

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BL 125249/0

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Addendum to Summary Review for Regulatory Action

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|---|---|
| Date | February 27, 2008 |
| From | Bob A. Rappaport, M.D. <i>Bob Rappaport</i> Director Division of Anesthesia, Analgesia and Rheumatology Products |
| Subject | Division Director Summary Review |
| BLA # | 125249 |
| Applicant Name | Regeneron Pharmaceuticals, Inc. |
| Date of Submission | May 29, 2007 |
| PDUFA Goal Date | February 28, 2008 |
| Proprietary Name / Established (USAN) Name | Arcalyst/riloncept (IL-1 Trap [®]) |
| Dosage Forms / Strength | Lyophilized powder for reconstitution with WFI <ul style="list-style-type: none">• 160 mg subcutaneous injection q week for adults• 4.4 mg/kg subcutaneous injection q week for children |
| Proposed Indication(s) | For the treatment of Cryopyrin-Associated Periodic Syndromes |
| Recommended Action | Approval |

On February 26, 2008, the Division of Medication Errors and Technical Support (DMETS) in the Office of Surveillance and Epidemiology signed off on and submitted a second review. This review addresses a number of remaining concerns that the DMETS review team recommends be resolved prior to approval.

1. DMETS believes that the graphic on the left side of the principal display panel on the carton and container labeling is "...more prominent than other important information such as the established name, product strength, and storage information." They propose that this graphic be minimized or deleted. I do not concur with their concern. The established name, product strength and storage information are clearly legible and the blue and gold graphic at the left edge of the panel does not, to my eye, in any way distract from this information.

2. DMETS believes that the one-time training to be provided in the prescriber's office is not adequate to assure that a patient will be able to properly prepare and administer the product. For the reasons delineated in my primary review, I do not concur with their concerns. They also express concern that the "...plan does not provide assurance that the patient will take the drug vials back to the physician's office for the initial one time hands-on training..." and that "It is also possible that the patient may read the proposed patient brochure booklet and attempt to prepare and administer the product without proper training by their healthcare provider." This seems to be a highly speculative and highly unlikely set of assumptions. Patients are not likely to be cavalier with an injectable medication and a complex administration procedure unless they, or their caregiver happens to be a trained specialist as well, e.g., R.N., pharmacist. There are other products that require reconstitution and injection that have been approved and there have been no signals of concern related to casually careless preparation and administration of these products. Certainly, isolated situations may arise, but I do not feel that the risk is so significant that a more restrictive set of rules and regulations is necessary in this case.
3. DMETS believes that "...all the information pertaining to the disease and treatment along with the drugs/supplies should go directly to the physician's office so that the physician can go over the information in detail with the patient/caregiver in person." They also note that the "

I disagree with their recommendation and do not concur with their concerns. It is not at all uncommon for patients to be given prescriptions for medication and/or equipment, pick up these products at the pharmacy, and then return to the prescriber's office for detailed instruction in proper use. I see no reason to impose a special restriction in this case.



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Summary Review for Regulatory Action

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| Date | February 8, 2008 |
| From | Bob A. Rappaport, M.D. <i>R Roca for B. Rappaport 2/8</i> Director Division of Anesthesia, Analgesia and Rheumatology Products |
| Subject | Division Director Summary Review |
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| Proposed Indication(s) | For the treatment of Cryopyrin-Associated Periodic Syndromes |
| Recommended Action | Approval |

| Material Reviewed/Consulted | |
|--------------------------------------|---|
| OND Action Package, including: | |
| Medical Officer Review | Keith K. Burkhart, M.D., Jeffrey Siegel, M.D. |
| Statistical Review | Ruthanna C. Davi, M.S., Dionne Price, Ph.D. |
| Pharmacology Toxicology Review | Mamata De, Ph.D., R. Daniel Mellon, Ph.D. |
| OBP CMC Review | Ruth Cordoba-Rodriguez, Ph.D., Gurpreet Gill-Sangha, Ph.D., Jun Park, Ph.D., Chana Fuchs, Ph.D. |
| Office of Compliance/TFRB CMC Review | Michelle Y. Clark-Stuart, MGA/MIS, MT, Bo Chi, Ph.D., Patricia Hughes, Ph.D., Gilbert Salud |
| Clinical Pharmacology Review | Lei Zhang, Ph.D., Suresh Doddapaneni, Ph.D., Hao Zhu, Ph.D., Jogarao Gobburu, Ph.D. |
| DDMAC | Michelle Safarik, PA-C |
| DSI | Sheryl Gunther, Pharm. D. |
| CDTL Review | Jeffrey Siegel, M.D. |
| OSE/DMETS | Walter Fava, R.Ph. |
| OSE/DDRE | |
| OSE/DSRCS | |
| OSE/Risk Management | Suzanne Berkman, Pharm.D., |

