

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BL 125249/0**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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BLA	STN 125249
Submission Dates:	5/25/2007; 7/26/2007; 9/24/2007; 9/27/2007; 10/3/2007
Brand Name	ARCALYST™
Generic Name	Rilonacept (or IL-1 Trap), monoclonal antibody (fusion protein to human IgG1 Fc)
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OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sponsor	Regeneron Pharmaceuticals
Relevant IND	BB-IND 11,781
Submission Type; Code	NME; 1P
Formulation; Strength(s); Administration Route	Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution; Subcutaneous
Proposed Indication	An Orphan Indication- For _____ treatment, _____ _____ of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).
Proposed Dosage Regimen	<ul style="list-style-type: none"><li>• Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2 mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly.</li><li>• Pediatric patients ages &lt;math&gt;\leq 17&lt;/math&gt;: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. Do not administer ARCALYST more often than once weekly.</li></ul>

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### 1 Executive Summary

#### 1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

#### 1.2 Phase IV Commitments

None.

### 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG<sub>1</sub>. Rilonacept has a molecular weight of approximately 251 kDa, ( ). Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

The Sponsor developed rilonacept (or IL-1 Trap) as a novel therapeutic molecule for blockade of inflammation caused by overproduction of the cytokine IL-1. Rilonacept is indicated for treatment of cryopyrin-associated periodic syndromes (CAPS), such as Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS). Currently there are about 200-300 CAPS patients in the U.S. There is no approved therapy for the CAPS indication. Anakinra (an IL-1 receptor antagonist) approved for rheumatoid arthritis (RA) or NSAIDs are used off-label for the treatment of CAPS. The Sponsor received orphan drug designation in Dec, 2004 and Fast Track designation for the development of IL-1 Trap for CAPS in May 2006. This BLA is under priority review.

The clinical development program included a single pivotal study (Study IL1T-AI-0505, or Study 505) designed to provide two independent assessments of the efficacy of rilonacept to reduce the signs and symptoms of CAPS diseases when used for long term therapy: one evaluated efficacy for reduction in signs and symptoms and the other evaluated maintenance of efficacy for reduction of signs & symptoms.

**Mechanism of Action:** CAPS refers to rare genetic syndromes caused by mutations in the gene, Cold-Induced Autoinflammatory Syndrome 1 (*CIAS1*). These syndromes include FCAS, MWS, and Neonatal Onset Multisystem Inflammatory Disease (NOMID). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

*CIAS1* encodes a protein called cryopyrin or NALP3 that is a component of the "inflammasome", which is a protein complex that includes caspase-1 and controls activation of the proinflammatory cytokine, IL-1 $\beta$ . Pharmacologically, the gene mutation in *CIAS1* results in an overactive inflammasome leading to excessive release of activated IL-1 $\beta$  that drives inflammation. Rilonacept blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1 (both IL-1 $\alpha$  and IL-1 $\beta$ ) and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1 receptor antagonist (IL-1ra) with somewhat reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1 $\beta$ , IL-1 $\alpha$  and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

**Comparability among Product Lots:** During product development, there were four major drug substance processes (DS P1 to P4) and five drug product processes. The final to-be-marketed product is designated DP P4B made from DS P4. It was the product used in the Part B (randomized withdrawal phase) of the pivotal clinical study, Study 505, and its on-going open

label extension (OLE) phase. No bioequivalence study was conducted to determine PK comparability of different drug product processes.

Comparability between different drug substances (DS P1 to P2, P2 to P3, and P3 to P4) and drug products (DP P4A and P4B) were determined by Product review of physicochemical property assessment from stability and release data. The results indicated comparability. Refer to Product review for details.

With respect to the pivotal clinical trial formulation changes, drug products, DP P4A and DP P4B, were used in Study 505. They only differed in lyophilization process. Data obtained from the same subjects who received P4A in the single-blinded phase of Part B and P4B in the randomized withdrawal phase of Part B indicated that drug exposures (trough concentrations) were comparable between formulations. Data from Study 505 also suggested that the formulation process change did not appear to affect efficacy and safety outcomes.

***Pharmacokinetics Findings:***

***Healthy Subjects:*** Two PK studies were conducted in healthy subjects with drug product P3A and assay method IL1T-AS-03034R.1. Study IL1T-RA-0401 (or Study 401) was a single-ascending dose study with doses of 80-320 mg following subcutaneous injection. Study IL1T-RA-0402 (or Study 402) was a single ascending dose study with single doses of 100-2000 mg administered via intravenous injection. The results from healthy volunteer studies suggested that following SC route, exposure of rilonacept in healthy subjects was dose proportional in the range of 80 to 320 mg. Rilonacept had a  $T_{max}$  of about 3 days and a half-life of 6 days via SC administration. Absolute bioavailability via SC route estimated via cross study comparison was about 43%.

***CAPS Patients:*** No dense PK data was collected in CAPS patients. In Study 505, trough plasma samples were collected on Day 0, and every 3 weeks thereafter until Week 24. Patients received a loading dose of 320 mg on Week 1 and thereafter weekly injection of 160 mg. Additional trough plasma samples were also collected for patients who continued the 24-week OLE portion of the study or who were newly enrolled to OLE on Day 0 and every 3-12 weeks thereafter until Week 24. Mean trough levels at the end of 24-week OLE in adults were 24  $\mu\text{g/mL}$  (range 7-56  $\mu\text{g/mL}$ ). Steady-state seemed to be reached by Week 6 as no further increase in trough levels was observed after Week 6.

Quantitative PK results from healthy subjects could not be used to compare to patient PK data as different drug products and bioanalytical assay methods were used. No formal cross-validation was conducted to compare the assay methods.

***Pharmacokinetics in Special Populations:*** No formal PK studies in subjects with hepatic impairment, renal impairment or in pediatric populations were conducted.

Four pediatric patients (age 13-16 years) were enrolled in OLE of Study 505. Mean trough levels were 20  $\mu\text{g/mL}$  (range 3.6-33  $\mu\text{g/mL}$ ) at Week 24 at a weekly dose of 2.2 mg/kg up to 160 mg.

No study was conducted to evaluate the age, gender and body weight effect on rilonacept exposure. We evaluated the age, gender and body weight effect by using the trough levels data collected in Study 505. It was found that rilonacept steady state trough concentrations were similar between male and female subjects, and did not appear to change with body weight (within the range of 50 -120 kg) and age (within the range of 26 -78 years).

Although a POP-PK analysis was conducted by the Sponsor, majority of these data were from a different patient population with different formulations and analytical assay methods. The PK characteristics and trend observed in these data may not reflect those of the CAPS population. In the absence of blood samples collected at various timepoints covering the full profile in CAPS patients, PK characterization in CAPS patients remains incomplete.

***Pharmacodynamic Findings:***

***Cytokine Complexes:*** The equilibrium dissociation constants for rilonacept binding to IL-1 $\beta$ , IL-1 $\alpha$  and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively. Trough levels for rilonacept:IL-1 $\beta$  complex and rilonacept:IL-1ra complex were determined in the pivotal study. Rilonacept:IL-1 $\alpha$  complex levels were not detectable with the available method. Complexes with IL-1ra generally comprised less than 15% of the total rilonacept concentrations, and IL-1 $\beta$  complexes comprised less than 0.05% of the total.

***Inflammation Markers:*** C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are monitored as biomarkers and indicators of inflammatory disease activity in CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with rilonacept resulted in significant reductions from baseline in mean serum CRP and SAA to normal levels following rilonacept administration. In Study 505, rilonacept treatment decreased median CRP from 20.1 to 1.3 mg/L ( $p < 0.0001$ ) during the double blind Part A portion of the study, and SAA decreased from 49.5 to 2.5 mg/L ( $p = 0.006$ ).

***Exposure-Response:*** Only one dose was studied in CAPS patients. It is not clear whether the dosage regimen selected (160 mg weekly) is the lowest effective dose.

***Rationale for Dose Selection:*** No formal dose-ranging study was conducted in CAPS patients. Dose selection was based on experience with studies in a different indication, and a pilot study (Study IL1T-AI-0406) in 5 CAPS patients in which following the initial 300 mg (100 mg/day for 3 days) loading dose, doses were escalated from 100 mg/week, to 160 mg/week, and up to 320 mg/week based on clinical evaluation. Evaluation of cytokine complex formation suggested an increase in IL-1 $\beta$  complex levels for CAPS subjects following dose escalation from 100 mg to 160 mg weekly. Therefore 160 mg was selected because it provided higher systemic levels of rilonacept than 100 mg throughout the dosing interval, maintaining levels that seemed to be associated with biological activity. It was also the highest dose that could be delivered with a single 2 mL injection of the formulation of rilonacept.

***Immunogenicity:*** As with all therapeutic proteins, rilonacept has the potential to induce an immune response. Twenty of 46 patients (43%) tested positive for binding antibodies on at least

one occasion during the first 24 weeks of Study 505. Seven patients also developed neutralizing antibodies. Additional 2 patients who were continued to the 24-week OLE tested positive for binding antibodies. And one adult and one pediatric patient who directly enrolled to OLE of Study 505 also tested positive for binding antibodies. Therefore, twenty-four of 58 patients (41%) tested positive for treatment-emergent binding antibodies on at least one occasion during the 48 week treatment (Study 505 and OLE). At least 6 patients showed persistent antibody reaction up to 48 weeks. Although some subjects who tested positive to antibody showed decrease in exposure but overall, there was no clear trend between antibody titer to the exposure of riloncept as this was within the large inter-individual variability of trough concentrations (CV: 40% - 50%). There does not appear to be any relationship between the appearance of antibodies to riloncept and the safety or efficacy of the molecule. Data from subjects who developed neutralizing antibody also did not show an effect on efficacy.

**Drug Metabolism and In Vivo Drug-Drug Interaction:** No studies on the metabolism of riloncept have been performed in humans. No formal drug-drug interaction assessment for riloncept and other drugs or biologics was performed. Metabolism studies are not generally performed for monoclonal antibodies because they are proteins which are degraded into amino acids that are then recycled into other proteins. Several pathways have been described that may contribute to antibody metabolism, all of which involve biodegradation of the antibody to smaller molecules, i.e., small peptides or amino acids. Although not studied, the concomitant use of riloncept and other immune modulators such as TNF inhibitors or anakinra should be avoided due to potential increased risk of serious infection. Cytochrome P450 enzymes in the liver are down-regulated by infection and inflammation stimuli. A recent publication showed gene-specific effect of inflammatory cytokines on P450 regulation in human hepatocytes.<sup>1</sup> IL-1 was shown to down-regulate CYP2C8 and CYP3A4 while having no effect on CYP2B6, 2C9, 2C18 and 2C19. Because riloncept binds to IL-1, it may reverse the down-regulation effect of IL-1 leading to increased metabolism of drugs that are metabolized by CYP2C8 and CYP3A4. Caution should be exercised when ARCALYST is coadministered with CYP2C8 and CYP3A4 substrates such as repaglinide and oral contraceptives.

**QT/QTc Evaluation:** A thorough QT/QTc study was not conducted for riloncept since it is generally not required for a biological product.

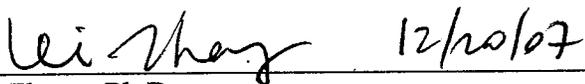
**Adverse Events:** The most common adverse events reported with riloncept in CAPS patients were injection-site reaction (ISR) and upper respiratory tract infection. The ISRs were mild to moderate in severity. They only lasted one day for most subjects and did not require medication therapy. The one potential adverse event of concern is infections. There were no serious infections seen in the pivotal trial. In the open label, however, there was one death secondary to streptococcal meningitis. Another patient in the development program developed an opportunistic infection from mycobacteria intracellulare.

**Conclusion:** Overall, acceptable Clinical Pharmacology information has been presented in this BLA. The pivotal clinical trial demonstrated acceptable safety and efficacy of riloncept in

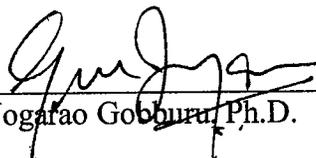
<sup>1</sup> Artkin and Morgan. Gene-Specific Effects of Inflammatory Cytokines on Cytochrome P450 2C, 2B6, and 3A4 mRNA Levels in Human Hepatocytes. *Drug Metab. Disp.* 35(9):1687-1693, 2007.

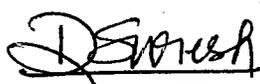
**Conclusion:** Overall, acceptable Clinical Pharmacology information has been presented in this BLA. The pivotal clinical trial demonstrated acceptable safety and efficacy of riloncept in CAPS patients with the proposed dose regimen. Even though, full PK profile has not been determined in CAPS patients, exposure in the form of trough levels in CAPS patients has been submitted. In view of the successful clinical findings, lack of full PK information in patients is not considered a deficiency that would impact the approval of this BLA. If clinical trials are conducted in the future in CAPS patients, then sponsor should collect full PK information.

The Required Office-Level Clinical Pharmacology briefing took place on Nov 1, 2007.

 12/20/07  
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## 2 Question-Based Review (QBR)

*Reviewer's Notes: Rilonacept and IL-1 Trap were used interchangeably in this review.*

### 2.1 General Attributes

**2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?**

**Chemistry and Physico-Chemical Properties:** ARCALYST (rilonacept) is a recombinant fusion protein containing the extracellular domains of the human IL-1RI receptor (IL-1RI) and the IL-1 receptor accessory protein (AcP), fused inline with the Fc domain from human IgG<sub>1</sub> (Figure 2.1.1.1).

Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

Figure 2.1.1.1.

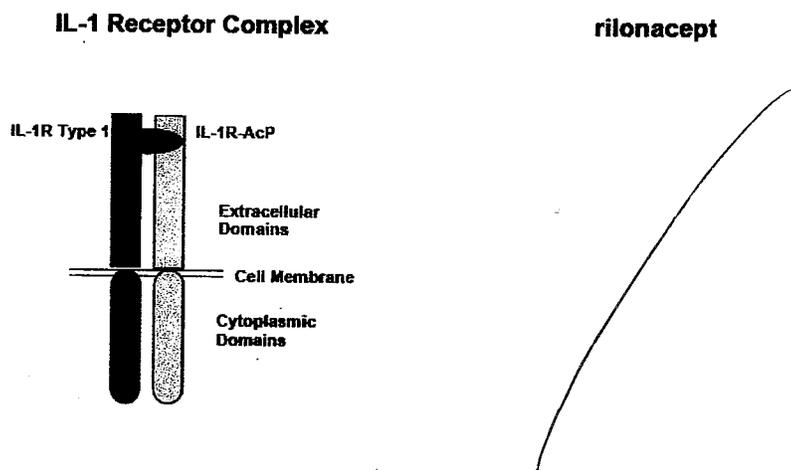


Figure 2.1.1.1. The rilonacept is created by fusing the sequences encoding the extracellular domains of the AcP, IL-1RI, and Fc inline

**Table 2.1.1.1. Characteristics of Rilonacept.**

Characteristic	Information
Description	Dimeric in-line fusion glycoprotein with MW ~251 kDa:
Ligand binding specificity	IL-1 $\beta$ , IL-1 $\alpha$ , IL-1ra
Binding affinity (KD) by BiaCore	IL-1 $\beta$ = 0.5 pM IL-1 $\alpha$ = 1.4 pM IL-1ra = 6.1 pM

**Formulation:** ARCALYST (Rilonacept) is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection (SWFI). Each vial contains 220 mg rilonacept (160 mg/2 mL after reconstitution), histidine, arginine, polyethylene glycol 3350, sucrose, and glycine at a pH of  $6.5 \pm 3$ . No preservatives are present.

**2.1.2 What is the proposed mechanism of drug action and therapeutic indication? What is the proposed dosage and route of administration?**

**Mechanism of Action:** Cryopyrin-Associated Periodic Syndromes (CAPS) refers to rare genetic syndromes caused by mutations in the gene, Cold-Induced Autoinflammatory Syndrome 1 (CIAS1). The gene mutation in CIAS1 results in an overactive inflammasome leading to excessive release of activated IL-1 $\beta$  that drives inflammation. Rilonacept blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1 (both IL-1  $\alpha$  and IL-1  $\beta$ ) and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1 receptor antagonist (IL-1ra) with somewhat reduced affinity. The equilibrium dissociation constants for rilonacept binding to

IL-1 $\beta$ , IL-1 $\alpha$  and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively determined by BiaCore surface plasmon resonance technology.

**Proposed Indication:** ARCALYST is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

**Dosage and Route of Administration:**

- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2 mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly.
- Pediatric patients age 6 to 17: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. Do not administer ARCALYST more often than once weekly.

## 2.2 General Clinical Pharmacology

### 2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

The PK of rilonacept was studied in healthy subjects via SC and IV routes. A drug product (P3A) generated from an older process and an earlier analytical method were used for these studies. In addition, trough levels were collected from CAPS patients in the pivotal clinical trial (Study 505 and its OLE). In this study, the final-to-be marketed drug product (P4B) and a newer analytical method were used.

The clinical development program included a single pivotal study (Study IL1T-AI-0505, or Study 505) designed to provide two independent assessments of the efficacy of rilonacept to reduce the signs and symptoms of CAPS diseases when used for long term therapy.

Study 505 was a multi-center, double-blind, placebo-controlled study. Weekly subcutaneous (SC) doses of 160 mg of rilonacept were dosed in adult subjects with active CAPS in 27 study sites in the United States. The study consisted of a 3-week screening period, a 6-week, double-blind, randomized, placebo-controlled treatment period (Part A, 1:1 ratio), a 9-week single-blind active-treatment period followed by a 9-week double-blind, placebo-controlled, randomized withdrawal phase (Part B, 1:1 ratio), a 24-week open-label extension phase (OLE), a 64-week long-term open-label extension (LTOLE), and a 6-week post-treatment follow-up period. Amendments 4 and 6 allowed eligible adult and pediatric subjects to enroll directly into the open-label phases of the trial. At the beginning of the study, subjects received 320 mg SC as a loading dose and 160 mg weekly SC dose was administered subsequently.

**2.2.2 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?**

**Efficacy:**

The primary endpoint was Mean Change from Baseline in the Mean Key Symptom Score (KSS) (based on Daily Health Assessment Form (DHAF)). The key symptoms included: rash, feeling of fever/chills, joint pain, eye redness/pain, and fatigue. The DHAF has a scale from 0=no severity to 10=very severe, which is a 21-point scale with 0.5-point intervals. For each day, the 5 scores were summed and divided by 5 (daily mean score). For each observation period, the daily mean scores were summed and divided by 21 (the number of days in the observation period) to result in a mean key symptom score (KSS) for the observation period.

**Part A of Study 505:**

The group randomized to treatment with rilonacept showed significant improvement in key symptom score from a Baseline mean of 3.1 to an endpoint (Week 6) mean of 0.5 (1-sample t-test  $p < 0.0001$ ) (Table 2.2.2.1). Tertiary and exploratory measures for efficacy were listed in Table 2.2.2.2.

**Table 2.2.2.1.**

**Table 11 Summary of Mean Change from Baseline to Endpoint in Mean Key Symptom Score (KSS) – Primary Analysis in Part A**

Assessment Period	Statistic	Rilonacept (n=23)	Placebo (n=24)	Comparison p-value*
Baseline Part A	Mean KSS	3.1	2.4	P<0.0001
	Median KSS	2.8	2.0	
	SD	1.9	1.5	
	(min – max)	(0.7, 8.1)	(0.6, 5.4)	
	n	23	24	
Endpoint Part A (Week 6)	Mean KSS	0.5	2.1	
	Median KSS	0.3	1.5	
	SD	0.5	1.6	
	(min – max)	(0.0, 1.7)	(0.4, 6.5)	
	n	23	24	
Change from Baseline Part A to Endpoint Part A	Mean Change	-2.6	-0.3	
	Median Change	-2.3	-0.3	
	SD of Change	1.9	0.7	
	(min – max)	(-8.1, -0.1)	(-1.8, 1.1)	
	n	23	24	
	p-value of significance of change from Baseline†	p<0.0001	NS	

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

SD: standard deviation

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

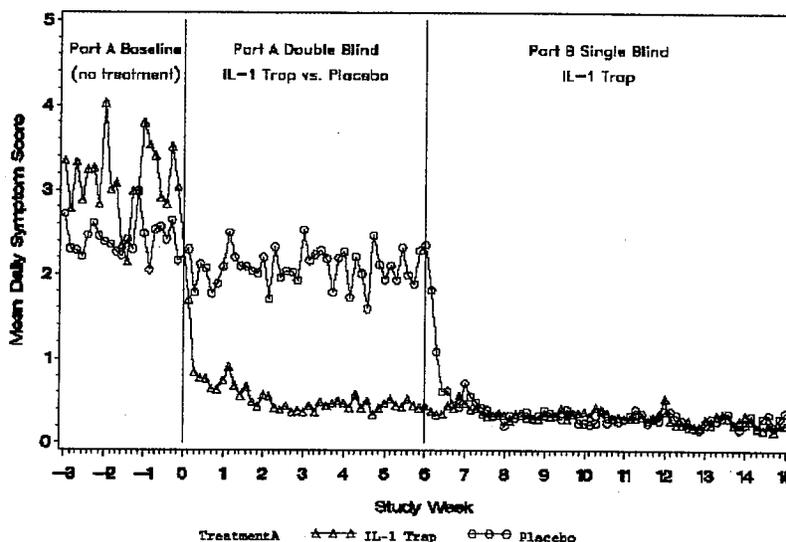
† p-value of significance of change from Baseline is 1-sample t-test

NS: not significant

Source: Post-text Table 9.2.1.1.1 and Analysis Output in Statistical Appendix 11.1.9/T1.1A

Figure 2.2.2.1.

