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

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name Keith K. Burkhardt, MD *KKB 12-18-2007*  
Through Jeffrey Siegel, MD *J 512-18-07*  
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Established Name Rilonacept  
(Proposed) Trade Name Arcalyst  
Therapeutic Class Interleukin-1 blocker  
Applicant Regeneron

Priority Designation P

Formulation Lyophilized powder  
Dosing Regimen Adult: 160 mg SC q weekly  
Pediatrics: 4.4 mg/kg  
Indication Familial Cold Autoinflammatory  
Syndromes  
Intended Population Adults and Pediatrics

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## 1 EXECUTIVE SUMMARY

### 1.1 Recommendation on Regulatory Action

At the time of this review, there are several unresolved CMC issues. If these CMC issues are resolved then the application for rilonacept should be approved for the indication of \_\_\_\_\_ Cryopyrin Associated Periodic Syndromes (CAPS), an autoinflammatory disease. The Applicant has provided substantial evidence of efficacy in an adequately controlled two-part trial. The first part was a 6-week double-blind placebo controlled study. Following Part A all subjects were placed on rilonacept for 9 weeks (Part B single-blind phase). After the 9 weeks, subjects underwent randomized withdrawal for another 9-week study period. In Part A rilonacept reduced five key symptoms (feeling of fever/chills, rash, eye redness/pain, fatigue, and joint pain) of CAPS within days of initiating therapy. This benefit was maintained while subjects continued on rilonacept. In Part B those subjects withdrawn from rilonacept to placebo had a return of their symptoms over the following weeks.

In the development program no significant safety concerns emerged that would prevent licensure. Injection site reactions (ISRs) are common after the injection of rilonacept. The ISRs are mild to moderate in severity. ISRs last approximately one day for most subjects and do not require medication therapy. The one potential risk is infection. There were no serious infections seen in the pivotal trial. In the open label extension, however, there was one death secondary to streptococcal meningitis. Another patient in the clinical program developed an opportunistic infection from mycobacteria intracellulare. Therefore, use of rilonacept is associated with a risk of serious infections. In addition, there is a possibility that off-label use of rilonacept that involves the concomitant use of other immune modulators may synergistically increase the risk of infectious complications.

The report of a second death in a young patient in the open-label study is concerning, since there are now two deaths in an exposed CAPS population of less than 100 patients. There are no natural history or epidemiology reports on CAPS to know the prevalence of premature sudden death. At this time, however, mechanistically there is no information on this latest fatality to suggest a role for rilonacept. Specifically there was no preceding infection reported. Systemic hypersensitivity has not been seen within the safety database of rilonacept exposed patients. Additionally no disparities were seen between placebo and study drug in regards to chest pain, myocardial infarction, arrhythmias, or pulmonary embolus. This second death, therefore, does not change this reviewer's recommendation for licensure.



## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Arcalyst, generic name rilonacept, is an interleukin-1 (IL-1) antagonist. Rilonacept is a fusion protein that consists of the human IL-1 receptor extracellular domains and the Fc portion of human IgG1. This new molecular entity binds IL-1 thereby inhibiting the cytokine. Rilonacept is administered subcutaneously.

In early development rilonacept was studied in other inflammatory diseases including rheumatoid arthritis and osteoarthritis.

CAPS is an Orphan disease with too few patients available to conduct two independent randomized clinical trials. Therefore, one pivotal trial was performed. This trial analyzed the same study population, first in a double-blind, placebo-controlled phase (Part A), and then in a withdrawal phase (Part B) after re-randomization, when all subjects had been on rilonacept for 9 or 15 weeks. A total of 47 CAPS patients were studied in the pivotal trial. An additional 42 subjects with CAPS were studied in the development program. In all 600 subjects have been treated with rilonacept. A total of 85 and 65 subjects have been treated at the 160 mg dose for 6 months and one year, respectively.

The clinical program has a number of ongoing trials in other auto-inflammatory diseases and a number of diseases where inflammation is part of the disease process including; Adult Still's, systemic juvenile idiopathic arthritis, coronary heart disease and gout.

### 1.3.2 Efficacy

Efficacy for CAPS was evaluated in a single pivotal trial with two parts including two separate randomizations. During a three week screening and baseline period CAPS subjects recorded their disease symptoms on Daily Health Assessment Forms (DHAFs). This form was used to produce a mean composite score, 0-10, on five key symptoms: feeling of fever/chills, rash, eye redness/pain, fatigue, and joint pain. A reduction in mean disease activity as measured by the DHAF was the primary endpoint. Part A was a double-blind placebo-controlled comparison of symptoms of CAPS during 6 weeks of treatment. The mean DHAF score for rilonacept treated patients decreased from 3.1 to 0.5, a change of -2.6. Subjects receiving placebo had a change of -0.3 in the mean DHAF score. This difference in change between groups (reduction in DHAF mean score) was statistically significant at  $p < 0.0001$ . This reduction in disease activity represents a significant clinical benefit to the rilonacept treated patients.

In Part B following a 9-week period when all subjects received rilonacept, subjects underwent a second randomization to assess the change in disease activity of subjects remaining on rilonacept compared to those switching to placebo. Prior to withdrawal, the mean DHAF scores of both treatment groups were low (means 0.2 and 0.3) and were similar. After rilonacept was

withdrawn, the mean scores of the placebo group increased from 0.2 to 1.2, a change of 0.9, while the group remaining on rilonacept had essentially no change in their mean scores ( $p < 0.0001$ ).

All secondary endpoints demonstrated a statistically significant benefit ( $p < 0.05$ ) in favor of rilonacept. Secondary endpoints included the mean number of disease flare days, mean number of single symptom disease flare days, and reduction in the mean maximum single symptom scores. In addition each individual symptom of the DHAF was evaluated.

All tertiary and exploratory endpoints tested demonstrated a statistically significant benefit ( $p < 0.05$ ) in favor of rilonacept. These tertiary endpoints included physician and patient global assessments, a decrease in the limitations on activities, and reductions in serum levels of the acute inflammatory phase reactants, C-reactive protein and serum amyloid A.

### 1.3.3 Safety

Six hundred patients have been exposed to rilonacept to date. 85 of these have had exposure greater than 6 months. No significant safety signals have emerged at this time. A significant number of patients (43% in the pivotal trial) develop injection site reactions (ISRs). ISRs are a common complication of biologic agents. In the pivotal trial these reactions were mild to moderate in intensity and self-limited without additional medication therapy.

Since rilonacept is an immune modulator, there is concern that treated patients may be at risk for infectious complications. In the pivotal trial in Part A more infections were seen in the rilonacept treated patients compared to the placebo group. The difference appeared to be due to more upper respiratory infections. An evaluation of these URIs in the rilonacept group did not indicate an increase in intensity or a prolonged recovery period. In the open-label trial there was one death from streptococcal meningitis. In another trial a patient with Adult Still's developed an opportunistic infection, mycobacteria intracellulare bursitis. No increased incidence rate for serious infections was noted when comparing rilonacept to placebo treated subjects, when all controlled trials of rilonacept were aggregated.

Overall, the safety profile for rilonacept indicates a favorable risk-benefit relationship that in the CAPS population is satisfactory for licensure.

### 1.3.4 Dosing Regimen and Administration

The proposed dose is a loading dose of 320 mg followed by 160 mg weekly administered subcutaneously. This dose is effective, although the safety and efficacy of lower doses or longer dosing intervals in the CAPS population have not been evaluated.

### 1.3.5 Drug-Drug Interactions

As a large biologic protein, rilonacept should not interact with other small molecule drugs. Therefore, formal drug-drug interaction studies are not warranted and were not performed. Since

a synergistic increase in the incidence of serious infections has been seen with the combination of anakinra, another IL-1 blocker, and TNF blockers, coadministration of rilonacept with TNF blockers should be avoided.

### 1.3.6 Special Populations

Rilonacept is effective in both sexes, and elderly patients. The elimination of rilonacept should not be significantly impacted by hepatic and renal disease.

Six pediatric CAPS patients, ages 12 to 16, have been administered the drug in the open-label extension. The dose is weight based, 2.2 mg/kg, not to exceed the adult dose of 160 mg. The mean trough level in 4 subjects was 20 µg/mL. This result was comparable to the mean adult trough level of 24 µg/mL. Exposure ranged from 12 to 40 weeks. The pediatric subjects have demonstrated favorable responses, similar to adult subjects. The reported adverse reactions were comparable to adult subjects. Injection site reactions were common at 3/6 subjects, while one subject reported upper respiratory congestion.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

The Applicant has proposed the name Arcalyst as the trade name and rilonacept as the generic name for their product. Rilonacept, a new molecular entity, is an immune modulator. It is a fusion protein that consists of the human IL-1 receptor extracellular domains and the Fc portion of human IgG1. Both extracellular portions of the IL-1 receptor, IL-1 R1 and the receptor accessory protein, are contained in the structure of rilonacept. Rilonacept binds IL-1 $\alpha$ , and IL-1 $\beta$  with high affinity. Rilonacept binding subsequently blocks IL-1 activity and the downstream signaling involved in an autoinflammatory disease such as CAPS.

### 2.2 Currently Available Treatment for Indications

There are no approved medications for the treatment of CAPS.

### 2.3 Availability of Proposed Active Ingredient in the United States

The Sponsor, Regeneron, is the sole manufacturer of the active ingredient. Since there are only 200-300 patients in the United States with CAPS, sufficient product should be available.

### 2.4 Important Issues With Pharmacologically Related Products

Rilonacept is an immune modulator, inhibiting a cytokine that signals many inflammatory processes. Therefore, as with most immune modulators, subjects may be at increased risk for infectious complications. There is some evidence for an increased risk of malignancy,

specifically of the hematopoietic system, for example lymphomas, with drugs that inhibit another cytokine, tumor necrosis factor.

There is one approved medication, anakinra, which also inhibits IL-1. To date there have been reports of opportunistic infections with anakinra, but no clinical evidence for increased cancer rates.

## **2.5 Presubmission Regulatory Activity**

### **SPA Review: 11/18/2005**

In general, the Division agreed with the trial design for the pivotal trial, but communicated several concerns to the Applicant. The protocol (IL-T-AI-0505.0) was entitled, "A Multicenter Double-blind, Placebo-controlled, study of the Safety, Tolerability, and Efficacy of IL-1 Trap in Subjects with *CIAS1* Associated Periodic Syndromes (CAPS) Using both Parallel Group and Randomized Withdrawal Designs." The trial contained two randomizations within the trial, thereby allowing two independent assessments of efficacy. After a three week-baseline period, patients would be randomized to treatment with study drug or placebo for 6 weeks. The efficacy analysis would compare symptoms during the last half (3 weeks) of the treatment period. For the next nine weeks placebo subjects would cross over to single-blind (patient only) active treatment, while active subjects remained on study drug. After this additional 9 weeks, all remaining subjects would then undergo randomized withdrawal for an additional 9 weeks. Again the last 3 weeks of this time period would be used for the efficacy analysis. The primary outcome measure is a composite score of CAPS signs and symptoms. The proposed primary analysis was acceptable. The Division communicated that the data as a whole would be evaluated for efficacy and not only the achievement of a certain p-value. While a responder analysis might not demonstrate efficacy due to the small sample size, one would be performed as a secondary endpoint. Subjects must have *CIAS1* mutations to be enrolled into the trial. Subjects must have more than the proposed greater than 1 of 21 days with baseline measurements to be enrolled. The fever assessment (10-point VAS) was not felt to be adequate and needed more definition. A clarification was requested as to whether the last 21 days were to be those with diary entries or the last three weeks of the defined efficacy period. A new Special Protocol Amendment was to be submitted to address the above issues.

### **EOP2 Meeting (Type B CMC): February 16, 2006**

The Applicant acknowledged that their Phase 3 study had begun prior to reaching agreement on a recently submitted SPA. It is this reviewer's interpretation that the Applicant wanted to start the trial in the cold winter months believing that this time represented the peak disease activity for the subjects that were being enrolled into the trial.

The Division raised concerns about potential bias because of the method of blinding. Subjects mix their drug for subcutaneous administration within a closed box and are told not to look

inside. This issue will need to be addressed to insure that the study is adequate and well-controlled.

At this meeting many CMC issues were addressed. The Applicant developed a new manufacturing process referenced as Process B compared to Process A. The Applicant was informed that full comparability data (including \_\_\_\_\_) would be required before using the Process B drug product in trials. Stability data would also be required. Antibody level comparisons within subjects receiving both products and between subjects receiving different products would also need to be carried out. The Division also requested that process validation studies for removal of impurities be submitted for the to-be-marketed product. At the time of this meeting an immunogenicity assay was still under development.

### **Review to Determine Fast Track Development Program: April 7, 2006**

The Division granted the development program fast track designation. CAPS patients have increased morbidity defined as severe impairment in patients' activities of daily living. The drug in open-label studies demonstrated marked improvement in physical symptoms and laboratory parameters. Anakinra, an IL-1 antagonist, has also shown clinical activity in CAPS patients. The drug development program was assessing a serious aspect of the disease via the primary endpoint (reduction of 5 core signs and symptoms). Finally there is no accepted/approved treatment for CAPS.

### **Pre-BLA: 9/19/2006**

The Division stated the requirement that the BLA submission must include one-year safety data. A BLA submission with just 6 months data followed with the one-year data at the time of the safety update would not be a complete submission.

The Safety data is to be organized into 4 Tiers. Tier one is to include the Pivotal Study Part A. Tier 2 is to include all data from CAPS patients. Tier 3 is to include all subjects from all completed studies excluding healthy volunteers. The Division requested and the Applicant agreed to specify that Tier 4 would compare all patients treated with IL-1 Trap to subjects receiving placebo.

Since IL-1 Trap is an Orphan Product pediatric studies are not required under PREA. The Division, however, encouraged the Applicant to perform pediatric studies since it is likely that post-approval the drug would be used in pediatric patients. Specifically, the Division suggested a trial in Neonatal Onset Multi-system Inflammatory Disease (NOMID). The Applicant informed the Division that IL-1 Trap has been administered to 20 pediatric patients including 6 open-label CAPS patients. Information on pediatric use may in principle be included in the product label. The Applicant also agreed to provide a detailed safety monitoring plan with the submission.

At the time of the meeting the Applicant was still working on a new binding antibody assay including a neutralizing antibody assay. The Applicant did commit to providing a validation

package within the BLA review cycle. The binding assay

Pharmacokinetic analyses will pool CAPS subjects with subjects from other trials. Currently there are 4 SOPs for the assay. These assays will each be used to evaluate all samples and report differences and similarities to the Division. Trough level data will be provided including pediatric patients.

The Division agreed to a rolling BLA submission and the Applicant stated that it would not pursue a Pilot 1 program. The Clinical Team detailed the analyses and tables to submit with the BLA and the Applicant agreed to provide them.

### **Pre-BLA CMC Quality Module 3: 12/12/2006**

The Applicant understood that all available — validation data would be submitted with the CMC reviewable unit. The shelf-life of the product would be determined after the stability data was reviewed by the Division. The assays that were to be used for characterization and for future comparability studies should be well qualified with controls. Finally, the Applicant understood that the manufacturing facilities were to be ready for inspection at the time of the submission of the final reviewable unit.

**Proprietary Name Review:** DMETS review finds that the proprietary name, Arcalyst, is presently acceptable and communicated to the Applicant on 4/9/2007.

## **3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES**

### **3.1 CMC (and Product Microbiology, if Applicable)**

A number of CMC issues remain open at the writing of this primary review. Manufacturing control processes are still being reviewed. Immunogenicity assays remain under review. Extractable and leachable data from product-contact materials are under review. In order to ensure consistency in drug product administration, data supporting consistency in withdrawable drug product volume from the drug product vial is needed. See the primary review for a detailed review and conclusions on these issues.

### **3.2 Animal Pharmacology/Toxicology**

The non-clinical pharmacology/toxicology review has identified toxicity issues for reproductive toxicology and growth. In the Segment I studies in the surrogate mouse model there was early resorption of embryos and lower female and male fertility indices. In the Segment II cynomolgous monkey model an increase in fetal death and skeletal abnormalities were seen in treated versus control animals. In Segment III studies using the surrogate mouse model animals had decreased estrogen levels and decreased learning behavior.

Injection site reactions were common in the monkey models. The histopathology demonstrated findings consistent with a local inflammatory reaction with infiltration of neutrophils, macrophages, lymphocytes and eosinophils.

Preclinical studies did not identify any evidence for rilonacept to induce EKG changes. In a 6-month intravenous toxicity study with doses of rilonacept up to 100 mg/kg once every two weeks in male and female cynomolgus monkeys (IL1T-TX-03050) and in a 26-week subcutaneous toxicity study with doses of rilonacept up to 60 mg/kg three times per week in male and female cynomolgus monkeys (IL1T-TX-03021), no treatment-related changes in ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc interval [Fridericia formula]) were found and no arrhythmias reported. Rilonacept is a large molecule with a molecular weight of about 250 Kd. Large molecules (e.g. antibodies) have not been known to interact with cardiac ion channels.

See the primary review by the pharm-tox reviewer, Mamata De, for detailed reports on the above toxicology concerns.

#### 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

##### 4.1 Sources of Clinical Data

The data used to conduct this review included the clinical trials conducted by the Applicant and the natural history trial conducted by the NIH.