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMETS=Division of Medication Errors and Technical Support
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DSRCS=Division of Surveillance, Research, and Communication Support
 CDTL=Cross-Discipline Team Leader

1. Introduction

Regeneron Pharmaceuticals, Inc. has submitted this BLA in support of approval of Arcalyst (riloncept) for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS). CAPS is a rare disease with approximately 200 to 300 affected patients in the US. The Agency granted CAPS orphan designation. Due to the rarity of the disease, the applicant requested that they be required to perform only one adequate and well-controlled study of Arcalyst. Working with the Agency, Regeneron designed a two-phase study that allowed replication of the results to provide more compelling support of the effectiveness of the product in a single trial. The Agency approved the use of this trial as the sole support for efficacy in the application.

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While it appears that the applicant has provided clear evidence of efficacy for Arcalyst in the treatment of CAPS, the safety data submitted raises concerns regarding an increased risk of serious, potentially life-threatening infectious diseases in patients treated with this drug. In addition, due to the extremely limited exposure of pediatric subjects in the database, and concerning findings from the reproductive toxicity studies, the review team has raised the question of whether Arcalyst should be approved for use in pediatric patients at this time.

2. Background

As per Dr. Siegel's CDTL review, page 4:

CAPS comprises 3 distinct autoinflammatory diseases that are all characterized by mutations in the gene for the protein cryopyrin. Cryopyrin is a protein component of the inflammasome, an intracellular complex of proteins that responds to external dangers (e.g., bacterial infection) by activating caspase 1 and releasing interleukin-1 β (IL-1 β). CAPS is inherited in an autosomal dominant manner.

The three autoinflammatory disorders comprising CAPS are:

- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS); and
- Neonatal Onset Mutisystem Inflammatory Disorder (NOMID)

All three disorders are characterized by rash, fever, conjunctivitis, arthralgias, fatigue and polymorphonuclear leukocytosis with organ infiltration. NOMID, the most severe of the three, presents early in life with severe dermatologic, rheumatologic and neurologic manifestations. MWS is associated with sensorineural deafness and an increased risk of amyloidosis. FCAS patients develop urticarial skin lesions, swollen and painful joints, conjunctivitis and fever following exposure to cold.

The pathogenesis of CAPS is thought to be due to uncontrolled overproduction and release of IL-1, with resultant inflammation. Riloncept is a dimeric fusion protein consisting of the extracellular domains of the IL-1 (interleukin-1) Type I receptor and the IL-1 receptor accessory protein fused to the Fc portion of human IgG1. Riloncept binds IL-1, interfering with its interaction with the receptor. There are no approved products to treat CAPS, although the IL-1 blocker anakinra is used widely off label to treat the disorder. Anakinra requires daily subcutaneous dosing, so the weekly dosing schedule for Arcalyst would clearly provide some advantage to patients.

During development, Regeneron was advised by the Agency on a number of study design and analysis concerns for their pivotal efficacy trial. In particular, they chose a composite endpoint that consisted of a number of clinical outcomes after having been

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cautioned not to use an endpoint heavily weighted towards unvalidated acute phase reactants that are elevated in CAPS. Also, they designed their trial to be inclusive of the summer months after being cautioned that a study only incorporating the colder part of the year would not support continued treatment into the warmer months. Finally, the applicant incorporated genetic testing into the protocol, at the Agency's request, in order to document that the patients did, indeed, have the cryopyrin mutation that is the underlying cause of CAPS.

3. CMC

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of up to 18 months stored at 2 to 8° centigrade. There are no outstanding issues.

Dr. Fuchs's team leader summary review delineates an extensive list of post-marketing commitments and agreements. These include: revision and reassessment of drug substance and product specifications; continued stability testing of formulated drug substance and product; validation studies and modification of specifications for _____ content; qualification of additional _____ assays for _____; a study to evaluate _____ for IL1-Trap; an adequate study to _____

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology review team that there are no outstanding pharm/tox issues that preclude approval for use in adult CAPS patients. Drs. De and Mellon have recommended a Category C pregnancy rating for the product label based on a number of findings in the reproductive toxicity studies including increased skeletal variations, skeletal malformations, apparent decreases in 17-beta-estradiol levels in monkeys, stillborn pups, litter losses, unscheduled deaths of offspring, and gestational abortions. I agree with their recommendation. They also recommend that a juvenile animal study be performed prior to approval of Arcalyst for use in pediatric patients, due in particular to the hormonal and bone growth and deformity changes found in the reproductive toxicity studies. The clinical review team has reviewed these recommendations and does not concur as this product will have its most important impact on pediatric patients, the animal findings are not clearly translatable to the clinical setting, and these findings can be clearly denoted in the product

labeling so that prescribers can make an informed decision and discuss their conclusions and recommendations with the patients and their families. I agree that the animal findings should not preclude approval for pediatric patients. Further non-clinical and clinical evaluation should be performed in the post-marketing period.