Figure 4 Mean Daily Key Symptom Score by Treatment Group from Week -3 to Week 15 in Study Part A and Part B Single-blind Phase



Source: Post-test Figure 9.4.2.1

Table 2.2.2.2.

Table 16

Summary of Tertiary and Exploratory Measures of Efficacy for Part A (Physician's Global Assessment, Patient's Global Assessment, Limitation of Activities Assessment, CRP, SAA)

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	
Limitation of Activities	Rilonacept (n=23)	3.0	0.8	-2.2	0.006
	Placebo (n=24)	2.4	1.6	-0.8	
CRP <sup>†</sup> (0.0 – 8.4 mg/L)	Rilonacept (n=23)	20.1 <sup>†</sup>	1.3 <sup>†</sup>	-18.4 <sup>†</sup>	<0.0001
	Placebo (n=24)	25.2 <sup>†</sup>	21.8 <sup>†</sup>	-2.1 <sup>†</sup>	
SAA <sup>†</sup> (0.7 – 6.4 mg/L)	Rilonacept (n=23)	49.5 <sup>†</sup>	2.5 <sup>†</sup>	-48.5 <sup>†</sup>	0.006
	Placebo (n=24)	63.5 <sup>†</sup>	39.7 <sup>†</sup>	-2.8 <sup>†</sup>	

Note: Sample sizes differ due to missing data for laboratory parameters

\*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.

<sup>†</sup>The values displayed for CRP and SAA change from Baseline are median values.

CRP=C-reactive protein; SAA=serum amyloid A

Source: Post-test Tables 9.2.3.1.1, 9.2.3.2.1, 9.2.4.1.1, 9.2.4.2.1, 9.2.4.3.1, and Analysis Output in Statistical Appendix 11.1.9/T5.2A, T5.4A, T7.2A

Part B of Study 505:

The group randomized to treatment with rilonacept maintained low mean key symptom score from a Baseline mean of 0.3 to an endpoint (Week 24) mean of 0.4 (the change was not significant with a 1-sample t-test). Beginning with a Baseline mean of 0.2 on rilonacept therapy, the group then randomized to placebo had an endpoint mean of 1.2, which was nominally highly significant (1-sample t-test  $p < 0.0001$ ) (Table 2.2.2.3). Tertiary and exploratory measures for efficacy were listed in Table 2.2.2.4.

**Table 2.2.2.3.**

**Table 18**

**Summary of Mean Change from Baseline to Endpoint in Mean Key Symptom Score (KSS): Primary Analysis for Part B**

Assessment Period	Statistic	Rilonacept (n=22)	Placebo (n=23)	Comparison p-value*
<b>Baseline Part B (Ending at Week 15)</b>	Mean KSS	0.3	0.2	
	Median KSS	0.2	0.1	
	SD	0.3	0.4	
	(min – max)	(0.0, 1.0)	(0.0, 2.1)	
	n	22	23	
<b>Endpoint Part B (Ending at Week 24)</b>	Mean KSS	0.4	1.2	
	Median KSS	0.2	0.7	
	SD	0.5	1.0	
	(min – max)	(0.0, 2.0)	(0.0, 3.2)	
	n	22	23	
<b>Change from Baseline Part B to Endpoint Part B in Mean KSS</b>	Mean Change	0.1	0.9	P=0.0002
	Median Change	0.0	0.6	
	SD of Change	0.4	0.9	
	(min – max)	(-0.7, 1.5)	(-0.2, 2.7)	
	n	22	23	
	p-value of significance of change from Baseline <sup>†</sup>	NS	$p < 0.0001$	

Mean Key Symptom Score is derived from the Daily Health Assessment Form (diary questionnaire); symptom scale is 0=no severity to 10=very severe.

SD: standard deviation

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

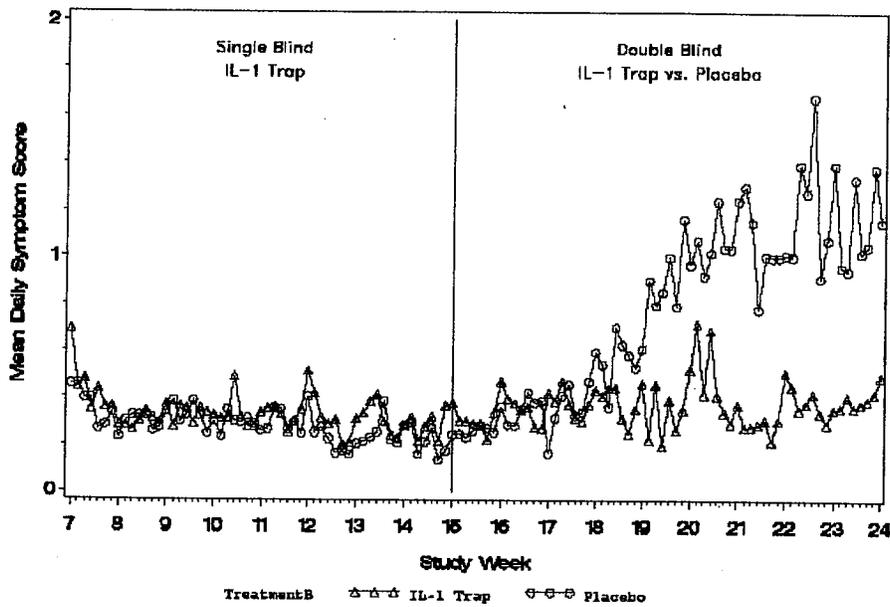
†p-value of significance of change from Baseline is 1-sample t-test

NS: not significant

Source: Post-text Table 9.2.1.1.3 and Analysis Output in Statistical Appendix 11.1.9/T2.1A

Figure 2.2.2.2.

Figure 5 Mean Daily Key Symptom Score by Treatment Group from Week 6 Single-Blind Phase to Week 24 Randomized Withdrawal Phase in Part B



Source: Post-text Figure 9.4.2.2

Table 2.2.2.4.

Table 23

Summary of Tertiary and Exploratory Measures of Efficacy for Part B (Physician's Global Assessment, Patient's Global Assessment, Limitation of Activities Assessment, CRP, SAA)

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)	1.5 <sup>†</sup>	1.7 <sup>†</sup>	0.0 <sup>†</sup>	0.0001
	Placebo (n=23)	1.5 <sup>†</sup>	16.3 <sup>†</sup>	13.3 <sup>†</sup>	
SAA (0.7 - 6.4 mg/L)	Rilonacept (n=22)	2.5 <sup>†</sup>	2.8 <sup>†</sup>	0.0 <sup>†</sup>	0.01
	Placebo (n=23)	3.8 <sup>†</sup>	28.3 <sup>†</sup>	26.3 <sup>†</sup>	

\*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.

<sup>†</sup>The values displayed for CRP and SAA change from Baseline are median values.

Sample sizes differ due to missing data for laboratory parameters and missing physician's evaluation.

Higher scores indicate worse disease activity.

Source: Tables 9.2.3.1.3, 9.2.3.2.3, 9.2.4.1.3, 9.2.4.2.3, 9.2.4.3.3, and Analysis Output in Statistical Appendix 11.1.9/T6.2A, T6.4A, T8.2A

**Safety:**

There were no deaths in this study. There was one SAE reported during the course of the study; sciatica was reported by a 62-year-old white female treated with rilonacept, with a prior history of osteoarthritis and sciatica, judged not related to study medication by the Investigator. There was one withdrawal from the study due to adverse events.

Injection site reaction is the most frequent adverse event (AE). Overall, injection site reactions were reported in approximately one-third to one-half of subjects treated with rilonacept, a rate approximately three-fold greater than that reported for subjects treated with placebo.

Upper respiratory tract infection (URTI) is another most frequent AE that may be related to cold season. While there was an increased incidence of URI with rilonacept compared with placebo during Part A, there were no URITs reported during the randomized withdrawal phase, the other double blind comparison (Table 2.2.2.5).

**Table 2.2.2.5. Number (%) of Patients Reporting Treatment-Emergent Adverse Events of Infections by Treatment Group and Study Phase.**

Treatment Assignment	Part A Double-blind Phase (6 weeks)	Part B (Segment A) Single-blind, Rilonacept Treatment Phase (9 weeks)	Part B (Segment B) Double-blind, Randomized, Withdrawal Phase (9 weeks)
Rilonacept	11 (48%) n=23	9 (20%) n=46	4 (18%) n=22
Placebo	4 (17%) n=24	--	5 (22%) n=23

**2.2.3 What pharmacodynamic markers were evaluated?**

Trough concentrations of rilonacept/cytokine complexes (e.g., rilonacept:IL-1 $\beta$ ) were monitored. In general, concentrations for rilonacept:IL-1ra was less than 15% of total rilonacept concentrations, and rilonacept:IL-1 $\beta$  was less than 0.05% of total total rilonacept concentrations. Rilonacept:IL-1 $\alpha$  complex levels were not detectable with the available method.

Inflammatory disease is associated with well-established changes in acute phase response proteins in the blood, such as C-reactive protein (CRP) and serum amyloid A (SAA) that serve as pharmacodynamic biomarkers. Chronic elevation of SAA can lead to amyloidosis resulting in kidney disease and mortality in subjects with CAPS. Inflammation also gives rise to elevated white blood count, platelets and neutrophils. Normalization of these values provides evidence of a rilonacept pharmacodynamic effect. In Study 505, CRP and SAA were measured as exploratory endpoints suggesting pharmacodynamic effect of rilonacept. Data in Tables 2.2.2.2

and 2.2.2.4 showed decrease in CRP and SAA levels in the presence of rilonacept and increase in CRP and SAA levels when switching from rilonacept to placebo.

**2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?**

Total IL-1 Trap (free plus various complex) levels in plasma were measured with an ELISA method to assess PK parameters. Separate assays were used to measure IL-1 Trap:IL-1 $\beta$  complex and IL-1 Trap: IL-1ra complex for potential PD assessment.

**2.2.5 What was exposure-response relationship of rilonacept in terms of efficacy and safety?**

Only one dose was studied. No exposure-response relationship was explored.

**2.2.6 What are PK characteristics of rilonacept in healthy subjects? Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

Two PK studies were conducted in healthy subjects with product (P3A) and assay method (IL1T-AS-03034R.1). Study IL1T-RA-0401 (or Study 401) was a single-ascending dose study with doses of 80-320 mg following subcutaneous injection. Study IL1T-RA-0402 (or Study 402) was a single ascending dose study with single doses of 100-2000 mg via intravenous injection. The results from healthy volunteer studies suggest that following SC route, exposure of rilonacept in healthy subjects was dose proportional in the range of 80 to 320 mg. Rilonacept had a Tmax of about 3 days and half-life of 6 days via SC administration. Absolute bioavailability via SC route estimated via cross study comparison was about 43%.

**Table 2.2.6.1. Study 401: Summary of Mean PK Parameters following the Rilonacept (P3A) at Doses 80 to 320 mg (SC).**

Treatment	N	Dose (mg)	Cmax ( $\mu\text{g/mL}$ )	AUCinf ( $\mu\text{g/mL}\cdot\text{hr}$ )	AUCt ( $\mu\text{g/mL}\cdot\text{hr}$ )	Tmax (hr)	T <sub>1/2</sub> (hr)
D	13	80	4.4	1195	1158	61	154
E	13	104	5.5	1774	1682	92	164
F	13	120	5.5	1621	1593	96	147
G	5	240	11.6	3755	3712	120	147
I	5	160	8.8	2286	2263	67	126
J	4	320	16.5	5263	5195	66	152

**Table 2.2.6.2. Study 402: Summary of the Pharmacokinetic Parameters of Rilonacept (60-min IV Infusion).**

Dose	N	Cmax ( $\mu\text{g/mL}$ )	AUCinf ( $\mu\text{g/mL}\cdot\text{hr}$ )	AUCt ( $\mu\text{g/mL}\cdot\text{hr}$ )	Tmax (hr)	T <sub>1/2</sub> (hr)	V <sub>ss</sub> (L)
100 mg	5	19.6	3235	3185	4.8	188	7.0
300 mg	3	71.6	12755	12427	3.2	216	5.8
1000 mg	5	187	31568	30923	6.8	195	7.5
2000 mg	5	455	71629	69688	7.6	254	6.8

**2.2.7 What is PK of riloncept in patients? How does the PK of riloncept in healthy volunteers compare to that in patients?**

No dense PK data was collected for CAPS patients. Trough levels for CAPS patients at steady state were approximately 24 µg/mL (range 7-56 µg/mL) following 160 mg weekly SC dosing of riloncept.

Quantitative PK results from healthy subjects could not be used to compare to patient PK data where different drug products and bioanalytical assay methods were used. No formal cross-validation was conducted to compare the assay methods.

**2.3 Intrinsic Factors**

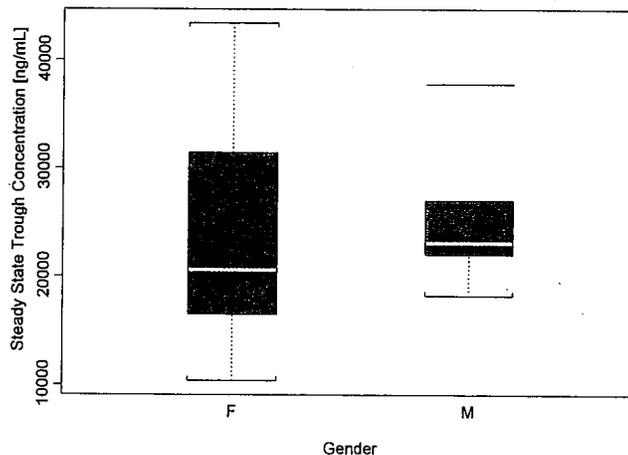
**2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?**

**Pharmacokinetics in Special Populations:** No dedicated studies in subjects with hepatic impairment, renal impairment or in pediatric populations were conducted. No study was conducted to evaluate the age, gender and body weight effect on riloncept exposure. Clinical Pharmacology review team evaluated the age, gender and body weight effect by using the exposure data collected in Study 505. Refer to Pharmacometrics (PM) review (Section 4.3) for details.

**a) Gender**

The steady state trough concentrations were similar between male and female subjects based on Week 9 exposure data from 14 females and 9 males in randomized withdrawal phase of Part B of Study 505 (Table 2.3.1.1 and Figure 2.3.1.1).

**Figure 2.3.1.1. Steady state trough concentration distribution in different gender groups**



Note: F = Female, M= male

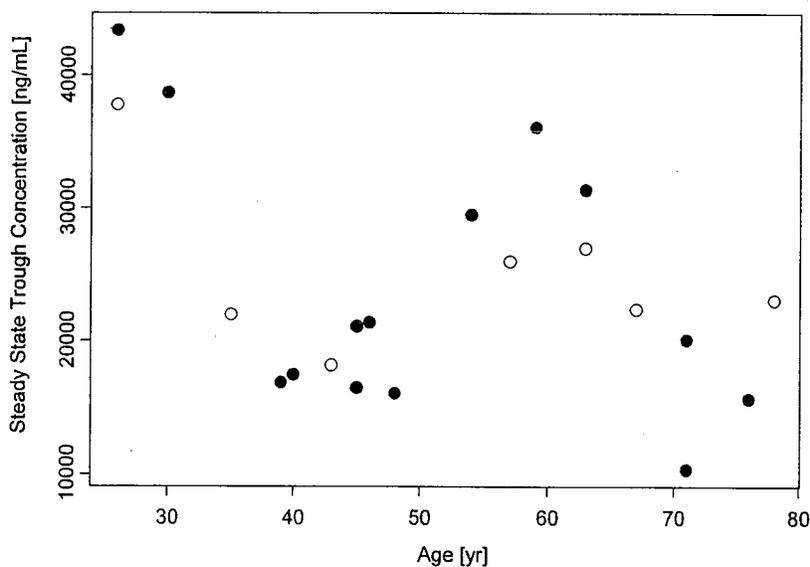
**Table 2.3.1.1. Summary of the gender effect effect on steady state trough concentration following market formulation administration**

	Gender Effect	
	Female	Male
Number of observations	14	7
Trough Concentration [ng/mL] Mean (SD)	23914.29 (10074.02)	25214.29 (6246.713)
Median (10th - 90th percentile)	20600 (15820 - 37920)	23100 (20480 - 31320)

**b) Elderly**

Age does not appear to have an effect on trough concentrations. Efficacy was demonstrated in patients with CAPS who were either older or younger than the median age of 51 years in Study 505.

**Figure 2.3.1.1. Steady state trough concentrations at week 24 from male (blue open circle) and female (red solid circle) subjects versus age.**



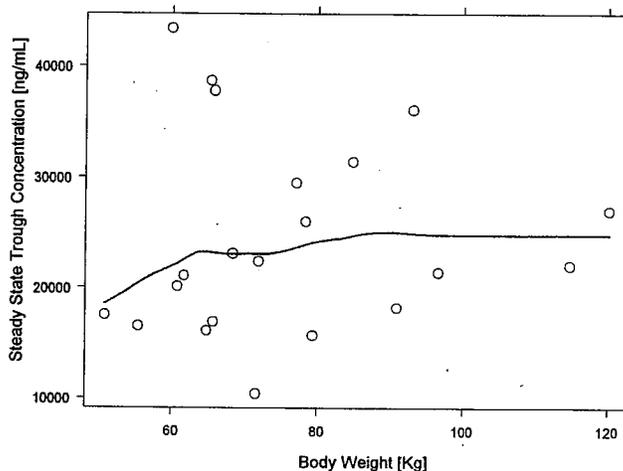
**c) Pediatric Patients**

Four pediatric patients were enrolled in OLE of Study 505. Mean trough levels were 20 µg/mL (range 3.6-33 µg/mL) at Week 24 following weekly SC dose of 2.2 mg/kg up to 160 mg.

**d) Body Weight**

Rilonacept trough exposure does not appear to change with body weight (within the range of 50 - 120 kg) (Figure 2.3.1.3).

**Figure 2.3.1.3. Steady state trough concentration versus body weight**



Note: open circle = observation, red line = lowest smooth line

**e) Race**

Only Caucasian patients participated in Study 505 because *CAIS-1* gene mutation is rare with 90% traced to one family tree.

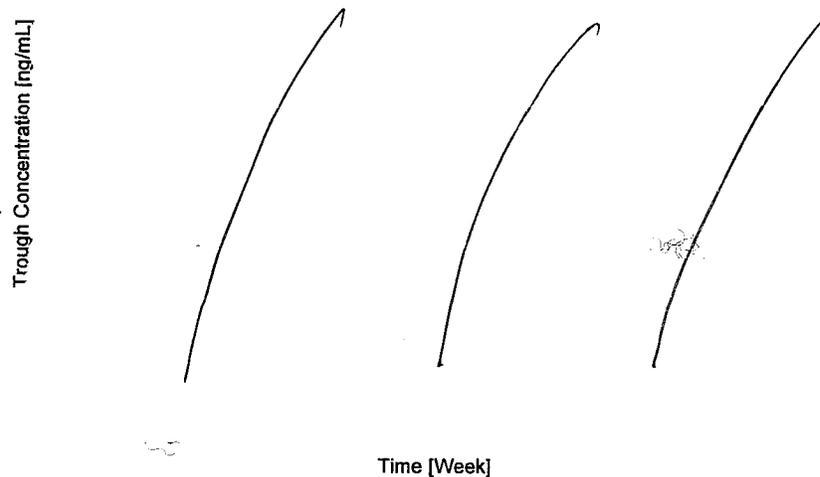
**2.3.2 What were the immunogenicity findings for rilonacept? What was the impact of immunogenicity on exposure and/or safety and efficacy?**

Twenty of 46 patients (43%) tested positive for binding antibodies on at least one occasion during the first 24 weeks of Study 505. Seven patients also developed neutralizing antibodies. Additional 2 patients who were continued to the 24-week OLE tested positive for binding antibodies. And one adult and one pediatric patient who directly enrolled to OLE of Study 505 also tested positive for binding antibodies. Therefore, twenty-four of 58 patients (41%) tested positive for treatment-emergent binding antibodies on at least one occasion during the 48 week treatment (Study 505 and OLE). At least 6 patients showed persistent antibody reaction up to 48 weeks.

We investigated the relationship between immunogenicity and rilonacept trough exposure and found that immunogenicity appears to affect the exposure for some of the subjects; however, given the large inter-individual variability of trough concentrations, the trough concentrations in antibody positive group appears to be comparable to those in antibody negative group (Figure 2.3.2.1). Refer to PM review (Section 4.3) for details.

There also does not appear to be any relationship between the appearance of antibodies to rilonacept and the safety or efficacy of the molecule. Data from subjects who developed neutralizing antibody also did not show an effect on efficacy.

**Figure 2.3.2.1. Trough concentrations in antibody negative group (blue open circle) versus trough concentrations in antibody positive group (red solid circle)**



Note: Blue open circle = Trough concentration with negative antibody  
Red solid circle = Trough concentration with positive antibody

## 2.4 Extrinsic Factors

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?**

None has been studied.

### **Effect of other drugs on rilonacept:**

Concomitant medicines were allowed in clinical trials. The most common ones used were anti-inflammatory/anti-rheumatic products, non-steroids, and analgesics and antipyretics. There was no evidence to suggest an interaction between concomitant use of rilonacept and anti-inflammatory or anti-rheumatic products (non-steroids).

Interleukin-1 (IL-1) blockade may interfere with immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking rilonacept.

The use of anakinra or anti-TNF agents during the course of the study was prohibited. Receipt of a live (attenuated) vaccine during the 3 months prior to the Screening visit or during the course of the study was prohibited.

