

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BL 125249/0

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST™ (rilonacept)
Injection for Subcutaneous Use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

DOSAGE AND 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 on the same day at two different sites. 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. (2)
- Pediatric patients aged 12 to 17 years: 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. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

DOSAGE FORMS AND STRENGTHS

Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with ARCALYST. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST™ (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated 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. Dosing should be continued 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. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80-mg/mL solution is sufficient to allow a withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Prior to injection, the reconstituted solution should be carefully inspected for any discoloration or particulate matter. If there is discoloration or particulate matter in the solution, the product in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug.

Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin -1 (IL-1) blockade may interfere with the 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

ARCALYST [see *Clinical Studies (14)*]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [see *Adverse Reactions (6.3)*]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [see *Adverse Reactions (6.3)*]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST.

Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control. <http://www.cdc.gov/vaccines/recs/schedules/>).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted [see *Adverse Reactions (6.7)*].

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [see *Adverse Reactions (6.3)*].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [see *Adverse Reactions (6.2)*]. The next most commonly reported adverse reaction was upper respiratory infection [see *Adverse Reactions (6.3)*].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [see *Clinical Studies (14)*]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	ARCALYST 160 mg (n = 23)	Placebo (n = 24)
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritis, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One subject receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with *Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[see Warnings and Precautions (5.2)].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia ($ANC < 1 \times 10^9/L$) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 subjects (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five subjects tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety.

The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rilonacept with the incidence of antibodies to other products may be misleading.

6.7 Lipid profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 19 mg/dL, 2 mg/dL, 10 mg/dL, and 57 mg/dL respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

7 DRUG INTERACTIONS

7.1 TNF-blocking agent and IL-1 blocking agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [see *Warnings and Precautions* (5.1)].

The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus.

Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analogue of rilonacept at doses of 20, 100, 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F₁ offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and upper respiratory symptoms as were commonly seen in the adult subjects.

The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7-56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [see *Use in Specific Populations* (8.1)]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [see *Adverse Reactions* (6.3)]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

In case of overdose, it is recommended that the subject be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

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 IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST 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. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept (80 mg/1 mL after reconstitution), histidine, arginine, polyethylene glycol 3350, sucrose, and glycine at a pH of 6.5 ± 0.3 . No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [CIAS1]). 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.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1 β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1 β that drives inflammation.

Rilonacept blocks IL-1 β signaling by acting as a soluble decoy receptor that binds IL-1 β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1 α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1 β , IL-1 α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady state trough concentrations were similar between male and female subjects. Age (26-78 years old) and body weight (50-120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all subjects received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

Table 2: Mean Symptom Scores

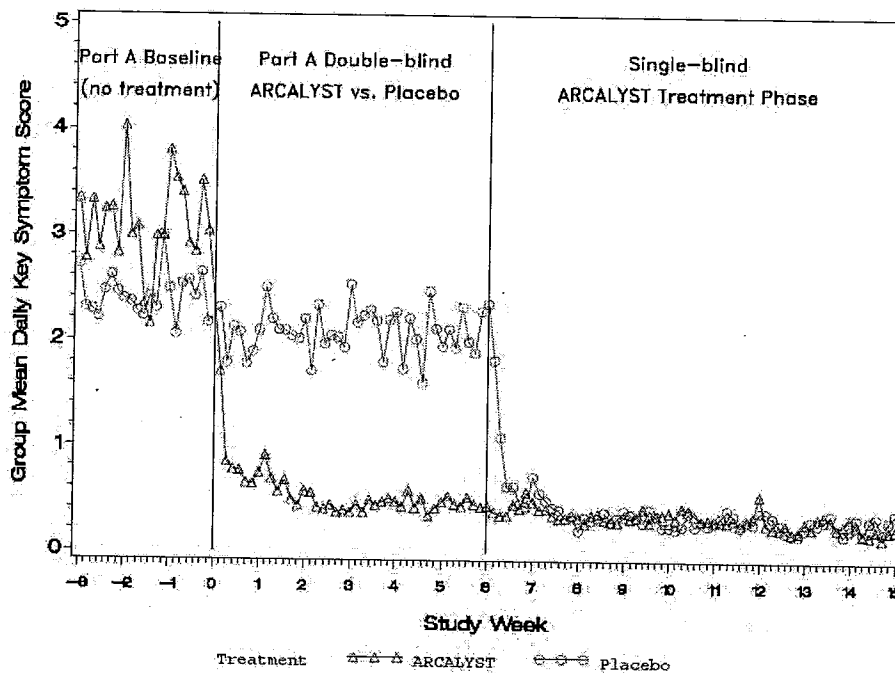
Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.

** A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3. Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

16 HOW SUPPLIED/ STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials.

The lyophilized ARCALYST product is to be stored refrigerated at 2 to 8 °C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and

should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST™*). Arcalyst should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritis, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

Manufactured and distributed by:
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