Drs. De and Mellon have also recommended that, due to a paucity of information on the carcinogenicity of riloncept, the label should include information indicating that the product has the potential to increase the risk of immunosuppression-related tumors. I agree that some language regarding the potential for exposure to immunosuppressant drugs to lead to an increased risk of malignancies should be included in the labeling under warnings and precautions. However, I think that the following language would be less speculative: Treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics review team that there are no outstanding clinical pharmacology issues that preclude approval. Complete pharmacokinetic data was not captured in CAPS patients during clinical development. Trough levels were collected from patients in some of the studies, but it is not possible to compare the pharmacokinetic data captured from normal subjects to the CAPS patients due to the fact that different drug products and bioanalytical assay methods were used. Nevertheless, the successful clinical outcomes preclude the necessity for a full pharmacokinetic profiling as a basis for approval. Any future studies in CAPS patients should attempt to capture this data, however.

Forty-one percent of the Arcalyst-treated subjects tested positive for binding antibodies to the receptor portion of the molecule on at least one occasion in the combined controlled-trial and open-label follow-on studies. Seven patients also developed neutralizing antibodies. However, there was no clear association between these findings and the safety and/or efficacy of the treatment.

It is worth noting that the applicant chose the dosing regimen used in the clinical studies to completely bind calculated, expected quantities of IL-1 molecules and IL-1 receptors. While the efficacy of 160 mg weekly was demonstrated in the clinical trial, it remains possible that a lower dose may be equally efficacious, and possibly associated with a lower risk of infectious complications. It also remains unclear whether a less frequent dosing regimen would maintain efficacy. Due to the limited patient population, it will be difficult to develop studies to test these possibilities. Nevertheless, those studies should be performed in the post-marketing period if at all possible.

6. Clinical Microbiology

I concur with the conclusions reached by Dr. Chi that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

As noted above, the applicant was only required to perform one adequate and well-controlled clinical trial, but worked with the Agency to design a trial that would provide some degree of internal replication of the efficacy results. Study IL1T-AI-0505 included an initial randomized, double-blind, parallel-arm phase, followed by a double-blind withdrawal phase. Adult patients with FCAS or MWS were enrolled and randomized 1:1 to Arcalyst or placebo treatment for 6 weeks. The placebo-treated subjects were then switched to treatment with Arcalyst and the study continued for 9 weeks. Subjects were then rerandomized to Arcalyst or placebo for an additional 9 weeks. Subsequently, all subjects were rolled over into a 24-week, open-label extension study of Arcalyst.

The primary outcome measure was a composite score based on subscores of 5 key symptoms (rash, fatigue, joint pain, fever/chills, and eye redness/pain) on a 21-point scale. A daily symptom score from "0" (best) to "10" (worst) was calculated by summing the ratings on each symptom and dividing by five. Baseline for the first phase of the study was calculated as the average daily symptom score over the first 21 days of the screening period. The primary outcome for the first phase of the study was the difference between the baseline score for the first phase of the study and the average score over the last 21 days of the first randomized period. For the second phase of the study, the randomized withdrawal phase, baseline was calculated as the average daily symptom score over the last 21 days immediately before the first day of the randomized withdrawal period. For the randomized-withdrawal phase of the study, the primary outcome was the difference between the baseline score for the randomized withdrawal period and the average score over the last 21 days of the randomized withdrawal period.

Dr. Siegel's Table 2, page 12 of his review, summarizes the results of both of the randomized periods and is reproduced below:

Table 1: Primary Analysis for Study IL1T-AI-0505

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

Arcalyst-treated subjects clearly had a statistically significant treatment effect compared to placebo-treated subjects in both Parts A and B of the controlled clinical trial. The effects appeared to be maintained in the open-label study for out to 6 months. This assessment is, of course, limited by the lack of a control or blinding in that study.