### Effect of riloncept on other drugs

Cytochrome P450 in the liver are down-regulated by infection and inflammation stimuli. A recent publication showed gene-specific effect of inflammatory cytokines on P450 regulation in human hepatocytes.<sup>1</sup> IL-1 was shown to down-regulate CYP2C8 and CYP3A4 while having no effect on CYP2B6, 2C9, 2C18 and 2C19. Because riloncept binds to IL-1, it may reverse the down-regulation effect of IL-1 leading to increased metabolism of drugs that are metabolized by CYP2C8 and CYP3A4. Caution should be exercised when riloncept is coadministered with CYP2C8 and CYP3A4 substrates such as repaglinide and oral contraceptives. The in vivo effect of riloncept on P450 may be confirmed with a cocktail study where probe substrates for main P450 enzymes are studied simultaneously.

**2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.**

None.

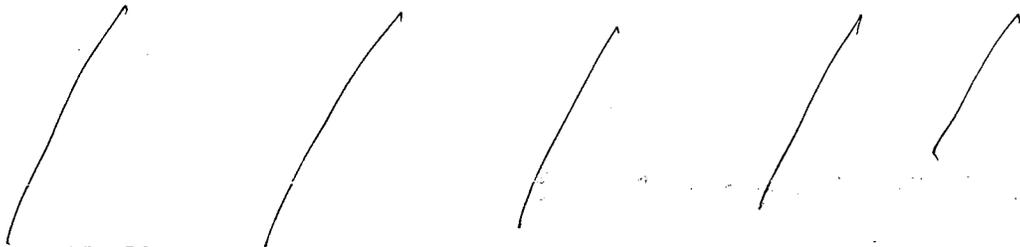
## 2.5 General Biopharmaceutics

**2.5.1 What is the final-to-be marketed formulation (drug substance and drug product) of riloncept (aka IL-1 Trap)?**

IL-1 Trap Drug Substance (DS) is formulated in \_\_\_\_\_ at pH 6.5 containing \_\_\_\_\_ nistidine, \_\_\_\_\_ (w/v) polyethylene glycol 3350, \_\_\_\_\_ (w/v) Glycine, \_\_\_\_\_ arginine, and \_\_\_\_\_ (w/v) sucrose.

\_\_\_\_\_ yield a solution of pH 6.5. IL-1 Trap DS is called Formulated Drug Substance (FDS) after the IL-1 Trap DS is \_\_\_\_\_

To manufacture the drug product (DP),



IL-1 Trap Drug Product (DP) is supplied as a lyophilized powder in a 20 mL glass vial for reconstitution with 2.3 mL of sterile WFI. The solution contains 80 mg/mL IL-1 Trap in an aqueous buffered solution at pH 6.5 containing — histidine, — (w/v) polyethylene glycol 3350 (PEG 3350). — (w/v) Glycine, — arginine, and — (w/v) sucrose. Two mL can be withdrawn from the vial, which provides a dose of 160 mg IL-1 Trap.

Table 2.5.1.1

Table 2.3.P.1-1: Nominal Composition of IL-1 Trap Formulation

Component	Function / Characteristic	Reference to Quality Standard	Formulated Drug Substance	Diluted Formulated Drug Substance (Pre-Lyophilized)	Reconstituted Drug Product
			Concentration (mg/mL)	Concentration (mg/mL)	Concentration (mg/mL)
Water for Injection	Solvent	USP, Ph. Eur.	NA	NA	NA
IL-1 Trap	Active ingredient	Not applicable	—	—	80
Histidine	/	USP, Ph. Eur.	/	/	/
Polyethylene glycol 3350	/	NF, Ph. Eur.	/	/	/
Glycine	/	USP, Ph. Eur., JP	/	/	/
-Arginine	/	USP, Ph. Eur., JP	/	/	/
Sucrose	/	NF, Ph. Eur., JP	/	/	/

NA = not applicable

**2.5.2 What are the major development processes for drug substance and formulations for drug product?**

**Drug Substance:**

Four drug substance (DS) manufacturing processes, designated P1 to P4, were used to manufacture riloncept during the clinical development program.

- The P1 process was used in the first phase 1 study in subjects with rheumatoid arthritis (RA; IL1T-RA-0004).
- The manufacturing process was subsequently transferred from Regeneron’s Tarrytown, New York facility to the Rensselaer, New York facility, modified and designated as Process P2.
- The most substantive changes in the drug substance manufacturing process occurred between P2 and P3, and included modifications to the \_\_\_\_\_ manufacturing process scale, and purification process \_\_\_\_\_). The changes in the P3 process resulted in increased scale, productivity and yield.

- The final commercial-scale, manufacturing process, designated P4, is similar to P3 with the exception of the \_\_\_\_\_

**Drug Product:**

- Drug substance from processes P1 and P2 was manufactured as a liquid formulation at concentrations up to 50 mg/mL for SC administration.
- DS from processes P3 and P4 was manufactured as a lyophilized form that was reconstituted for either a SC or intravenous (IV) delivery (lyophilization process designated as Process A). The lyophilized form was developed : \_\_\_\_\_
- The lyophilization cycle was further optimized to reduce the reconstitution time of the lyophilized cake (lyophilization process designated as Process B).

See Table 2.5.1.2 below (from the Product Team) for summary.

**Table 2.5.1.2. Manufacturing Development.**

Process	P1	P2	P3	P4*
Facility	Regeneron, Tarrytown (TT)	Regeneron, Rensselaer (R)	R	R
Cell line	CHO	CHO	CHO	CHO
Production Scale				
DS Concentration				
Facility	_____			
Concentration	25.0 mg/ml	12.5 mg/ml, 25 mg/ml, 50 mg/ml	80, 120, 160, 500 mg/ml	160 mg/ml
Batch Size (# vials)	_____			
Presentation	liquid	Liquid	Lyophilized – Process A	Lyophilized – Process A and B

**2.5.3 Which batches were used in the pivotal clinical and bioavailability studies?**

Refer to Table 2.5.2.1 for drug substance/products used in clinical studies.

The pivotal clinical trial IL1T-AI-0505 (or Study 505) Part B (randomized withdrawal phase) and its OLE used the drug product intended for marketed use (DP P4B). Trough plasma samples were collected to determine IL-1 Trap exposure levels. Drug product P4A was used in Part A and Part B (single blind phase) of Study 505.

**Table 2.5.2.1. Summary of Drug Substance Process Used in Clinical Studies of Riloncept**

<b>DS process</b>	<b>DP Dose Form</b>	<b>Study Number</b>	
<b>P1</b>	<b>Liquid, 25 mg/mL</b>	<b>IL1T-RA-0004</b>	P1
		<b>IL1T-RA-0111</b>	
<b>P2</b>	<b>Liquid, 12.5, 25, 50 mg/mL</b>	<b>IL1T-RA-0102</b>	P2
		<b>IL1T-RA-0401</b>	
<b>P3</b>	<b>Lyophilized, Process A, 80 mg/mL after recon</b>	<b>IL1T-RA-0401</b>	P3A
		<b>IL1T-RA-0402</b>	
		<b>IL1T-RA-0404</b>	
		<b>IL1T-RA-0408</b>	
		<b>IL1T-RA-0409</b>	
		<b>IL1T-AI-0406</b>	
		<b>IL1T-AI-0504</b>	
		<b>IL1T-OA-0425</b>	
		<b>IL1T-PR-0423</b>	
<b>IL1T-CV-0503</b>			
<b>P4</b>	<b>Lyophilized, Process A, 80 mg/mL after recon</b>	<b>IL1T-AI-0505, Part A</b>	Pivotal, P4A
<b>P4</b>	<b>Lyophilized, Process B, 80 mg/mL after recon</b>	<b>IL1T-AI-0505, Part B</b> <b>IL1T-AI-0505, open-label extension</b>	Pivotal, P4B

PK data from healthy subjects were obtained with DP P3A.

**2.5.4 Were various drug products used in clinical studies comparable in terms of PK exposure?**

No bioequivalence study was conducted to determine PK comparability of different drug products, in particular, P3A vs. P4B and P4A vs. P4B.

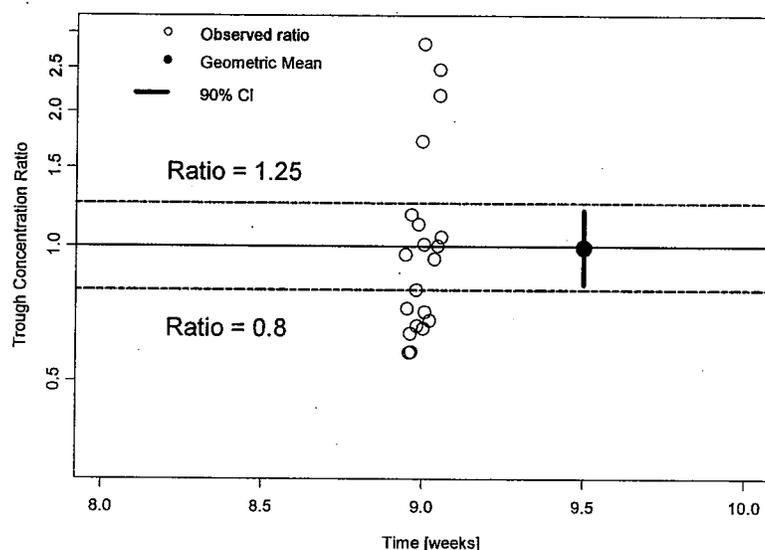
Comparability between different drug substances (DS P1 to P2, P2 to P3, and P3 to P4) and drug products (DP P4A and P4B) were determined by Product review of physicochemical property assessment from stability and release data. The assessment indicated comparability.

Drug products, DP P4A and DP P4B, were used in Study 505. They only differed in lyophilization process. We conducted analysis to determine whether manufacturing process change would affect the riloncept exposure in patient population. Namely, steady-state trough concentrations determined in Study 505 from subjects who received both drug products were compared. The analyses were based on subgroup of subjects who received riloncept with the sequence of Drug-Drug-Drug or Placebo-Drug-Drug. There were totally 22 subjects, with PK samples obtained every 3 weeks following the riloncept administration. Our analyses were performed to compare the steady state trough exposure within the same subject after 9 weeks of receiving P4A as well as P4B, and we found the formulation change did not appear to lead to

major changes in trough exposure. The ratios of trough concentrations in market formulation (P4B) to those in previous formulation (P4A) for each individual and the geometric mean ratio with its 90% confidence interval were presented in Figure 2.5.4.1. A paired-t test was conducted using log-transformed trough concentrations. The results were listed in Table 2.5.4.1. At week 9 after receiving market formulation or previous formulation, the trough concentrations were comparable because the 90% confidence interval of the trough concentration ratio was within 0.8 – 1.25 under normal scale and the paired-t test showed no statistical significance.

Refer to PM review (Section 4.3) for details.

**Figure 2.5.4.1. Ratio of trough concentration in market formulation to that in previous formulation 9 weeks after receiving each formulation.**



**Table 2.5.4.1. Paired-t test results for log-transformed trough concentrations 9 weeks after receiving market formulation or previous formulation.**

Number of Observation	Mean	90% CI	Method
20	-0.005	(-0.192 ~ 0.181)	Log-transformed
20	0.995	(0.825 - 1.198)	normal scale

In addition, the exposure in patients who participated in the single blinded phase of Part B (used formulation P4A) and 24-week OLE (used formulation P4B) were compared. The mean trough concentration during OLE (Week 6 to 24) for those subjects initially enrolled in Parts A and B was 25.2 µg/mL. And the mean trough concentration for the same groups of patients was 27.0 µg/mL in the first 24 weeks (as measured by the mean of weeks 12 and 15 during the single-

blind portion of the study). The data were comparable suggesting little impact of process change between P4A and P4B on PK of rilonacept.

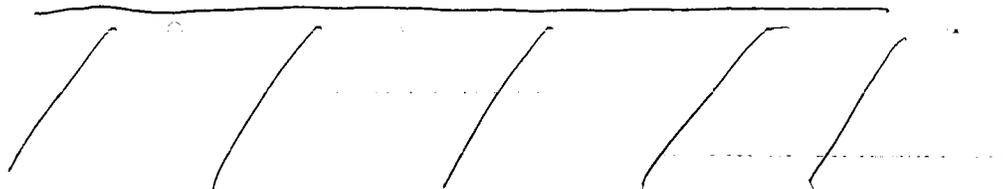
**2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Not applicable because rilonacept is given via subcutaneous injection.

## 2.6 Analytical

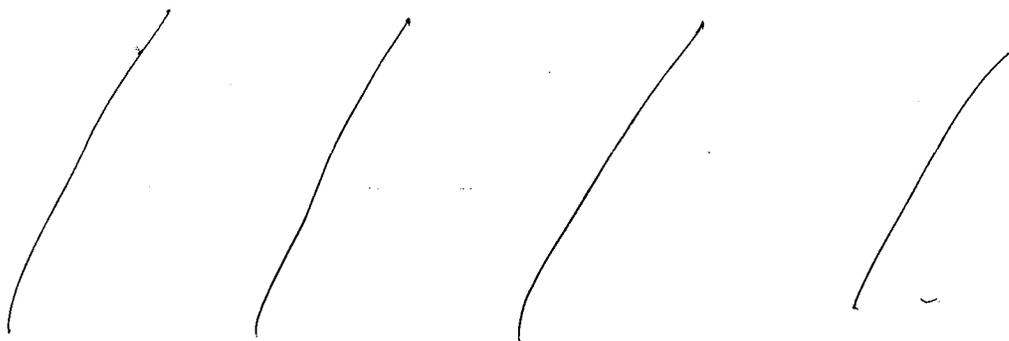
**2.6.1 How were the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

Four ELISA methods have been used to determine concentrations of total rilonacept (free plus various complex) in human serum or plasma from various studies (Table 2.6.1.1). All assays used

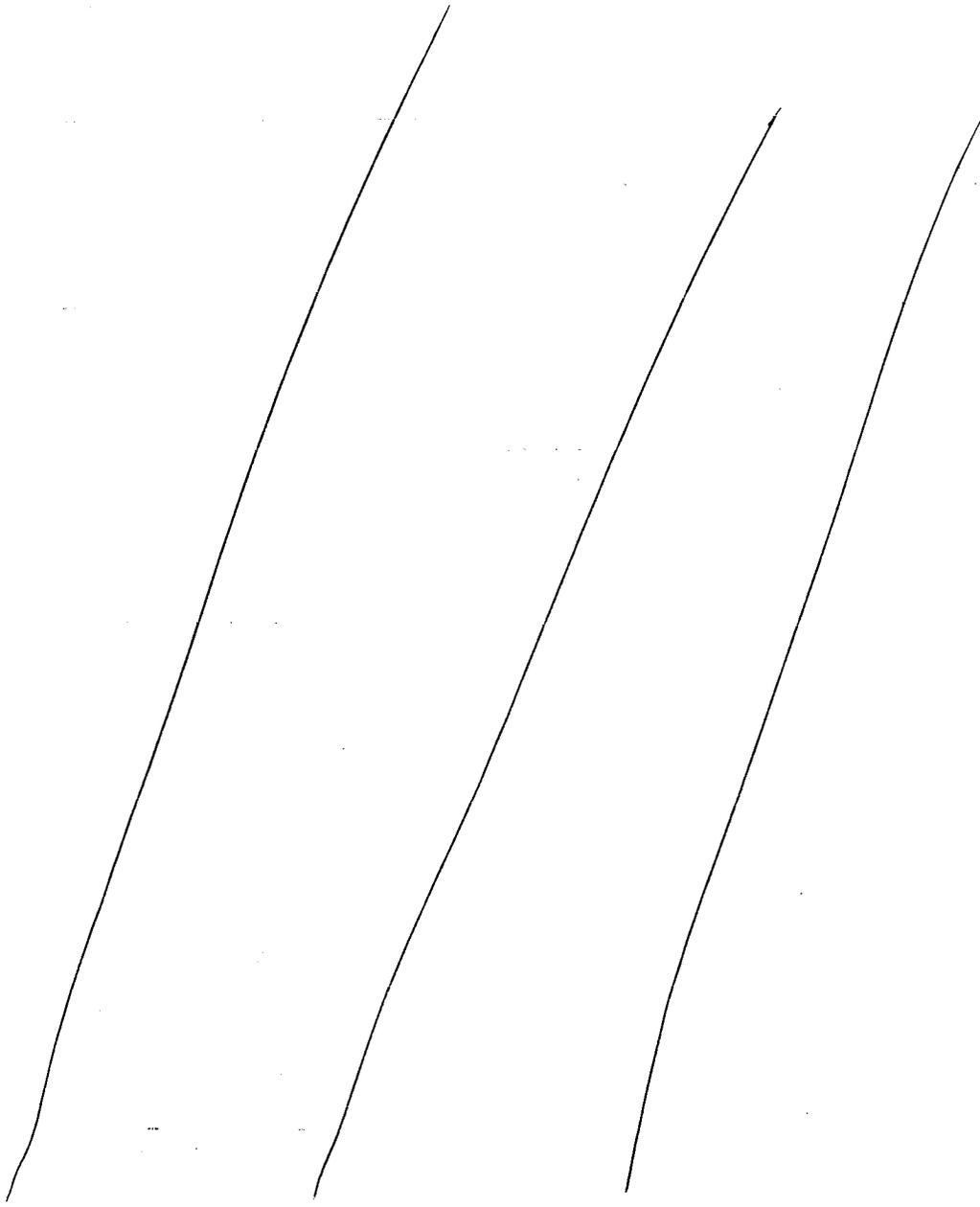


Although all assays were validated with IL-1 Trap, formal cross-validation studies were not performed. Consult review from Division of Monoclonal Antibodies confirmed that it was difficult to determine whether these methods would generate similar quantitative results without cross-validation (See Section 4.4). Therefore, pooling exposure data from various studies as the Sponsor did for POP-PK analysis was not appropriate if different methods were used for quantitation without cross-validation.

Method IL1T-AS-05006: For analysis of samples from the pivotal study IL1T-AI-0505, the ELISA employed:



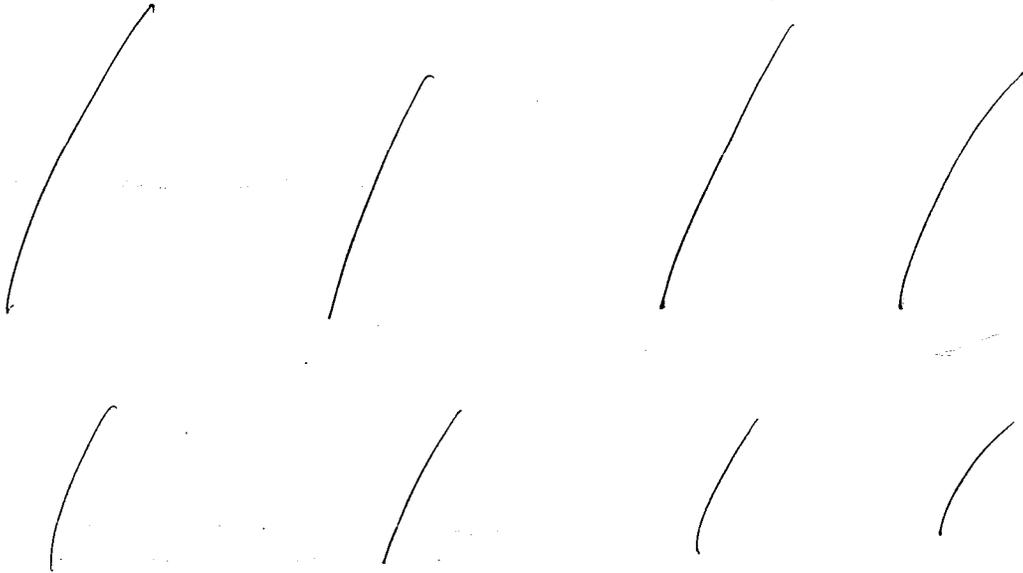
The validation report (IL1T-AS-05006R.0) provides evidence that the assay is substantially more sensitive than previous assays, as shown in Table 2.6.1.1,



**2.6.2 *What bioanalytical methods were used to detect anti-drug antibodies and those that were neutralizing antibodies in serum or other biological fluids?***

The antibody screening and selectivity assays used in early- and late-stage clinical studies, up to the pivotal CAPS study, were similar in that they were all ELISA-based, \_\_\_\_\_

The pivotal trial used BA3 assay (IL1T-AV-06015). The BA3 assay is \_\_\_\_\_

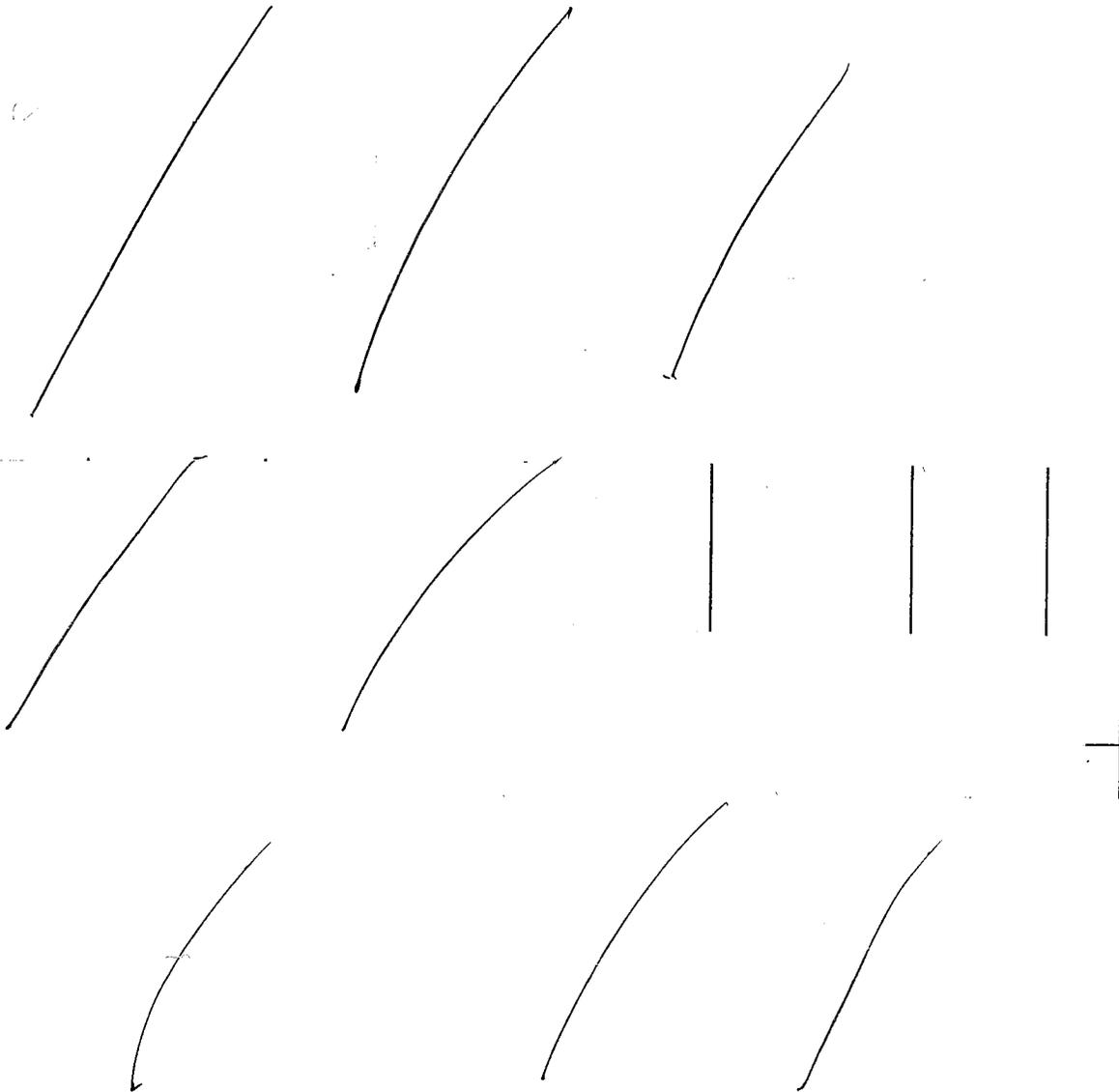


Samples that were positive in the binding antibody assays (BA3) were further evaluated in an assay to assess antibody-dependent drug neutralization.

