai-0505\listings\dhaf.xpt

All submitted data sets were found to be adequately documented and organized.

## 3. STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

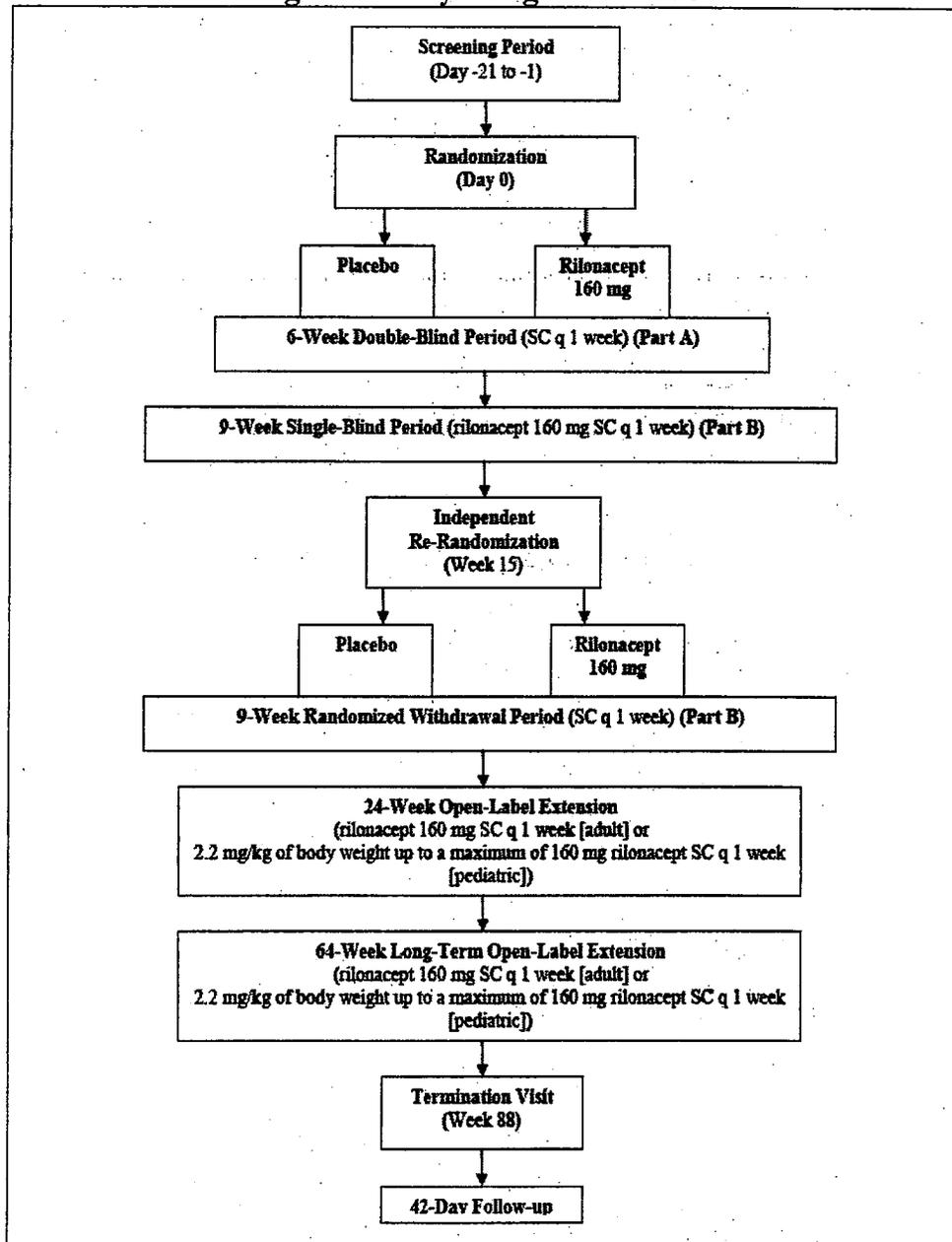
#### 3.1.1 Study Design (Study IL1T-AI-0505)

Study IL1T-AI-0505 was a multi-center study including a three-week screening period, a six-week, double-blind, randomized, placebo-controlled treatment period (referred to as part A), a nine-week single-blind active-treatment period followed by a nine-week double-blind, placebo-controlled, randomized withdrawal phase (referred to as part B). In addition, there were open label extensions and follow-up for this study extending as late as 94 weeks post-part B; however, these were not intended to contribute to the evaluation of the efficacy of IL-1 Trap.