##### 4.2 Table of Clinical Studies

Study #	Phase	Subject Population	Number Enrolled and Treated	Number Treated with Rilonacept	Dosage and Route of Administration of Study Drug	Treatment Duration
IL1T-AI-0505	3 Pivotal	CAPS (FCAS/MWS)	89	89	Multiple SC injections: Placebo & 160 mg	≤88 weeks ongoing
IL1T-AI-0406	1	Auto-Inflammatory Diseases (FCAS/ MWS/ FMF/ Adult Still's Disease)	10	10	Multiple SC injections: 100, 160, & 320 mg	105 weeks ongoing
IL1T-RA-0102	2	Active Rheumatoid Arthritis	201	145	Multiple SC injections: Placebo, 25, 50, & 100mg	12 weeks

IL1T-RA-0401	1	Normal volunteers	103	71	Single SC injection Placebo, 50, 80, 104, 120, 160, 240, & 320 mg	Single dose
IL1T-RA-0402	1	Normal volunteers	28	20	Single IV infusion: 100, 300, 1000, & 2000mg	Single dose
IL1T-RA-0004	2b	Rheumatoid Arthritis	107	82	Part A, Single injections Part B, Multiple SC injections: Placebo, 50, 100, 200, 400, & 800mcg/kg	≤6 weeks
IL1T-RA-0408	2a	Active Rheumatoid Arthritis	26	25	Multiple IV infusions: Placebo, 1000, & 2000mg	≤24 weeks
IL1T-RA-0409	2a	Active Rheumatoid Arthritis	25	24	Multiple SC injections: Placebo, 240, & 320mg	≤24 weeks
IL1T-RA-0404	2b	Active Rheumatoid Arthritis	3	2	Multiple SC injections: Placebo, 160, & 320mg	≤11 weeks
IL1T-RA-0111	1b	Active Rheumatoid Arthritis	30	14	Multiple SC injections: Placebo, & 100 mg	6 weeks
IL1T-OA-0425	2a	Osteoarthritis	79	38	Single IV infusion: Placebo, & 2000mg	Single dose
IL1T-CV-0503	2a	History or Risk of Atherosclerotic Coronary Artery Disease	35	26	Single or multiple SC injections: Placebo, 80 mg, & 320 mg	≤18 weeks
IL1T-AI-0504	1	Active Systemic Juvenile Idiopathic Arthritis	24	24	Multiple SC injections: Placebo, 2.2mg/kg, & 4.4mg/kg (up to 320 mg)	4 weeks double-blind, 96 weeks ongoing
/	2a	/ /	14	14	Multiple SC injections: Placebo, & 320mg	≤26 weeks
/	1	/ /	6	6	Single SC injection: 160mg	Single dose

Clinical Review  
 Keith K. Burkhart, MD  
 BLA 125249  
 Arcalyst™ (Rilonacept)

IL1T-RA-0608	1	Chronic Active Gout	10	10	Multiple SC injections: Placebo, & 160mg (320 mg loading dose)	6 weeks
Total			790	600		

### 4.3 Review Strategy

This review focused upon the pivotal trial, IL1T-AI-0505, of rilonacept for the treatment of the signs and symptoms of CAPS to determine efficacy. The integrated safety dataset from all trials was analyzed to evaluate safety.

The primary review team included;

Biometrics: Ruthi Davi

Clinical Pharmacology: Lei K. Zhang

Pharmacology/Toxicology: Mamata De

Product Reviewers: Ruth Cordoba-Rodriguez

Gurpreet Gill-Sangha

Facility Reviewers: Bo Chi

Michelle Clark-Stuart

### 4.4 Data Quality and Integrity

The Division of Scientific Integrity was asked to audit four sites that were selected based upon two factors, high enrollment or high response rates in favor of the study drug.

Indication(s)	Protocol #	Site (Name and Address)	Number of Subjects
CAPS	ILIT-AI-0505	Martin Throne, MD Radiant Research, Atlanta 1100 Lake Hearn Drive, Suite 360 Atlanta, GA 30342	7
CAPS	ILIT-AI-0505	Eugene Boling, MD Boling Clinical Trials 510 N. 13 <sup>th</sup> Avenue, Suite 302 Upland, CA 91786	5
CAPS	ILIT-AI-0505	Michael Noss, MD Radiant Research 11500 N. Lake Drive, Suite 320 Cincinnati, OH 45249	3
CAPS	ILIT-AI-0505	Ronald Fogel, MD Clinical Research Institute of Michigan, LLC 30795 23 Mile Road, Suite 207 Chesterfield, MI 48047	3

The DSI report concluded that the data generated at the above clinical sites appeared acceptable for use in support of the BLA.

#### **4.5 Compliance with Good Clinical Practices**

All studies were conducted in compliance with Good Clinical Practices.

#### **4.6 Financial Disclosures**

The Applicant attested to not having any financial arrangements with investigators that raised any concerns for potential conflicts of interest.

### **5 CLINICAL PHARMACOLOGY**

#### **5.1 Pharmacokinetics**

The pharmacokinetics was determined in healthy subjects. The bioavailability of rilonacept is about 43%. The half-life of rilonacept is approximately 6-8 days.

There was a process formulation change that occurred between the single-blinded phase of Part B and the randomized withdrawal phase of Part B of the pivotal trial. The 90% confidence interval analysis of the trough concentration ratios (at Week 9) and the paired t-test suggested that trough levels were comparable between the two products. The process change did not impact drug efficacy (Section 6).

In the pivotal study, mean trough levels of total rilonacept at steady-state was approximately 24  $\mu\text{g/mL}$  in adults (n=48) and 20  $\mu\text{g/mL}$  for pediatrics (n=4). Steady state trough concentrations were similar between male and female subjects, and the mean trough concentrations in elder patients (age  $\geq 65$ ) were about 30% lower than the younger patients (age  $< 65$ ).

As with all therapeutic proteins, rilonacept has the potential to induce an immune response. 43% of subjects tested positive for treatment-emergent binding antibodies on at least one occasion during the 48 week treatment during the pivotal study and its open-label extension. Although some subjects who tested positive to antibody showed a decrease in exposure, overall, there was no clear trend between antibody titer to the exposure of rilonacept possibly due to large inter-individual variability of trough concentrations.

Although not studied the concomitant use of rilonacept and other immune modulators such as TNF inhibitors or anakinra should be avoided due to the potential increased risk for serious infections. As a large biologic protein, rilonacept should not alter the metabolism of other drugs.

For an in-depth review see the primary review by Lei Zhang.

## 5.2 Pharmacodynamics

C-reactive protein and serum amyloid A are acute phase reactants. They are markers of inflammation, not necessarily specific for CAPS. These markers were studied as tertiary endpoints in the pivotal trial. The serum levels of C-reactive protein and serum Amyloid A were reduced while subjects were on rilonacept. A review of individual subjects suggests that the fall in serum levels correlates with the resolution of the signs and symptoms of CAPS.

## 5.3 Exposure-Response Relationships

Only one dose of rilonacept for CAPS has been tested, so there is inadequate information to reach conclusions about the exposure-response relationship. In addition improvement in symptoms, was so large and uniform that it would be difficult to find exposure-response relationships.

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

The indication for rilonacept proposed by the Applicant is for the \_\_\_\_\_ treatment \_\_\_\_\_, of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

### 6.1.1 Methods

The efficacy review analyzed the single phase 3 study in CAPS patients; Study IL1T-AI-0505: A Multi-center, Double-blind, Placebo-controlled Study of the Safety, Tolerability, and Efficacy of Rilonacept in Subjects with Cryopyrin-Associated Periodic Syndromes (CAPS) Using Both Parallel Group and Randomized Withdrawal Designs – Part A and B. This was the only trial in the development plan that specifically tested rilonacept in patients with CAPS.

### 6.1.2 General Discussion of Endpoints

The primary endpoint for the CAPS pivotal trial was a reduction in the signs and symptoms of the disease. There are no other approved drugs for the treatment of CAPS. Therefore there was no pre-established consensus study endpoint to use for the pivotal trial. A natural history study of CAPS over a period of 6 months was performed by the NIH. This study (IL1T-AI-0507) identified key clinical signs and symptoms that were impacted by the level of disease activity. Five of these were used to create a composite endpoint for scoring. These five symptoms were rash, fatigue, joint pain, feeling of fever/chills, and eye redness/pain.

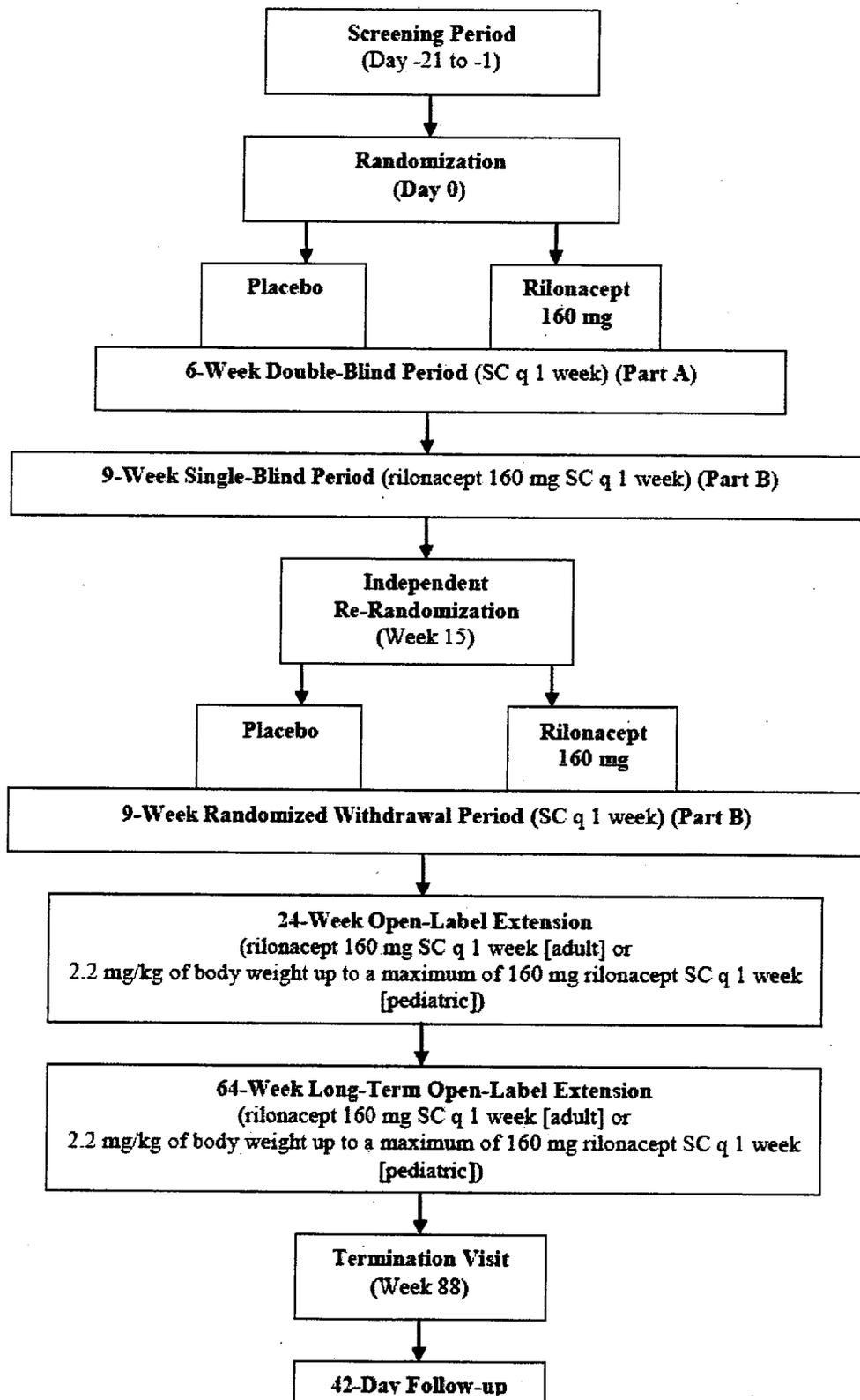
The Applicant originally proposed to use the reduction of two acute phase reactants, C-reactive protein and serum amyloid A, as primary endpoints. While these serum tests may be surrogate markers, they have not been validated. While significant reductions in these biomarkers may occur with treatment, a correlation with clinical benefit may not necessarily follow. Changes in the acute phase reactants were therefore to be analyzed as secondary or tertiary endpoints.

Additional secondary endpoints include analyses of the number of disease flare days over the final three weeks of drug treatment. Since some patients have single symptom disease flares, another secondary endpoint analyzed single symptom disease flare days. Another secondary endpoint compared the maximum score for any single symptom and the change with therapy. Taken as a whole these secondary endpoints also contribute to understanding the clinical benefit of therapy for CAPS.

### 6.1.3 Study Design

The pivotal trial, Study IL1T-AI-0505, was a two-part controlled trial in patients with CAPS. Part A was a randomized, double-blind, placebo-controlled trial designed to assess the efficacy, safety, and tolerability of weekly subcutaneous (SC) doses of 160 mg of rilonacept in adult subjects with active CAPS. Part B was a randomized, double-blind, placebo-controlled withdrawal in the same subjects. CAPS is a rare genetic disease with a small population of subjects available to enroll into randomized clinical trials. Therefore, the Division agreed to the aforementioned study design that included two separate randomizations in one trial, since it would be impossible to enroll subjects into two separate trials (**Figure 1**). Part A randomized subjects (1:1) into either rilonacept treatment or the control placebo group. This randomization followed a 21 day screening period that determined average baseline disease activity. Part A of the study lasted 6 weeks. The final 3-week period was scored like the 3-week screening period and the results were compared to baseline for the efficacy analysis. Part B of the trial began after the conclusion of Part A. The first nine weeks of Part B was a single-blind phase. All subjects were administered rilonacept. The last 3-week period was used to determine baseline disease activity on rilonacept. Subsequently subjects entered a randomized (1:1) withdrawal phase for another 9-week period. Similar to Part A the final 3-week period of Part B was compared to baseline for the efficacy analysis. This overall study design was determined to be consistent with FDA *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998, Section 3.a, “Multiple studies in a single study”).

**Figure 1: Study Design**



Subjects completed Daily Health Assessment Forms (DHAFs). The DHAF was designed in consultation with the Division (See Regulatory History). The DHAF assessed five key symptoms of CAPS; rash, fatigue, joint pain, feeling of fever/chills, and eye redness/pain (**Figure 2**). Each of the key symptoms was rated on a 21-point scale, 0 to 10 with 0.5 point measurements included. The total of all five symptom scores were divided by 5 to give a daily symptom score that could range from 0 (no symptoms) to 10 (most severe). The baseline score was the average of the available scores (maximum 21) during the 3-week screening period.

The original study plan was to analyze subjects separately who had more severe disease. Therefore randomization included stratification by disease activity at baseline. Stratum 1 included subjects with active CAPS as evidenced by a score of three or more in at least one key diary symptom during the 21-day baseline period. Stratum 2 (less severe) included all subjects with scores less than 3 at screening. Since only one Stratum 2 patient was enrolled, all patients were analyzed together.

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The entry criteria were adequate. The inclusion criteria (**Figure 3**) appropriately allowed a washout period for anakinra, another IL-1 antagonist. The exclusion criteria (**Figure 4**) were also appropriate to decrease the risk for infections from an IL-1 antagonist. Many illnesses that may have confounded the interpretation of the results were appropriately excluded.

### **Figure 3: Inclusion Criteria**

1. Adult ( $\geq 18$  years of age)

2. Diagnosis of FCAS, MWS based upon:

- Genetic evidence of mutation in *CIAS1* through analysis of subject or relative, and
- Classic signs and symptoms of CAPS

FCAS:

- Recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g., air conditioning) or both types of generalized cold exposure.

MWS:

- Syndrome of chronic fever and rash that may wax and wane in intensity; sometimes exacerbated by generalized cold exposure. This syndrome is sometimes associated with deafness or amyloidosis.

3. If taking anakinra, subjects were required to stop treatment following the informed consent procedure at the screening visit.

4. Must have been able to read, understand and complete the study-related questionnaires. Subjects must have completed their symptom diaries for  $\geq 11$  of 21 days.

5. Must have been able to read, understand and willing to sign the informed consent form and follow study procedures. Informed consent included permission to confirm mutation in *CIAS1* gene via DNA sequence analysis.

6. Must have been willing, committed and able to return for all clinic visits and complete all study-related procedures, including willingness to self-administer subcutaneous (SC) injections or have available a qualified person(s) to administer SC injections.

7. A woman was to be considered not of childbearing potential if she was postmenopausal for greater than 2 years or surgically sterile. Men and women of childbearing potential must be willing to utilize adequate contraception and not become pregnant (or have their partner become pregnant) during the full course of the study.

### **Figure 4: Exclusion criteria**

1. Treatment with a live (attenuated) virus vaccine during 3 months prior to baseline visit.
2. Current or recent treatment (less than 5 half lives) with a tumor-necrosis factor (TNF) inhibitor.
3. A positive intradermal skin tuberculin test (PPD 5 TU)  $\geq 5$  mm induration read at 48 to 72 hours and had:
  - a. An abnormal chest radiograph consistent with TB, whether or not previously treated with anti-tuberculosis agents or previously BCG vaccinated, OR
  - b. A normal chest radiograph with no documented prior prophylaxis for tuberculosis and was unwilling or unable to receive prophylaxis or therapeutic anti-tuberculosis treatments from their primary physician concurrently during the conduct of the study.
4. Testing is negative intradermal skin tuberculin test (PPD 5 TU)  $< 5$  mm induration read at 48 to 72 hours and had a history or a chest radiograph consistent with prior tuberculosis infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This did not include non-caseating granulomata.
5. A history of listeriosis, active tuberculosis, persistent chronic or active infection(s) requiring treatment with parenteral antibiotics, parenteral antivirals, or parenteral antifungals within 4 weeks, or oral antibiotics, oral antivirals, or oral antifungals within 2 weeks prior to the screening visit.
6. Significant concomitant illness such as cardiac, renal, neurological, endocrinological, metabolic, or lymphatic that would adversely affect the subject's participation or evaluation.
7. Active systemic inflammatory condition including rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, vasculitis, or myositis.
8. History of fibromyalgia or chronic fatigue syndrome.
9. Evidence of current HIV, hepatitis B, or hepatitis C infection by clinical or serological history.
10. History of malignancy other than a successfully treated non-metastatic cutaneous, basal, or squamous cell carcinoma and/or *in situ* cervical cancer within 5 years of the screening visit.
11. History of a de-myelinating disease or multiple sclerosis.
12. Severe respiratory disease, including, but not limited to severe bronchiectasis, chronic obstructive pulmonary disease, bullous lung disease, uncontrolled asthma, or pulmonary fibrosis.
13. Known hypersensitivity to Chinese hamster ovary (CHO) cell derived therapeutics or proteins or any components of rilonacept.

## 6.1.4 Efficacy Findings

### 6.1.4.1 Study Conduct

#### Baseline Characteristics:

All subjects were white and non-Hispanic (Table 1). This result stems from the genetic basis for the disease. All subjects were tested and found to be positive for the CIAS1 mutation.

A comparison of baseline demographics between the study drug and placebo groups did not identify clinically relevant imbalances between the groups. There was a preponderance of females enrolled into the trial which was unexpected, since CAPS is a genetic and not sex-linked disease the prevalence rate in the population is expected to be 50:50, not the 2:1 ratio seen in the trial.