Neutralizing Anti-IL-1 Trap antibodies were indirectly detected in human serum using a validated ELISA (IL1T-AV-06016). This bioanalytical method involved \_\_\_\_\_



**Table 2.6.2.1. Characteristics of Immunogenicity Assays.**



**2.6.3 What bioanalytical methods were used to assess the pharmacodynamic effect of the drug?**

Riloncept binds and blocks IL-1 $\beta$ , IL-1 $\alpha$  and IL-1ra; therefore, assays to detect complexes of the drug with each of these species were developed. The levels of these complexes are a function of the *in vivo* synthesis rate of the ligand, the fractional capture by riloncept, and the clearance rate of the complex. At high doses, riloncept should capture all of the ligand that is synthesized by the body; therefore examination of the complex levels at different doses may provide a surrogate measure of the riloncept dose response.



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           Trade Secret / Confidential

  ✓   Draft Labeling

           Deliberative Process

## 4.2 Individual Study Review

### 4.2.1 Study IL1T-RA-0401(or Study 401): A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Pharmacokinetics and Tolerability of Two Formulations of IL-1 Trap

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Duration of Study: June 7, 2004 to October 9, 2004

Principal Investigator: \_\_\_\_\_

Study Site: \_\_\_\_\_

Analytical Dates: July 6, 2004 to October 6, 2004

October 18 to October 28, 2006 (Anti-IL-1 Trap analysis)

Analytical Site: Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road,  
Tarrytown, NY 10591

Objectives: Determine single dose PK via SC dosing and safety in healthy subjects

Study Design: This was a six-week, single-center, double-blind, placebo-controlled, randomized, parallel group study in normal subjects.

PK sampling for plasma IL-1 Trap was performed at the following time points: Groups A, B, and C: predose (0 hour), and 2, 4, 8, 12, 24, 30, 48 (Day 3), 72 (Day 4), 120 (Day 6), 168 (Day 8), 216 (Day 10), 264 (Day 12), 360 (Day 16), 672 (Day 29), 888 (Day 38), and 1008 (Day 43) hours postdose; and Group D: predose (0 hour), 168 (Day 8), 360 (Day 16), and 672 (Day 29) hours postdose. PK parameters were computed for Treatment L (Group D) from the sparse sampling timepoints at predose (0 hour), 168, 360, and 672 hours postdose. An enzyme-linked immunosorbent assay (ELISA) was used to determine the plasma concentrations of total IL-1 Trap (both free Trap and that bound to IL-1 and its analogues) (Validation Report No. IL1T-AS-03034R.1: Quantitative Analysis of Total Interleukin-1 Trap in Human Serum). The dynamic range of the assay \_\_\_\_\_, with a lower limit of quantitation (LLOQ) of \_\_\_\_\_ ng/mL in the assay. Any subject sample that presented drug levels below this limit was reported as BLQ (Below Limit of Quantitation). Samples that exceeded the upper limit of the range were further diluted to reach a value within the assay's dynamic range (Sample analysis report No. IL1T\_RA\_401\_SA\_03V2).

Serum IL-1 Trap antibody concentration samples were collected at each scheduled time point. The immunogenicity of the Trap was assessed using an ELISA selective for IL-1 Trap.

#### Investigational Products:

Reference formulation: DP P2 liquid formulation

Test formulation: DP P3A lyophilized formulation

### Summary of Groups and Treatments

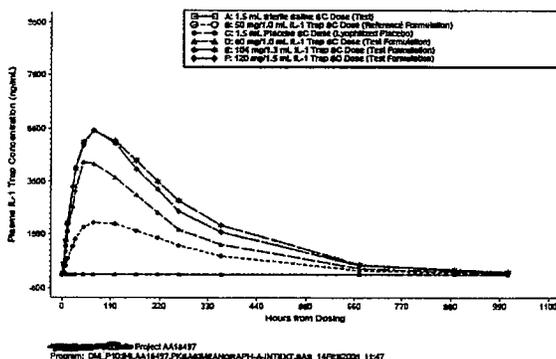
Group	Treatment	Number of Injections	Number of Subjects	Total Dose	Lot Number
A	A	1	12	1.5 mL sterile saline	342143
	B	1	12	50 mg/1.0 mL IL-1 Trap (Reference Formulation)	TP1F02022AB
	C	1	12	1.5 mL Lyophilized Placebo	B04001P910F01A
	D	1	13	80 mg/1.0 mL IL-1 Trap (Test Formulation)	B03015M810E11A
	E	1	13	104 mg/1.3 mL IL-1 Trap (Test Formulation)	B03015M810E11A
	F	1	13	120 mg/1.5 mL IL-1 Trap (Test Formulation)	B03015M810E11A
B	G	2	5	240 mg/3.0 mL IL-1 Trap (Test Formulation)	B03015M810E11A
	H	2	2	3.0 mL Lyophilized Placebo	B04001P910F01A
C	I	2	5	160 mg/2.0 mL IL-1 Trap (Test Formulation) and 2.0 mL Lyophilized Placebo	B03015M810E11C/ B04001P910F01A/ B04001P910F01C
	J	2	5	320 mg/4.0 mL IL-1 Trap (Test Formulation)	B03015M810E11C
	K	2	4	4.0 mL Lyophilized Placebo	B04001P910F01A/ B04001P910F01C
	L	2	5*	320 mg/4.0 mL IL-1 Trap (Test Formulation)	B03015M810E11A/ B03015M810E11C
	M	2	2	4.0 mL Lyophilized Placebo	B04001P910F01C

#### Results:

A total of 103 subjects were enrolled and included in safety analysis. PK parameters were calculated only for the 71 subjects who received the active IL-1 Trap SC doses. Subject 704, who discontinued after 8 blood draws was excluded from PK summary statistics. Moreover, Subjects 601, 602, 604, 605, and 607 (Group D, Treatment L), who had sparse data, were excluded from the dose proportionality analysis and the comparison of the test vs. reference treatments.

The overall study population was predominantly female (55 of 103 subjects) and predominantly Caucasian (56 of 103 subjects). The mean age for all subjects was 38.2 years (range 19 - 69 years), the mean weight was 79.95 kilograms (range 43.8 - 110.7 kg), and the mean height was 169.0 centimeters (range 145.3 - 196.9 cm).

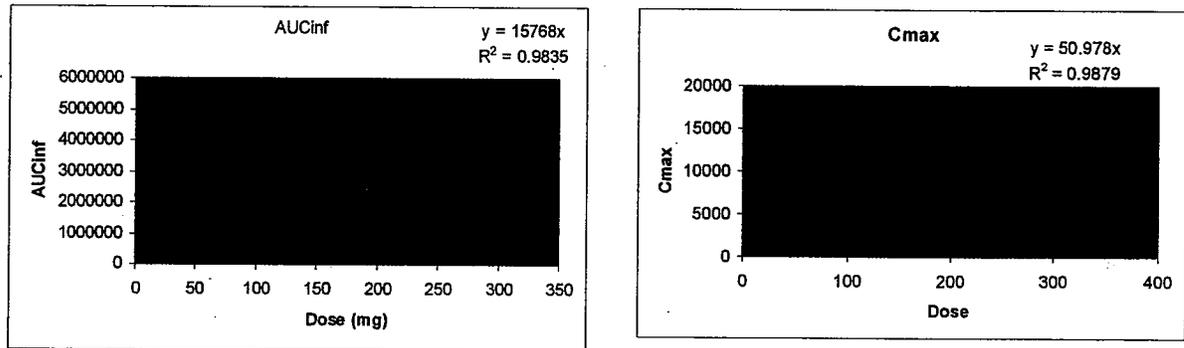
Figure 11.4.2.1:1 Mean Plasma IL-1 Trap Concentrations Versus Time; Group A (Linear Scale)



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**Table 1. Summary of Mean PK Parameters following the Test Formulation (P3A) at Doses 80 to 320 mg.**

Treatment	N	Dose (mg)	Cmax (µg/mL)	AUCinf (µg/mL*hr)	AUCt (µg/mL*hr)	Tmax (hr)	T <sub>1/2</sub> (hr)
D	13	80	4.4	1195	1158	61	154
E	13	104	5.5	1774	1682	92	164
F	13	120	5.5	1621	1593	96	147
G	5	240	11.6	3755	3712	120	147
I	5	160	8.8	2286	2263	67	126
J	4	320	16.5	5263	5195	66	152



**Figure 1. AUC and Cmax vs. Dose.**

**Table 11.4.2.2:3 Dose Proportionality Assessment of Plasma IL-1 Trap Pharmacokinetic Parameters Following the Test Treatments D, E, F, G, I, and J**

Pharmacokinetic Parameter	Slope	SE	P-Value
C <sub>max</sub>	-0.0524	0.1072	0.6272
AUC <sub>(0-t)</sub>	0.0557	0.0992	0.5767
AUC <sub>(0-inf)</sub>	0.0277	0.0977	0.7783

Parameters were dose-normalized and log-transformed prior to analysis. Dose was log-transformed.  
Dose proportionality is concluded if the slope is not significantly different from zero at 0.05 probability level.  
Source Table: 14.2.6.1

Dose proportionality assessment of dose-normalized and log-transformed plasma IL-1 Trap PK parameters C<sub>max</sub>, AUC(0-t), and AUC(0-inf) indicated that there was a dose proportional increase in IL-1 Trap exposure within the investigated 80 mg/1.0 mL to 320 mg/4.0 mL IL-1 Trap dose range. The slope of the lines of the dose-normalized PK parameters C<sub>max</sub>, AUC(0-t), and AUC(0-inf) vs. dose were not significantly different from zero, as all the p-values were > 0.05.

**Table 2. PK Parameter Comparison between P3A Formulation and P2 formulation.**

	<b>Dose (mg)</b>	<b>C<sub>max</sub>/D (1/kL)</b>	<b>AUC(0-t)/D (hr/kL)</b>	<b>AUC(0-inf)/D (hr/kL)</b>	<b>T<sub>max</sub> (hr)</b>	<b>T<sub>1/2</sub> (hr)</b>
<b>Test Formulation (P3A) (N=53)</b>	80-320	49.0	14199.6	14637.2	77.92	148.0
<b>Reference Formulation (P2) (N=12)</b>	50	38.1	11643.1	12196.5	92.43	162.3

P3A formulation appeared to have higher exposure (dose-adjusted) than P2 formulation (20% higher in AUC and 29% higher in C<sub>max</sub>). As of note, the formulations were studied at difference dose ranges.

One (1) subject (Subject 105) in Treatment D, 80 mg/1.0 mL, exhibited a serum IL-1 Trap antibody level of – ng/mL on Day 43. Serum IL-1 Trap antibody levels were below the limit of quantification (BLQ) for all remaining subjects at the assessed time points.

Conclusion: IL-1 Trap showed dose-proportional PK in healthy subjects via single-dose SC injection of P3A formulation (80-320 mg). Maximum level of IL-1 Trap reached about 3 days (2.5-5 days) after SC administration and half-life was around 6 days.

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**4.2.2 Study IL1T-RA-0402 (or Study 402): A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose-Escalation Safety Study to Evaluate the Pharmacokinetics and Tolerability of Intravenous IL-1 Trap in Normal Human Volunteers**

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Duration of Study: May 19, 2004 to September 17, 2004

Principal Investigator: \_\_\_\_\_

Study Site: \_\_\_\_\_

Analytical Dates: July 12, 2004 to August 20, 2004

October 22, 2004 to October 25, 2004 (Anti-IL-1 Trap analysis)

Analytical Site: Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road,  
Tarrytown, NY 10591

Objectives: To determine the pharmacokinetics, safety profile, and tolerability of a single dose of IL-1 Trap administered intravenously in healthy subjects.

Study Design: This was a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study of IL-1 Trap in healthy subjects.

The test product was IL-1 Trap (lyophilized powder, P3A) given in a single 100 mg dose (0.4 mg/mL) (Cohort 1); 300 mg dose (1.2 mg/mL) (Cohort 2); 1000 mg dose (4 mg/mL) (Cohort 3); and 2000 mg dose (8 mg/mL) (Cohort 4), by IV infusion. All cohorts were dosed with IL-1 Trap or placebo diluted in 250 mL of sterile normal saline administered at 250 mL/hr (hour) over 60 minutes. Batch number was B03015M810E11B for IL-1 Trap and B04001P910F01B for placebo.

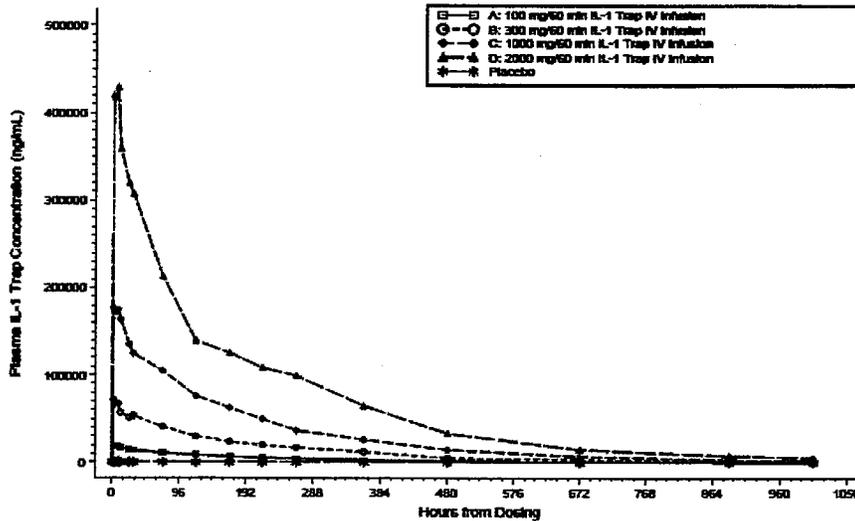
PK sampling for plasma IL-1 Trap was performed at the following time points: Predose (0 hour), 3, 5, 9, 13, 25, 31, 73, 121, 169, 217, 265, 361, 481, 673, 889, and 1009 hours postdose (start of infusion). Same analytical method as Study 401 were used for sample analysis.

Serum IL-1 Trap antibody concentration samples were collected prior to dosing on Day 1, and at the off drug/follow-up visits on Days 6, 16, 29, and 43 or upon early withdrawal. The immunogenicity of the Trap was assessed using an ELISA selective for IL-1 Trap.

Results:

A total of 28 subjects were enrolled in the study, and all 28 subjects completed the study. Eighteen were female and 10 were male. Regarding race, 12 subjects were Caucasian, 8 subjects were Hispanic, 7 subjects were Black, and 1 subject was of "other" race. The mean age for all subjects was 40 years (range 19 to 58 years). The mean weight for all subjects was 74.9 kg (range 50.5 to 123.6 kg).

PK parameters were calculated for all 20 subjects who received the active IL-1 Trap dose; however, summary statistics of concentration and PK parameters, as well as dose proportionality analysis, were based on the data from the 18 subjects who received the correct dose of IL-1 Trap, excluding results from the 2 subjects (001-201 and 001-202) who had errors in dosing.



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Figure 1. Mean Plasma IL-1 Trap Concentrations Versus Time-Linear Scale.

Table 1. Summary of the Pharmacokinetic Parameters of Plasma IL-1 Trap.

Dose	N	C <sub>max</sub> (µg/mL)	AUC <sub>inf</sub> (µg/mL*hr)	AUC <sub>t</sub> (µg/mL*hr)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	V <sub>ss</sub> (L)
100 mg	5	19.6	3235	3185	4.8	188	7.0
300 mg	3	71.6	12755	12427	3.2	216	5.8
1000 mg	5	187	31568	30923	6.8	195	7.5
2000 mg	5	455	71629	69688	7.6	254	6.8

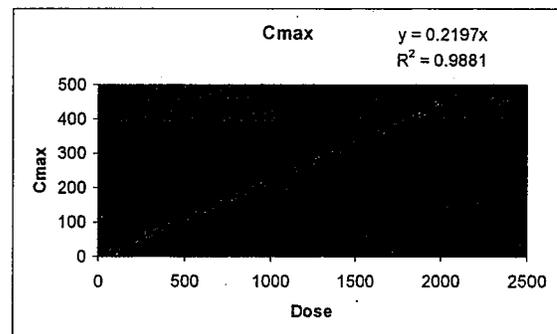
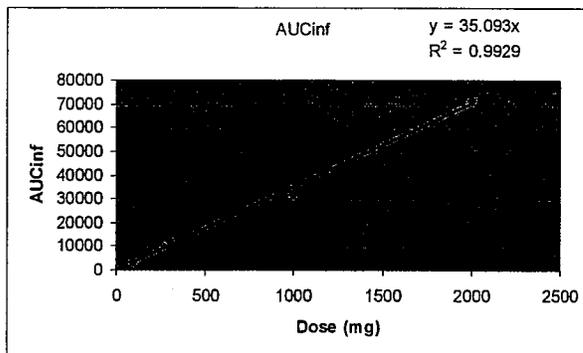


Figure 2. AUC and C<sub>max</sub> vs. Dose.

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**Table 11.4.1.2:2 Dose Proportionality Assessment of Plasma IL-1 Trap Pharmacokinetic Parameters Among 100 mg, 300 mg, 1000 mg, and 2000 mg Doses**

Pharmacokinetic Parameter	Slope	SE	P-Value
C <sub>max</sub>	0.0284	0.0433	0.5221
AUC(0-t)	0.0091	0.0451	0.8433
AUC(0-inf)	0.0121	0.0462	0.7963

Parameters were dose-normalized and ln-transformed prior to analysis.  
Dose proportionality is concluded if the slope is not significantly different from zero at 0.05 probability level.  
Source: Table 14.2.3

Dose proportionality assessment of dose-normalized ln-transformed plasma IL-1 Trap PK parameters C<sub>max</sub>, AUC(0-t), and AUC(0-inf) indicated that there was a dose proportional increase in the rate and extent of IL-1 Trap exposure within the investigated 100 mg to 2000 mg IL-1 Trap dose range. The slope of the lines of PK parameters C<sub>max</sub>, AUC(0-t), and AUC(0-inf) were not significantly different from zero, as all the p-values were > 0.05.

T<sub>max</sub> appeared to occur 3-8 hours post-dose. No plasma sample was collected at the end of infusion which may represent the true C<sub>max</sub> and T<sub>max</sub>. Volume of distribution was approximately 6-7 L suggesting limited extravascular distribution.

All serum IL-1 Trap antibody levels were below the limit of quantification (BLQ) for all subjects at the assessed time points.

Estimation of absolute bioavailability of IL-1 Trap via SC administration:

Absolute bioavailability of SC=Mean (AUC/D)<sub>sc</sub>/Mean (AUC/D)<sub>iv</sub>=15.42/35.56=43%

Conclusion: IL-1 Trap showed dose-proportional PK in healthy subjects via single-dose IV infusion of P3A formulation. The half-life was around 8-9 days. Across study comparison of data suggested that the absolute bioavailability of SC was approximately 43%.