Figure 1 was provided by the sponsor in the clinical study report and reflects the study design. As indicated in Figure 1, the study began with a screening period which continued for three weeks during which time subjects were to record their daily diary data regarding disease symptoms (i.e., data relevant to efficacy evaluation, measurement tool is described later in this section). Subsequently, subjects were randomized (1:1) to receive IL-1 Trap or placebo during the six-week double blind phase (i.e., part A). Subjects were to continue to record their daily diary data throughout this period. The efficacy data from part A is therefore an assessment of whether, relative to placebo, IL-1 Trap reduces the signs and symptoms of CAPS in patients not currently receiving IL-1 Trap. Following part A, all

subjects received IL-1 Trap under single blind conditions (i.e., subjects blinded) for nine weeks. In the phase referred to as the double-blind phase of part B, subjects were then randomized (1:1) to either continue treatment with IL-1 Trap or be switched to placebo while continuing to record their daily diary data thus allowing evaluation of the maintenance of the reduced signs and symptoms of CAPS. The randomizations associated with parts A and B were independent of one another. Both randomizations were stratified by disease activity as assessed at the part A baseline (i.e., all key symptoms at visit 2, day 0 rated less than three versus not).

**Figure 1: Study Design Schematic \***



\*Source: Clinical Study Report for Study IL1T-AI-0505, page 5

For parts A and B, the target population consisted of adult subjects with confirmed *CLAS1* mutation. In instances where more than one family member diagnosed with CAPS lived in the same household, only one person from that household was to be enrolled in parts A and B of the study. In this case, the patient chosen for study participation was at the Investigator's discretion. In total, the protocol specified 7 inclusion and 19 exclusion criteria for parts A and B of the study.

Clinical assessment of disease activity was conducted using the Daily Health Assessment Form (DHAF), which was a one-page questionnaire that asked subjects to rate the severity of their key symptoms (rash, feeling of fever/chills, joint pain, eye redness/pain, and fatigue) over the previous 24 hours on a scale from 0=no severity to 10=very severe with 0.5 increments. Subjects were asked to complete the form every evening at approximately the same time. Subjects were to return the forms at the next study visit. The study coordinator reviewed the completed DHAFs with the subjects for accuracy and completeness. For efficacy analysis purposes, the daily means (across symptoms) were calculated ignoring missing data. Then for each 21-day observation period, the mean of the daily means was calculated ignoring missing data and resulting in a mean key symptom score (KSS) for the primary efficacy analysis. The primary efficacy variable was the mean change from part A baseline (i.e., the mean of the last 21 days of the screening period) to endpoint (i.e., the mean of either the last 21 days of part A or the last 21 days of part B) in the mean key symptom score (KSS).

For each part, A and B, the primary efficacy analysis was protocol-specified as a conditional sequence of superiority hypothesis tests beginning with a test of subjects in stratum 1 and proceeding to a test of the overall group (i.e., subjects in either strata) only if significance is achieved in stratum 1. This controlled for multiplicity while permitting the initial evaluation of efficacy to be in a population expected to have adequate disease activity for demonstration of efficacy (i.e., stratum 1). The protocol-specified primary analysis for comparison of IL-1 Trap to placebo was analysis of covariance (ANCOVA) using part A baseline mean KSS as a covariate and treatment for the relevant part, A or B, as a main effect. The protocol specifically highlights that the part A baseline should be used as the covariate in both part A and B analyses since part B baseline is collected during the final three weeks of a nine-week period of IL-1 Trap treatment. As agreed upon with the Division (see section 2.1), no multiplicity correction accounting for multiple analyses resulting due to the two parts of this study was applied.