**Table 1. Demographics for Randomized Subjects in Part A and B**

Trait	Part A Rilonacept N=23	Part A Placebo N=24	Part B Rilonacept N=22	Part B Placebo N=23
Age (years, mean +/- SD)	46 +/- 16	56 +/- 15	52 +/- 16	50 +/- 17
Female Gender N (%)	15 (65%)	16 (67%)	14 (64%)	16 (70%)
Race (White)	100%	100%	100%	100%
CIAS 1 Mutation Positive	100%	100%	100%	100%
Height (cm +/- SD)	168 +/- 8	169 +/- 7	170 +/- 9	167 +/- 6
Weight (kg, mean +/- SD)	72 +/- 15	76 +/- 17	76 +/- 18	74 +/- 14

The baseline disease activity for the rilonacept group averaged slightly higher than the placebo group. Out of a maximum score of 10, rilonacept averaged 3.1 compared to 2.4 for the placebo group. Compliance rates with recording daily scores were high, averaging 20 out of 21 days for both groups (Table 2). Likewise the baseline disease activity prior to Part B, the randomized withdrawal phase, was similar between the two groups (Table 3).

**Table 2. Baseline Disease Activity for Part A**

Screening DHAF Scores*	Rilonacept (N=23)	Placebo (N=24)
Mean 21 Day Average Score	3.1 +/- 1.9	2.4 +/- 1.5
(Minimum and Maximum)	(0.7, 8.2)	(0.6, 5.4)
Number of days (Max = 21)	20.0	20.2
(Minimum and Maximum)	(15, 21)	(16, 21)

Footnote: \*Range for DHAF Score is 0 to 10.

**Table 3. Baseline Disease Activity for Part B Randomized Withdrawal**

Baseline Scores	Rilonocept (N=22)	Placebo (N=23)
Mean 21 Day Average Score	0.3 +/- 0.3	0.2 +/- 0.4
(Minimum and Maximum)	(0, 1.0)	(0, 2.1)
Number of days (Max = 21)	20.3	20.4
(Minimum and Maximum)	(18, 21)	(13, 21)

Footnote: \*Range for DHAF Score is 0 to 10.

### Disposition

Overall, the withdrawal rate for the pivotal trial was low (Table 4). Only one subject withdrew or was removed from the study during each of the three phases, double-blind (Part A), single-blind and randomized withdrawal (Part B). All three withdrawals were subjects taking rilonocept at the time. See Section 7.1.3.2 for the detailed review of these subjects.

**Table 4. Disposition of Subjects in Parts A and B**

Disposition	RANDOMIZATION A		RANDOMIZATION B	
	Part A and Part B Single-Blind		Part B Randomized-Withdrawal	
	Rilonocept (n=23)	Placebo (n=24)	Rilonocept (n=22)	Placebo (n=23)
Completed	22	24	21	23
Withdrew for any reason	2 (8%)	0	1 (4%)	0
<b>Reason for Withdrawal</b>				
Adverse Event	0	0	1 (4%)	0
Noncompliance with protocol	1 (4%)	0	0	0
Decision by Investigator or sponsor	0	0	0	0
Request for withdrawal by the subject	0	0	0	0
Lost to follow-up	0	0	0	0
Other	1 (4%)	0	0	0
Death	0	0	0	0

### Protocol Deviations:

1. Eligibility waivers:
  - a. SID 018-9001 had baseline LFTs that were 2.2-2.3 X ULN. On repeat these became <2.0 X ULN, the defined eligibility criteria limit.
  - b. SID 010-9001 was enrolled despite history of SLE, as the disease was considered inactive.

- c. SID 025-9001 had a baseline platelet count of 132K/mm<sup>3</sup>. This result was within the normal range for the reference lab where the result was obtained.
  - d. SID 004-9002 had a PPD read 5 hours before the 48-72 hour window.
2. Drug dosing errors (Table 5):
- a. Single-blind phase: Three subjects continued placebo for the first week of the single-blind rilonacept phase. One subject missed the clinic visit and took the extra vial provided for such an event. Two other subjects were also administered the extra (placebo) vial rather than rilonacept.
  - b. Withdrawal phase: The randomization schedule for Part A was inadvertently used for Part B. This error resulted in 11 subjects receiving the wrong drug assignment for the first 3 weeks of the 9 week randomized withdrawal study, Part B. Subsequently, the error was corrected and for the final 6 weeks all subjects received their correct randomized drug assignment for Part B.

**Table 5. Incorrect Medication Use in the Study**

Subject ID	Study Days receiving incorrect treatment	Intended Treatment	Actual Treatment
001-6287	106 – 126	Placebo	Rilonacept
002-6379	106 – 126	Rilonacept	Placebo
004-6983	43 – 49	Rilonacept	Placebo
	106 – 126	Rilonacept	Placebo
006-6572	43 – 49	Rilonacept	Placebo
007-6456	106 – 126	Rilonacept	Placebo
007-6525	106 – 126	Rilonacept	Placebo
007-6632	109 – 129	Placebo	Rilonacept
007-6875	106 – 126	Placebo	Rilonacept
008-6334	106 – 126	Rilonacept	Placebo
011-6826	106 – 126	Placebo	Rilonacept
015-6060	43 – 49	Rilonacept	Placebo
	106 – 126	Rilonacept	Placebo
016-6997	106 – 126	Placebo	Rilonacept

**Compliance and Extent of Exposure**

- 1. Part A: Four subjects, two each rilonacept and placebo missed a single dose of study medication.

2. Single-blind phase: 41 of 46 subjects took all doses. The minimum number of doses taken was 6 out of 9 doses.
3. Part B: Subjects assigned to placebo did not miss any study doses. 15 of 22 rilonacept subjects took all doses. The mean number of doses taken was 8.4 out of 9. One subject only took one dose, while three subjects took 10 doses, one extra dose.

### Concomitant Medication Use during the Pivotal Trial

The use of concomitant medications was examined to determine if use may have confounded the efficacy results. There was a disparity between the groups in the use of concomitant medications during the 6-week randomization treatment period, Part A, (Table 6). 17/23 (74%) of the rilonacept subjects took analgesics and antipyretics compared to 9/24 (38%) for the placebo group. Anti-inflammatory use was higher in the rilonacept group compared to the placebo group, 8/23 (35%) and 6/24 (25%) respectively. Rilonacept subjects (9/23, 39%) also used multivitamin preparations at a rate higher than placebo subjects (2/24, 8%). Cough suppressant use was only by rilonacept subjects (5/23, 22%).

The difference in the use of concomitant medications was determined not to be related to rilonacept use. An analysis by the review team determined that randomization resulted in a difference in subjects taking these medications in the rilonacept compared to the placebo group beginning in the baseline period before initiation of treatment with study medication and continuing into Part A. While the increased use of antihistamines, anti-inflammatory agents, analgesics/antipyretics, multivitamins and cough suppressants might have been consistent with rilonacept patients treating common adverse events including viral syndromes and injection site reactions, these medications were used to treat the underlying CAPS symptoms beginning at baseline.

**Table 6. Concomitant Medication Class Used By 20% or more of Subjects in a group in Part A**

Medication Class and Preferred Term*	IL-1 Trap (n=23)	Placebo (n=24)
<b>ANY CONCOMITANT MEDICATIONS</b>	22 (96%)	22 (92%)
<b>OTHER ANALGESICS AND ANTIPYRETICS</b>	17 (74%)	9 (38%)
Tylenol	6 (26%)	3 (13%)
Aspirin	5 (22%)	1 (4%)
Advil	2 (9%)	1 (4%)
Nyquil	2 (9%)	0 (0%)
Tylenol arthritis	2 (9%)	0 (0%)
Bc headache	1 (4%)	1 (4%)
Ibuprofen	1 (4%)	1 (4.2%)
Alka-seltzer plus night-time	1 (4%)	0 (0%)
Anacin	1 (4%)	0 (0%)
Excedrin migraine	1 (4%)	0 (0%)

Midol	1 (4%)	0 (0%)
Neurontin	1 (4%)	0 (0%)
Salsalate	1 (4%)	0 (0%)
Tylenol extra-strength	1 (4%)	0 (0%)
Tylenol sinus	1 (4%)	0 (0%)
Acetylsalicylic acid	0 (0%)	1 (4%)
Asa	0 (0%)	1 (4%)
Naproxen	0 (0%)	1 (4%)
<b>ANTIINFLAMMATORY NON-STEROIDALS</b>	<b>8 (35%)</b>	<b>6 (25%)</b>
Ibuprofen	4 (17%)	2 (8%)
Advil	2 (9%)	3 (13%)
Aleve	1 (4%)	0 (0%)
Chondroitin w/glucosamine	1 (4%)	0 (0%)
Advil cold & sinus	0 (0%)	1 (4%)
Neurontin	1 (4%)	0 (0%)
Salsalate	1 (4%)	0 (0%)
Tylenol extra-strength	1 (4%)	0 (0%)
Tylenol sinus	1 (4%)	0 (0%)
Acetylsalicylic acid	0 (0%)	1 (4%)
Asa	0 (0%)	1 (4%)
Naproxen	0 (0%)	1 (4%)
Ibuprofen w/ pseudoephedrine hydrochloride	0 (0%)	1 (4%)
Lodine	0 (0%)	1 (4%)
Osteo bi-flex	0 (0%)	1 (4%)
<b>MULTIVITAMINS, PLAIN</b>	<b>9 (39%)</b>	<b>2 (8%)</b>
Multivitamin	9 (39%)	2 (8%)
<b>ANTIHISTAMINES: SYSTEMIC USE</b>	<b>6 (26%)</b>	<b>4 (17%)</b>
Zyrtec	1 (4%)	3 (13%)
Benadryl	1 (4%)	0 (0%)
Dramamine	1 (4%)	0 (0%)
Fexofenadine	1 (4%)	0 (0%)
Meclizine	1 (4%)	0 (0%)
Reactine	1 (4%)	0 (0%)
Desloratadine	0 (0%)	1 (4%)
Loratadine	0 (0%)	1 (4%)
Periactin	0 (0%)	1 (4%)
<b>COUGH SUPPRESSANTS EXCLUDES COMBINED WITH EXPECTORANTS</b>	<b>5 (22%)</b>	<b>0 (0%)</b>
Cough and cold preparations	1 (4%)	0 (0%)
Dayquil	1 (4%)	0 (0%)

Promethazine dm	1 (4%)	0 (0%)
Promethazine w/codeine	1 (4%)	0 (0%)
Tessalon perle	1 (4%)	0 (0%)

In the single-blind phase of Part B all subjects were placed on rilonacept for 9 weeks. Concomitant medication use became similar between the group continuing rilonacept compared to subjects starting rilonacept (Table 7). The rate of analgesic/antipyretic use for those subjects continuing on the rilonacept decreased to 15/22 (68%), while the placebo group starting rilonacept had the rate increase to 11/24 (46% from 38%). Anti-inflammatory and antihistamine use also became similar between the groups. There was no reported cough suppressant use. This result may reflect that the cough and cold season had ended when the single-blind phase began.

**Table 7. Concomitant Medication Class Use ( $\geq 20\%$ ) in Subjects During the Single-Blind Phase of Part B**

Medication Class and Preferred Term*	IL-1 Trap in Part A (N=22)	Placebo in Part A (N=24)
<b>ANY CONCOMITANT MEDICATIONS</b>	20 (91%)	23 (96%)
<b>ANALGESICS AND ANTIPYRETICS</b>	15 (68%)	11 (46%)
Tylenol	6 (27%)	3 (13%)
Aspirin	3 (13%)	2 (8%)
Advil	2 (9%)	1 (4%)
Tylenol arthritis	2 (9%)	0 (0%)
Bc headache	1 (5%)	1 (4%)
Ibuprofen	1 (5%)	1 (4%)
Alka-seltzer plus night-time	1 (5%)	0 (0%)
Anacin	1 (5%)	0 (0%)
Midol	1 (5%)	0 (0%)
Neurontin	1 (5%)	0 (0%)
Nyquil	1 (5%)	0 (0%)
Salsalate	1 (5%)	0 (0%)
Tylenol cold	1 (5%)	0 (0%)
Tylenol extra-strength	1 (5%)	0 (0%)
Tylenol sinus	1 (5%)	0 (0%)
Acetylsalicylic acid	0 (0%)	1 (4%)
Asa	0 (0%)	1 (4%)
Naproxen	0 (0%)	1 (4%)
Tylenol extra strength	0 (0%)	1 (4%)
<b>ANTIINFLAMMATORY NON-STEROIDALS</b>	6 (27%)	6 (25%)
Advil	2 (9%)	3 (13%)

Ibuprofen	2 (9%)	2 (8%)
Advil cold & sinus	1 (5%)	1 (4%)
Chondroitin w/glucosamine	1 (5%)	0 (0%)
Ibuprofen w/ pseudoephedrine hydrochloride	0 (0%)	1 (4%)
Lodine	0 (0%)	1 (4%)
Osteo bi-flex	0 (0%)	1 (4%)
<b>MULTIVITAMINS, PLAIN</b>	8 (36%)	2 (8%)
Multivitamin	8 (36%)	2 (8%)
<b>ANTIHISTAMINES: SYSTEMIC USE</b>	4 (18%)	4 (17%)
Zyrtec	1 (5%)	3 (13%)
Benadryl	1 (5%)	0 (0%)
Fexofenadine	1 (5%)	0 (0%)
Reactine	1 (5%)	0 (0%)
Loratadine	0 (0%)	1 (4%)
Periactin	0 (0%)	1 (4%)
<b>COUGH SUPPRESSANTS</b>	0 (0%)	0 (0%)

During the randomized withdrawal phase there were smaller differences in concomitant medication use between groups (Table 8). Analgesic and antipyretic use for rilonacept subjects was 13/22 (59%), while 12/23 (52%) placebo subjects used these medications. Anti-inflammatory use was higher in the rilonacept group, 7/22 (32%) vs 5/23 (22%) in the placebo group. Antihistamine use was also higher in the rilonacept subjects, 7/22 (32%) compared to 4/23 (17%) in the placebo subjects.

**Table 8. Concomitant Medication Class Use ( $\geq 20\%$ ) in Subjects During the Randomized Withdrawal Phase Part B**

Medication Class and Preferred Term*	IL-1 Trap (n=22)	Placebo (n=23)
<b>CONCOMITANT MEDICATIONS</b>	21 (96%)	21 (91%)
<b>ANALGESICS AND ANTIPYRETICS</b>	13 (59%)	12 (52%)
Tylenol	4 (18%)	5 (22%)
Aspirin	2 (9%)	2 (9%)
Bc headache	2 (9%)	0 (0%)
Ibuprofen	2 (9%)	0 (0%)
Tylenol arthritis	2 (9%)	0 (0%)
Advil	0 (0%)	2 (9%)
Tylenol extra-strength	0 (0%)	2 (9%)
Acetylsalicylic acid	1 (5%)	0 (0%)
Excedrin migraine	1 (5%)	0 (0%)
Neurontin	1 (5%)	0 (0%)

Alka-seltzer plus night-time	0 (0%)	1 (4%)
Anacin	0 (0%)	1 (4%)
Asa	0 (0%)	1 (4%)
Midol	0 (0%)	1 (4%)
Salsalate	0 (0%)	1 (4%)
Tylenol sinus	0 (0%)	1 (4%)
<b>ANTIINFLAMMATORY: NON-STEROIDALS</b>	<b>7 (32%)</b>	<b>5 (22%)</b>
Advil	3 (14%)	3 (13%)
Ibuprofen	3 (14%)	1 (4%)
Chondroitin w/glucosamine	1 (5%)	0 (0%)
Ibuprofen w/ pseudoephedrine hydrochloride	1 (5%)	0 (0%)
Motrin	1 (5%)	0 (0%)
Advil cold & sinus	0 (0%)	1 (4%)
Advil cold and sinus	0 (0%)	1 (4%)
Celecoxib	0 (0%)	1 (4%)
<b>ANTIHISTAMINES FOR SYSTEMIC USE</b>	<b>7 (32%)</b>	<b>4 (17%)</b>
Zyrtec	4 (18%)	0 (0%)
Loratadine	2 (9%)	0 (0%)
Reactine	0 (0%)	2 (9%)
Desloratadine	1 (5%)	0 (0%)
Fexofenadine	1 (5%)	0 (0%)
Periactin	1 (5%)	0 (0%)
Aerius	0 (0%)	1 (4%)
Benadryl	0 (0%)	1 (4%)
Claritin	0 (0%)	1 (4%)
<b>MULTIVITAMINS, PLAIN</b>	<b>5 (23%)</b>	<b>5 (22%)</b>
<b>COUGH SUPPRESSANTS</b>	<b>1 (5%)</b>	<b>1 (4%)</b>

#### 6.1.4.2 Study Results

##### Primary Efficacy Analysis

In Part A of the study efficacy was assessed by comparing changes in disease activity, as measured using the DHAF score, between rilonacept treated subjects compared to placebo. Rilonacept treated patients had a statistically significantly greater reduction in their DHAF scores (Table 9 and Figure 5). The average baseline DHAF score was compared to the final three week average score on therapy using a parametric ANCOVA main effects model. The mean DHAF score for rilonacept treated patients decreased from 3.1 to 0.5, a change of -2.6. Subjects receiving placebo had a change of -0.3 in the mean DHAF score. This difference in change between groups (reduction in DHAF mean score) was statistically significant at  $p < 0.0001$ . This

reduction in disease activity represents a significant clinical benefit to the rilonacept treated patients.

The subjects underwent a second randomization for the withdrawal phase of Part B. Prior to withdrawal, the mean DHAF scores of both treatment groups were low (means 0.2 and 0.3) and were similar. After rilonacept was withdrawn, the mean scores of the placebo group increased from 0.2 to 1.2, a change of 0.9, while the group remaining on rilonacept had essentially no change in their mean scores ( $p < 0.0001$ ). See Table 9 and Figure 6.