***4.2.3 Study IL1T-RA-0505 (or Study 505): 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 (Parts A & B, and Open Label Extension)***

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Duration of Study: Part A: December 27, 2005 to June 21, 2006  
Part B: February 28, 2006 to October 9, 2006  
24-week open label extension (OLE): July 5, 2006 to March 26, 2007  
64-week OLE: ongoing

Principle Investigators: Multi-centers and PIs

Analytical Dates: July 5, 2006 to February 1, 2007 (Parts A and B)

November 28, 2006 to February 21, 2007 (Anti-IL-1 Trap analysis in

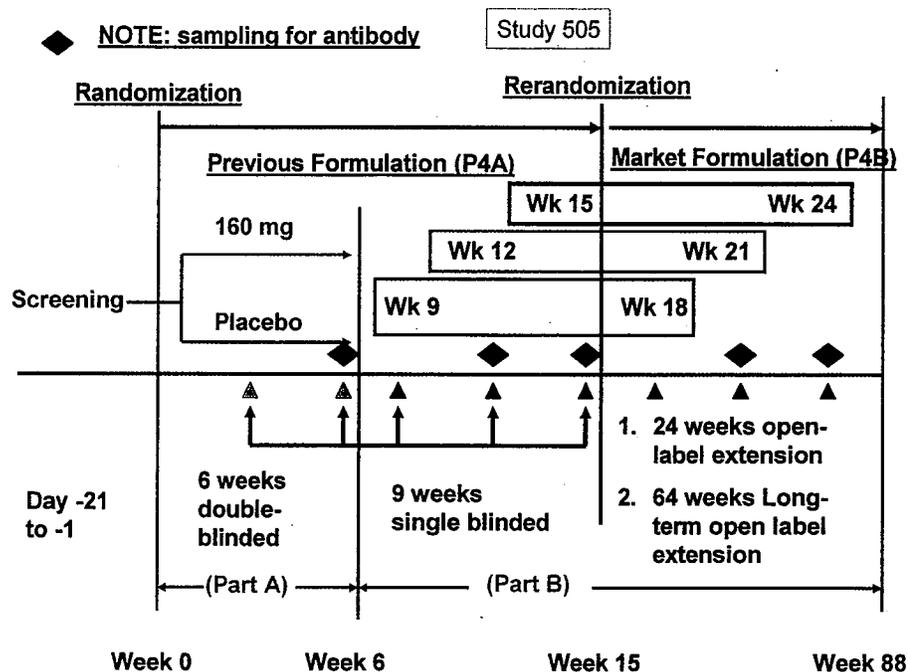
Parts A and B)

Analytical Site: Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road,  
Tarrytown, NY 10591

***Objectives:*** To assess the effect, safety and tolerability of rilonacept on the clinical signs and symptoms of CAPS when used for chronic therapy. To assess the effect of rilonacept on laboratory measures of inflammation such as acute phase reactants.

***Study Design:*** This was a multi-center, double-blind, placebo-controlled study. Weekly subcutaneous (SC) doses of 160 mg of rilonacept were dosed in adult subjects with active CAPS in 27 study sites in the United States. The study consisted of a 3-week screening period, a 6-week, double-blind, randomized, placebo-controlled treatment period (Part A, 1:1 ratio), a 9-week single-blind active-treatment period followed by a 9-week double-blind, placebo-controlled, randomized withdrawal phase (Part B, 1:1 ratio), a 24-week open-label extension phase (OLE), a 64-week long-term open-label extension (LTOLE), and a 6-week post-treatment follow-up period. Amendments 4 and 6 allowed eligible adult and pediatric subjects to enroll directly into the open-label phases of the trial.

Subjects received a loading dose of 320 mg of rilonacept or placebo, with subsequent weekly SC injections of 160 mg of rilonacept or placebo for a total of 6 doses in Part A. Following completion of the double-blind period, subjects received weekly SC injections of rilonacept for 9 weeks in the single-blind phase of Part B, and were then re-randomized at Week 15 (Visit 7) in a 1:1 ratio to receive weekly SC injections of 160 mg of rilonacept or placebo for a 9-week randomized withdrawal period of Part B (Figure 1). Upon completion of this phase of the trial, subjects were eligible to receive weekly SC injections of 160 mg of rilonacept in the 24 week open-label extension phase, and then a 64-week long-term open-label extension.



**Figure 1. Schematic of Study 505 (first 24-weeks).**

Dose for pediatric patients were based on adult dose divided by body weight so 2.2 mg/kg weekly SC doses up to 160 mg were given to pediatric patients (7-17 years).

All subjects underwent testing to confirm the diagnosis of mutation-positive CAPS via bi-directional sequencing of exon 3 of the *CIAS1* gene (

Drug product P4A and P4B were used in the study. P4A (Lot No. B05003M810E21A) was used in Part A and single-blinded phase of Part B, and P4B (Lot No. B05006M810E12A) was used in randomized withdrawal phase of Part B and OLE.

*(Reviewer's Note: This review will focus on PK and immunogenicity data generated from the study. Refer to Medical and Statistics' reviews for efficacy and safety analysis.)*

Sampling for PK: Blood samples to determine plasma rilonacept levels were collected prior to dosing on study Day 0 and Weeks 3, 6, 9, 12, 15, 18, 21 and 24 (Parts A & B), open-label extension Day 0 and Weeks 6, 12, 18, and 24 (for currently randomized subjects and new subjects enrolled under Amendment #4) and Day 0 and Weeks 6, 12, and 24 for subjects randomized under Amendment #6.

Sampling for immunogenicity: Blood samples to determine serum anti-rilonacept antibody levels were collected prior to dosing on study Day 0, Weeks 6, 12, 15, 21, and 24 (Parts A & B), 24-week open-label extension Day 0, Week 6, 12, 18, and 24 (for currently randomized subjects and new subjects enrolled under Amendment #4) and 24-

week open-label extension Day 0, Week 6, 12, and 24 (for new subjects enrolled under Amendment #6).

Sample Analysis: An enzyme-linked immunosorbent assay (ELISA) was used to determine the plasma concentrations of total IL-1 Trap (both free Trap and that bound to IL-1 and its analogues) (Validation Report No. IL1T-AS-05006R.0: Validation of a Bioanalytical Method for Quantitative Measurement of Total Interleukin- 1 Trap in Human Plasma Using Regeneron \_\_\_\_\_ The lower limit of quantitation (LLOQ) of the assay was \_\_\_\_\_

\_\_\_\_\_. Any subject sample that presented drug levels below this limit was reported as BLQ (Below Limit of Quantitation). Samples that exceeded the upper limit of the range were further diluted to reach a value within the assay's dynamic range (Sample analysis report No. IL1T\_AI\_0505\_SA\_01V2). Plasma levels were converted from ng/mL to nM using \_\_\_\_\_ kDa as the molecular weight of IL-1 Trap.

The immunogenicity of the Trap was assessed using an ELISA selective for IL-1 Trap (IL1T-AV-06015\_SA\_01V1). \_\_\_\_\_

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Neutralizing Anti-IL-1 Trap antibodies were indirectly detected in human serum using a validated ELISA method (IL1T-AV-06016\_SA\_01V1) that : \_\_\_\_\_

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\_\_\_\_\_  
\_\_\_\_\_

Results:

A total of 46 subjects participate in Part A and B of Study 505 (Table 1 below).

The study population was White-non-Hispanic (100%) and predominantly female (66%). Age ranged from 22 to 78 years with a mean of 51 years. All subjects were positive for CIAS1 gene mutation (Table 2).

There were 12 subjects who received wrong study medication at some time during the 24-week period. Eleven of these subjects received the incorrect study medication for a 3-week period due to a programming error in the drug allocation system. The error was limited to the first 3 weeks of randomized withdrawal.

Table 1.

Table 8 Disposition of Subjects in Parts A and B

Disposition	Randomization A Part A and Part B Single-Blind		Randomization B Part B Randomized-Withdrawal	
	Rilonacept (n=23)	Placebo (n=24)	Rilonacept (n=22)	Placebo (n=23)
	Completed	22	24	21
Withdrawn for any reason	2 (8%)	0	1 (4%)	0
<b>Reason for Withdrawal</b>				
Adverse Event	0	0	1	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

\*This subject was removed from the study in the Part B single-blind phase of the study due to non-compliance with study drug dosing and study visits.

† Subject 018-6891 was removed from the study during Part A while being treated with rilonacept due to hepatitis C that was diagnosed after dosing but determined to have a pre-dose start date based upon Screening liver function test results

Source: Post-text Tables 9.1.3.1, 9.1.3.2

Table 2. Demographic and Baseline Characteristics

Demographic Trait	Statistic	Open-label		Total (n=56)
		Participants of Parts A and B (n=44)	Direct Enrollees (n=12)	
CAPS Disease Diagnosis	Number with FCAS	41	11	52
	Number with MWS	3	1*	4*
Age (years)	Mean (min-max)	51 (22-78)	27 (13-56)	46 (13-78)
Gender	Number (%) Female	30 (68%)	8 (67%)	38 (68%)
	Number (%) Male	14 (32%)	4 (33%)	18 (32%)
Ethnic Origin	Number (%) White Non-Hispanic	44 (100%)	12 (100%)	56 (100%)
	Number Black Non-Hispanic	0	0	0
	Number Hispanic	0	0	0
	Number Other	0	0	0
CIAS1 Gene Mutation	Number (%) Positive	44 (100%)	12 (100%)	56 (100%)
Height (cm)	Mean (min-max)	168 (155-190)	168 (152-180)	168 (152-190)
Weight (kg)	Mean (min-max)	75 (50-119)	66 (38-97)	73 (38-119)
Baseline Key Symptom Score	Mean (min-max)	2.8 (0.6-8.2)	2.1 (0.3-3.9)	2.6 (0.3-8.1)

\* Includes one pediatric subject with FCAS/MWS overlap

Source: Post-Text Tables 9.1.3, 9.1.4, 9.1.6; Subject Profiles/Appendix 11.4.2

Following Parts A and B, 44 subjects were eligible to enter a 24-week open label extension (OLE) during which rilonacept was administered at a dose of 160 mg weekly. Twelve additional subjects were directly enrolled in the OLE, four of whom (subjects 007-8004, 007-8007, 014-8009 and 027-8012) were pediatric subjects who were dosed with 2.2 mg/kg rilonacept, up to 160 mg, weekly. Their ages were 13, 13, 15, and 16.

Exposure of rilonacept:

Part A and B:

**Table 3. Summary of Baseline and Endpoint Levels of Drug Concentrations (Part A and Part B)**

Randomization	Treatment Group (Part A Randomization)	Baseline Mean (mg/L)	Endpoint Mean (mg/L)	Endpoint Range Minimum to Maximum (mg/L)
Randomization A (Part A)	Rilonacept (n=22)	0.00	22.41	0.68 to 32.20
	Placebo (n=23)	0.00	0.00	0.00 to 0.00
Randomization B (Part B)	Rilonacept (n=21)	26.82	24.35	10.40 to 43.40
	Placebo (n=23)	28.39	0.28	0.00 to 3.09

Source: Post-text Tables 9.3.5.2.1, 9.3.5.2.2

24-Week OLE:

The mean steady state trough plasma levels for subjects in the 24-week OLE were consistent with those in the initial, 24-week blinded portions of the study. The mean trough level at the end of Part B was 24 µg/mL (N=21) (Table 3) and the mean trough level at the end of 24-week OLE in adults was also 24 µg/mL (N=48) (Table 4). The range was 7-56 µg/mL. Steady-state seemed to be reached by Week 6 as no further increase in trough levels was observed after Week 6 (Table 4).

**Table 4. Drug Levels (µg/mL) in Adult Patients at OLE.**

	Trough Levels				~Cmax
	Wk 6 (N=52)	Wk 12 (N=8)	Wk 18 (N=49)	Wk 24 (N=48)	Post 2-3 days (N=23)
Mean	26	28	26	24	32
Std.	12	13	11	9.9	14

Source: Table 9.3.5.4.

The mean blood levels of rilonacept for the four pediatric subjects at the end of the 24-week OLE were similar at 20.0 µg/mL (Table 5). The range was 3.6-33 µg/mL.

**Table 5. Drug Levels (µg/mL) in Pediatric Patients.**

	Trough Levels				~Cmax
	Wk 6	Wk 12	Wk 18	Wk 24	Post 2-3 days
007-8004					
007-8007					
014-8009					
027-8012					
<b>Mean</b>	<b>22.9</b>	<b>18.0</b>	<b>13.1</b>	<b>20.0</b>	<b>35.4</b>
<b>Std.</b>	<b>18.9</b>	<b>3.9</b>	<b>N/A</b>	<b>12.2</b>	<b>9.3</b>

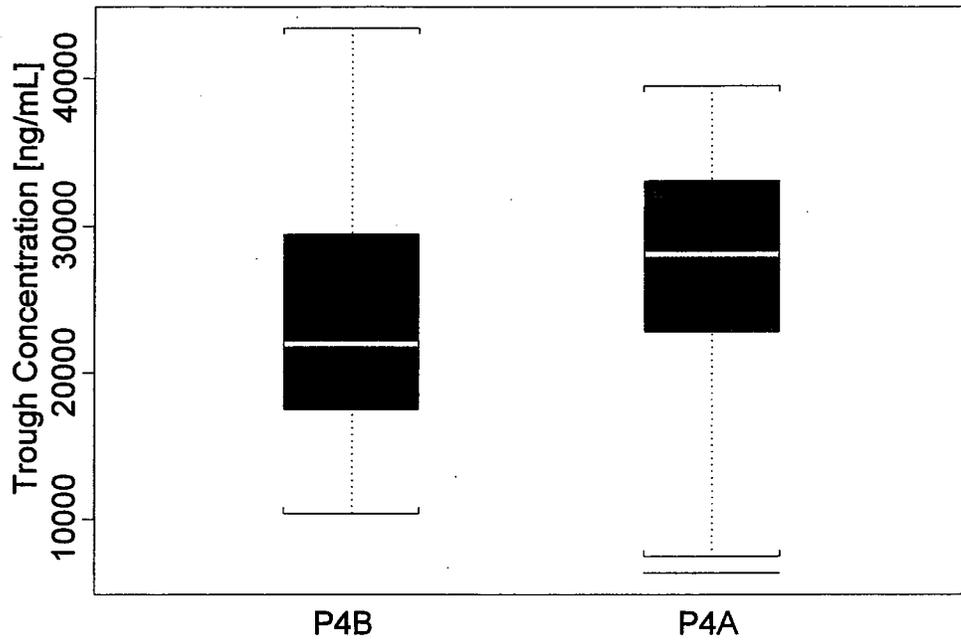
The mean rough Cmax values determined by samples collected 2-3 days post Week 24 dose in the open-label phase was 32 µg/mL for the adult population and 35 µg/mL for the pediatric subjects.

**Comparability of P4A and P4B:**

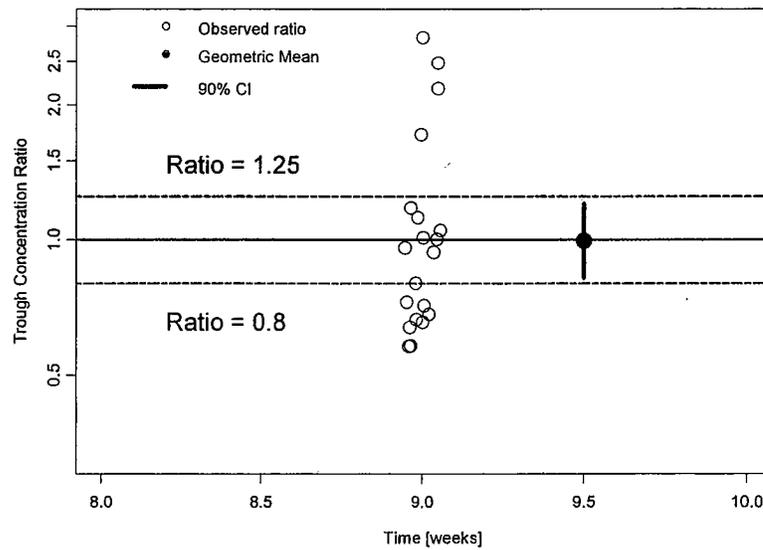
1) Comparing exposure at Week 15 vs. Week 24 of subjects who received drugs at both the single-blinded phase (P4A) and randomized withdrawal phase (P4B) of Part B:

No. of Subjects	Process A Formulation		Process B Formulation
	Part A of Study 505	Part B of Study 505	
	Week 1-6 (6 weeks) 1:1 D: P (N=47) 23 D 24 P	Week 6-15 (9 weeks) All on drug (N=46) 46 D	Week 15-24 (9 weeks) Randomized withdrawal 1:1 D: P (N=45) 22 D 23 P
PK Sampling	Wk 0, 3, 6	Wk 9, 12, 15	Wk 18, 21, 24
N=11	D		
N=12	P		
N=12	P	D	P
N=11	D	D	P

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**Figure 1. Trough level comparison between Process A (wk 15) and Process B (wk 24).**



**Figure 2. Ratio of trough concentration in market formulation (P4B) to that in previous formulation (P4A) 9 weeks after receiving each formulation.**

Although the median exposure level from P4B was approximately 25% lower than the median levels from P4A (Figure 1), the 90% confidence interval of the trough concentration ratio (at Week 9) was within 80-125% and the paired-t test showed no statistical significance (Figure 2).

Refer to PM review for details of analysis (Section 4.3).

2) Comparing the exposure in patients who participated in the single blinded phase of Part B (used formulation P4A) and 24-week OLE (used formulation P4B):

The mean trough concentration during OLE (Week 6 to 24) for those subjects initially enrolled in Parts A and B was 25.2 µg/mL. And the mean trough concentration for the same groups of patients was 27.0 µg/mL in the first 24 weeks (as measured by the mean of weeks 12 and 15 during the single-blind portion of the study). The data were comparable suggesting little impact of process change between P4A and P4B on PK of rilonacept.

#### Immunogenicity:

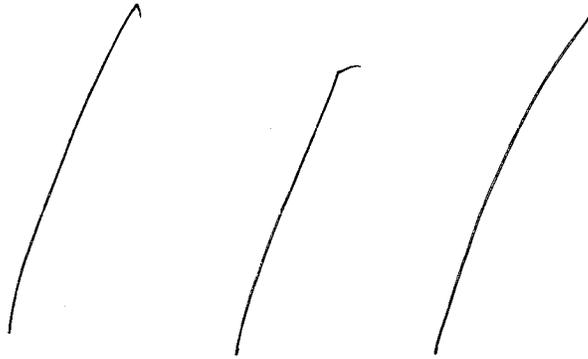
Parts A and B:

Antibodies directed against the receptor domains of rilonacept were detected by a highly sensitive ELISA assay. Twenty of 46 evaluable subjects (43%) dosed with rilonacept for up to 24 weeks in Parts A and B of the study tested positive for treatment-emergent anti-rilonacept binding antibodies on at least one occasion. Seven of them (Subjects 002-6255, 002-6379, 002-6492, 002-6824, 007-6525, 007-6746, and 029-6814) also showed positive for neutralizing antibodies on at least one occasion.

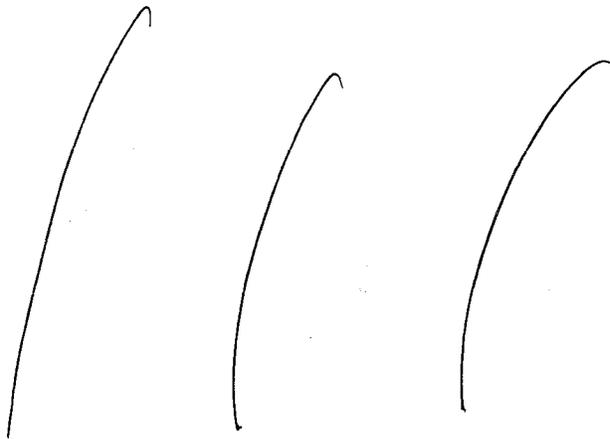
The relationship between immunogenicity and rilonacept trough exposure were examined. Although the presence of antibody appeared to cause decrease of exposure in some subjects (e.g., Subjects 009-6025, 014-6666, 016-6277, 020-6566, 021-6003, 025-6386, and 025-6905) (Figure 3), there is no clear trend between antibody status and exposure, possibly due to large interindividual variability of trough concentrations. Overall, the trough concentrations in antibody positive group appeared to be comparable to those in antibody negative group (Figure 4 and Table 6).

Refer to PM review for detail of analysis (Section 4.3).

Trough Concentration and Antibody Titer vs. Time,  
Subject = ( 009-6025 )



**Figure 3. Trough Concentrations vs. Antibody Titer for Subject 009-6025.**



**Figure 4. Trough concentrations with negative antibody versus trough concentrations with positive antibody.**

Note: Blue open circle = Trough concentration with negative antibody  
Red solid circle = Trough concentration with positive antibody

**Table 6. Mean (SD) of trough concentrations (ng/mL) with antibody negative and positive over time**

	Week									
	0	6	12	15	21	24	30	42	48	
<b>Antibody Negative</b>										
N	43	41	36	32	27	41	28	35	45	
Mean	1.525814	9805.634	25555.56	27094.06	9091.659	7275.849	26125	25026.29	24082.4	
SD	8.906794	11746.77	8780.024	9541.842	10298.18	12013.96	14289.36	10956.25	10110.98	
<b>Antibody Positive</b>										
N	1	4	7	12	17	15	10	11	5	
Mean	0	22750	30771.43	29433.33	13238.88	14622.63	25260	22474.55	22478	
SD	-	15245	10980.39	7637.864	11873.3	14317.21	11118.87	10905.39	10696.2	

Based on individual case report forms, no relationship between antibody positivity and plasma levels of rilonacept, safety, or efficacy parameters was apparent (for either binding or neutralizing antibodies).