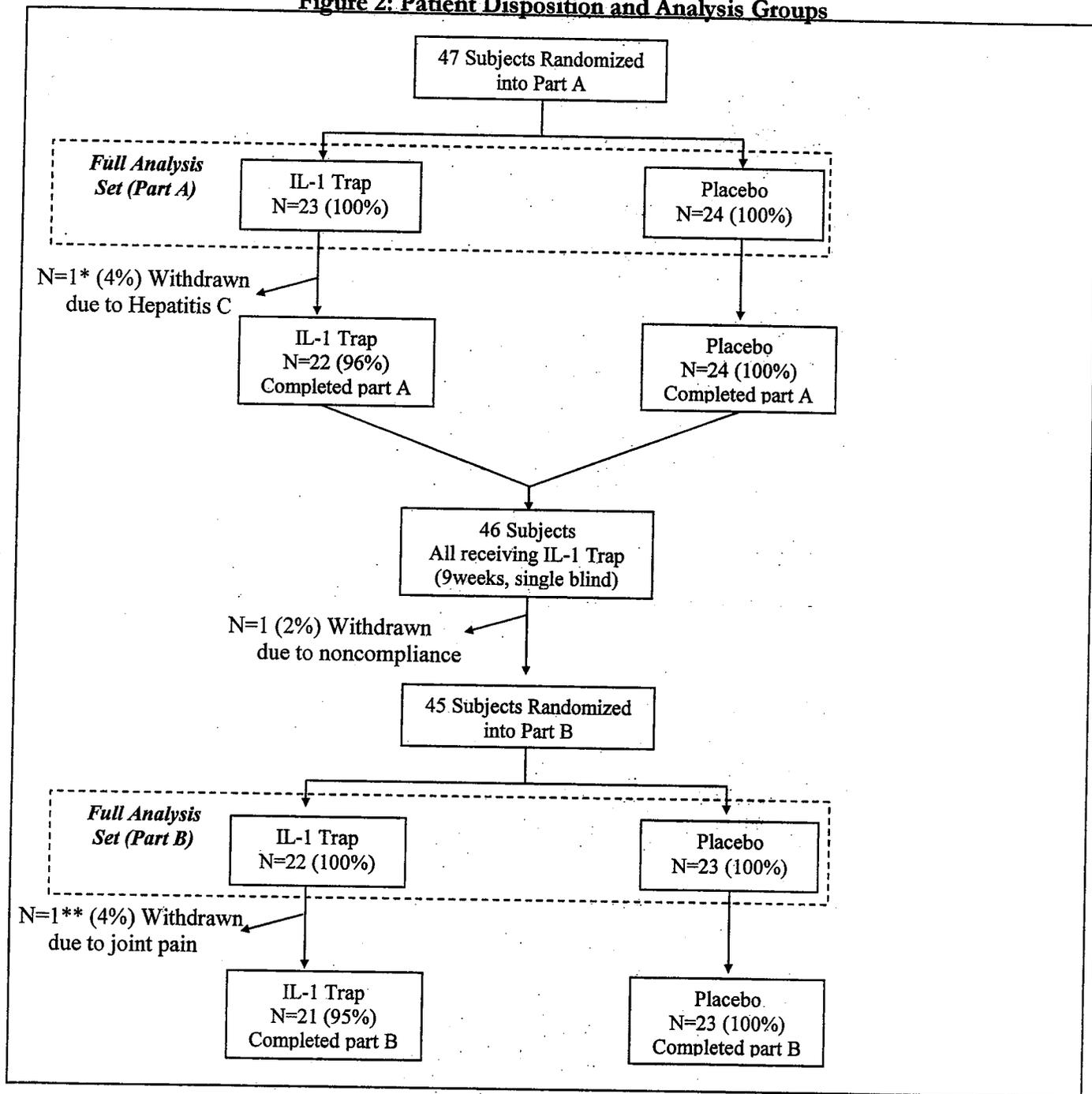
The protocol defines a "full analysis set" as including all randomized subjects for part A/B who are known to be genotype positive for CAPS (an inclusion criteria) and who receive at least one dose of study medication. The full analysis set is protocol-specified for use in the primary efficacy analysis.

### **3.1.2 Results (Study IL1T-AI-0505)**

Fifty-three subjects were screened and 47 of these were randomized (1:1) into part A: 23 to receive IL-1 Trap and 24 to receive placebo. All 47 subjects randomized received study medication and therefore were included in the "full analysis set". Forty-six subjects enrolled in part B. All received IL-1 Trap for the single blind nine week period followed by 45 of

these subjects being randomized into the double blind portion of part B: 22 to continue to receive IL-1 Trap and 23 to be switched to placebo. Figure 2 describes the randomizations and the inclusion or exclusion of subjects from the “full analysis set” for each part.

**Figure 2: Patient Disposition and Analysis Groups**



\* Subject included in part A efficacy analysis using primary efficacy endpoint calculated from last 21 days of participation.  
 \*\* Subject included in part B efficacy analysis using primary efficacy endpoint calculated from last 21 days of participation.

As per-protocol, both randomizations were stratified by disease activity as assessed at the part A baseline (i.e., all key symptoms at visit 2, day 0 rated less than three versus not). However, since only a single subject was enrolled into stratum 2 (i.e., lesser disease activity) the results within stratum 1 (i.e., more severe disease activity) and the overall group are very similar as they include the same set of subjects with the exception of one. Therefore, only the results of the overall group are reported herein. It should be noted that the protocol specified multiple comparison plan requiring significance in stratum 1 before testing the overall group for the primary efficacy analysis was satisfied.

Demographic and baseline characteristics for the full analysis sets for parts A and B were provided by the sponsor in the clinical study report and are summarized in Table 1. Reviewer analyses indicate that the difference between treatment groups in age in part A is associated with a nominal p-value less than 0.05 ( $p=0.04$ ); however from a statistical perspective, this may be a spurious finding and is not considered a significant detriment to the study or an indication that the random treatment assignment was inadequate. No other differences between treatment groups with associated p-values less than 0.05 were noted in demographic and background characteristics in the full analysis sets for part A or B.