**Table 9. Primary Efficacy Analyses for Parts A and B**

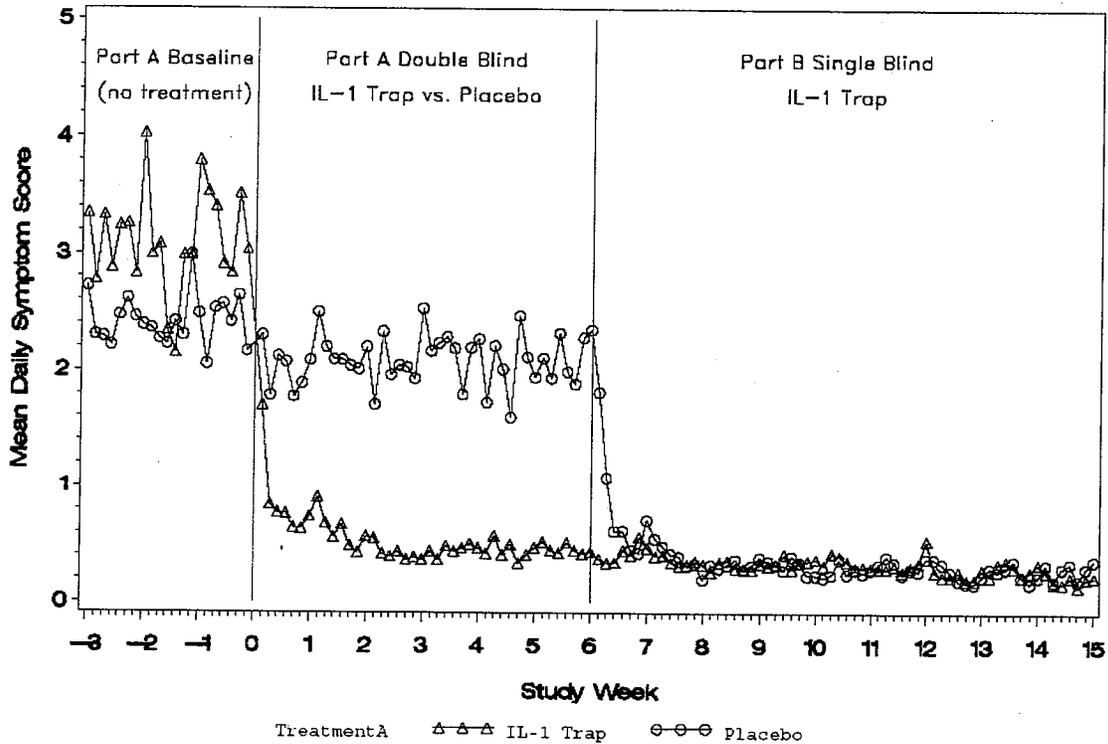
STUDY PHASE	TIME POINT	RILONACEPT MEAN +/- SD	PLACEBO MEAN +/- SD	COMPARISON P-VALUE*
Part A		N=23	N=24	
	Baseline	3.1 +/- 1.9	2.4 +/- 1.5	
	Endpoint	0.5 +/- 0.5	2.1 +/- 1.5	
	Change	-2.6 +/- 1.9	-0.3 +/- 0.7	<0.0001
Part B:		N=22	N=24	
Single-Blind	Baseline	0.5 +/- 0.5	2.1 +/- 1.5	
	Endpoint	0.3 +/- 0.3	0.3 +/- 0.4	
	Change	-0.2 +/- 0.4	-1.8 +/- 1.4	
Part B:		N=22	N=23	
Withdrawal	Baseline	0.3 +/- 0.3	0.2 +/- 0.4	
	Endpoint	0.4 +/- 0.5	1.2 +/- 1.0	
	Change	0.1 +/- 0.4	0.9 +/- 0.9	0.0002

Mean key symptom score derived from the: Daily Health Assessment Form (diary questionnaire); symptom scale is 0=none to 10=very severe.

The results are from the Intention to Treat population. Imputation method for missing data was Last Observation Carried Forward.

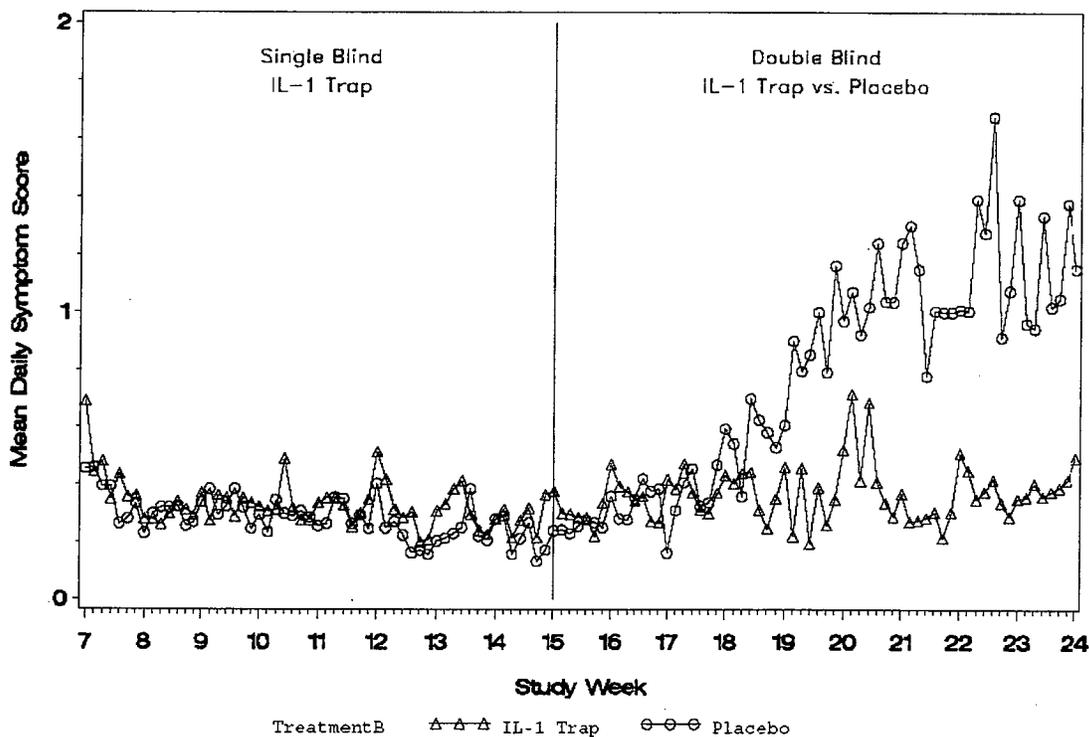
\* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment

**Figure 5. Mean Daily Key Symptom Score by Treatment Group from Week -3 to Week 15 in Study Part A and Part B Single-Blind Phase.**



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**Figure 6. Mean Daily Key Symptom Score by Treatment Group from Week 6 Part B Single-Blind Phase to Week 24 End of Study Part B Randomized Withdrawal Phase.**



The clinical benefit of riloncept appears after a single injection within a few days. (See Figure 5 Part A double blind phase, week 0 to 6). When the placebo group was switched to riloncept after week 6, their scores decreased in a similar manner in a few days. (Figure 5 Part B single blind, weeks 6 to 15). Once disease activity fell, it remained low, while subjects continued on q weekly riloncept. Because of the randomization error for the first 3 weeks, it is difficult to determine how long it takes before the benefit of riloncept dissipates. **Figure 6** suggests that some benefit may be lost as soon as one week. On the other hand, some benefit may persist for three weeks.

### Secondary Analyses

In order to further address the effect of riloncept on disease activity the Applicant performed several additional pre-specified secondary analyses. These secondary analyses included change in the mean number of disease flare days during the 21 day efficacy analysis period, change in the mean number of single-symptom disease flare days, and change in the mean maximum score for any single symptom (Table 10). All three secondary endpoints demonstrated reductions (improvements) for the riloncept group compared to the placebo group,  $p$  values  $< 0.0001$ . Specifically, the mean number of disease flare days for the riloncept group decreased from 8.6 to 0.1, while the placebo group decreased from 6.2 to 5.0.

The same secondary analyses were also assessed in Part B: randomized withdrawal. The mean number of disease flare days over the 21 day efficacy analysis period remained 0 for rilonacept, while the mean number for the placebo group increased to 1.9. Statistically significant differences ( $p \leq 0.01$ ) between rilonacept and placebo were also seen for these three secondary endpoints for Part B withdrawal phase (Table 11).

**Table 10. Results of Analysis of Secondary Endpoints for Part A.**

Assessment	Assessment Period	Rilonacept (n=23)	Placebo (n=24)	Comparison p-value*
Number of disease flare days	Baseline Part A	8.6 +/- 7.2	6.2 +/- 6.0	
	Endpoint Part A (Week 6)	0.1 +/- 0.5	5.0 +/- 6.1	
	Change	-8.4 +/- 7.1	-1.2 +/- 3.6	<0.0001
Single-symptom Disease Flare Days	Baseline Part A	13.2 +/- 6.0	11.6 +/- 7.3	
	Endpoint Part A (Week 6)	1.1 +/- 2.8	10.4 +/- 6.6	
	Change	-12.1 +/- 6.2	-1.3 +/- 4.1	<0.0001
Maximum Score for any Single Symptom	Baseline Part A	8.1 +/- 2.0	8.1 +/- 2.1	
	Endpoint Part A (Week 6)	2.7 +/- 2.5	7.6 +/- 2.3	
	Change	-5.4 +/- 2.8	-0.5 +/- 2.0	<0.0001

Footnote: \* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment

**Table 11. Results of Analysis of Secondary Endpoints for Part B.**

Assessment	Assessment Period	Rilonacept (n=22)	Placebo (n=23)	Comparison p-value*
Number of disease flare days	Baseline Part B (Week 15)	0 +/- 0	0.1 +/- 0.4	
	21 day period	0 +/- 0.2	1.9 +/- 3.1	
	Change	0 +/- 0.2	1.8 +/- 1.9	0.003

Assessment	Assessment Period	Rilonacept (n=22)	Placebo (n=23)	Comparison p-value*
Single-symptom Disease Flare Days	Baseline Part B (Week 15)	0.8 +/- 1.5	0.8 +/- 3.7	
	Endpoint Part B (Week 24)	2.1 +/- 4.4	6.3 +/- 7.1	
	Change	1.4 +/- 3.7	5.6 +/- 6.5	0.01
Maximum Score for any Single Symptom	Baseline Part B (Week 15)	2.5 +/- 2.2	1.5 +/- 1.3	
	Endpoint Part B (Week 24)	2.2 +/- 1.8	5.0 +/- 3.1	
	Change	-0.3 +/- 2.5	3.6 +/- 3.0	<0.0001

Footnote: \* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment

To address whether the positive results on the primary endpoint were driven by a single symptom or subset of the CAPS symptoms, the effects of rilonacept were analyzed on each component of the DHAF composite. The rilonacept group for each of the individual mean scores in Part A was found to have a statistically significant reduction from baseline compared to the placebo group; all p values  $\leq 0.0001$  (Table 12). Similarly during Part B, withdrawal phase, the placebo group had statistically significant increases in all the individual mean key symptom scores when compared to those subjects remaining on rilonacept (Table 13).

**Table 12. Change in Individual Key Symptom Scores in Part A.**

Key Symptom	Treatment Group Part A	Baseline Mean	Endpoint Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Feeling of Fever/Chills	Rilonacept (n=23)	3.0	0.4	-2.7	<0.0001
	Placebo (n=24)	2.0	1.7	-0.3	
Rash	Rilonacept (n=23)	4.0	0.5	-3.5	<0.0001
	Placebo (n=24)	3.5	3.3	-0.2	
Eye Redness/pain	Rilonacept (n=23)	1.7	0.2	-1.5	0.0001
	Placebo (n=24)	1.3	1.2	-0.1	
Fatigue	Rilonacept (n=23)	3.6	0.8	-2.8	<0.0001
	Placebo (n=24)	2.7	2.3	-0.5	
Joint Pain	Rilonacept (n=23)	3.1	0.5	-2.6	<0.0001
	Placebo (n=24)	2.6	2.0	-0.5	

Footnote: \* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment

**Table 13. Change in Individual Key Symptom Scores in Part B.**

Symptom	Treatment Group (Part B Randomization)	Baseline (Week 15) Mean	Endpoint (Week 24) Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Feeling of Fever/Chills	Rilonacept (n=22)	0.1	0.2	0.1	0.008
	Placebo (n=23)	0.1	1.1	1.0	
Rash	Rilonacept (n=22)	0.4	0.6	0.2	<0.0001
	Placebo (n=23)	0.4	2.3	1.9	
Eye Redness/pain	Rilonacept (n=22)	0.2	0.2	-0.0	0.03
	Placebo (n=23)	0.1	0.4	0.3	
Fatigue	Rilonacept (n=22)	0.5	0.5	-0.0	0.0005
	Placebo (n=23)	0.3	1.1	0.9	
Joint Pain	Rilonacept (n=22)	0.4	0.5	0.1	0.02
	Placebo (n=23)	0.3	0.9	0.6	

Footnote: \* comparison p-value is parametric ANCOVA main effects model with Part A Baseline mean KSS as covariate and treatment

The tertiary endpoints analyzed also demonstrate the clinical benefit of rilonacept. Both the physicians' and patients' mean global scores demonstrated a statistically significant clinical benefit for rilonacept compared to placebo Tables 14 and 15.

The serum levels of the acute phase reactants, C-reactive protein and serum amyloid A, are markers of inflammation, not necessarily specific for CAPS. The serum levels fell as the signs and symptoms of CAPS abated on rilonacept treatment (data not shown). The mean differences between rilonacept treated patients compared to placebo were statistically significantly lower at the study endpoint (Table 14). Statistically significant differences on these tertiary endpoints were again seen in Part B randomized withdrawal phase (Table 15).

**Table 14. Tertiary and Exploratory Measures of Efficacy (Physician's Global Assessment, Patient's Global Assessment, Limitation of Activities Assessment, C-Reactive Protein, and Serum Amyloid A)**

Symptom (Reference Range)	Treatment Group (Part A Randomization)	Baseline Mean	Endpoint Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Physician's Global	Rilonacept (n=23)	5.6	1.5	-4.2	<0.0001
	Placebo (n=24)	4.7	5.0	0.2	
Patient's Global	Rilonacept (n=23)	3.6	0.9	-2.7	<0.0001
	Placebo (n=24)	3.1	2.7	-0.4	

Symptom (Reference Range)	Treatment Group (Part A Randomization)	Baseline Mean	Endpoint Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Limitation of Activities	Rilonacept (n=23)	3.0	0.8	-2.2	0.006
	Placebo (n=24)	2.4	1.6	-0.8	
CRP (0.0 – 8.4 mg/L)	Rilonacept (n=23)	22.5	2.4	-20.1	
	Placebo (n=24)	29.7	28.4	-1.3	
SAA (0.7 – 6.4 mg/L)	Rilonacept (n=23)	60.4	3.8	-56.6	
	Placebo (n=24)	109.9	109.8	-0.1	

\*Comparison p-value is parametric ANCOVA main effects model with Part A Baseline variable as covariate and treatment. The p-value represents the between-group comparison for placebo vs rilonacept treatment. All comparison p-values are calculated from the mean change from Baseline.

**Table 15. Tertiary and Exploratory Measures of Efficacy for Part B (Physician’s Global Assessment, Patient’s Global Assessment, Limitation of Activities Assessment, C-Reactive Protein, and Serum Amyloid A)**

Parameter (Reference Range)	Treatment Group (Part B Randomization)	Baseline (Ending at Week 15) Mean	Endpoint (Ending at Week 24) Mean	Mean Change from Baseline to Endpoint	Comparison p-value*
Physician’s Global	Rilonacept (n=22)	1.3	1.4	0.1	<0.0001
	Placebo (n=23)	1.0	4.3	3.4	
Patient’s Global	Rilonacept (n=22)	0.5	0.7	0.2	0.003
	Placebo (n=23)	0.4	1.7	1.3	
Limitation of Activities	Rilonacept (n=22)	0.5	0.5	-0.0	0.05
	Placebo (n=23)	0.1	0.8	0.7	
CRP (0.0 – 8.4 mg/L)	Rilonacept (n=22)	2.7	2.6	-0.1	
	Placebo (n=23)	2.5	20.7	18.2	
SAA (0.7 – 6.4 mg/L)	Rilonacept (n=22)	4.5	4.2	-0.3	
	Placebo (n=23)	4.3	71.7	67.4	

\*Comparison p-value is parametric ANCOVA main effects model with Part A Baseline variable as covariate and treatment.

All comparison p-values are calculated from the mean change from Baseline.

The Applicant performed responder analyses at the request of the Division. A large and statistically significant difference in response rates was seen between rilonacept compared to placebo subjects in Part A (Table 16). In fact most rilonacept, 16/23 subjects, achieved a 75% improvement in their mean key symptom score, while no subject on placebo achieved this degree of improvement in Part A.

**Table 16. Responder Analysis: Rates of Improvement in Key Symptom Scores (KSS) from Baseline to Endpoint (Week 6) in Part A.**

Responders with Improvement in Mean KSS	Rilonacept (n=23)		Placebo (n=24)		Comparison with Fisher's Exact Test
	Number Responding	% Responding	Number Responding	% Responding	
≥ 30%	22	96%	7	29%	<0.0001
≥ 50%	20	87%	2	8%	<0.0001
≥ 75%	16	70%	0	0%	<0.0001

Demographic and disease subset analyses were performed to evaluate for gender, and age differences in the response to rilonacept (Table 17). Despite the smaller sample sizes, both male and female subset analyses demonstrated statistically significant differences for rilonacept compared to placebo. A statistically significant reduction in mean key symptom score for rilonacept compared to placebo was demonstrated for the subset based on age less than or greater than 50. Likewise for subsets of patients with lower and higher levels of disease activity (based upon the mean key symptom score), there was a statistical benefit in favor of rilonacept compared to placebo.