**OLE:**

Two additional subjects (Subjects 003-6192 and 004-6256) who tested negative for binding antibodies during Parts A and B tested positive on at least one occasion during the 24 week OLE. Two of the 12 subjects who enrolled directly into the OLE, an adult (007-8002) and a pediatric subject (007-8007), also tested positive for treatment-emergent binding antibodies on at least one occasion. One additional subject, Subject 025-6386, also showed positive for neutralizing antibodies on at least one occasion.

Overall, during the 48-week period (Parts A, B, and 24-week OLE), 24 of 58 subjects (41%) tested positive for treatment-emergent binding antibodies on at least one occasion and eight of them also showed positive for neutralizing antibodies on at least one occasion.

**Rilonacept (IL-1 Trap) complex levels:**

In general, concentrations for IL-1 Trap:IL-1ra was less than 15% of total IL-1 Trap concentrations, and for IL-1 Trap:IL-1 $\beta$  was less than 0.1% of total total IL-1 Trap concentrations (Table 7).

**Table 7. Mean Concentrations for Each Riloncept (IL1-Trap) Species (nM; for IL-1 $\beta$  is pM).**

Visit	Mean	StdDev												
OL-Day 0	46	64	5.3	7.5	4.9	7.9	4.5	7.2	0.21	0.49	4.7	7.5	41	59
OL-Wk6	129	68	25.6	21.8	16.3	8.8	14.7	7.2	0.77	0.92	15.5	8.0	113	60
OL-Wk12	130	62	20.8	17.1	14.9	3.8	13.7	2.8	0.58	0.48	14.3	3.3	116	64
OL-Wk18	127	53	29.7	24.5	18.4	8.3	16.3	6.7	1.04	1.37	17.3	7.4	110	54
OL-Wk24	117	50	28.6	24.9	16.6	8.1	15.0	6.7	0.81	0.81	15.8	7.4	102	50
D2-3 POST	163	66	27.4	31.4	15.7	7.1	14.6	6.3	0.57	0.69	15.2	6.7	147	67

Notes: Concentrations are in nM except for IL-1 $\beta$  Complex which is in pM; BLQ = 0 for all average calculations; StdDev: standard deviation  
 Mean Wk6-24: mean levels between OL-Week 6 to 24 for each subject; Table was generated using Microsoft® Office Excel 2003  
 Values rounded to either 2 or 3 significant figures to provided needed accuracy

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### 4.3 Pharmacometrics Review

## PHARMACOMETRIC REVIEW

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BLA:	STN 125249
Drug name:	Riloncept
Indication:	Treatment of Cryopyrin-Associated Periodic Syndromes (CAPS)
Proposed Regimen (Sponsor):	Adult: loading dose of 320 mg S.C., then 160 mg once weekly, S.C. Pediatric: loading dose of 4.4 mg/kg (up to 320 mg), then 2.2 mg/kg (up to 160 mg/kg) once weekly, S.C.
Applicant:	Regeneron Pharmaceuticals
OCP Reviewer	Lei Zhang, Ph.D.
PM Reviewer:	Hao Zhu, Ph.D.
PM Team Leader:	Joga Gobburu, Ph.D.
Type of Submission:	BLA
Submission Date:	05/25/2007
PDUFA Date:	11/29/2007

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## 1 EXECUTIVE SUMMARY

This review highlighted the pharmacometric findings from riloncept BLA submission. Specifically, we found that:

- Riloncept steady state trough concentrations for both manufacturing process A and process B (to-be-marketed) were similar (Mean ratio was 0.995 with 90% confidence interval of 0.825 ~ 1.198).
- We found that immunogenicity affected the exposure for some subjects; however, given the large inter-individual variability of trough concentrations (CV: 40% - 50%), the trough concentrations in antibody positive group appeared to be comparable with those in antibody negative group.
- We found that riloncept steady state trough concentrations using the to-be-marketed formulation were similar between male and female subjects, and did not appear to change with body weight (within the range of 50 -120 kg) and age (within the range of 26 -78 yr).

## 2 QUESTION BASED REVIEW

### 1. Is there evidence to suggest whether the manufacturing process change (from process A to process B) will affect the riloncept exposure?

Riloncept formulation manufacturing process was changed during the pivotal trial (Study IL1T-AI-0505). As a result, two different formulations were used at two phases of the study. The question then arises whether formulation manufacturing process change would affect the riloncept exposure in patient population. Based on our analyses, we found that riloncept steady state trough concentrations for both manufacturing processes (Process A and Process B) were bioequivalent and subsequently, the safety and efficacy outcomes were comparable.

Two formulations were used in different phases of Study IL1T-AI-0505, which consisted of a 3-week screening period, a 6-week, double-blind randomized, placebo-controlled treatment period (Part A), a 9-week single-blind active treatment period followed by a 9-week double-blind, placebo-controlled, randomized withdrawal phase (Part B), a 24-week open-label extension phase (OLE), a 64-week long-term open-label extension (LTOLE), and a 6-week post-treatment follow-up period. The manufacturing process for drug product used in the Part B of randomized withdrawal portion of the study and for subsequent open-label extension phases was modified to result in a drug product that would reconstitute more quickly in sterile water for injection. This modified manufacturing process is referred to as Process B (market formulation). According to the sponsor, the process B would be used to manufacture the market formulation. Drug product used during the Part A and the Part B single-blind phase of the study was made using the prior manufacturing process which is denoted as Process A (previous formulation).

We compared the steady state trough concentrations collected 9 weeks after market formulation or previous formulation was used. Typically, to demonstrate whether two different formulations yield comparable exposure, a bioequivalence or a PK comparability study is desirable. Because the sponsor did not conduct such a study, we compared trough concentrations collected in Study IL1T-AI-505. The analyses were based on subgroup of subjects who received riloncept with the sequence of Drug-Drug-Drug or Placebo-Drug-Drug (**Table 1**). There were totally 22 subjects, with PK samples obtained every 3 weeks following the riloncept administration. It is to note that subject "029-6529" had missing trough concentrations at week 6 and 9 after receiving market formulation, and subject 025-6386 had missing trough concentration at week 9 after receiving market formulation. The two subjects were excluded from our analyses. Because riloncept has an estimated terminal half-life of 6-8 days, 6-week administration of riloncept is generally sufficient to reach steady-state. However, because 35% of the subjects (002-6379, 004-6983, 006-6572, 007-6456, 007-6525, 008-6334, and 015-6060) erroneously received placebo rather than market formulation for

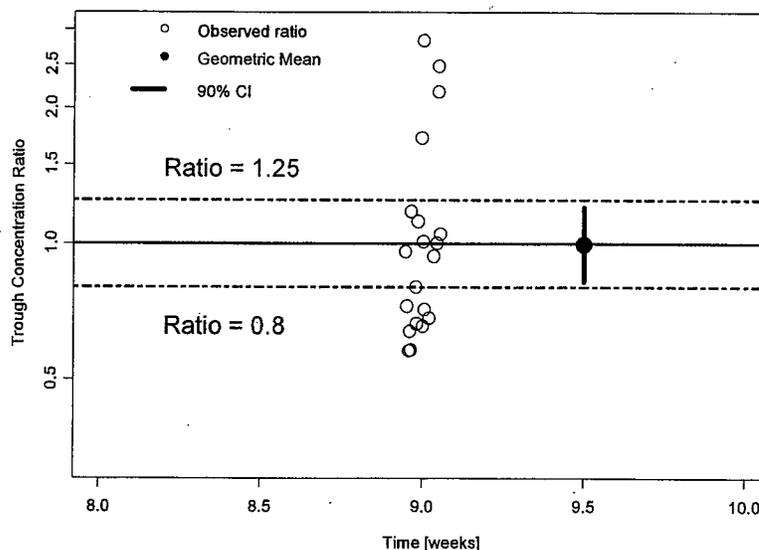
the first 3 weeks, the trough concentrations of the 7 subjects at week 6 would be about 12.5% lower than the steady state values. Nevertheless, using concentrations collected at week 9 would allow every subject to reach steady state (including the 7 subjects with dosing deviation), hence are more reliable for comparison.

**Table 1 Study design of IL1T-AI-0505 and PK samples**

	Process A Formulation		Process B Formulation
	Part A of Study 505	Part B of Study 505	
	Week 1-6 (6 weeks) 1:1 D: P (N=47) 23 on Drug 24 on Placebo	Week 6-15 (9 weeks) All on drug (N=46) 46 on Drug	Week 15-24 (9 weeks) Randomized withdrawal 1:1 D: P (N=45) 22 on Drug 23 on Placebo
PK Sampling		Wk 3, 6, 9	Wk 3, 6, 9
N=11	D		
N=12	P		
N=12	P	D	P
N=11	D	D	P

\* Note: D = Drug (Rilonacept); P = Placebo; Shaded area in the table represents the subjects involved in the trough concentration comparison.

**Figure 1 Ratio of trough concentration in market formulation to that in previous formulation 9 weeks after receiving each formulation**



Our analyses were performed to compare the steady state trough exposure within the same subject after 9 weeks of receiving the previous formulation as well as the market formulation, and we found the formulation change did not affect steady state trough concentrations. The ratios of trough concentrations in market formulation to those in previous formulation for each individual and the geometric mean ratio with its 90% confidence interval were presented in Figure 1. A paired-t test was conducted using log-transformed trough concentrations. The results were listed in Table 2. At week 9 after receiving market formulation or previous formulation, the trough concentrations were comparable because the 90% confidence interval of the trough concentration ratio was within the bioequivalence limits (0.8 – 1.25 under normal scale) and the paired-t test showed no statistical significance.

**Table 2 Paired-t test results for log-transformed trough concentrations 9 weeks after receiving market formulation or previous formulation**

Number of Observation	Mean	90% CI	Method
20	0.995	(0.825 - 1.198)	normal scale

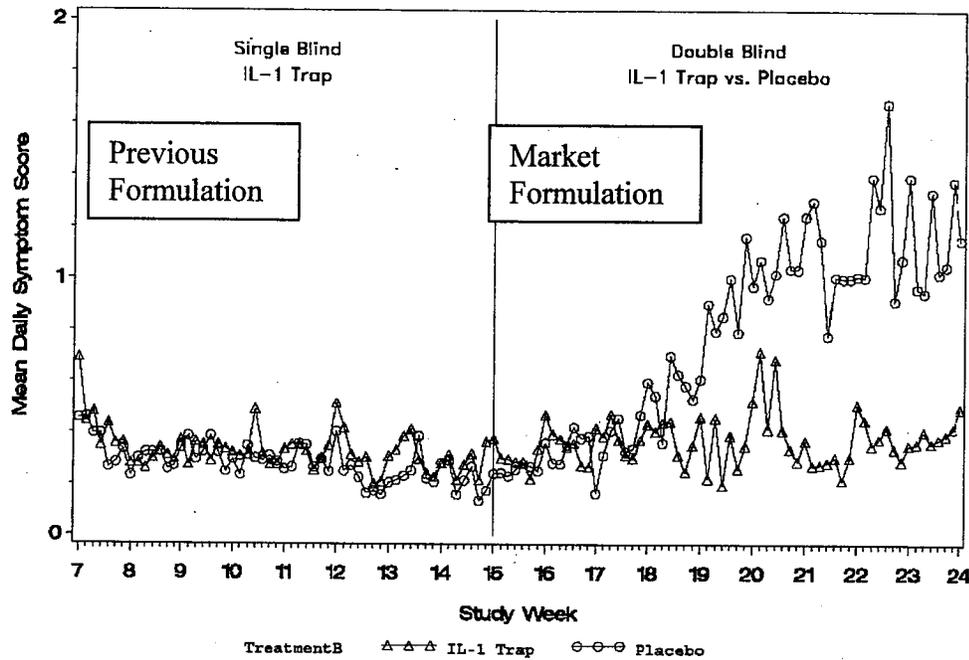
Note: \*: not statistically significant

In addition, the efficacy, safety outcomes were comparable between the two formulations treated periods. For example, one of the major safety concerns is infection; the incidence of infection by using previous formulation in the single-blind active treatment period was 20%, which was similar with 18% incidence observed in the double-blinded randomized withdrawal period by using the marked formulation (Table 3). The primary efficacy variable is the symptom score. As demonstrated in Figure 2, changing formulation did not result in mean symptom score change over time in riloncept treated group.

**Table 3 Number (%) of the subjects reporting treatment emergent adverse event of infection by treatment group and study phase**

Study Group Time Formulation	Single-blind active treatment period (By week 9)	Double-blinded randomized withdrawal (By week 9)
	Pervious Formulation	Market Formulation
Rilocept	9 (20%) N=46	4(18%) N =22
Placebo	-	5(23%) N =23

**Figure 2 Mean daily symptom score by treatment group from week 6 single blind phase to week 24 random withdrawal phase in Part B**



Although there are assumptions pertaining to potential period effect; for the following reasons, the two formulations are bioequivalent. 1.) no approved expectation that period effect is important, 2.) PK is comparable, 3.) new formulation demonstrated significant effectiveness over placebo, 4.) safety profile is not different, 5.) similar immunogenicity for both formulations.

**2. Is there evidence to suggest that the immunogenicity will affect riloncept exposure?**

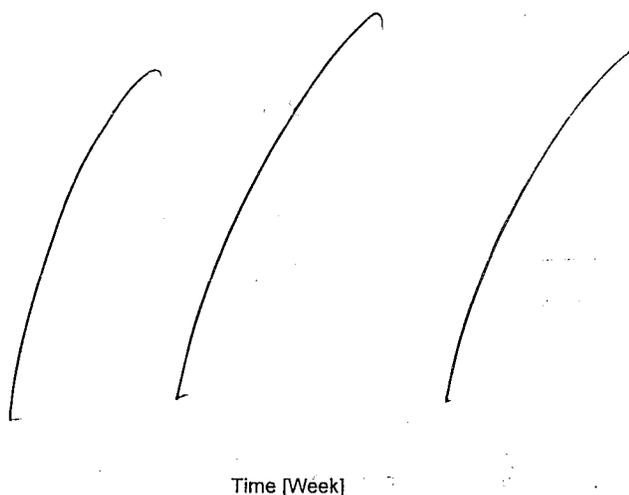
We investigated the relationship between immunogenicity and riloncept trough exposure and we found that immunogenicity affected the exposure for some subjects; however, given the large interindividual variability of trough concentrations (CV: 40-50%), the trough concentrations in antibody positive group were comparable to those in antibody negative group.

Our analyses were based on the riloncept trough concentrations and antibody measurements collected in Study IL1T-AI-0505, including double-blind, randomized, placebo-controlled treatment period (Part A), a 9-week single-blind active treatment period followed by a 9-week double-blind, placebo-controlled, randomized withdrawal phase (Part B), a 24-week open-label extension phase (OLE). Totally 58 subjects were included in the analyses, with longest duration of 48 weeks. PK samples were collected at weeks 0, 3, 6, 9, 12, 15, 18, 21, 24, 30, 42, 48 and antibody samples were collected at

weeks 0, 6, 12, 15, 21, 24, 30, 36, 42, 48. Within the controlled study phase (Part A and Part B) up to 24 weeks, 20 subjects were antibody positive in at least one occasion. Within the 48 weeks, 24 subjects were detected antibody positive in at least one occasion.

A comparison for all mean trough concentrations in antibody negative group versus antibody positive group cross 48 weeks was performed, we found comparable trough concentrations between antibody positive and antibody negative groups cross all time points. The results were shown in Figure 2. The means and standard deviations of trough concentrations in negative antibody group and in positive antibody group were presented in **Table 4**. Ideally, to evaluate immunogenicity effect on exposure requires sufficient number of subjects receiving the same dosing regimen for the same length of treatment duration. However, subjects with different treatment (placebo or drug) and treatment duration were pooled together for our comparison, because only small number of subjects was available from the clinical study for this orphan indication. We specifically compared the trough concentrations at week 15, 30, 42, and 48. Week 15 is the last observation for the Part B single-blinded period, where every subject was exposed to rilonacept for at least 9 consecutive weeks. From week 30 to 48, every subject was given rilonacept during the OLE period. Including the 12 new patients, the treatment duration was at least 6 to 24 weeks. We also found comparable trough concentrations between antibody positive and antibody negative groups at week 15, 30, 42, and 48.

**Figure 3 Trough concentrations in antibody negative group (blue open circle) versus trough concentrations in antibody positive group (red solid circle)**



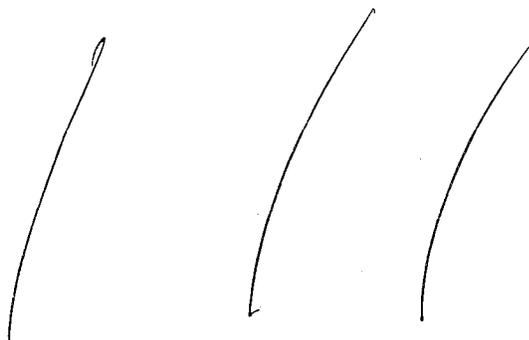
**Table 4. Mean (SD) of trough concentrations with antibody negative and positive over time.**

	Week									
	0	6	12	15	21	24	30	42	48	
Antibody Negative										
N	43	41	36	32	27	41	28	35	45	
Mean	1.525814	9805.634	25555.56	27094.06	9091.659	7275.849	26125	25026.29	24082.44	
SD	8.906794	11746.77	8780.024	9541.842	10298.18	12013.96	14289.36	10956.25	10110.98	
Antibody Positive										
N	1	4	7	12	17	15	10	11	5	
Mean	0	22750	30771.43	29433.33	13238.88	14622.63	25260	22474.55	22478	
SD	-	15245	10980.39	7637.864	11873.3	14317.21	11118.87	10905.39	10696.21	

Furthermore, a detailed comparison of trough concentration and antibody titer over time within the controlled phase of Study IL1T-AI-0505 (Part A and Part B) up to week 24 was conducted, and we found that for some individual, riloncept exposure appeared to be affected by antibody formation. The 20 subjects who were at least in one occasion detected positive antibody were plotted in the Appendices (**Figure 11**). By examining the time trend, we identified that the trough exposure appears to be affected for some of the subjects. For example, subject 021-6003 received riloncept for 24 consecutive weeks (**Figure 4**). However, the trough concentration dropped about 50% when antibody titer increased from — . . . . . When the antibody titer reduced to 0 at week 24, the trough concentration started to increase. Similar trend can be see on subject 016-6277, 009-6025, and 025-6386.

**Figure 4 Trough concentration and antibody titer plot for subject 021-6386**

Trough Concentration and Antibody Titer vs. Time,  
Subject = (021-6003)



Note: D = Drug, P=Placebo

In summary, immunogenicity appeared to affect the riloncept trough exposure for some individuals. However, given the large interindividual variabilities (CV: 40-50%), the trough exposure in antibody positive group was comparable in antibody negative group.

**3. Is there age, gender and body weight effect on riloncept exposure?**

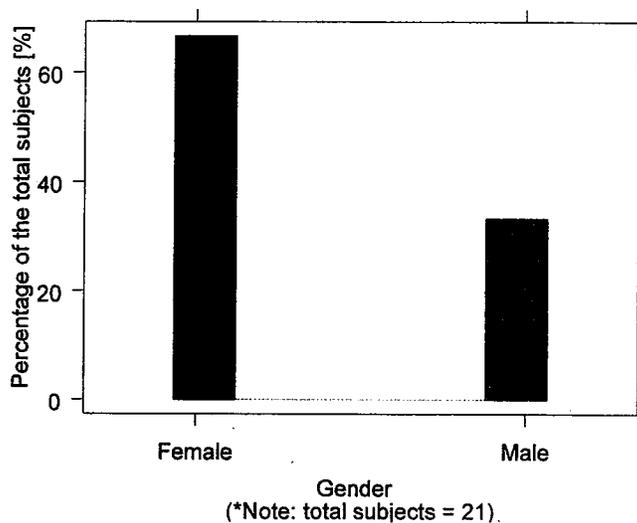
We evaluated the age, gender, and body weight effect by using the exposure data collected in Study IL1T-AI-0505. We found that steady state trough concentrations using market formulation were similar between male and female subjects, riloncept trough exposure does not to change with body weight (within the range of 50 -120 kg), and no age relationship can be identified.

Our analyses were based on trough concentrations collected 9 weeks after receiving market formulation, in order to account for formulation manufacturing process change, different analytical assays, dosing deviation, and different patient population. There were totally 21 subjects, with 7 male subjects and 14 female subjects (**Figure 5**). The trough concentration distribution between the two gender groups was demonstrated in **Figure 6**. As Shown in **Table 5**, the mean and median values were similar between the male and female subjects. **Figure 7** shows that no trend was identified within the observed range (26 – 78 yr). Among the 21 subjects, the body weight changes from 50 -120 kg. The steady state trough concentration versus body weight was plotted in **Figure 8**, no tend can be identified.