**Table 1: Demographic and Baseline Characteristics (Full Analysis Sets)**

Demographic/Baseline Characteristic		Part A			Part B		
		IL-1 Trap (n=23)	Placebo (n=24)	p-value*	IL-1 Trap (n=22)	Placebo (n=23)	p-value*
Age (years)	mean (min, max)	46 (22, 76)	56 (24, 78)	.04	52 (26, 78)	50 (22, 78)	0.78
Gender	Female N(%)	15 (65%)	16 (67%)	0.92	14 (64%)	16 (70%)	0.67
	Male N(%)	8 (35%)	8 (33%)		8 (36%)	7 (30%)	
Ethnic Origin	White Non-Hispanic N(%)	23 (100%)	24 (100%)	1.00	22 (100%)	23 (100%)	1.00
CIAS1 Gene Mutation	Yes N(%)	23 (100%)	24 (100%)	1.00	22 (100%)	23 (100%)	1.00
Height (cm)	mean (min, max)	168 (155, 190)	169 (158, 183)	0.76	170 (155, 190)	167 (158, 179)	0.32
Weight (kg)	mean (min, max)	72 (50, 114)	76 (50, 119)	0.35	76 (50, 119)	74 (50, 114)	0.68
Baseline Key Symptom Score	mean (min, max)	3.08 (0.73, 8.15)	2.41 (0.64, 5.4)	0.18	0.32 (0, 1)	0.23 (0, 2.07)	0.42

\*p-values correspond to a test of the difference between treatment groups using the independent t-test for means for continuous variables and binomial test of proportions for categorical variables.

All primary efficacy analyses were conducted using the statistical procedures specified in the protocol and described in section 3.1.1 of this document. The primary efficacy results (for both disease severity strata combined) for both parts A and B are given in Table 2. With the exception of inferential statistics (i.e., p-values), the sponsor reports unadjusted results for the primary efficacy analysis. The least squares means and inferential statistics (i.e., p-values and confidence intervals) reported in Table 2 were conducted by this reviewer and are adjusted using the protocol-specified primary efficacy analysis of covariance model.

Therefore, there are slight numerical differences between the results displayed in Table 2 and the primary efficacy results displayed by the sponsor in the study report. The qualitative conclusions using the adjusted and unadjusted results are the same.

<b>Table 2: Primary Efficacy Analysis – Change from Baseline to Endpoint in the Mean Key Symptom Score (Full Analysis Sets)</b>						
	<b>Part A</b>			<b>Part B</b>		
	<b>IL-1 Trap (n=23)</b>	<b>Placebo (n=24)</b>	<b>Diff</b>	<b>IL-1 Trap (n=22)</b>	<b>Placebo (n=23)</b>	<b>Diff</b>
<b>Mean KSS at Endpoint (scale: 0=none to 10=severe)</b>	0.5	2.1		0.4	1.2	
<b>LS Mean Change from Baseline <sup>1,2</sup></b>	-2.4	-0.5	-1.9	0.1	0.9	-0.8
<b>p-value &amp; 95% CI for By-Trt. Diff. in LS Mean Change from Baseline <sup>2</sup></b>	p<0.0001 (-2.4, -1.3)			p=0.0002 (-1.3, -0.4)		

1. Part A evaluates IL-1 Trap for the reduction in signs and symptoms in patients not currently receiving IL-1 Trap. A negative value for the mean change from baseline represents a reduction in the KSS from part A baseline. Part B evaluates IL-1 Trap for the maintenance of the reduced signs and symptoms in subjects who were already receiving IL-1 Trap. A value for the mean change from baseline that is close to zero represents maintenance of the KSS from part B baseline.

2. Least squares (LS) means and associated p-values and confidence intervals calculated using the protocol specified primary analysis method, an analysis of covariance model with part A baseline mean KSS as a covariate and the main effect for treatment of the relevant part.

For part A, the mean change from baseline in the KSS score for the IL-1 Trap subjects was statistically significantly smaller than that of the placebo subjects demonstrating that IL-1 Trap produced a significant reduction in signs and symptoms (as measured by the mean KSS) relative to the placebo group.

For part B, the mean change from baseline in the KSS score for the IL-1 Trap subjects was statistically significantly smaller than that of the placebo subjects demonstrating that IL-1 Trap produced significantly better maintenance of signs and symptoms (as measured by the mean KSS) relative to the placebo group.

Additional analysis of the primary efficacy endpoint employing slight variations in the ANCOVA model were conducted by both the sponsor and this reviewer and indicate that the qualitative conclusions supported by Table 2 are robust against the choice of the terms in the ANCOVA model (e.g., inclusion/exclusion of the baseline term did not impact the significance of the treatment effect).

By-treatment group comparisons of each of the individual components of the KSS are given in Table 3. These results are consistent with the results for the KSS.

Mean Change from Baseline <sup>1,2</sup>	Part A			Part B		
	IL-1 Trap (n=23)	Placebo (n=24)	p-value	IL-1 Trap (n=22)	Placebo (n=23)	p-value
Feeling of Fever/Chills	-2.7	-0.3	<0.001	0.1	1.0	0.008
Rash	-3.5	-0.2	<0.001	0.2	1.9	<0.001
Eye Redness/pain	-1.5	-0.1	<0.001	0.0	0.3	0.030
Fatigue	-2.8	-0.5	<0.001	0.0	0.9	<0.001
Joint Pain	-2.6	-0.5	<0.001	0.1	0.6	0.020

1. Part A evaluates IL-1 Trap for the reduction in signs and symptoms in patients not currently receiving IL-1 Trap. A negative value for the mean change from baseline represents a reduction in the KSS from part A baseline. Part B evaluates IL-1 Trap for the maintenance of the reduced signs and symptoms in subjects who were already receiving IL-1 Trap. A value for the mean change from baseline that is close to zero represents maintenance of the KSS from part B baseline.