**Table 17. Demographic and Disease Severity Subgroup Analyses in Part A**

Symptom	Treatment Group (Part A Randomization)	Part A Baseline Mean	Part A Endpoint (Week 6) Mean	Mean (SD) Change from Baseline to Endpoint	Comparison p-value*
Males	Rilonacept (n=8)	2.8	0.3	-2.6 (1.7)	0.002
	Placebo (n=8)	2.7	2.4	-0.3 (1.0)	
Females	Rilonacept (n=15)	3.2	0.6	-2.6 (2.1)	<0.0001
	Placebo (n=16)	2.3	1.9	-0.3 (0.6)	
Age 51 years or older	Rilonacept (n=10)	2.6	0.6	-2.0 (1.6)	<0.0001
	Placebo (n=14)	2.4	2.1	-0.3 (0.6)	

Symptom	Treatment Group (Part A Randomization)	Part A Baseline Mean	Part A Endpoint (Week 6) Mean	Mean (SD) Change from Baseline to Endpoint	Comparison p-value*
Age < 51 years	Rilonacept (n=13)	3.5	0.4	-3.1 (2.1)	0.0006
	Placebo (n=10)	2.5	2.1	-0.4 (1.0)	
Part A Baseline Mean KSS < 2.4	Rilonacept (n=10)	1.4	0.3	-1.1 (0.6)	<0.0001
	Placebo (n=14)	1.4	1.2	-0.2 (0.5)	
Part A Baseline Mean KSS ≥ 2.4	Rilonacept (n=13)	4.4	0.6	-3.8 (1.8)	<0.0001
	Placebo (n=10)	3.8	3.3	-0.5 (1.0)	

\*Comparison p-value is parametric ANCOVA main effects model with Part A Baseline variable as covariate and treatment

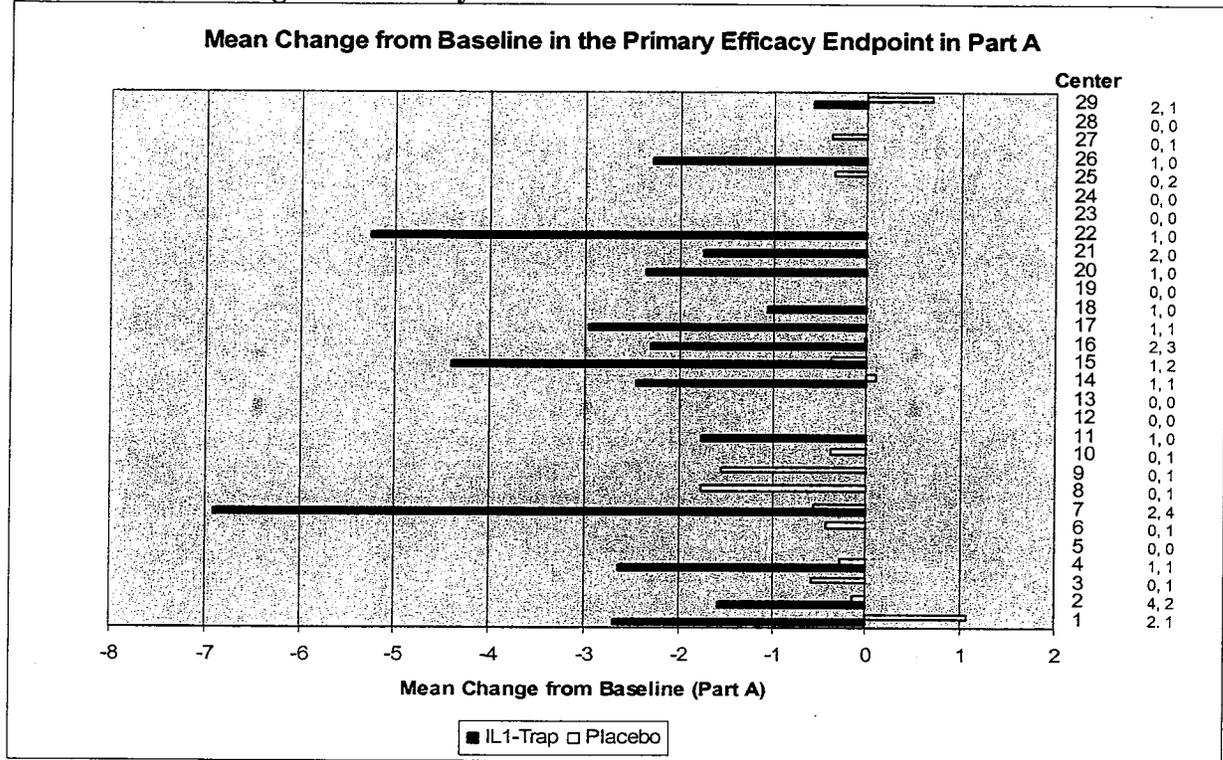
A biometric analysis was performed to see if any one site was responsible for confounding the results. The Sponsor enlisted many sites such that the patients were spread around at multiple sites throughout the country in both cold and warmer or moderate weather states (Table 18). While there was much variability regarding the mean change in scores in patients treated at different sites, there was no evidence that one center's results skewed the overall study outcome (Figure 7).

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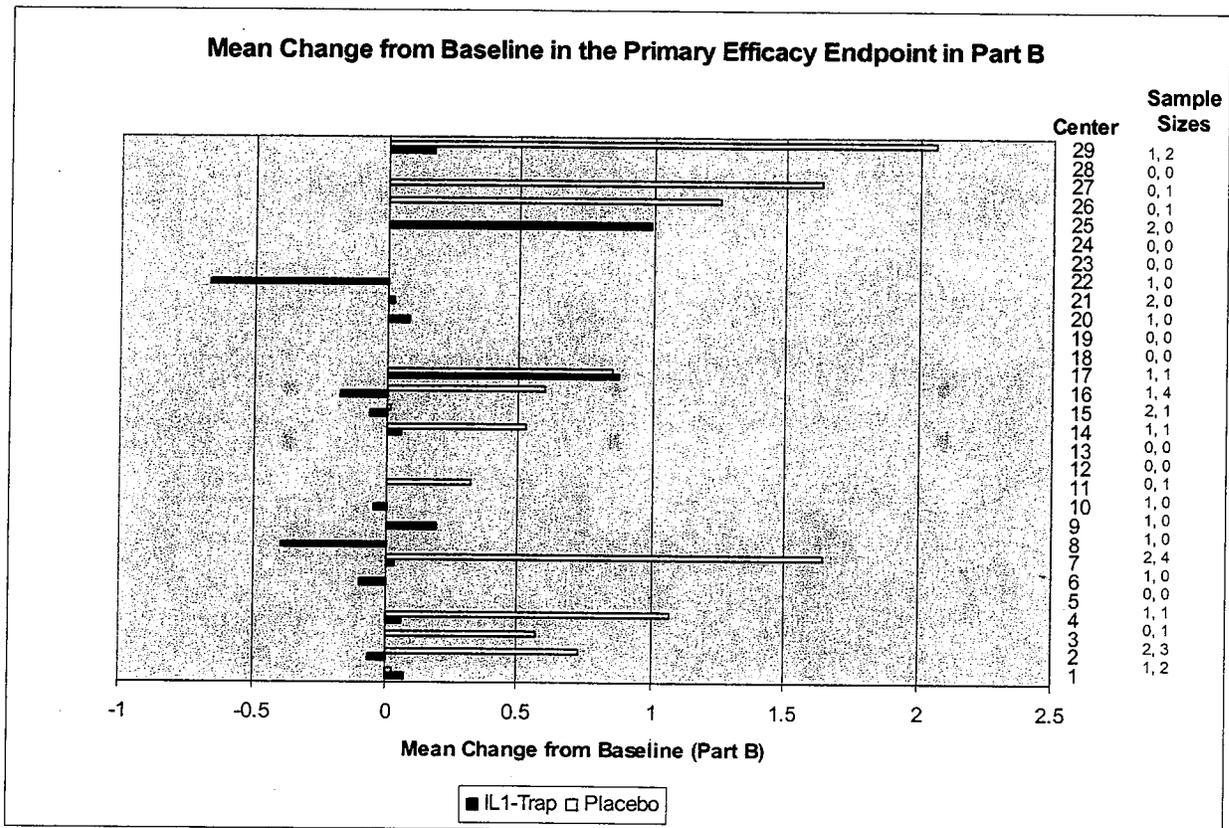
**Table 18. Individual Site enrollment**

Investigator Number	Stratum 1		Stratum 2		Total		
	Investigator	IL-1 Trap	Placebo	IL-1 Trap	Placebo	IL-1 Trap	Placebo
001	Michael Noss, MD, Cincinnati, OH	2	1	0	0	2	1
002	N.J. Amar, MD, Waco, TX	4	2	0	0	4	2
003	Arthur Kavanaugh, MD, LaJolla, CA	0	1	0	0	0	1
004	Bruce Berwald, MD, St. Louis, MO	1	1	0	0	1	1
005	Dennis Riff, MD, Anaheim, CA	0	0	0	0	0	0
006	John Rubino, MD, Raleigh, NC	0	1	0	0	0	1
007	Martin Throne, MD, Atlanta, GA	2	4	0	0	2	4
008	Robert Cartwright, MD, Columbus, GA	0	1	0	0	0	1
009	Wayne Larson, MD, Lakewood, WA	0	1	0	0	0	1
010	Darrell Fiske, MD, Stuart, FL	0	1	0	0	0	1
011	Alan Kivitz, MD, Duncansville, PA	1	0	0	0	1	0
012		0	0	0	0	0	0
013	Philip Toth, MD, Indianapolis, IN	0	0	0	0	0	0
014	Stephen Pollard, MD, Louisville, KY	1	1	0	0	1	1
015	F.L. Hamilton, MD, Chattanooga, TN	1	2	0	0	1	2
016	Eugene Boling, MD, Upland, CA	2	2	0	1	2	3
017	Maria Greenwald, MD, Palm Desert, CA	1	1	0	0	1	1
018		1	0	0	0	1	0
019	Harold A. Moore, MD, Columbia, SC	0	0	0	0	0	0
020	Santosh K Gill, MD, Aurora, IL	1	0	0	0	1	0
021	Stanley B. Cohen, MD, Dallas, TX	2	0	0	0	2	0
022	Lansing Ellsworth, MD, Cedar City, UT	1	0	0	0	1	0
023	Steven Mathews, MD, Jacksonville, FL	0	0	0	0	0	0
024	Wesley Robertson, MD, Forest, VA	0	0	0	0	0	0
025	Willard Washburne, MD, Shreveport, LA	0	2	0	0	0	2
026	Joe Hargrove, MD, Little Rock, AR	1	0	0	0	1	0
027	Susanna Goldstein, MD, New York, NY	0	1	0	0	0	1
028		0	0	0	0	0	0
029	Ronald Fogel, MD, Chesterfield, MI	2	1	0	0	2	1
030		0	0	0	0	0	0
<b>Subtotal</b>		<b>23</b>	<b>23</b>	<b>0</b>	<b>1</b>	<b>23</b>	<b>24</b>

Figure 7. Mean Change in Scores by Site



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### 6.1.5 Clinical Microbiology

Not applicable.

### 6.1.6 Efficacy Conclusions

The Applicant has provided substantial evidence for a significant clinical benefit for rilonacept in reducing the signs and symptoms of CAPS.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### 7.1.1 Deaths

There were no deaths during the pivotal trial, Part A or B. One death occurred in the open-label extension study. A 71 yo female died as a result of streptococcal pneumoniae meningitis. Her

PMH was significant for hypertension, cardiac arrhythmia, meth-resistant staph aureus cellulitis, seasonal allergic rhinitis, arthritis, and basal cell carcinoma. The subject participated in the CAPS trial receiving riloncept during the Part A double-blind phase and placebo during Part B withdrawal phase. She then participated in the open-label 24-week study and started the long-term trial, having completed one month of this continued riloncept therapy on 04/16/2007. The patient's concomitant medications included aspirin 81 mg po prn anticoagulant, salicylate 750 mg po TID, MVI qd, Tums, po qd, NTG prn chest pain, Desonide CR topically prn and pseudoephedrine prn allergic rhinitis. On 4/15/2007 the patient had signs and symptoms of a URI (non-productive cough and runny nose). On — the husband found the patient unresponsive. In the ED she was immediately intubated and transferred by helicopter to another hospital. There a lumbar puncture was performed that confirmed meningitis. A head CT documented maxillary and ethmoid sinusitis as a possible source. Decadron was initiated and antibiotics were started including clindamycin, ceftriaxone, vancomycin, and Zyvox. The patient's course seemed to improve including extubation, but the Investigator reported her death on — This death is considered probably related to the immuno-suppression from riloncept therapy.

#### 7.1.2 Other Serious Adverse Events

During the pivotal trial there was one serious adverse event reported. Subject 017-6405, a 62-year old white female was hospitalized for sciatica. She had a previous history of sciatica since 2003. The subject was allocated to placebo during Part A and developed worsening low back pain with sciatica after the first dose of riloncept in the Part B single-blind phase. Her concurrent medications included Advair, Prilosec, Tricor, albuterol, hydroxyzine, Lodine, Osteo Bi-Flex, Vitamin C, Vitamin A, B Complex, Black Cohosh, Vitamin E, Lotrisone cream, Vicodin, Tylenol. Her hospitalization was for an elective lumbar decompression and fusion at vertebrae positions L4 through L5. She had an uncomplicated course in the hospital and continued in the study. The Investigator judged the event not related to study drug.

In Tier 4, all controlled trials with a placebo group, the overall reported rate of SAEs was similar between riloncept and placebo (Tables 19 and 20). There were a total of 19 different SAEs. Nine of 360 (2.5%) of the riloncept treated subjects had SAEs, while 5/179 (2.8%) placebo subjects had SAEs. Four of the riloncept treated subjects had two or more SAEs. The only SOC with more than one subject reporting an SAE where the rate was different between placebo and riloncept was the respiratory system. Two subjects (2/360, 0.6%) of the riloncept subjects developed pneumonitis, pleural effusion, and pulmonary embolism, while there were no respiratory SAEs for placebo subjects. Infections and infestations are an SAE of special interest, but an increased reporting rate for riloncept was not seen, 2/179, 1.1% for placebo vs 1/360, 0.3% for riloncept.

**Table 19. Serious Adverse Events in Double-Blind Riloncept Trials by Dose.**

System Organ Class (SOC)	N = 179	Placebo %	N= 241	R<160 %	N= 32	R=160 %	N= 87	R>160 %	N= 360	All R %
<b>MedDRA Preferred Term</b>										
<b>Any Serious TEAE</b>	<b>5</b>	<b>3%</b>	<b>6</b>	<b>3%</b>	<b>1</b>	<b>3%</b>	<b>2</b>	<b>2%</b>	<b>9</b>	<b>3%</b>
<b>Infections and infestations</b>	<b>2</b>	<b>1%</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
Gastroenteritis salmonella	1	1%	0	0%	0	0%	0	0%	0	0%
Lobar pneumonia	1	1%	0	0%	0	0%	0	0%	0	0%
Pneumonia	0	0%	1	<1%	0	0%	0	0%	1	<1%
<b>Musculoskeletal and connective tissue disorders</b>	<b>1</b>	<b>1%</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>1%</b>	<b>2</b>	<b>1%</b>
Arthralgia	0	0%	0	0%	0	0%	1	1%	1	<1%
Osteoarthritis	0	0%	1	<1%	0	0%	0	0%	1	<1%
Rheumatoid arthritis	1	1%	0	0%	0	0%	0	0%	0	0.0%
<b>Neoplasms benign, malignant and unspecified inclusion cysts and polyps</b>	<b>1</b>	<b>1%</b>	<b>2</b>	<b>1%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>2</b>	<b>1%</b>
Metastatic neoplasm	0	0.0%	1	<1%	0	0%	0	0%	1	<1%
Non-small cell lung cancer	0	0.0%	1	<1%	0	0%	0	0%	1	<1%
Uterine leiomyoma	1	1%	0	0%	0	0%	0	0%	0	0%
<b>General disorders and administration site conditions</b>	<b>1</b>	<b>1%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>3%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
Chest pain	1	1%	0	0%	0	0%	0	0%	0	0%
Pyrexia	0	0%	0	0%	1	3%	0	0%	1	<1%
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>0</b>	<b>0%</b>	<b>2</b>	<b>1%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>2</b>	<b>1%</b>
Pleural effusion	0	0%	1	<1%	0	0%	0	0%	1	<1%
Pneumonitis	0	0%	1	<1%	0	0%	0	0%	1	<1%
Pulmonary embolism	0	0%	1	<1%	0	0%	0	0%	1	<1%
<b>Blood and lymphatic system disorders</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>3%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
Pancytopenia	0	0%	0	0%	1	3%	0	0%	1	<1%
<b>Cardiac disorders</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
Acute myocardial infarction	0	0%	1	<1%	0	0%	0	0%	1	<1%
<b>Gastrointestinal disorders</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>1%</b>	<b>1</b>	<b>&lt;1%</b>
Gastric ulcer perforation	0	0%	0	0%	0	0%	1	1%	1	<1%
Small intestinal obstruction	0	0%	0	0%	0	0%	1	1%	1	<1%
<b>Hepatobiliary disorders</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>	<b>0</b>	<b>0%</b>	<b>0</b>	<b>0%</b>	<b>1</b>	<b>&lt;1%</b>
Bile duct stone	0	0%	1	<1%	0	0%	0	0%	1	<1%

**Table 20. Serious Adverse Events in Double-Blind Riloncept Trials ay any dose**

SOC	PREFERRED TERM	PLACEBO N=179 (%)	RILONACEPT N=360 (%)
Total SAE		5 (3%)	9 (3%)
Blood and lymphatic	Pancytopenia	0	1 (<1%)
Cardiac disorders	Acute MI	0	1 (<1%)
Gastrointestinal	Gastric ulcer perforation	0	1 (<1%)
	Small intestinal obstruction	0	1 (<1%)
General disorders	Chest pain	1 (1%)	0
	Pyrexia	0	1 (<1%)
Hepatobiliary	Bile duct stone	0	1 (<1%)
Infections and infestations	Pneumonia	0	1 (<1%)
	Lobar pneumonia	0	1 (<1%)
	Gastroenteritis salmonella	0	1 (<1%)
Musculoskeletal	Rheumatoid arthritis	1 (1%)	0
	Osteoarthritis	0	1 (<1%)
	Arthralgia	0	1 (<1%)
Neoplasms	Non-small cell lung cancer	0	1 (<1%)
	Metastatic neoplasm	0	1 (<1%)
	Uterine leiomyoma	1 (1%)	0
Respiratory and Thoracic	Pulmonary embolism	0	1 (<1%)
	Pneumonitis	0	1 (<1%)
	Pleural effusion	0	1 (<1%)

Narratives of these SAEs and others from the open-label studies are included in Appendix 10.1.3.

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

In the CAPS pivotal trial there were only 3 dropouts (Section 6.1.4.1) at the 160 mg dose (Table 21). In the overall development program

**Table 21. Overall Dropout Rate in Tier 4 (Controlled Trials)**

<b>Dropout Reason</b>	<b>Placebo N=179</b>	<b>R&lt;160 mg N=241</b>	<b>R=160 mg N=32</b>	<b>R&gt;160 mg N=87</b>	<b>All R N=360</b>
Completers	128 (72%)	173 (72%)	30 (94%)	59 (68%)	262 (73%)
Lack of efficacy	26 (15%)	47 (20%)	0	5 (6%)	52 (14%)
Adverse event	1 (1%)	8 (3%)	0	4 (5%)	12 (3%)
Lost to follow-up	2 (1%)	0	0	2 (2.3%)	2 (0.6%)
Other	22 (12%)	13 (5%)	2 (6%)	17 (20%)	32 (9%)
<b>Total dropouts</b>	<b>51 (29%)</b>	<b>68 (28%)</b>	<b>2 (6%)</b>	<b>28 (32%)</b>	<b>98 (27%)</b>

#### 7.1.3.2 Adverse events associated with dropouts

In the pivotal trial three subjects dropped out for elevated liver function tests as a result of hepatitis C, non-compliance and an adverse event. During Part A one subject coded as other was removed from the study. This subject had elevated liver function tests at baseline. It was later determined that the subject had hepatitis C, when LFTs became further elevated while taking rilonacept. The other dropout during Part A was withdrawn for non-compliance with the protocol. This withdrawal occurred during the single-blind phase when all subjects were taking rilonacept before the randomized withdrawal phase. Incidentally, this subject reported that her partner was determined to have hepatitis C; upon testing she was also determined to have hepatitis C. One subject assigned to stay on rilonacept was withdrawn for an adverse event during Part B, the randomized withdrawal phase. The reason for withdrawal was coded as an adverse event. The subject developed finger joint pain and discontinued. The study site investigator determined that the AE was not related to study drug. This AE occurred at a time when the patient might have believed that he/she was assigned to placebo. It is therefore possible that the AE could have been a therapeutic failure.