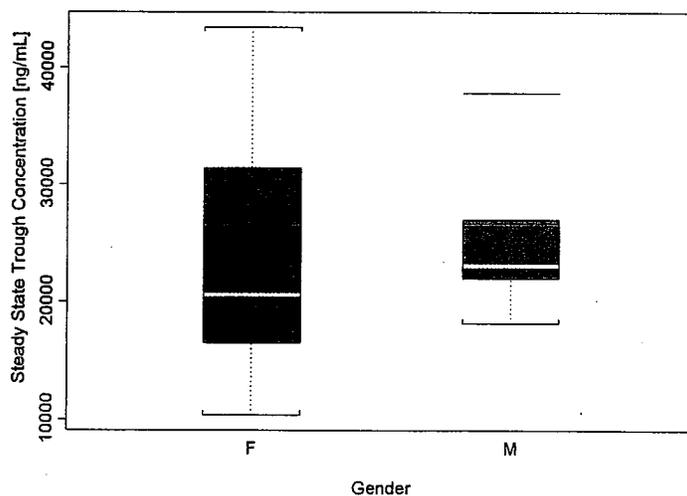
**Table 5. Summary of the gender effect and age effect on steady state trough concentration following market formulation administration**

	Gender Effect	
	Female	Male
Number of observations	14	7
Trough Concentration [ng/mL]	23914.29	25214.29
Mean (SD)	(10074,02)	(6246.713)
Median	20600	23100
(10th - 90th percentile)	(15820 - 37920)	(20480 - 31320)

**Figure 5 Percentage of subjects in different gender groups**

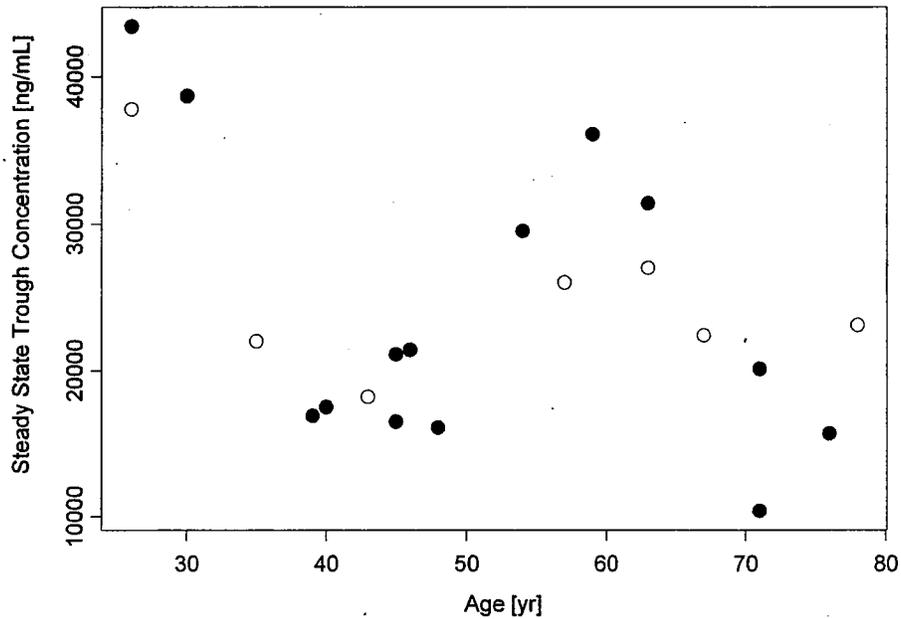


**Figure 6 Steady state trough concentration distribution in different gender groups**

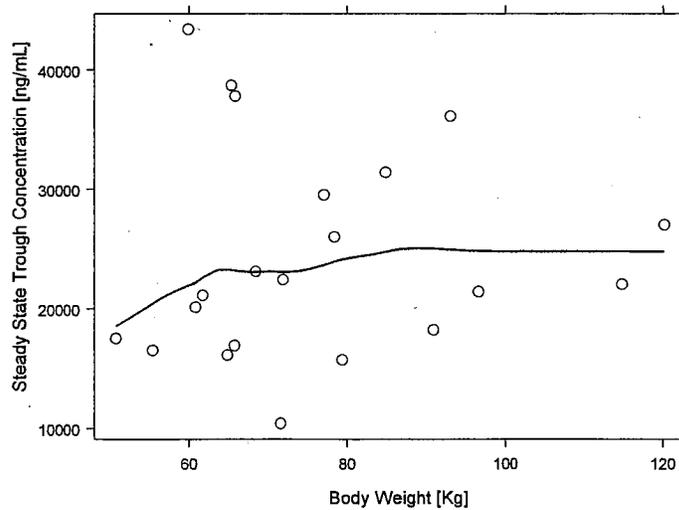


Note: F = Female, M= male

**Figure 7 Steady state trough concentrations at week 24 from male (blue open circle) and female (red solid circle) subjects versus age**



**Figure 8 Steady state trough concentration versus body weigh**



Note: open circle = observation, red line = lowess smooth line

## 3 INTRODUCTION

### 3.1 BACKGROUND

Rilonacep (IL-1 trap, BLA STN 125249) is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human Interleukin-1 receptor complex linked in-line to the Fc portion of human IgG1. Rilonacep has a molecular weight of approximately 252 kDa. Rilonacep is expressed in recombinant Chinese hamster ovary cells and is purified by a process that includes

This submission is a Biological License Application (BLA) number 125249 for the treatment of cryopyrin-associated periodic syndromes (CAPS). CAPS refers to three rare genetic syndromes caused by mutations in gene CIAS1. The syndromes include Neonatal Onset Multi-system Inflammatory Disorder (NOMID), (also called Cutaneous and Articular Syndrome [CINCA]), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS). It is estimated that approximately 200 to 300 adults and children in the U.S. have been diagnosed with FCAS and even fewer with NOMID or MWS. Inflammation in CAPS arises from mutations in NALP3, which is involved in the regulations of the protease caspase-1 and the activation of interleukin-1 beta (IL-1 $\beta$ ). The mutation in NALP3 results in an overactive inflammasome resulting in excessive release of activated IL-1 $\beta$  and drives inflammation. Blocking bioactivity of IL-1 $\beta$  with rilonacep may have therapeutic benefit by preventing clinical and laboratory features of Familial Cold Autoinflammatory Syndrome (FCAS) and possibly other inflammatory conditions.

### 3.2 STUDIES

There was 1 major clinical effectiveness and safety study (Study IL1T-AI-0505) that the sponsor included in this submission. It is summarized as the following:

#### **Study IL1T-AI-0505:**

Study IL1T-AI-0505 is a multi-center, double-blind, placebo-controlled study of the safety, tolerability, and efficacy of rilonacep in subjects with CIAS1-associated periodic syndromes (CAPS) using both parallel group and randomized withdrawal designs - parts A & B. The primary objective of this study was to assess the effect of rilonacep on the clinical signs and symptoms of CAPS when used for chronic therapy. The secondary objectives were to determine the safety and tolerability of rilonacep in subjects with CAPS, and to assess the effect of rilonacep on laboratory measures of inflammation such as phase reactants. The study consisted of a 3-week screening period, a 6-week, double-blind randomized, placebo-controlled treatment period (Part A), a 9-week single-blind active treatment period followed by a 9-week double-blind, placebo-controlled, randomized withdrawal phase (Part B), a 24-week open-label

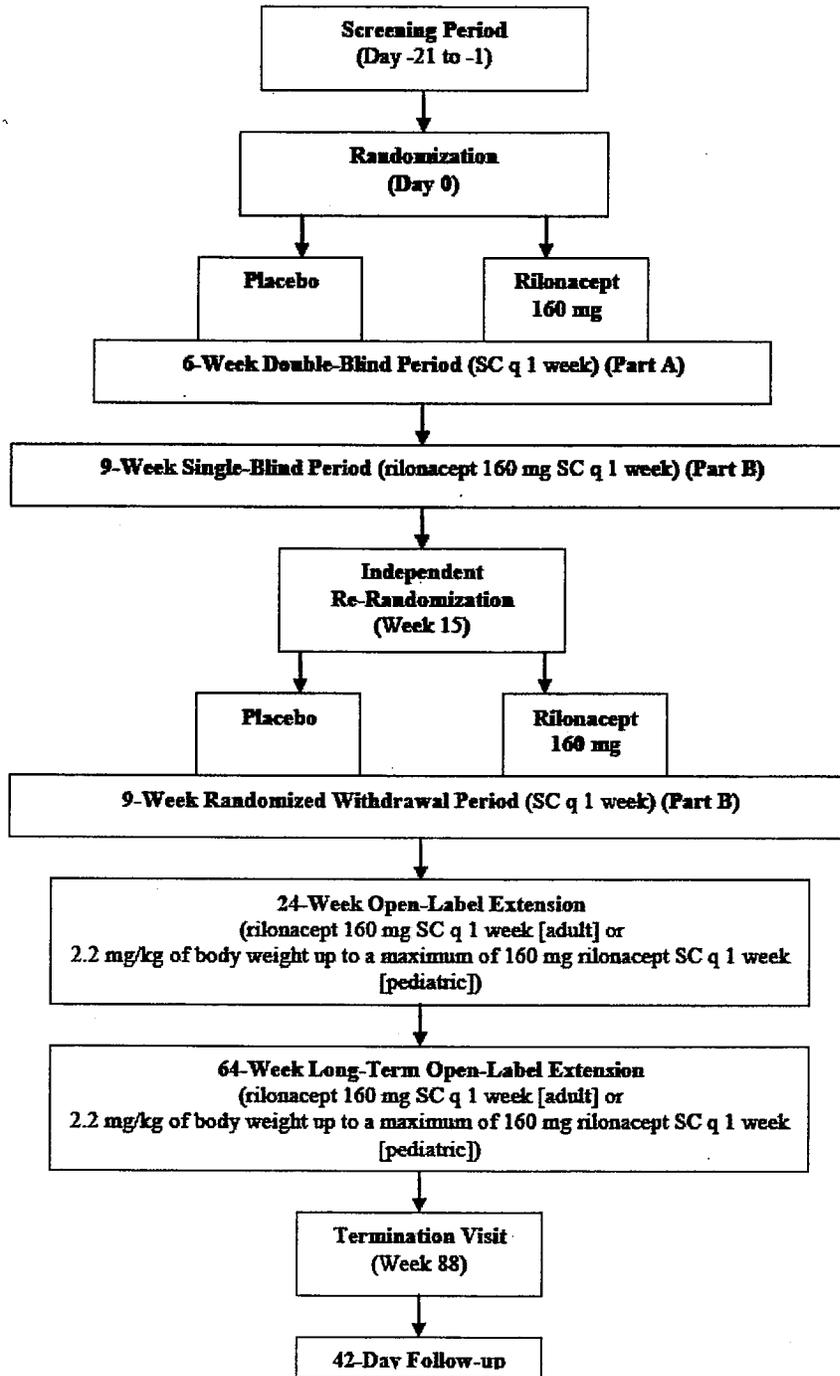
extension phase (OLE), a 64-week long-term open-label extension (LTOLE), and a 6-week post-treatment follow-up period.

47 subjects were randomized on Day 0 (Visit 2) in a 1:1 ratio to receive a loading dose of 320 mg of rilonacept or placebo, with subsequent weekly SC injections of 160 mg of rilonacept or placebo for a total of 6 doses. Following completion of the double-blind period, subjects were eligible to receive weekly single-blind SC injections of rilonacept for 9 weeks, and were then re-randomized at Week 15 (Visit 7) in a 1:1 ratio to receive weekly SC injections of 160 mg of rilonacept or placebo for a 9-week randomized withdrawal period. Upon completion of this phase of the trial, subjects were eligible to receive weekly SC injections of 160 mg of rilonacept in the 24 week open-label extension phase, and then a 64-week long-term open-label extension; a second informed consent process was required prior to participation in the open-label extension phase of the study. A total of 60 subjects were planned to be screened at approximately 25 study centers in order to obtain 50 evaluable subjects for participation in Parts A & B of the study. Approximately 35 additional subjects, including pediatric subjects aged 7 to 17, are to be screened for entry directly into the open-label extension of the study as a result of protocol Amendments 4 and 6.

The manufacturing process for drug product used in the Part B randomized withdrawal portion of the study and for subsequent open-label extension phases was modified to result in a drug product that would reconstitute more quickly in sterile water for injection. This modified manufacturing process is referred to as Process B. Drug product used during the Part A and the Part B single-blind phase of the study was made using the prior manufacturing process which is denoted as Process A.

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**Figure 9 Study Design Schematic**



### 3.3 AIM OF ANALYSIS

The aims for population pharmacokinetic analysis were as follows:

1. To estimate the population PK parameters in CAPS subjects, as well as in healthy volunteers and rheumatoid arthritis (RA) subjects;
2. To measure variability in PK parameters;
3. To explain variability in PK parameters.

## 4 SPONSOR'S ANALYSIS

### 4.1 BACKGROUND

Rilonacept is initiated with a loading dose of 320 mg S.C. in adult patients, followed by 160 mg dose once weekly S.C. In pediatric patients aged  $\geq$  to 17, the loading dose is 4.4 mg/kg (up to 320 mg). Then the dose is continued with a once-weekly S.C. injection of 2.2 mg/kg (up to 160 mg). The sponsor did not recommend dose adjustment for renal impaired patients, hepatic impaired patients and geriatric patients.

### 4.2 SPONSOR'S POPULATION PK ANALYSIS

The sponsor submitted 1 population PK report (Population Pharmacokinetic Analysis Report for IL-1 Trap).

#### **Population Pharmacokinetic Analysis Report for IL-1 Trap:**

The population pharmacokinetic analysis report for IL-1 Trap presented a population PK model developed from 6 clinical studies, including 333 adult and 17 pediatric subjects (Table 6). Among them, 47 were CAPS patients; others were healthy subjects and rheumatoid arthritis (RA) subjects. The adult analysis population was predominantly female (72.7%), Caucasian (77.8%) and had a mean age of 50.8 years, a mean weight of 79.0 kg, a mean calculated creatinine clearance of 111.2 mL/min, and a mean high sensitivity C-reactive protein of 1.60 mg/dL. The Study IL1T-AI-0505 analysis population was predominantly female (66.7%), Caucasian (100%) and had a mean age of 51.4 years, a mean weight of 75.7 kg, a mean calculated creatinine clearance of 86.1 mL/min, and a mean high sensitivity C-reactive protein of 2.64 mg/dL.

**Table 6. Description of the clinical studies included in the population PK report**

<b>Study Description and Code</b>	<b>Subjects Exposed to IL-1 Trap / Samples per Subject</b>	<b>Active Doses</b>
Pivotal Phase 3 Study IL1T-AI-0505	47/8	Weekly SC 160 mg
Rheumatoid arthritis Phase 2a Study IL1T-RA-0102	145/10	Weekly SC 25, 50, 100 mg
Rheumatoid arthritis Phase 1a Study IL1T-RA-0004	82/14-25	Weekly SC 50, 100, 200, 400, 800 mcg/kg
Normal volunteer Phase 1 Study IL1T-RA-0401	71/16	Single SC 50, 80, 104, 120, 160, 240, 320 mg
Normal volunteer Phase 1 Study IL1T-RA-0402	20/16	Single IV 100, 300, 1000, 3000 mg
Systemic Juvenile Idiopathic Arthritis Phase 1 Study IL1T-AI-0504	21/4	Weekly SC 2.2, 4.4 mg/kg (up to 320 mg)

### 4.3 POPULATION PK METHOD AND RESULTS

The sponsor performed population PK analysis by using NONMEM Version VI with g77 FORTRAN compiler in Windows environment.

The primary dataset included data from studies with rich data and studies with trough levels. Standard one- and two-compartment linear models with zero-order input were considered for subjects receiving IV infusions. Standard one- and two-compartment linear models with first-order input were considered for subjects receiving subcutaneous (SC) injections. The two-compartment model was selected as the primary one. This structure of the pharmacokinetic model was based on observations from the noncompartmental analyses of intravenous (IV) Study IL1T-RA-0402 and on statistical tests. From Study IL1T-RA-0402, it was known that intravenous administration of IL-1 Trap results in biphasic behavior with a distribution phase and a log-linear terminal phase. However, with subcutaneous administration, the distribution phase was obscured. Although adding the peripheral compartment improved the objective function (OF) significantly, it was found that the peripheral distribution volume was estimated as being much smaller than that of the central compartment. A combined constant coefficient of variation (CV) and additive model of errors was used. Different CVs were implemented for IV and SC studies. Two different additive errors were implemented for studies with different assay sensitivity. The exponential model was used as the primary model of random effects. The covariance matrix of the vector of random effects (vector  $\eta$ ) had the following structure for the IV study and the SC studies with sparse data:

$$\Omega_{IV} = \begin{pmatrix} \omega_{11} & \omega_{12} \\ \omega_{21} & \omega_{22} \end{pmatrix},$$

and the following structure for the SC studies with rich data:

$$\Omega_{SCR} = \begin{pmatrix} \omega_{11} & \omega_{12} & 0 \\ \omega_{21} & \omega_{22} & 0 \\ 0 & 0 & \omega_{33} \end{pmatrix}$$

Because the exponential model of the random effect was used, the diagonal elements of the matrix approximate squared coefficients of variation.

The first order conditional estimation method with interaction was implemented.

The covariate model was developed for the adult population and tested on the pediatric population. The following demographic and baseline covariates were explored: Age, [years; continuous variable], Sex [male, female], Race [white, other], Weight, Predicted creatinine clearance, High sensitivity C-reactive protein (hs-CRP), Albumin, Aspartate transaminase (AST/SGOT), Alanine transaminase (ALT/SGPT), Alkaline phosphatase (ALP), MTX use [yes, no].

Indicators of studies were used as dichotomous covariates (assigned a value of 0 and 1) to account for the differences in the assays and some other study-specific factors. The indicators in the regression analyses of Bayesian parameter estimates and in the NONMEM analyses were specified for four out of five studies to avoid multicollinearity (Studies IL1T-RA-0401, IL1T-RA-0402, IL1T-RA-0102, and IL1T-RA-0004). Thus, in the regression models, the regression coefficients on the indicators represented the adjusted differences between Study IL1T-AI-0505 and the other studies. It is noteworthy to mention that such differences are equal to the differences in least-squared means between studies if the variable STUDY is a categorical predictor in a general linear model. In the NONMEM covariate models, the indicators have similar interpretation.

Three different assays were used to detect antibodies. The first assay was used in Study IL1T-RA-0004. The second assay was used in Studies IL1T-RA-0401, IL1T-RA-0402, IL1T-RA-0102, and IL1T-AI-0504. Antibodies were detected in very few subjects. The third assay was used in Study IL1T-AI-0505 and was more sensitive than the first two assays. Therefore, it was not feasible to use an indicator of antibody in the NONMEM models. Conditional estimates of PK parameters were analyzed instead. Because low and high laboratory values were similar across the studies, normalization procedures were not used to adjust for differences in data provided by different laboratories.

From the Bayesian parameter estimates a regression screening was conducted to explore the covariates. A linear regression analysis of clearance, volume of the central compartment, terminal half-life, and absorption rate constant was conducted. A forward inclusion was used to select covariates. A variable had to be significant at the 0.1 level before it was entered into the model. The final covariate selection was done using NONMEM. Limited analysis of covariates of  $K_a$  was conducted because only two out of five studies had rich data and because the pivotal study had sparse data. Both additive and multiplicative models were screened. The multiplicative model was selected because it was more flexible than the additive model. The full model was tested. All potential covariates were used to predict clearance and central volume. Only

covariates selected using forward regression screening were used to predict  $K_a$ . The model was parameterized as follows:

$$V_{2S}/F_S = V_2/F \prod_{i=1}^{i_{max}} e^{\theta_{vi} (\ln(\text{Covariate}_{vi}) - \text{Median}(\ln(\text{Covariate}_{vi})))} \prod_{j=1}^{j_{max}} \theta_{vj}^{\text{Covariate}_{vj}}$$

$$Cl_S/F_S = Cl/F \prod_{i=1}^{i_{max}} e^{\theta_{ci} (\ln(\text{Covariate}_{ci}) - \text{Median}(\ln(\text{Covariate}_{ci})))} \prod_{j=1}^{j_{max}} \theta_{cj}^{\text{Covariate}_{cj}}$$

$$K_{aS} = K_a \prod_{i=1}^{i_{max}} e^{\theta_{kai} (\ln(\text{Covariate}_{kai}) - \text{Median}(\ln(\text{Covariate}_{kai})))}$$

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where  $\theta_{vi}$ ,  $\theta_{ci}$ , and  $\theta_{kai}$  are the coefficients for the continuous covariates,  $\theta_{vj}$ , and  $\theta_{cj}$  are the coefficients for the binary covariates,  $F$  is bioavailability, and  $S$  is the subject number. In the full model, the optimization terminated. A backward elimination was used to remove covariates from the model. A covariate remained in the final model when its removal resulted in increase of  $\geq 7.88$  in the objective function assuming chi-square distribution and alpha of 0.005. The covariates were removed in the following order: a) the covariates, which were not selected for both central volume and clearance at the multivariate regression step; b) the covariates, which were not selected for central volume or clearance at the multivariate regression step; c) the covariates, which were selected for  $K_a$  at the multivariate regression step; d) all other covariates.