2. P-values calculated using the protocol specified primary analysis method, an analysis of covariance model with part A baseline mean KSS as a covariate and the main effect for treatment of the relevant part.

According to the clinical study report, eleven subjects were provided the wrong study medication for at least a portion of the first three weeks of the randomized withdrawal period of part B. Nine subjects who should have received IL-1 Trap actually received placebo and five subjects who should have received placebo actually received IL-1 Trap. The primary efficacy analysis shown in Table 2 is conducted using the intended treatment assignment rather than the treatment actually received. As such this error would cause the treatments to look artificially similar in the primary efficacy analysis. Since a statistically significant difference between treatment groups was established despite this error, the conclusions discussed above regarding the efficacy of IL-1 Trap remain reliable.

While the unique study design utilized in this trial offers the opportunity to evaluate IL-1 Trap for the reduction and maintenance of signs and symptoms of CAPS, it has the limitation that the results seen in the randomized withdrawal portion of part B of the study may be affected by the treatment assignment during part A if the single blind portion of part B where all subjects received IL-1 Trap was not sufficient to wash-out the effects of the part A treatment. This was investigated using the analysis of covariance model specified for the primary efficacy analysis with the modification that the main effect for the part A treatment assignment was included in the analysis of the part B results. The treatment assignment for part A was not a significant predictor in this regard, indicating that the results observed in the randomized withdrawal period of part B were not affected by the treatment assignment in part A. In addition, the interaction between the treatment assignments in part A and part B was evaluated in this model and was found to be non-significant as was expected since the randomization scheme for each part were independent of one another.

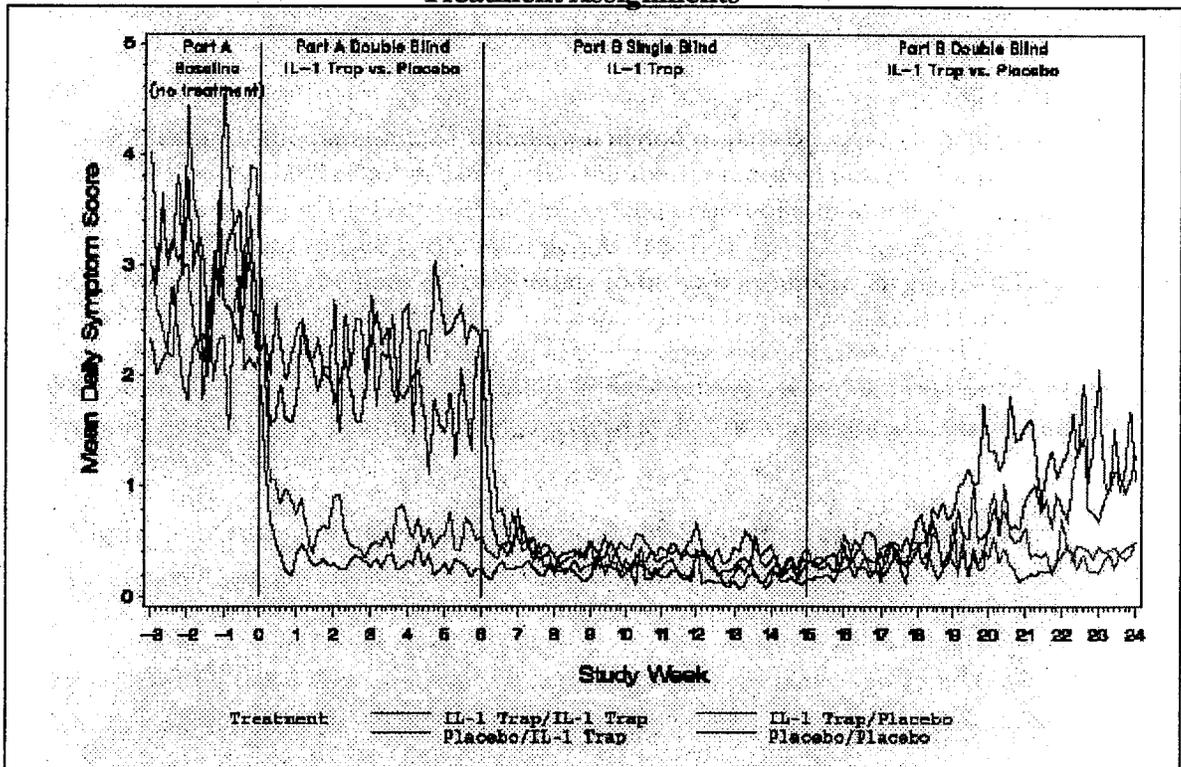
Figure 3 was provided by the sponsor in the clinical study report and is provided herein as additional support for the conclusion that the results observed in the randomized withdrawal portion of part B of the study were not affected by the treatment assignment in part A.