Sixteen of 360 (4.4%) rilonacept subjects dropped out for an AE. Injection site reactions (ISRs) were the primary reason accounting for 8/16 (50%) of these terminations. In the pivotal trial no subject dropped out for an ISR. The reactions appeared self-limited, lasting about one day and did not require medical intervention (See next Section 7.1.3.3)

#### 7.1.3.3 Other significant adverse events

Although no Injection Site Reaction (ISR) was reported as serious, these ISRs were the most common AE reported in the pivotal trial and were more frequent in rilonacept subjects compared to placebo subjects (Table 22). 171 of 200 (86%) of the ISR AE reports were rated mild, while the other 29 reports were moderate and all occurred in rilonacept treated subjects. Most of the

reactions included erythema, but the descriptions of other symptoms were variable such as pruritus, itching, swelling, and mass as common examples (Table 23).

**Table 22. Total Injection Site Reactions by Study Part**

STUDY PHASE	RILONACEPT	PLACEBO
Part A	11/23 (48%)	3/24 (13%)
Part B (Single-blind)	9/22 (41%)	7/24 (29%)
Part B (Withdrawal)	8/22 (36%)	3/23 (13%)

**Table 23. Types of Injection Site Reactions by Study Part**

PART A: ISR PREFERRED TERM	RILONACEPT (N=23) MILD	RILONACEPT (N=23) MODERATE	PLACEBO (N=24) MILD
Erythema	7 (30%)	2 (9%)	1 (4%)
Mass	2 (9%)	2 (9%)	0
Pruritus	3 (13%)	0	0
Swelling	3 (13%)	0	0
Bruising	2 (9%)	0	1 (4%)
Inflammation	2 (9%)	0	0
Pain	1 (4%)	0	1 (4%)
Dermatitis	1 (4%)	0	0
Discomfort	1 (4%)	0	0
Edema	1 (4%)	0	0
Urticaria	1 (4%)	0	0
Vesicles	1 (4%)	0	0
Warmth	1 (4%)	0	0
Hemorrhage	0	0	0
PART B Withdrawal	N = 22	N=22	N=23
Erythema	4 (18%)	1 (5%)	1 (4%)
Mass	0	1 (5%)	1 (4%)
Pruritus	1 (5%)	0	1 (4%)
Swelling	1 (5%)	0	0
Bruising	1 (5%)	0	1 (4%)
Inflammation	0	0	0
Pain	0	1 (5%)	0
Dermatitis	0	0	0
Discomfort	0	0	0
Edema	2 (9%)	0	0
Urticaria	0	0	0
Vesicles	0	0	0
Warmth	0	0	0
Hemorrhage	2 (9%)	0	0

In the pivotal trial there were no SAEs for infections or infestations, nor any that required parenteral antibiotics. Two subjects did temporarily discontinue study medication for infections. Part A of the pivotal trial was initiated in February during the winter cough and cold season. In Part A of the trial a greater percentage of subjects treated with rilonacept reported infections, 11/23, 48% compared to 4/24%, 17% for placebo subjects (Table 24). In Part A the increase was mostly secondary to more upper respiratory infections (Table 25). During the Part B withdrawal phase the reported infection rate became similar for the rilonacept and placebo groups. This phase would have been mostly in the summer months. It is also important to note that there was an error in dosing during the first three weeks of the 9 week phase. In addition with a half-life of one week those subjects switched to placebo would have a continued rilonacept effect potentially for a few weeks after the switching to placebo.

**Table 24. Total Number of Infections in the Pivotal Trial**

STUDY PHASE	RILONACEPT	PLACEBO
Part A	11/23 (48%)	4/24 (17%)
Part B (Single-blind)	5/22 (23%)	4/24 (17%)
Part B (Withdrawal)	4/22 (18%)	5/23 (22%)

**Table 25. Specific Infections during the Pivotal Trial**

PART A: INFECTION PREFERRED TERM	RILONACEPT (N=23) MILD	RILONACEPT (N=23) MODERATE	PLACEBO (N=24) MILD	PLACEBO (N=24) MODERATE
Infection/Infestations	6 (26%)	5 (22%)	3 (13%)	1 (4%)
URI	3 (13%)	3 (13%)	1 (4%)	0
Sinusitis	2 (9%)	0	0	1 (4%)
UTI	0	1 (4%)	1 (4%)	0
Nasopharyngitis	0	1 (4%)	0	0
Influenza	1 (4%)	0	0	0
Tooth Abscess	1 (4%)	0	0	0
Viral labyrinthitis	1 (4%)	0	0	0
Localized infection	0	0	1 (4%)	0
Part B: Single-Blind	N=22	N=22	N=24	N=24
Infection/Infestations	4 (18%)	1 (5%)	4 (17%)	0
URI	1 (5%)	0	3 (13%)	0
Nasopharyngitis	0	0	1 (4%)	0
Pharyngitis	1 (5%)	0	0	0
Bronchitis	1 (5%)	0	0	0
Hepatitis C	0	1 (4.5%)	0	0
Furuncle	1 (5%)	0	0	0

	Rilonacept Mild	Rilonacept Moderate	Placebo Mild	Placebo Moderate
Part B: Withdrawal	N=22	N=22	N=23	N=23
Infection/Infestations	2 (9%)	2 (9%)	5 (22%)	1 (4%)
UTI	0	0	1 (4%)	1 (4%)
Sinusitis	1 (5%)	0	1 (4%)	0
URI	0	1 (5%)	0	0
Nasopharyngitis	0	0	1 (4%)	0
Pharyngitis	0	0	1 (4%)	0
Herpes simplex	0	0	1 (4%)	0
Oral fungal infection	1 (5%)	0	0	0

There were three subjects who had prolonged (>2 weeks) treatment with antibiotics. A 48 yo white female, SID# 002-6965, on rilonacept during Part A, reported on study Day 7 sinusitis, treated with 500 mg oral ciprofloxacin BID for 19 days. The subject was removed from the study during the single-blind phase of Part B for non-compliance.

A 40 yo white female, SID# 017-6775, receiving rilonacept during both Part A and the randomized withdrawal phase of Part B, was treated with oral antibiotics for an upper respiratory infection for 19 consecutive days. A Z-Pack [Zithromax®] was taken for 5 days followed by Augmentin, 500 mg, TID, for 14 days. The subject remained on study drug.

A 59 yo white female, SID# 022-6528, receiving rilonacept during both Part A and the randomized withdrawal phase of Part B, reported a *Clostridium difficile* positive chronic intermittent bowel infection that was not reported as a TEAE because the Investigator documented this chronic, intermittent condition during the study medical history assessment; it was originally diagnosed in April 2005. This infection was treated with two courses of Flagyl 500 mg po TID, and then vancomycin 125 mg po QID. The subject remained on study drug.

The combined safety database also demonstrated an increased rate of URIs in rilonacept versus placebo treated subjects, 8% compared to 5% (Table 26). This difference was mostly secondary to the increased rate from the 160 mg dose in the pivotal trial. Urinary tract infections were also higher in the rilonacept subjects (20/360, 6%) compared to placebo subjects (3/179, 2%). Most other infection rates were similar.

**Table 26. Infections in all rilonacept trials**

MedDRA	Placebo N=179	R<160 N=241	R=160 N=32	R>160 N=87	All R N=360
<b>Preferred Term</b>					
<b>Any Infection</b>	<b>48 (27%)</b>	<b>86 (36%)</b>	<b>15 (47%)</b>	<b>23 (26%)</b>	<b>124 (34%)</b>
Nasopharyngitis	10 (6%)	22 (9%)	2 (6%)	6 (7%)	30 (8%)
Upper respiratory tract infection	9 (5%)	20 (8%)	8 (25%)	2 (2%)	30 (8%)
Sinusitis	9 (5%)	12 (5%)	2 (6%)	2 (2%)	16 (4%)
Urinary tract infection	3 (2%)	14 (6%)	1 (3%)	5 (6%)	20 (6%)
Bronchitis	3 (2%)	7 (3%)	0	3 (3%)	10 (3%)
Gastroenteritis viral	3 (2%)	6 (3%)	0	2 (2%)	8 (2%)
Influenza	1 (1%)	2 (1%)	1 (3%)	1 (1%)	4 (1%)
Vaginal infection	2 (1%)	3 (1%)	0	0	3 (1%)
Otitis media	2 (1%)	2 (1%)	0	0	2 (1%)
Pharyngitis streptococcal	1 (1%)	0	0	3 (3%)	3 (1%)
Tooth abscess	1 (1%)	2 (1%)	1 (3%)	0	3 (1%)
Cystitis	1 (1%)	2 (1%)	0	0	2 (1%)
Fungal infection	1 (1%)	2 (1%)	0	0	2 (1%)
Gastroenteritis	0	3 (1%)	0	0	3 (1%)
Herpes simplex	0	2 (1%)	0	1 (1%)	3 (1%)
Laryngitis	0	3 (1%)	0	0	3 (1%)
Localized infection	2 (1%)	1 (<1%)	0	0	1 (<1%)
Lower respiratory tract infection	0	3 (1%)	0	0	3 (1%)
Pharyngitis	1 (1%)	2 (1%)	0	0	2 (1%)
Viral upper respiratory tract infection	1 (1%)	2 (1%)	0	0	2 (1%)
Bronchitis acute	0	2 (1%)	0	0	2 (1%)
Ear infection	1 (1%)	1 (<1%)	0	0	1 (<1%)
Pneumonia	0	2 (1%)	0	0	2 (1%)
Vulvovaginal mycotic infection	0	1 (<1%)	0	1 (1%)	2 (1%)

**Serious infections:**

At the time of this review there have been 5 reports of serious infections. Cases of lobar pneumonia (SID# 004-007) and salmonella gastroenteritis (SID# 079-005) occurred in subjects receiving placebo. A patient (SID# 079-181) suspected of having pneumonia was ultimately diagnosed with adenocarcinoma of the lung. One subject, SID# 001-008, on rilonacept developed an olecranon bursitis from mycobacteria intracellulare. Another subject, SID# 014-004, developed sinusitis and bronchitis on rilonacept. The only death in this review occurred in a

subject during open-label rilonacept from streptococcal pneumonia meningitis. This death and SAEs are detailed further in Appendix 10.3 Deaths and SAE Narratives.

#### 7.1.4 Other Search Strategies

No other search strategies were employed.

#### 7.1.5 Common Adverse Events

##### 7.1.5.1 Eliciting adverse events data in the development program

Adverse events were collected on case report forms (CRFs) or electronic case report forms (eCRFs). General instructions were provided to record any untoward events reported by the subject, observed by the physician, or identified through any test procedures, including laboratory testing, vital signs measures, electrocardiography, or any other specialty test. Subjects were assessed at every study visit. There were no checklists that asked about adverse events, e.g. infections, of particular interest. This general approach was the same across all studies. Severity and relatedness was judged by the investigator.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

MedDRA preferred terms were used by the Applicant. These were grouped by broad terms when evaluating AEs of particular interest.

##### 7.1.5.3 Incidence of common adverse events

##### 7.1.5.4 Common adverse event tables (Table 27)

**Table 27. Adverse Effects Seen in at Least Two Patients in the Pivotal Trial**

MedDRA Preferred Term v9.0	Rilonacept (n=23)	Placebo (n=24)
Injection site erythema	7 (30%)	1 (4%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Diarrhea	1 (4%)	3 (13%)
Nausea	1 (4%)	3 (13%)
Injection site pruritus	3 (13%)	0
Injection site swelling	3 (13%)	0
Injection site bruising	2 (9%)	1 (4%)
Sinusitis	2 (9%)	1 (4%)
Cough	2 (9%)	0

MedDRA Preferred Term v9.0	Rilonacept (n=23)	Placebo (n=24)
Hypoaesthesia	2 (9%)	0
Injection site pain	1 (4%)	1 (4%)
Injection site inflammation	2 (9%)	0
Injection site mass	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)
Abdominal pain upper	0	2 (8%)

#### 7.1.5.5 Identifying common and drug-related adverse events

The most common drug-related adverse event is an injection site reaction. A difference between rilonacept and placebo was seen in both Part A and B in the pivotal trial. In Part A of the trial there was an increased rate of infections, predominantly URIs. This difference was not as significant in Part B of the trial. Note that in Part A, most patients were enrolled in the winter and early spring months. The Part B randomized withdrawal phase occurred predominantly in the summer months.

#### 7.1.5.6 Additional analyses and explorations

Injection site reactions were generally mild and self-limited. All subjects who developed an injection site reaction were individually analyzed. No ISR was graded as serious. No generalized hypersensitivity reaction was associated with an ISR. Subjects quickly recovered with most ISRs lasting only one day. Subjects did not take medications to treat the symptoms of the ISR. There was no correlation seen between those subjects who developed antibodies and those subjects who manifested ISRs.

Subjects who developed infections appeared to recover well without prolonged illness. Individual subject profiles were reviewed for all patients who developed an infection. In most cases subjects recovered from the various infections with normal courses of antibiotics. Those subjects with URIs seemed to recover in a pattern consistent with natural recovery. A pattern of significant medication use to treat the URI symptoms was not seen. In fact some patients had documented URIs and did not take medications for their symptoms. All subjects who continued on open label into the second winter season were followed for a full winter. The subjects did not develop frequent multiple URIs. Most subjects had one or two URIs for the season which is not an uncommon number for the normal population.

#### 7.1.6 Less Common Adverse Events

Malignancy is a rare adverse event of concern for immunosuppressants. The incidence was similar for rilonacept and placebo. Lymphoma has been a cancer of particular concern for

immunosuppressants such as the TNF inhibitors. No reports were seen in the pivotal CAPS trial or in the integrated safety dataset.

### 7.1.7 Laboratory Findings

#### 7.1.7.1 Overview of laboratory testing in the development program

Standard hematology testing was performed including white blood cell differential counts to especially see if the impact on lymphocyte and neutrophil counts. Clinical chemistry testing included serum LFTs (ALT, AST, alkaline phosphatase, bilirubin, and albumin), renal function tests (blood urea nitrogen and creatinine), urate, glucose, calcium, lipid profiles, electrolytes (sodium, potassium, carbon dioxide, and chloride), amylase, and creatinine kinase. The acute phase reactants, C-reactive protein and serum amyloid A, were also measured. These are discussed as endpoints in Section 6.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

All studies, all subjects, were used for the analysis of the laboratory parameters.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

##### 7.1.7.3.1 *Analyses focused on measures of central tendency*

Subjects on rilonacept develop a slight mean increase in their hemoglobin and hematocrit (Table 28). In the pivotal trial, the 160 mg dose, the mean increase in hemoglobin and hematocrit was 0.5 g/dL and 1.2%, respectively. Platelet counts also fell significantly; mean fall of 75 K/mm<sup>3</sup> (Table 28). These increases are most likely consistent with a decrease in the inflammation of the chronic disease. With reduced inflammation the total white blood cell count decreased. The decrease was predominantly a fall in the total number of neutrophils (Table 29).

**Table 28. Mean Change from Baseline for Hematologic Parameters Tier 3**

Hematology Analyte (Range)	Mean	Placebo N=179	R>160mg N=241	R=160mg N=32	R>160mg N=87	All R N=360
<b>Hemoglobin</b> 11-17 g/dL	Baseline	13.2	13.1	12.7	13.1	13.0
	Change to First on-treatment	-0.1	-0.1	0.4	0.2	0.0
	Change to Last on-treatment	-0.1	0.0	0.5	0.1	0.1
<b>Hematocrit</b> 33-51%	Baseline	40.5	40.4	38.2	40.4	40.2
	Change to First on-treatment	-0.4	-0.6	0.9	0.5	-0.2
	Change to Last on-treatment	-0.5	-0.5	1.2	0.3	-0.1
<b>RBC</b> 3.7-5.6 10 <sup>6</sup> /cu mm	Baseline	4.5	4.4	4.4	4.6	4.5
	Change to First on-treatment	-0.0	-0.0	0.1	0.1	-0.0
	Change to Last on-treatment	-0.0	-0.0	0.1	0.0	0.0
<b>WBC</b> 3.7-11 K/cu mm	Baseline	8.2	8.5	10.1	7.0	8.3
	Change to First on-treatment	-0.1	-0.2	-2.4	-1.2	-0.6
	Change to Last on-treatment	0.1	-0.2	-2.9	-1.2	-0.6

**Table 29. Mean Change from Baseline for WBC Differential Counts and Platelets in Tier 3**

Hematology Analyte	Mean	Placebo	R>160mg	R=160mg	R>160mg	All R
(Range)		N=179	N=241	N=32	N=87	N=360
<b>Neutrophils</b> 1.7-7.9 K/cu mm	Baseline	5.6	6.5	7.5	4.7	6.0
	Change to First on-treatment	-0.2	-0.3	-2.3	-1.2	-0.8
	Change to Last on-treatment	-0.0	-0.3	-2.9	-1.2	-0.9
<b>Basophils</b> 0-0.3 K/cu mm	Baseline	0.05	0.06	0.05	0.04	0.05
	Change to First on-treatment	0.00	0.01	0.01	-0.01	0.00
	Change to Last on-treatment	0.01	0.00	0.01	-0.00	0.00
<b>Eosinophils</b> 0-0.8 K/cu mm	Baseline	0.19	0.20	0.22	0.16	0.19
	Change to First on-treatment	-0.01	-0.01	0.02	-0.00	-0.00
	Change to Last on-treatment	0.01	0.01	-0.04	0.01	0.00
<b>Lymphocytes</b> 0.4-5.1 K/cu mm	Baseline	1.9	1.9	1.9	1.8	1.9
	Change to First on-treatment	0.0	0.1	0.0	0.0	0.0
	Change to Last on-treatment	0.1	0.1	0.1	0.0	0.1
<b>Monocytes</b> 0-1.2 K/cu mm	Baseline	0.4	0.4	0.4	0.4	0.4
	Change to First on-treatment	-0.0	0.0	0.1	-0.0	0.0
	Change to Last on-treatment	0.0	0.0	0.1	-0.0	-0.0
<b>Platelets</b> 125-375 K/cu mm	Baseline	322	331	417	298	331
	Change to First on-treatment	-0.6	2.6	-57.8	-20.2	-8.3
	Change to Last on-	5.8	-9.4	-75.7	-23.0	-18.6

Riloncept produces changes in the lipid profiles of subjects (Table 30). Mean increases in total cholesterol, HDL cholesterol and total triglycerides were seen. Once again these may be physiologic changes that follow a decrease from an inflammatory state. Although the database is small, there were no cardiovascular SAEs seen.