The NOMEM results for the final covariate model were listed as following (Table 7 and Table 8):

**Table 7. OMEGA matrix for the basic model and covariate model**

Basic Model	Covariate Model
$\Omega_{IV} = \begin{pmatrix} 0.203 & 0.153 \\ 0.153 & 0.212 \end{pmatrix}$	$\Omega_{IV} = \begin{pmatrix} 0.155 & 0.0838 \\ 0.0838 & 0.113 \end{pmatrix}$
$\Omega_{SCr} = \begin{pmatrix} 0.203 & 0.153 & 0 \\ 0.153 & 0.212 & 0 \\ 0 & 0 & 0.289 \end{pmatrix}$	$\Omega_{SCr} = \begin{pmatrix} 0.155 & 0.0838 & 0 \\ 0.0838 & 0.113 & 0 \\ 0 & 0 & 0.279 \end{pmatrix}$

Table 8. Parameters of covariate model

Parameter	Estimate				Difference in Objective Function	P-value
	Value	Lower CL	Upper CL	SE		
V <sub>2</sub> /F [L]	6.27436	5.45377	7.09495	0.41867	N/A	N/A
Cl/F [L/day]	0.80758	0.75372	0.86144	0.02748	N/A	N/A
K <sub>a</sub> [1/day]	0.37743	0.29642	0.45844	0.04133	N/A	N/A
Lag [day]	0.06418	0.06079	0.06757	0.00173	N/A	N/A
Q [L/day]	0.24999	-0.004	0.50395	0.12957	N/A	N/A
V <sub>3</sub> /V <sub>2</sub>	0.22041	0.10698	0.33383	0.05787	N/A	N/A
θ <sub>Cl on ID401</sub>	3.17419	2.20249	4.14589	0.49576	119.266	<.0001
θ <sub>Cl on ID402</sub>	1.16115	0.87148	1.45082	0.14779	1.490	0.222
θ <sub>Cl on ID102</sub>	1.36006	1.19151	1.52861	0.086	19.616	<.0001
θ <sub>Cl on ID004</sub>	1.57923	1.38616	1.77231	0.09851	35.453	<.0001
θ <sub>V2 on ID401</sub>	2.28168	1.55133	3.01202	0.37262	49.900	<.0001
θ <sub>V2 on ID402</sub>	1.08042	0.79447	1.36638	0.1459	0.325	0.569
θ <sub>V2 on ID102</sub>	1.22146	1.04195	1.40098	0.09159	5.384	0.020
θ <sub>V2 on ID004</sub>	1.5014	1.00631	1.99648	0.25259	18.356	<.0001
θ <sub>Cl on Weight [1/kg]</sub>	0.37669	0.09431	0.65907	0.14407	15.323	<.0001
θ <sub>V2 on Weight [1/kg]</sub>	0.70722	0.4562	0.95824	0.12807	43.130	<.0001
θ <sub>Cl on Race</sub>	0.88682	0.81669	0.95695	0.03578	8.636	0.003
θ <sub>Cl on ALB [dL/g]</sub>	-1.0798	-2.0742	-0.0853	0.50736	20.967	<.0001
θ <sub>Cl on Creatinine [min/mL]</sub>	0.18837	-0.0901	0.46679	0.14205	8.472	0.004
θ <sub>Cl on CRP [dL/mg]</sub>	0.08003	0.02197	0.13809	0.02962	21.152	<.0001
θ <sub>V2 on CRP [dL/mg]</sub>	0.08003	0.02197	0.13809	0.02962	6.692	0.010
CV <sub>1</sub>	0.25582	0.23534	0.27629	0.01045	N/A	N/A
CV <sub>2</sub>	0.13506	0.11379	0.15633	0.01085	N/A	N/A

Parameter	Estimate				Difference in Objective Function	P-value
	Value	Lower CL	Upper CL	SE		
SD <sub>1</sub>	0.02918	0.01899	0.03937	0.0052	N/A	N/A
SD <sub>2</sub>	0.01481	0.00644	0.02317	0.00427	N/A	N/A
θ <sub>11</sub>	0.15541	0.09451	0.2163	0.03107	N/A	N/A
θ <sub>12</sub>	0.08378	0.05367	0.11389	0.01536	N/A	N/A
θ <sub>21</sub>	0.113	0.08613	0.13987	0.01371	N/A	N/A
θ <sub>33</sub>	0.27911	-0.7705	1.32876	0.53554	N/A	N/A

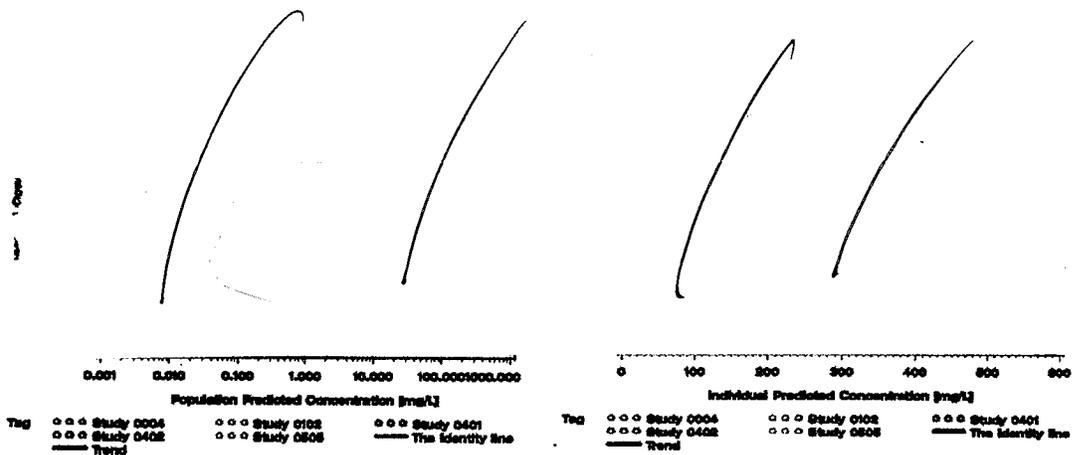
The parameters for CAPS patients from Study IL1T-AI-0505 were summarized in Table 9.

**Table 9. Parameters of covariate model at Study IL1T-AI-505 median of covariates**

Parameter	Estimate	
	Value	SE
$V_2/F$ [L]	6.79729	1.02202
$Cl/F$ [L/day]	0.78749	0.02605
$K_{el}$ [1/day]	0.37741	0.03229
Lag [day]	0.06418	0.00177
$Q$ [L/day]	0.25004	0.11404
$V_1/V_2$	0.22043	0.04635

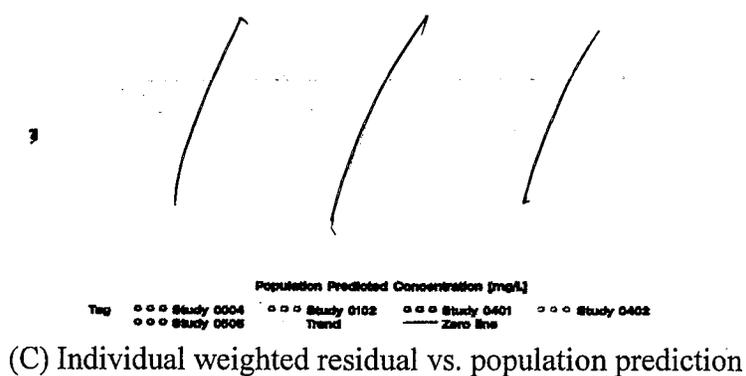
Diagnostic plots for the final covariate model were presented in Figure 10.

**Figure 10 Diagnostic plots for the final covariate model**

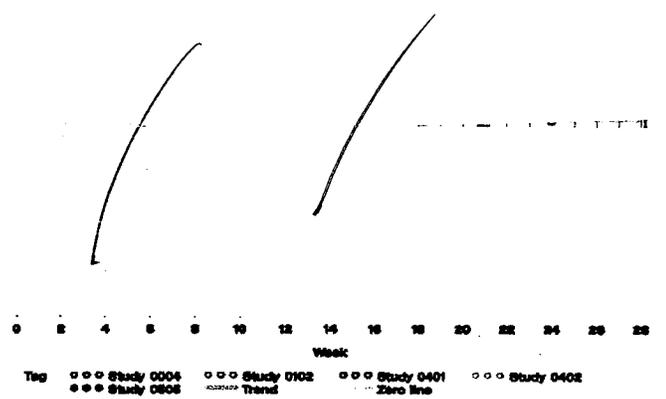
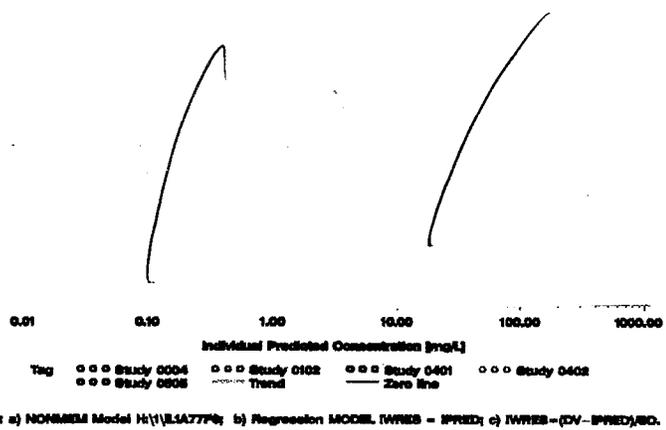


(A) Population Prediction vs. Observation

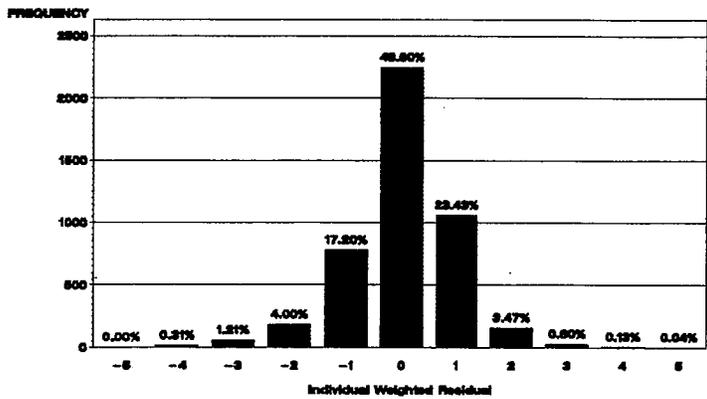
(B) Individual Prediction vs. Observation



(C) Individual weighted residual vs. population prediction



(E) Individual weighted residual vs. time



(F) Individual weighted residual

#### 4.4 SPONSOR'S CONCLUSIONS

Based on the Population Pharmacokinetic Analysis Report for IL-1 Trap, the sponsor found:

- Both the basic and covariate models produced an accurate representation of the data.
- The results were in agreement with linear pharmacokinetic principles. There was no evidence of unexpected accumulation of IL-1 Trap following weekly S.C. dosing.
- Significant association between CL/F and albumin, creatinine clearance, race, weight, and hs-CRP were not clinically important.
- There was no statistical evidence that binding or neutralizing antibodies significantly affect pharmacokinetics of IL-1 Trap.

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#### 4.5 REVIEWER'S COMMENTS ON SPONSOR ANALYSIS

- The population pharmacokinetic analysis for rilonacept in CAPS, RA patients, and healthy volunteers is acceptable.
- We found that no definitive conclusion can be drawn on whether antibody affect rilonacept exposure based on current population PK approach and available data, because:
  - Antibody information in the analysis dataset from various antibody assays with different detection sensitivity is inconsistent cross different trials. The sponsor developed 3 different assays to detect antibody. The first two assays (BA1 and BA2) were not very sensitive, but they were used in most of the trials (Studies IL1T-RA-0004, IL1T-RA-0401, IL1T-RA-0402, IL1T-RA-0102 and IL1T-AI-0504). The third assay was more sensitive than the first two assays. However the most sensitive and validated assay was mainly applied in a small patient group (47 CAPS subjects out of 350 subjects). It is insufficient to determine antibody effect on exposure in population PK analysis based on small number (or percentage) of subjects with reliable and sensitive antibody observation.
  - The sponsor excluded the adult subjects with less than 5 available PK trough samples (with concentrations above LOQ) and the pediatric subjects with less than 2 available PK trough samples (with concentrations above LOQ) for population PK analysis dataset. By applying this rule, a subject whose exposure is affected by antibody formation can be removed from analysis. One example is subject 019-007 (Study IL1T-RA-0102), who was antibody positive and demonstrated a considerable decrease in concentration of total IL-1 Trap at Day 35 and six later visits. This subject was excluded from analysis due to a small number of IL-1 Trap concentrations above LOQ.
  - The immunogenicity observation from Study IL1T-AI-0505 suggested that in some subjects, the appearance of anti-rilonacpet antibody seems to be variable. Therefore, investigating the time trend of weighted residual is not reliable, because the formation of antibody and subsequent exposure change, if exists, is random over time.
- This population PK model is mostly driven by RA patients and healthy subjects due to the sample size distribution in the population PK dataset. Because PK profile can be patient population specific for biological products, we investigated the age, gender, and body weight effect separately based on steady state trough concentration from CAPS patient using the market formulation. We found that consistent with the population PK findings, age, body weigh, and gender do not appear to remarkably affect the trough exposure.

## 5 PHARMACOMETRIC REVIEW CONCLUSIONS

This review highlighted the pharmacometric findings from rilonacept BLA submission. Specifically, we found that:

- Rilonacept steady state trough concentrations for both manufacturing process A and process B were comparable (Mean ratio is 0.995 with 90% confidence interval of 0.825 ~ 1.198).
- We found that immunogenicity affects the exposure for some subjects; however, given the large inter-individual variability of trough concentrations (40% - 50%), the trough concentrations in antibody positive group appear to be comparable with those in antibody negative group.
- We found that steady state trough concentrations using market formulation were similar between male and female subjects, rilonacept trough exposure does not appear to change with body weight (within the range of 50 -120 kg), and age ( within the range of 26 -78 yr).

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## 6 APPENDICES

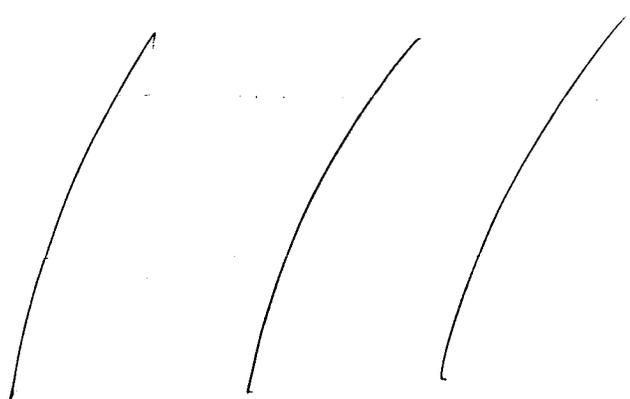
Table 10. Summary of incorrect medication in Part B of Study IL1T-AI-0505

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

Note: obtained from the clinical study report: IL1T-AI-0505 (P-72, section 4.3.2: Dosing deviation)

Figure 11. Rilonacept trough concentration and antibody titer time profile in the controlled phase of the Study IL1T-AI-505 for each individual

Trough Concentration and Antibody Titer vs. Time,  
Subject = ( 002-6255 )



Time [Weeks]

\* Positive in neutralizing Ab assay

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#### 4.4 Bioanalytical Validation Methods Consult Review (CMC)



DEPARTMENT OF HEALTH & HUMAN  
SERVICES

*Public Health Service*

Center for Drugs Evaluation and Research – Food and Drug Administration  
Office of Biotechnology Products / Office of Pharmaceutical Science  
Division of Monoclonal Antibodies, NIH Bldg 29B, HFM-555  
29B Lincoln Drive, Bethesda, MD 20892-4555

To: File  
From: Patrick Swann  
Date: October 9, 2007  
Subject: Bioanalytical Method Validation for Assays used to Detect Rilonacept

On September 20, Lei K. Zhang sent the following to the DMA review team for BLA 125249 (IL-1 Trap) requesting a consult on bioanalytical assays:

I wonder if you could help me determine whether the different analytical assays that the sponsor used for rilonacept (see table below) would generate similar quantitative results even without cross-validation studies. All of them were ELISA assays but used different                       
                     According to the sponsor, each assay was validated.

Table 2.7.1-2 Characteristics of Total Rilonacept Assays

Three large, hand-drawn curved lines that sweep across the page from the bottom left towards the top right, indicating that the content of the table has been redacted.

Per the BMV guidance (<http://www.fda.gov/cder/guidance/4252fnl.htm>):

Cross-validation is a comparison of validation parameters when two or more bioanalytical methods are used to generate data within the same study or across different studies. An example of cross-validation would be a situation where an original validated bioanalytical method serves as the *reference* and the revised bioanalytical method is the *comparator*. The comparisons should be done both ways.

Cross-validation should also be considered when data generated using different analytical techniques (e.g., LC-MS-MS vs. ELISA) in different studies are included in a regulatory submission.

Therefore, addressing Dr. Zhang's question will require an understanding of the impact of the differences listed in the above table. Do these differences constitute "different analytical techniques" as described in the BMV guidance?

According to DeSilva et al<sup>2</sup>, full validation should be performed for:

- Brand New Method
- Change in Species
- Change in Matrix within Species

1. Validation Report IL1T-AS-00022 - Quantitative Analysis of Total Interleukin-1 Trap in Human Serum

<sup>2</sup> B. DeSilva, W. Smith, R. Weiner, M. Kelley, J. Smolec, B. Lee, M. Khan, D. Tacey, H. Hill, and A. Celniker, "Recommendations for the Bioanalytical Method Validation of Ligand-binding Assays to Support Pharmacokinetic Assessments of Macromolecules," Pharm.Res. Vol. 20, No. 11, pp. 1885-1900.

5 Page(s) Withheld

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#### 4.5 OCP Filing Memo

Office of Clinical Pharmacology				
New Drug Application/Biologics License Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA/BLA Number	STN 125249	Brand Name	Arcalyst	
OCPB Division (I, II, III)	DCP2	Generic Name	Riloncept (IL-1 Trap)	
Medical Division	DAARP	Drug Class	IL-1 Blocker	
OCP Reviewers	Lei Zhang, Ph.D. Hao Zhu, Ph.D. (PM)	Indication(s)	CAPS (Cypropyrin-Associated Periodic Syndrome) in adults and pediatrics (≤17)	
OCP Team Leaders	Suresh Doddapaneni, Ph.D Jogarao Gobburu, Ph.D. (PM)	Dosage Form	Lyophilized powder for reconstitution	
		Dosing Regimen	Adult: loading dose 320 mg (2 X2 mL) and 160 mg wkly; Pediatric (≤17 yr): loading dose of 4.4 mg/kg up to 320 mg and weekly injection of 2.2 mg/kg up to 160 mg.	
Date of Submission	5/25/2007	Route of Administration	Subcutaneous Injection	
Estimated Due Date of OCP Review	9/29/2007	Sponsor	Regeneron Pharmaceuticals	
PDUFA Due Date	<del>11/29/2007</del> Revised due to major amendment submission: 2/28/2008	Priority Classification	1P	
Division Due Date	<del>10/29/2007</del> Revised due to major amendment submission: 12/20/2007		BB-IND 11,781	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Analytical and immunogenicity assays
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:	X	Study RA-0401 (SC) Study RA-0402(IV)	Study RA-0401 (SC) Study RA-0402 (IV)	Dense PK data in healthy subjects
multiple dose:				
<b>Patients-</b>				
single dose:				

alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	X		1	
<b>Total Number of Studies</b>		6	8	
<b>Filability and QBR comments</b>				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	X	Submit control files (basic and final models) used for POP-PK analyses with your BLA submission. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension.		
QBR questions (key issues to be considered)		<ul style="list-style-type: none"> <li>• Have the single and multiple dose PK of rilonacept been adequately characterized in healthy subjects and CAPS patients?</li> <li>• Is PK dose proportional?</li> <li>• What is the to-be-marketed formulation of rilonacept?</li> <li>• Are various formulations of rilonacept used throughout the clinical development adequately linked?</li> <li>• Have the analytical methods been adequately validated?</li> <li>• Do different analytical assays affect PK assessment?</li> <li>• What is the immunogenicity of the product?</li> <li>• Have the antibody assays been adequately validated?</li> <li>• Does immunogenicity affect PK, PD, and/or efficacy/safety?</li> <li>• Is POP-PK analysis acceptable?</li> <li>• What are main covariates for PK? <ul style="list-style-type: none"> <li>○ Is there a need for dose adjustment?</li> <li>○ Is formulation a significant covariate?</li> </ul> </li> <li>• Does exposure-response support the dose recommendation? <ul style="list-style-type: none"> <li>• Adult?</li> <li>• Pediatrics?</li> </ul> </li> </ul>		
Other Comments or information not included above				
Primary reviewer Signature and Date	Lei Zhang			
Secondary reviewer Signature and Date	Suresh Doddapaneni			

multiple dose:	X	Study AI-0505 and OLE	Study AI-0505 and OLE	The Study contains 24-week placebo-controlled phase and 24-week open label extension (OLE); Only trough levels measured in CAPS patients
		Study RA-0004 Study RA-0102 (trough levels)		Non-indication patients ; Used early liquid formulation and assay method; Assays were not cross-validated.
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	Study RA-0401 (SC) Study RA-0402 (IV)	Study RA-0401 (SC) Study RA-0402 (IV)	
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:	X	Study AI-0505 OLE	Study AI-0505 OLE	Four pediatric CAPS patients enrolled in 24-week OLE portion of the study; Only trough levels
		Study AI-0504 (trough levels)		Non-indication patients; Did not use to-be-marketed formulation ; Only trough levels
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:	X	Study AI-0406		Pilot study in 5 CAPS patients
Phase 3:	X	Study AI-0505	Study AI-0505	Biomarkers, CRP and SAA, were monitored as tertiary efficacy endpoints; Complex to IL-1 $\beta$ and IL-1ra levels were measured
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:	X	Study RA-0004 Study RA-0401 (SC) Study RA-0402 (IV)		Data were mainly from a different indication population that used an early liquid formulation with a $\rightarrow$ analytical assay
Data sparse:	X	Study RA-0102 (trough levels) Study AI-0504 (trough levels) Study AI-0505 (trough levels)		
<b>Absolute bioavailability:</b>	X	Study RA-0401 (SC) Study RA-0402 (IV)	Study RA-0401 (SC) Study RA-0402 (IV)	Healthy subjects
<b>Relative bioavailability -</b>				
solution as reference:				