Figure 3 displays the mean KSS across both parts A and B and distinguishes subjects according to the following treatment groups.

- “IL-1 Trap / IL-1 Trap” meaning that the subject received IL-1 Trap for part A followed by IL-1 Trap for the single blind period of part B followed by IL-1 Trap for the randomized withdrawal period of part B
- “IL-1 Trap / Placebo” meaning that the subject received IL-1 Trap for part A followed by IL-1 Trap for the single blind period of part B followed by placebo for the randomized withdrawal period of part B
- “Placebo / IL-1 Trap” meaning that the subject received placebo for part A followed by IL-1 Trap for the single blind period of part B followed by IL-1 Trap for the randomized withdrawal period of part B
- “Placebo / Placebo” meaning that the subject received placebo for part A followed by IL-1 Trap for the single blind period of part B followed by placebo for the randomized withdrawal period of part B

As indicated in Figure 3 the lines corresponding to the two groups receiving IL-1 Trap in the randomized withdrawal portion of part B overlap and follow the same general pattern. Similarly, the two groups receiving placebo in the randomized withdrawal portion of part B follow a related course. Therefore the results in the randomized withdrawal portion of part B appear to be due to the treatment being received at that time and not affected by the treatment received during part A.

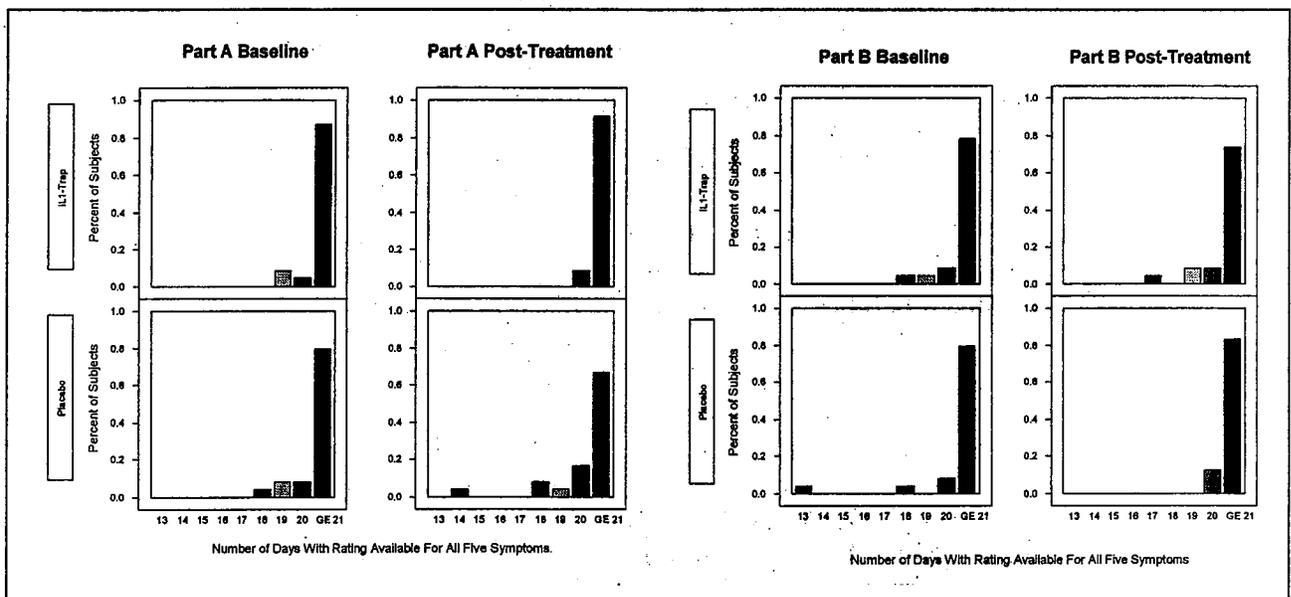
**Figure 3: Mean Daily Key Symptom Score by Sequence of Part A and Part B Treatment Assignments**



\*Source: Clinical Study Report for Study IL1T-AI-0505, page 5

The primary efficacy endpoint, mean KSS, was calculated for each subject by first obtaining the mean (across the subject's rating of the five symptoms) for each day and then averaging across the last 21 days of the relevant screening or baseline period. These means were calculated ignoring missing data which in effect is equivalent to imputing the mean score for values that were missing. Figure 4 provides the availability of symptom scores by treatment group for each measurement period, part A baseline, part A post-treatment, part B baseline, and part B post-treatment. The figure indicates that complete data for calculation of the primary efficacy endpoint was available for most subjects and that the distributions of missing data appear to be balanced across treatment groups providing reassurance that the efficacy conclusions given in Table 2 are not an artifact of missing evaluations or the imputation strategy employed and that the conclusions of the primary efficacy analysis remain reliable.