**Table 30. Mean Change from Baseline in Selected Serum Chemistry Results in Tier 3**

Chemistry Analyte	Time Point and Mean Change	Placebo	R>160mg	R=160mg	R>160mg	All R
(Range)		N=179	N=241	N=32	N=87	N=360
<b>Total Cholesterol</b> 125-200 mg/dL	Baseline	194	203	171	198	198
	Change to First on-treatment	-1	2	15	11	6
	Change to Last on-treatment	-3	4	16	7	6
<b>HDL Cholesterol</b> 35-60 mg/dL	Baseline	55	55	46	50	54
	Change to First on-treatment	-1	0	2	4	1
	Change to Last on-treatment	-2	-0	9	3	1
<b>LDL Cholesterol</b> 50-160 mg/dL	Baseline	107	115	78	105	112
	Change to First on-treatment	-2	1	3	6	2
	Change to Last on-treatment	-1	4	0	7	4
<b>Triglycerides</b> 45-200 mg/dL	Baseline	158	171	115	162	168
	Change to First on-treatment	4	9	33	36	14
	Change to Last on-	7	8	16	32	12

*7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal*

Because of the changes seen in hematologic parameters an in-depth analysis of outliers was performed (Table 31). While a few subjects developed some low counts, outside of the normal range, these were not severe such that subjects would be particularly at risk from infectious or bleeding complications.

More riloncept subjects developed triglyceride levels greater than 450 mg/dL. All riloncept was 16/286 (5.6%) vs 2/143 (1.4%) for placebo subjects.

**Table 31. Hematology Laboratory Outliers Tier 3**

Hematology Analyte	Criteria	Placebo	R<160mg	R=160mg	R>160mg	All R
(Range)		N=179	N=241	N=32	N=87	N=360
<b>Hemoglobin</b> (11-17 g/dL)	F: <9.0 g/dl M: <10.5 g/dl	0/175	3/239 (1%)	0/28	2/86 (2%)	5/353 (1%)
<b>WBC</b> (3.7-11 K/cc mm)	<2.5x10 <sup>9</sup> /L	0/177	2/240 (1%)	28/32 (3%)	1/87 (1%)	4/359 (1%)
<b>Neutrophils</b> (1.7-7.9 K/cc mm)	<1.0x10 <sup>9</sup> /L	0/149	0/158	0/32	1/87 (1%)	1/277 (0.4%)
<b>Neutrophils</b>	<1.5x10 <sup>9</sup> /L	0/149	4/158 (3%)	1/32 (3%)	2/87 (2%)	7/277 (3%)
<b>Eosinophils</b> (<0.8 K/cc mm)	>2.0x10 <sup>9</sup> /L	0	0	0	0	0
<b>Lymphocytes</b> (0.4-5.1 K/cc mm)	<0.4x10 <sup>9</sup> /L	0/150	1/158 (1%)	1/32 (3%)	1/87 (1%)	3/277 (1%)
<b>Platelets</b> (125-375 K/cc mm)	<75x10 <sup>9</sup> /L	0	0	0	0	0

## 7.1.8 Vital Signs

### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs (blood pressures, pulse, respiratory rate, and temperature) and body weight were assessed at baseline and all study visits.

### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Analyses compared baseline values to first and last assessment on treatment as well as off treatment follow-up. The analyses were performed in Tier 4 and the CAPS studies.

### 7.1.8.3 Standard analyses and explorations of vital signs data

#### *7.1.8.3.1 Analyses focused on measures of central tendencies*

In Tier 1 (Part A CAPS trial) the mean change +/- S.D. in systolic blood pressure was 2.4 +/- 13.5 for rilonocept compare to -0.5 +/- 12.9 for placebo subjects at the last on-treatment visit. The mean change for diastolic blood pressure was 2.6 +/- 9.6 for placebo and 1.2 +/- 10.9 for rilonocept. The Tier 4 analyses did not demonstrate clinically significant mean changes in blood pressure.

There were no clinically significant mean changes in pulse rate, respiratory rate and temperature in Tier 1 or 4 analyses. There was no clinically significant change in mean body weight in Tier 1 or 4.

#### *7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal*

The one difference noted in vital sign shift analyses was in subjects with an increase in systolic blood pressure greater than 20 mm Hg and over 150 mm Hg. The difference, however, seemed to be in subjects who received doses of rilonocept greater than the current proposed dose of 160 mg (Table 32).

**Table 32. Vital Sign Shift Analyses for Tier 3**

Blood Pressure (mm Hg)	Criteria	Placebo 178/179	R<160 240/241	R=160 32/32	R>160 87/87	All R 359/360
Systolic	>150 and Increase > 20	<b>10 (6%)</b>	25 (10%)	1 (3%)	<b>12 (14%)</b>	<b>38 (11%)</b>
	Increase > 30	7 (4%)	14 (6%)	1 (3%)	9 (10%)	24 (7%)
	< 90 and decrease > 20	0	0	0	0	0
	Decrease > 30	10 (6%)	20 (8%)	1 (3%)	4 (5%)	25 (7%)
Diastolic	> 100 and increase > 15	1 (1%)	5 (2%)	0	0	5 (1%)
	Increase > 20	5 (3%)	10 (4%)	4 (13%)	3 (3%)	17 (5%)
	< 60 and decrease > 15	4 (2%)	5 (2%)	1 (3%)	2 (2%)	8 (2%)
	Decrease > 20	9 (5%)	19 (8%)	0	1 (1%)	20 (6%)

*7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities*

The Applicant did perform outlier analyses, but there was no evidence for clinically significant differences between placebo and riloncept.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical studies did not demonstrate ECG alterations. See the Animal Pharmacology/Toxicology Section 3.2 for details.

No dedicated clinical studies were carried out to specifically evaluate for QT prolongation. ECGs were obtained from subjects prior to administration of study medication in all clinical studies. ECG measurements were taken and reviewed by the investigators. Selection of studies and analyses for overall drug-control comparisons

In three studies (IL1T-RA-0111, IL1T-OA-0425, and the pivotal trial in CAPS, IL1T-AI-0505), post-baseline on-treatment ECGs were obtained. If treatment-emergent abnormalities of ECG parameters were observed, the investigator was to record the observation as an AE. Review of AEs reported in the Cardiac Disorders System Organ Class (SOC) in Tiers 3 and 4 revealed a low frequency of cardiac rhythm disorders, and review of other SOCs (e.g., Nervous System; Injury) for events potentially related to cardiac rhythm disorder (e.g., dizziness, falls) did not reveal a signal of concern for subjects treated with riloncept. In The CAPS trial EKG

measurements were taken and analyzed while on treatment with the results provided by the Applicant.

#### 7.1.9.2 Standard analyses and explorations of ECG data

##### 7.1.9.2.1 *Analyses focused on measures of central tendency*

There was no evidence for any EKG alterations in comparing rilonacept and placebo treated subjects, nor evidence for a change while on therapy. It is important to note that there were only a few subjects on rilonacept that had on-treatment EKGs performed.

##### 7.1.9.2.3 *Marked outliers and dropouts for ECG abnormalities*

In the CAPS trials, two subjects developed abnormal PR intervals (>200 msec). One was a placebo subject and the other was on rilonacept. A few subjects developed QTc intervals greater than 450 msec (3/62 [4.8%] on placebo and 3/63 [4.8%] on rilonacept) or had their QTC increase by 30 msec (6/62 [9.7%] on placebo and 4/63 [6.3%] on rilonacept). Therefore there was no evidence for a QTc prolonging effect for rilonacept compared to placebo.

#### 7.1.10 Immunogenicity

Anti-rilonacept binding antibodies develop in some subjects exposed to rilonacept. Throughout the clinical program multiple assays were used. In the early development program two subjects did develop anti-rilonacept binding antibody levels that impacted rilonacept drug levels. In the pivotal CAPS trial, however, 43% of rilonacept-exposed subjects developed low level anti-rilonacept binding antibody titers. Antibody titers fluctuated throughout therapy, for example they might rise, then fall, but rise again. This pattern is different from immunogenicity seen with other biologics, where increasing exposure produces higher antibody levels. There was no clear evidence that immunogenicity impacted rilonacept drug levels, most cases where the rilonacept drug levels seem to fall were secondary to drug discontinuation errors caused by the randomization errors. Therefore there was no impact upon efficacy for those patients whom developed antibodies.

The development of antibodies did not affect safety. The development of antibodies did not correlate with the development or severity of injection site reactions. No association was seen between the development of antibodies and infections or their severity.

#### 7.1.11 Human Carcinogenicity

The Applicant did not perform formal human carcinogenicity studies. Three malignant neoplasms are reported in the integrated safety database in subjects treated with rilonacept. Two subjects were discovered to have lung cancers, both subjects were smokers. Another subject with a prior history of facial basal cell carcinomas was reported to have had recurrent basal cell

carcinomas removed.

#### 7.1.12 Special Safety Studies

In a phase 1 placebo-controlled study of a single SC administrations of rilonacept in healthy volunteers, IL1T-RA-0401, subjects self-administered questionnaires assessing pain (six categories: no pain, mild, discomforting, distressing, horrible, and excruciating) at the injection sites up to 30-hours post-dose and at subsequent visits. Injection sites were examined for erythema and edema up to 43 days post-injection. The Applicant reports that peak pain scores of no pain to discomforting (none, horrible or excruciating) typically occurred at 1 or 5 minutes post-injection. Mean injection site erythema diameter for all dose groups ranged from 10 to 87 mm. The erythema resolution time was variable, but often occurred within 1 to 3 days post-injection. Mean injection site edema for all groups ranged from 1 to 65 mm, and resolved within 1 day of dosing.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

In the pivotal CAPS trial (Part B) some subjects underwent a 9-week randomized withdrawal from rilonacept. Subjects who were randomized to withdrawal had received 9 to 15 weeks of rilonacept. No safety signals were identified. Subjects randomized to placebo experienced gradually increasing clinical signs and symptoms toward their initial baseline levels. Re-initiation of therapy in the open-label extension then saw improvement again with rilonacept therapy.

As a large molecule, rilonacept should not interact with CNS receptors that could lead to dependence phenomenon or cause abuse potential.

#### 7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of rilonacept in pregnant women. During clinical studies subjects were required to use effective methods of birth control (including males in the recent studies) to prevent exposure of rilonacept in pregnant women. Hence, no data exist to evaluate rilonacept in pregnant women or the effects of treatment with rilonacept on human reproduction. No reports of pregnancies occurred in clinical studies of rilonacept.

#### 7.1.15 Assessment of Effect on Growth

No pediatric studies on growth have been conducted.

#### 7.1.16 Overdose Experience

There have been no cases of inadvertent or intentional overdose with rilonacept. Early clinical studies intravenously administered up to 2000 mg in some subjects (12.5 times the proposed dose for the CAPS indication).

### 7.1.17 Postmarketing Experience

There is no postmarketing experience with rilonacept.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

#### 7.2.1.1 Study type and design/patient enumeration

See Section 4.2.

#### 7.2.1.2 Demographics

Phase 1 trials were conducted in rheumatoid arthritis patients. The healthy volunteers were typical of this population, mostly white Caucasians in their 40s.

See Section 6 for the detailed demographics for the pivotal CAPS trial.

#### 7.2.1.3 Extent of exposure (dose/duration) Table 33

**Table 33. Patient Exposure to Rilonacept by Dose and Time**

Dose	Duration of Treatment with rilonacept		
	At least one dose	At least 6 months	At least 1 year
Any dose	600	85	65
< 160 mg	316	1	0
=160 mg	135	63	48
> 160 mg	171	24	16
160 mg or more	293	84	65

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

#### 7.2.2.1 Other studies

The Applicant did not submit any secondary source data.

#### 7.2.2.2 Postmarketing experience

There is no postmarketing data, as rilonacept is not marketed in any other country.

#### 7.2.2.3 Literature

No additional literature was reviewed.

### 7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to rilonacept. The study design successfully utilized the available subjects with CAPS. Most of the subjects continued into the open-label extension trials to provide safety data for subjects administered rilonacept for one year. CAPS is a genetic-based disease predominantly in Caucasians. Therefore no data was available for other ethnic groups.

Most dose finding studies were performed in the rheumatoid arthritis population. It is not clear whether lower doses of rilonacept would demonstrate similar efficacy and produce less adverse reactions. See Section 8.1.

Infections, including opportunistic infections, are expected to be a class effect of agents that antagonize IL-1. The pivotal trial suggests that rilonacept subjects may develop more upper respiratory infections. In open-label trials opportunistic infections were seen. The potential for drug-drug interactions to increase the potential for serious infections is a concern as a class effect. If patients receive rilonacept off-label for other conditions where they are receiving other immunosuppressants, there is a risk of additive or synergistic immunosuppression. For example, patients on concomitant TNF inhibitors, anakinra, or other immunosuppressants such as corticosteroids when taken in combination with rilonacept also theoretically may elevate the risk for infections.

#### 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Carcinogenicity studies have not been done. No juvenile animal studies have been performed. These additional studies should be considered in the post-marketing phase.

#### 7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects was adequate. Case report forms were designed to capture adverse events. Investigators were provided instructions about adverse events and their reporting. Section 7.1.7 reviews the laboratory findings. Section 7.1.8 reviews the vital sign findings. Section 7.1.9 reviews the EKG findings.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic and clearance studies are adequate. No formal interaction studies were required for this large biologic fusion protein.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Rilonacept is a biologic fusion protein with immunosuppressant properties. Anticipated adverse events include infections (Sections 7.1.2 and 7.1.3.3), injection reactions (Section 7.1.3.3), immunogenicity (Section 7.1.10) and malignancy (Section 7.1.6). Refer to the designated sections for detailed reviews of these AEs. The Applicant's ability to fully evaluate adverse events was limited by the size of the patient population available for study. The integrated safety analysis does provide evidence that adverse events can be expected to be similar to anakinra, a drug with a similar mechanism of action. Infectious complications from drugs that antagonize interleukin-1 are the primary risk for this class. Post-marketing surveillance (active and passive) will be the mechanism to address the risks in the larger population especially cases where concomitant immunosuppressant therapy may be used.

A post-marketing study of a lower dose is recommended to see if efficacy can be maintained, as theoretically a lower dose may lower the risk for serious infections.

#### 7.2.8 Assessment of Quality and Completeness of Data

The data provided for the safety review is of good quality and conformed to the recommendations provided in the pre-NDA meeting with the Division.

#### 7.2.9 Additional Submissions, Including Safety Update

The safety update did not include any additional deaths or SAEs in subjects who received rilonacept. The safety update augmented the number of subjects who received the study drug for greater than one year. The safety update also added to the pediatric experience. The Applicant also responded to information requests including an analysis of immunogenicity and the relationship to adverse reactions. The data from the safety update and the information request have been included throughout the review.

Since the Safety Update another Death Report has been received. This report, Manufacturer Report # 0711-352, provides preliminary information about the death of a 37 yo male who was found at home. This patient was obese (BMI 38.2 kg/m<sup>2</sup>) with a weight of 109 kg. He had been diagnosed with CAPS since the first 6 months of life. He was first diagnosed with asthma around age 2 and also had seasonal allergies. He had stopped smoking about 10 years earlier. He also was diagnosed with hypertension. His concomitant medication was Astelin. He began open-label treatment, 160 mg SQ, March 29, 2007 and died ————— The patient did report some

mild injection site reactions with some of the first injections. Typical laboratory changes were noted. Serum CRP levels fell (61 – 1.4 mg/L) and platelets fell (387-342 K/mm<sup>3</sup>). Triglyceride levels were also elevated; 275 mg/dL increased to 865 mg/dL and was 566 mg/dL at last test 6 weeks before his death. The subject was last contacted 5 days before his death at which time no changes in medications or condition was reported. This 37 yo male died of sudden death. An autopsy is pending. Most likely etiologies for the sudden death include cardiovascular including an arrhythmia, myocardial infarction, pulmonary embolus, or severe asthma attack. There is no evidence for a preceding infection precipitating these events. The safety database does not show a difference in these cardiopulmonary events. In summary, this death is most likely cardiopulmonary in nature and not related to rilonacept.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

#### **7.3.1 Infections**

In the pivotal CAPS trial Part A conducted in the winter months there was an increased incidence of upper respiratory infections including nasopharyngitis, sinusitis, labyrinthitis, and influenza (Section 7.1.3.3). There was no evidence for prolonged use of antibiotics. Studies were not conducted to determine if subjects who might get influenza might be at greater risk for infectious complications. If subjects might be at greater risk, the use of antibiotics theoretically may still be effective in reducing this risk. Post-marketing surveillance should observe for this potential complication, especially in years when influenza rates may be greater. Concomitant use of medications and infectious complications also warrant pharmacovigilance.

#### **7.3.2 Injection Site Reactions**

Injection site reactions in rilonacept-treated subjects in the pivotal trial were experienced at a much higher rate than seen in placebo subjects. These included erythema, pruritus, swelling, bruising, inflammation, and mass. These reactions were rated as mild and moderate and did not result in any subject discontinuations. The formulation and route of administration changed during the course of product development, so the incidence and type of reactions from earlier trials may not reflect that of the current formulation. Therefore there is no data to know if a lower dose of the current product might reduce the incidence of injection site reactions. For some biologic products anaphylactic/anaphylactoid reactions have occurred. While the subcutaneous route rather than the intravenous route may reduce the risk for these reactions, hypersensitivity reactions remain a postmarketing concern.

## 7.4 General Methodology

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

#### 7.4.1.1 Pooled data vs. individual study data

The pooling of data combined sets into multiple tiers. Tiers 1 and 2 included only CAPS subjects, while Tiers 3 and 4 included all subjects exposed to rilonacept in Phase 2 and 3 trials. Tier 3 included all subjects, while Tier 4 included those subjects in double-blind studies.

#### 7.4.1.2 Combining data

There was no weighting of studies in the analyses. The review simply pooled studies and added the numerators and denominators together.

### 7.4.2 Explorations for Predictive Factors

Explorations for predictive factors of injection site reactions and infections, two drug-related AEs, were performed.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

There is no evidence for a dose effect on the rate of infections in the evaluation including all double-blind rilonacept trials. Section 7.1.3.3 (Other significant adverse events) details the findings for this exploration. Also, note that for CAPS the pivotal trial only tested one dose.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Most patients who develop ISRs will do so after one of the first three injections. However, there are some subjects who have an ISR occur months after starting therapy. The Applicant provided this evaluation in answering the Division's information request.

Infections may occur at any time while on rilonacept therapy. Serious infection rates (Section 7.1.2) were not different between rilonacept and placebo treated subjects. While no serious opportunistic infections were seen during the 6-month pivotal trial a death did occur in the open-label extension. IL-1 antagonism will place subjects at risk for serious infections at any time while on therapy.

#### 7.4.2.3 Explorations for drug-demographic interactions

Gender and age did not alter the response to rilonacept therapy (Section 6.1.4.2). A different response based upon ethnicity could not be evaluated, as all subjects were Caucasian.

#### 7.4.2.4 Explorations for drug-disease interactions

No other drug-disease evaluations were performed secondary to the small sample sizes available.

#### 7.4.2.5 Explorations for drug-drug interactions

No formal drug-drug interaction studies were performed, because biologics are not generally believed to interact with small molecules. The use of concomitant immune modulators that may further suppress the immune system is a concern that warrants post-marketing monitoring. The exclusion criteria prevented enrollment of subjects on immune modulators of concern by providing for an appropriate washout period.

#### 7.4.3 Causality Determination

The injection site reactions are related to rilonacept, based upon the markedly increased rates seen in Part A, 48%, and Part B, 36%, compared to the 13% rate for placebo in both Part A and B. Regarding infections opportunistic infections would be likely especially if rilonacept were given with other immune modulators. Further study is needed to determine if rilonacept may increase the risk of more minor infections such as upper respiratory infections. However, it is likely that rilonacept increases the risk of upper respiratory infections based on the higher rate observed with rilonacept in the pivotal trial and the immunosuppressive mechanism of action of the product.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The Applicant studied one dose for the treatment of CAPS. The selected dose, 160 mg weekly, per the Applicant was chosen to completely bind calculated amounts of IL-1 and its receptor. The pivotal trial demonstrated that this dose is efficacious. However, we do not have any data to address whether lower doses such as 100 mg might be as efficacious and demonstrate lower risks for infectious complications.

The optimal dosing interval is also uncertain. The dosing interval for rilonacept is one week which approximates the half-life of rilonacept. Different dosing intervals were not studied for CAPS. While q weekly dosing is efficacious, it is unknown whether less frequent dosing would also be efficacious.

### 8.2 Drug-Drug Interactions

Although not studied, anakinra, another IL-1 antagonist should not be used concomitantly with rilonacept. Other drug-drug interactions were not studied nor identified in the trials. In any case the use of concomitant immuno-modulators should be avoided whenever possible. If one is need

for another medical condition close monitoring of the patient and treatment for infectious complications should be provided by healthcare professionals.

### 8.3 Special Populations

Special populations beyond some demographic subpopulations were not studied by the Applicant. The study demonstrated efficacy for males and females, and young and old adults. All subjects were Caucasian, and therefore ethnicity was not studied. Pediatric patients were not included in the pivotal trial, although six pediatric subjects received rilonacept in the open-label trials.

No subjects with evidence of significant hepatic or renal insufficiency were studied. For pediatric population see Section 8.4.

### 8.4 Pediatrics

Rilonacept has received a pediatric waiver. Rilonacept is currently being studied in pediatric CAPS patients in the open-label extension. In addition there is an ongoing phase 1 trial in Systemic Juvenile Rheumatoid Arthritis. Six pediatric CAPS patients, ages 12 to 16, have been administered the drug in the open-label extension. The dose is weight based, 2,2 mg/kg, not to exceed the adult dose. The mean trough level, 4 subjects, was 20 µg/mL. This result was comparable to the mean adult trough level of 24 µg/mL. Exposure ranged from 12 to 40 weeks. The pediatric subjects have demonstrated favorable responses, similar to adult subjects. The reported adverse reactions were comparable to adult subjects. Injection site reactions were common at 3/6 subjects, while one subject reported upper respiratory congestion. The available data suggests that pediatric CAPS subjects appear similar to adults in their response to rilonacept treatment.

### 8.5 Advisory Committee Meeting

No advisory committee meeting related to rilonacept was convened.

### 8.6 Literature Review

Rilonacept is a new molecular entity without significant reports in the literature.

### 8.7 Postmarketing Risk Management Plan

The Applicant proposes

A registry is to include \_\_\_\_\_, pediatric patients. To facilitate reporting the Applicant proposes to establish a \_\_\_\_\_ toll-free number, website, \_\_\_\_\_

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## 8.8 Other Relevant Materials

At the time of this review, DMETS has found the proposed trade name of Arcalyst to be acceptable.

## 9 OVERALL ASSESSMENT

### 9.1 Conclusions

The Applicant has provided adequate evidence of efficacy for rilonacept in the treatment of CAPS. The overall safety profile provided by the randomized trials and open-label extension studies indicates a favorable risk-benefit relationship and supports a recommendation of licensure.

### 9.2 Recommendation on Regulatory Action

Assuming that the remaining CMC issues can be resolved satisfactorily rilonacept should be licensed for the treatment of CAPS. Rilonacept is efficacious in the treatment of CAPS and the data demonstrated a favorable risk-benefit relationship. Nonetheless, infectious complications represent a significant risk. One subject in an open-label trial died from a serious infection, streptococcal meningitis. Another subject developed an opportunistic infection, mycobacteria intracellulare. Therefore, pharmacovigilance will be required of the treating healthcare professional for the development of infections and aggressive treatment is warranted when infections are identified.

### 9.3 Recommendation on Postmarketing Actions

#### 9.3.1 Risk Management Activity

The Applicant proposes both an active and passive pharmacovigilance plan. In the passive method the Applicant proposes to collate spontaneous reports into quarterly updates to the FDA for three years. For active surveillance the Applicant proposes a rilonacept registry to monitor patients; the registry is to include pediatric patients. To facilitate reporting the Applicant proposes to establish a toll-free number that will be included in the Full Prescribing Information and the package insert. In addition a

\_\_\_\_\_ website will be created. \_\_\_\_\_

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Many unanswered safety questions remain for the pediatric population and young adults who may be considering pregnancy. Only six pediatric CAPS patients have been exposed in the open-label trial to rilonacept. Therefore, a registry of pediatric patients should be followed for a minimum of five years for safety evaluations. It is unknown whether rilonacept impacts pediatric growth. The immune system plays an important role in normal fetal development. Despite a lack of animal evidence for reproductive toxicity, rilonacept may pose a risk in humans.

### 9.3.2 Required Phase 4 Commitments

None.

### 9.3.3 Other Phase 4 Requests

The Applicant should continue the registry for 5 years for pediatric patients. The sample size should be a minimum of 20 subjects. The questionnaire should be expanded to include monitoring of growth parameters for these patients. The Applicant should collect information on the outcomes of pregnancy for any woman who becomes pregnant, while taking rilonacept including the spouses of male patients who become pregnant while taking rilonacept, as it is unknown what the impact of rilonacept is on reproduction and fetotoxicity in humans.

The dosing regimen has not been fully studied to determine the lowest efficacious dose or conversely the appropriate dosing interval. With the efficacy demonstrated in the pivotal trial lower doses of rilonacept, e.g. 100 mg, or a longer dosing interval such as every two weeks warrant further study. A lower dose or a longer dosing interval may still provide efficacy. The adverse event profile of most drugs is improved by the use of the lowest efficacious dose. Although the risk benefit ratio for rilonacept seems favorable in the current database, only a small number of CAPS patients have been exposed to long-term use. The Applicant should consider studying a lower dose and/or a longer interval. A longer interval may also provide

greater patient convenience, for example to those patients who have frequent injection site reactions.

It would be desirable to collect additional pediatric pharmacokinetic data in CAPS patients, as well as information on skeletal growth and hormone levels.

\_\_\_\_\_, the sponsor should report any off-label use of rilonacept that comes to their attention.

#### **9.4 Labeling Review**

The labeling review will follow the completion of this primary review.

#### **9.5 Comments to Applicant**

None.

### **10 APPENDICES**

#### **10.1 Review of Individual Study Reports**

For this Orphan drug, with one pivotal trial, the key elements have been incorporated into the Efficacy (Section 6) and Safety (Section 7) Sections of the review.

#### **10.2 Line-by-Line Labeling Review**

To be performed after this review.

#### **10.3 Death and SAE Narratives:**

A 32 yo male with adult-onset Still's disease developed a mycobacterium intracellulare olecranon bursitis. This adult-onset subject was receiving IL-1 Trap in trial IL1T-AI-0406. The dose was 100 mg from 11/3/2005 to 2/22/2005 and increased to 160 mg on 2/22/2005 until 5/24/2005 the time of the SAE. The olecranon bursitis was pre-existing. During the course of therapy the subject also received drainage and two corticosteroid injections. His concomitant medication also included oral prednisone. Other concomitant medications included naproxen 500 mg po BID, omeprazole 20 mg qd, calcium carbonate 1250 mg po BID, cetirizine 10 mg po qd, Actonel 35 mg po qweek, MVI qd, oxycodone/acetaminophen 5/500 mg po q6h prn, Cymbalta 30 mg po qd, Lisinopril 5 mg po qd, gemfibrozil 600 mg po BID, selenium sulfide shampoo 5-10 mL qd, and clonazapine 1 mg po qhs prn. At the 3-month post-dose escalation visit the fluid had re-accumulated. Pus was drained and acid fast stain identified the atypical mycobacterium. The Investigator attributed the cause as unrelated to IL-1 Trap, and related to the procedure and steroid injection upon later review the NIAMS Safety Monitoring Board changed the causality to

“possibly related.” (The subject states that shortly after this procedure he was cleaning his fish tank and let water run down his arm. This water was deemed by the investigator as the possible source for the infection.) The subject developed an antimicrobial-related drug rash early in the therapy of his mycobacterial infection. Initial therapy was with ceftriaxone and vancomycin for two days. On 05/26/2006 he was switched to rifampin, Moxifloxacin, and azithromycin. The next day his antibiotics were switched to alizarin and azithromycin. After identification of the organism his antibiotics were again changed to rifabutin, ethambutol and azithromycin on 5/30/2006. Six days later he developed what was determined to be a pruritic drug rash. Only amikacin was continued with oral ethambutol restarted and clarithromycin added. The later two were continued for six months with resolution of the mycobacterium infection.

13 yo white female (SID# 010-215, IL1T-AI-0504) was hospitalized for pneumonitis. She was in the open-label study receiving 4.4 mg/kg SC weekly for 7 months. She had previously been hospitalized for an SJIA flare and macrophage activation syndrome triggered by a viral infection. Her workup rather than finding an infectious etiology, a biopsy determined a diagnosis of pulmonary fibrosis consistent with her autoimmune disease or methotrexate toxicity. Initially the patient was continued on rilonacept, but after another month was discontinued. Subsequently the patient had more admissions for her pulmonary fibrosis and MAS.

A 52 yo female (SID# 075-136, ILIT-RA-0004) suffered an MI for which she was hospitalized. She was a smoker and had a family history for coronary artery disease. She was being treated for rheumatoid arthritis. Her concomitant medications included Prilosec, ibuprofen, aspirin, Pepcid, Albuterol inhaler, Nexium, Plendil, and Atrovent. Her PMH included esophagitis, COPD, asthma, and hyperthyroidism. She received 6 weekly doses of rilonacept, 200 µg/kg SC. 27 days after her last dose she developed chest pain and ten days later suffered an MI with cardiac catheterization and stent placement.

68 yo female (SID# 075-137, ILIT-RA-0004) received 6 weekly doses of rilonacept 200 µg/kg SC. 33 days later was found to have pulmonary nodules consistent with metastatic disease. Biopsy determined non-small cell carcinoma in this patient with a smoking history.

52 yo female (SID# 079-181, ILIT-RA-0004) received 3 weekly doses of rilonacept 800 µg/kg SC before being discontinued from the study. The patient received the first dose of rilonacept despite a cough productive of yellow-green sputum. Cultures would not grow any organisms, but biopsy demonstrated adenocarcinoma. 29 days after her third and last dose the subject also suffered a pulmonary embolism.

50 yo white female (SID# 158-216, ILIT-RA-0004) received 6 weekly doses of rilonacept 800 µg/kg SC. This obese patient despite a history of a cholecystectomy developed a common bile duct stone that required hospitalization. During treatment the patient had a mild transient bilirubin increase to 1.5 mg/dL at week 5. One month later the patient developed severe epigastric pain and had a bilirubin of 2.7 mg/dL and serum alkaline phosphatase of 331 U/L. ERCP found the stone that subsequently passed without surgery.

64 yo black female (SID# 004-007, ILIT-RA-0102) received placebo during the trial. Her PMH was significant for asthma, COPD and smoking. Five days after the last placebo injection was hospitalized for a right lower lobe pneumonia.

46 yo black female (SID# 007-006, ILIT-RA-0102) received placebo during the trial. This subject was hospitalized for possible of infection of her replaced joints. Cultures returned negative and patient responded well to oral steroids. The diagnosis was determined to be a flare of her rheumatoid arthritis.

50 yo white male (SID# 027-005, ILIT-RA-0102) received 12 weekly doses of 50 mg SC of rilonacept. After the 10<sup>th</sup> dose the subject developed 4 rib fractures secondary to coughing that required a hospitalization. The patient was a smoker and had a PMH significant for rheumatoid arthritis, chronic cough since a positive PPD test 35 years earlier, asthma, COPD, obesity, hypertension, and diabetes mellitus. The patient subsequently developed a pneumonitis and effusion.

69 yo white female (SID# 033-001, ILIT-RA-0102) received 12 weekly doses of 50 mg SC of rilonacept. 58 days after the last dose the patient developed worsening of preexisting left knee osteoarthritis. She was hospitalized and underwent total left knee arthroplasty.

41 yo white female (SID# 075-003, ILIT-RA-0111) was assigned to placebo. She developed chest pain. She was a smoker with a positive family history of heart disease. She ruled out for an MI and had a co-diagnosis of situational stress.

50 yo white female (SID# 079-005, ILIT-RA-0111) was assigned to placebo. She developed salmonella gastroenteritis requiring hospitalization. The subject had rheumatoid arthritis and was receiving naprosyn and prednisone. In addition the subject had a bacterial vaginitis treated with ampicillin and a UTI treated with Levaquin in the preceding two months. She recovered with medical management.

32 yo white male (SID# 001-008, ILIT-AI-0406) with adult onset Still's disease was assigned to rilonacept. He started at 100 mg SC weekly and was increased to 160 mg SC weekly. This subject was hospitalized for nephrolithiasis. His concurrent medications included prednisone, naproxen, omeprazole, calcium carbonate, cetirizine, Actonel, Vicodin, Cymbalta, Lisinopril, gemfibrozil, Klonopin, ethambutol, clarithromycin, and multivitamin. The subject had been on anakinra prior to enrollment. Prior to this admission the subject developed a Mycobacterium intracellulare infection and was taking ethambutol and clarithromycin. There was no reported history of previous kidney stones. The subject responded to medical management. This subject was again hospitalized for elective hip replacement for avascular necrosis that predated his enrollment into the trial.

67 yo white male (SID# 002-245, ILIT-RA-0408) was assigned to rilonacept 2 g IV monthly. The patient developed a worsening of right knee pain, arthralgia, 23 days after the first dose. He was hospitalized for total knee replacement after having received 3 doses of rilonacept.

72 yo white female (SID# 004-469, ILIT-RA-0408) received all 3 doses of rilonacept 1 g IV monthly. She was hospitalized for a perforated gastric ulcer and small bowel obstruction eight days after the last dose. Her concomitant medications included methotrexate, piroxicam, Tylenol Arthritis, levothyroxine, Lisinopril, hydrochlorothiazide, MVI, calcium, and glucosamine. Her PMH included hypertension, hypothyroidism, hypoglycemia, osteoporosis, osteoarthritis, depression, prior smoking, and breast cancer with radiation therapy. She underwent surgery and recovered. The study investigator attributed the ulcer to a concomitant medication, piroxicam. The patient did not continue into the open-label trial.

38 yo white female (SID# 002-259, ILIT-RA-0409) assigned to placebo developed vaginal bleeding secondary to uterine fibroids and underwent a hysterectomy.

46 yo white male (SID#004-417, ILIT-RA-0409) was taking open label rilonacept 320 mg SC weekly. He developed lower gastrointestinal bleeding secondary to colitis. This event occurred after the 18<sup>th</sup> dose of rilonacept. His PMH was significant for hypertension, hypothyroidism, hypercholesterolemia, GERD, bronchitis and cholecystectomy. His concomitant medications includes Fosamax, prednisone, diltiazem, Aciphex, folic acid, methotrexate, Ultracet, Lidoderm patch, zanaflex, Oscar + D, Centrum, Osteobiflex, Allegra, lisinopril, and Synthroid. His work-up was consistent with bacterial colitis although an organism was not identified. He did respond to antibiotic therapy, Flagyl, Colazol, and Bentyl. The investigator considered the AE drug-related and rilonacept was discontinued.

83 yo male (SID# 006-001, ILIT-PR-0423) on open-label rilonacept for 58 days developed flash pulmonary edema secondary to a contrast media reaction from CT scans that were part of his work-up for abdominal pain; diverticulitis. The investigator did not believe these reactions were drug related, but the subject had the rilonacept therapy discontinued. The patient had a previous history of drug sensitivity to oxycodone/acetaminophen and had previous history of diverticulosis, GERD, and peptic ulcer disease. His concomitant medications included Lotrel, Prevacid, aspirin, calcium with vitamin D, MVI, and prednisone.

68 yo white female (SID# 014-004, ILIT-PR-0423) was taking open-label rilonacept, 320 mg SC weekly for 39 days. She was hospitalized for sinusitis and bronchitis treated with IV antibiotics and nebulizer treatments. The AEs were judged to be study drug related.

74 yo white female (SID# 001-006, ILIT-CV-0503) with a history of coronary artery disease received one dose of study drug (rilonacept 80 or 320 mg or placebo). 17 days after her first dose she developed chest pain secondary to a arrhythmia. The patient had a preexisting history of stable angina and arrhythmias.

## 10. References

None.