**Figure 4: Distribution of Missing Data Relevant to Calculation of the Primary Efficacy Endpoint, Mean KSS, by Treatment**



\*Source: Reviewer Analyses

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

A descriptive summary of the primary efficacy variable, mean KSS, by gender and age for both parts A and B are given in Table 4. Subgroup analyses by race are not possible as all subjects in this study were white.

	Part A					Part B				
	IL-1 Trap		Placebo		95% CI for diff	IL-1 Trap		Placebo		95% CI for diff
	N	mean	N	mean		N	mean	N	mean	
Subjects <51 years of age	13	-3.1	10	-0.4	(-4.2, -1.2)	11	0.1	10	1.3	(-1.8, -0.6)
Subjects ≥51 years of age	10	-2.0	14	-0.3	(-2.7, -0.7)	11	0.0	13	0.6	(-1.2, -0.02)
Males	8	-2.6	8	-0.3	(-3.8, -0.8)	8	-0.1	7	0.6	(-1.5, 0.1)
Females	15	-2.6	16	-0.3	(-3.4, -1.2)	14	0.2	16	1.1	(-1.4, -0.4)

1. Part A evaluates IL-1 Trap for the reduction in signs and symptoms in patients not currently receiving IL-1 Trap. A negative value for the mean change from baseline represents a reduction in the KSS from part A baseline. Part B evaluates IL-1 Trap for the maintenance of the reduced signs and symptoms in subjects who were already receiving IL-1 Trap. A value for the mean change from baseline that is close to zero represents maintenance of the KSS from part B baseline.

2. Confidence Interval for difference between means calculated using t-distribution.

#### 4.2 Other Special/Subgroup Populations

A disparity between treatment groups in the use of concomitant medications, specifically anti-inflammatory and antipyretic use was noted by the medical reviewer in the course of reviewing this study. Nineteen of 23 (83%) IL-1 Trap subjects and 12 of 24 (50%) placebo subjects were identified by the medical reviewer as using anti-inflammatories or antipyretics during part A. Sixteen of 22 (73%) IL-1 Trap subjects and 14 of 23 (61%) placebo subjects were identified by the medical reviewer as using anti-inflammatories or antipyretics during the randomized withdrawal portion of part B. However, most of these subjects were using these products at baseline and merely continued their use throughout the trial suggesting that the disproportionate use was not related to treatment. Three (13%) IL-1 Trap and 3 (13%) placebo subjects who were not using these products at baseline used these products during part A. Three (14%) IL-1 Trap and 2 (9%) placebo subjects who were not using these products at baseline used these products during part B. Analysis of the primary efficacy variable, mean KSS, using the protocol specified primary efficacy analysis methods sub-grouped by **baseline** concomitant anti-inflammatory and/or antipyretics use during the relevant part, A or B, is given in Table 5. Baseline concomitant anti-inflammatory and/or antipyretics use/non-use is used as the sub-grouping factor in this analysis, not use/non-use of these products during a treatment period as the later may be influenced by the study treatment received and thus a by-treatment group comparison of efficacy in those subgroups could be misleading. As shown in Table 5, a treatment effect consistent with the treatment effect in the overall group is observed in all instances providing evidence that the effect of IL-1 Trap is independent of the baseline concomitant use of anti-inflammatories and/or antipyretics.

Table 5: Primary Efficacy Analysis by Baseline Concomitant Anti-inflammatory and/or Antipyretic Use – Change from Baseline to Endpoint in Mean KSS (Full Analysis Sets)							
		Part A			Part B		
		IL-1 Trap	Placebo	Diff	IL-1 Trap	Placebo	Diff
With Baseline Concomitant Anti-inflammatory and/or Antipyretic Use	Sample Size	18	12		13	16	
	LS Mean Change from Baseline <sup>1,2</sup>	-2.2	-0.5	-1.7	0.02	1.0	-0.9
	p-value & 95% CI for By-Trt. Diff. in LS Mean Change from Baseline <sup>2</sup>	p=0.0001 (-2.4, -0.9)			p=0.0012 (-1.5, -0.4)		
Without Baseline Concomitant Anti-inflammatory and/or Antipyretic Use	Sample Size	5	12		9	7	
	LS Mean Change from Baseline <sup>1,2</sup>	-3.1	-0.6	-2.5	0.1	1.0	-0.9
	p-value & 95% CI for By-Trt. Diff. in LS Mean Change from Baseline <sup>2</sup>	p=0.0002 (-3.6, -1.4)			p=0.0530 (-1.9, 0.01)		

1. Part A evaluates IL-1 Trap for the reduction in signs and symptoms in patients not currently receiving IL-1 Trap. A negative value for the mean change from baseline represents a reduction in the KSS from part A baseline. Part B evaluates IL-1 Trap for the maintenance of the reduced signs and symptoms in subjects who were already receiving IL-1 Trap. A value for the mean change from baseline that is close to zero represents maintenance of the KSS from part B baseline.

2. Least squares (LS) means and associated p-values and confidence intervals calculated using the protocol specified primary analysis method, an analysis of covariance model with part A baseline mean KSS as a covariate and the main effect for treatment of the relevant part.

Concern was raised by the medical reviewer that by experiencing an injection site reaction, a subject may have been unblinded to treatment assignment which may have affected the subject's rating of the symptom scores. For this reason a subgroup analysis using the protocol specified primary efficacy analysis methods for the primary efficacy endpoint, mean KSS, while excluding subjects with injection site reactions was performed. The results are given in Table 6. The results did not reveal any apparent effect of the injection site reaction on efficacy in that the results in this subgroup are consistent with those of the overall group. However, this analysis is not reliable in that the sub-grouping factor, occurrence/non-occurrence of an injection site reaction, is a characteristic that occurred after randomization and therefore has the potential to have been affected by treatment assignment. This type of relationship with treatment assignment may obscure or bias the by-treatment group comparison of efficacy in the subgroup(s) created by the post-randomization characteristic. The analysis in Table 6 should be viewed in that light.

		Part A			Part B		
		IL-1 Trap	Placebo	Diff	IL-1 Trap	Placebo	Diff
Without Injection Site Reaction	Sample Size	12	21		14	20	
	LS Mean Change from Baseline <sup>1,2</sup>	-2.0	-0.2	-1.8	0.1	0.9	-0.7
	p-value & 95% CI for By-Trt. Diff. in LS Mean Change from Baseline <sup>2</sup>	p<0.0001 (-2.4, -1.1)			p=0.0115 (-1.3, -0.2)		

1. Part A evaluates IL-1 Trap for the reduction in signs and symptoms in patients not currently receiving IL-1 Trap. A negative value for the mean change from baseline represents a reduction in the KSS from part A baseline. Part B evaluates IL-1 Trap for the maintenance of the reduced signs and symptoms in subjects who were already receiving IL-1 Trap. A value for the mean change from baseline that is close to zero represents maintenance of the KSS from part B baseline.

2. Least squares (LS) means and associated p-values and confidence intervals calculated using the protocol specified primary analysis method, an analysis of covariance model with part A baseline mean KSS as a covariate and the main effect for treatment of the relevant part.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

- Analysis of baseline and demographic factors indicate that the treatment groups were adequately balanced to allow attributing differences between the groups to the effect of treatment assignment. (Section 3.1.2)
- Using the full analysis set and the as-randomized treatment assignment, the main conclusions of the primary efficacy analyses are as follows.
  - The results for part A demonstrate that IL-1 Trap produced a statistically significant reduction in signs and symptoms (as measured by the mean KSS) relative to the placebo group.
  - The results for part B demonstrate that IL-1 Trap produced statistically significant better maintenance of the reduced signs and symptoms (as measured by the mean KSS) relative to the placebo group.

These results were found to be robust to the choice of the statistical model. In addition, by-treatment group comparisons of each of the individual components of the KSS were consistent with the results for the mean KSS. Finally, the primary efficacy results were found to be reliable despite a small number of missing daily symptom scores. (Section 3.1.2)

- Eleven subjects were provided the wrong study medication for at least a portion of the first three weeks of the randomized withdrawal period of part B. Discussion is provided indicating why the conclusions of the primary efficacy analyses for part B remain reliable. (Section 3.1.2)

- Although possible due to the unique study design employed for this trial, the efficacy observed in the randomized withdrawal period of part B does not appear to have been affected by the treatment assignment for part A. (Section 3.1.2)
- A descriptive summary of the primary efficacy variable, mean KSS, by gender and age for both parts A and B did not reveal any differing effects in those subgroups. Subgroup analyses by race were not possible as all subjects in this study were white. (Section 4.1)
- A disparity between treatment groups in the use of concomitant medications, specifically anti-inflammatory and antipyretic use was noted by the medical reviewer. Analyses of the primary efficacy variable, mean KSS, using the protocol specified primary efficacy analysis methods sub-grouped by baseline concomitant anti-inflammatory and/or antipyretics use are provided and do not reveal differing treatment effects for these subgroups. (Section 4.2)
- Concern was raised by the medical reviewer that by experiencing an injection site reaction, a subject may have been unblinded to treatment assignment which may have affected the subject's rating of the symptom scores. A subgroup analysis using the protocol specified primary efficacy analysis methods for the primary efficacy endpoint, mean KSS, while excluding subjects with injection site reactions is provided. The results in this subgroup are consistent with those of the overall group.

## 5.2 Conclusions and Recommendations

Study IL1T-AI-0505 adequately demonstrates that IL-1 Trap produced a statistically significant reduction in signs and symptoms (as measured by the mean KSS) relative to the placebo group. In addition, Study IL1T-AI-0505 demonstrates that IL-1 Trap produced statistically significant better maintenance of signs and symptoms (as measured by the mean KSS) relative to the placebo group. These conclusions are robust against the choice of the statistical methods, are consistent within each component of the KSS, and do not appear to differ within any of the subgroups examined.

The following recommendations are being made for the Clinical Studies section of the IL-1 Trap labeling.