8. Safety

The safety data base for this BLA included 47 patients with CAPS (6 pediatric patients, ages 12 to 16 years) and patients with rheumatoid arthritis (24 JIA pediatric patients), for a total of 600 patients exposed to rilonacept, 85 for at least 6 months and 65 for at least one year. Two deaths occurred in patients exposed to Arcalyst. One was 37 year old obese man with a history of untreated hypertension who died suddenly without explanation. As this was most probably a cardiovascular-related death, the review team concluded that the death was not likely to have been related to drug exposure. The second subject was a 71 year old woman treated with Arcalyst for 7 months. She developed symptoms of an upper respiratory infection and was later found unresponsive. Pneumococcal meningitis was diagnosed and the patient died despite antibiotic treatment. The review team has concluded that this death is likely to be due to immunosuppression resulting from exposure to Arcalyst, although there is no information regarding concomitant medications for this patient. I concur with these conclusions.

One subject developed a mycobacterium avium intracellulare dermal infection while being treated with Arcalyst. This infection eventually responded to antibiotic treatment. The other serious adverse events noted in the clinical data base occurred with a similar incidence in Arcalyst and placebo-treated subjects. The most frequent reason for subject discontinuation was injection site reactions in the Arcalyst-treated patients, but there were no discontinuations for injection site reactions in CAPS patients. The most common adverse events in Arcalyst-treated subjects were injection site reactions and infections, and both occurred at a greater rate compared to placebo-treated subjects. The most common infections were upper respiratory tract infections.

9. Advisory Committee Meeting

This application was not presented to an advisory committee. There are few CAPS experts. Based on the limited input that non-CAPS experts might be able to provide, and the extremely short time-line for the Priority review required for this BLA, it was determined that the Agency review team had the necessary expertise and experience to make a reasonable and informed risk-benefit assessment of Arcalyst for the treatment of CAPS.

10. Pediatrics

While, as noted above, there are some findings of concern in the non-clinical database, and there is very limited exposure to Arcalyst in children thus far, the most important impact that this product is likely to have is in pediatric CAPS patients. As this condition is a potentially severe one and there are no approved alternative treatments, and as the relevance of the animal findings remains unclear, I recommend approving the product as proposed by the applicant for children as young as _____ of age. Juvenile animal studies and appropriate clinical evaluations should be undertaken in the post-marketing period.

11. Other Relevant Regulatory Issues

DMETS

I. Volume to administer

Arcalyst will be packaged in single-use vials, each containing 220 mg of lyophilized powder, which is a dose greater than is recommended for subcutaneous injection. Each vial is to be reconstituted with 2.3 mL of Sterile Water for Injection (160 mg/2mL). DMETS questions whether having a larger dose of drug in each vial than what is approved for use creates the potential for overdose of the product. DMETS recommends that Regeneron should propose a vial size and/or concentration which is more conducive to the end user in order to mitigate the

potential for administration and dosing errors, especially since the proposed labeling indicates that the product is _____

However, neither the clinical nor the product review teams agree with this recommendation. First, because, even if the patient were to be dosed with the entire amount of drug in the vial, there would still be no additional safety concerns from this small increase in exposure; and, second, because the viscosity of the product would make it difficult for a patient to remove the entire contents of the vial. I concur with the clinical and products reviewers.

II. Preparation Errors

DMETS expressed concern regarding the potential for patients to be prescribed Arcalyst for use at home without proper supplies (preservative-free sterile water for injection, syringes and needles). The product is not co-packaged with sterile water for injection. Retail pharmacies may not stock vials of preservative-free sterile water for injection or the correct type of syringes and needles. DMETS recommends that, in order to minimize preparation errors in every setting of use (clinical outpatient, home, etc), the product should be packaged with all items necessary for proper reconstitution and administration of the product. There is also some concern as to whether patients or caregivers will be able to safely reconstitute the product while maintaining sterility. DMETS recommends that Regeneron should implement an educational campaign to educate healthcare providers, caregivers and patients about the product. This should include clear instructions on how to reconstitute and administer the product.

The sponsor has submitted an educational program to address these concerns. That submission is currently under review. In the clinical studies, subjects were sent home with appropriate supplies and instructions for use, and there were no instances of adverse events related to misuse. The sponsor also informed Ms. Davies in a teleconference on February 4, 2008,

_____ The sponsor is submitting detailed information on this plan to the BLA.

I think that, assuming the educational program is adequate and that acceptable labeling can be agreed upon, these risk minimization strategies should be sufficient to prevent patients or caregivers from improperly reconstituting or administering the product. While one could argue that the lack of concerning findings in the clinical studies may not be reflected in real world use of the product, this is always the case with drug development. Careful post-marketing monitoring will be necessary.

III. Labeling

DMETS' review contains the following proposed revisions to the label which are currently under consideration by the Division:

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Carton/Container:

- Font color should be changed to make the strength easier to read.
- The graphic in the label should be minimized.
- _____ should be changed to read _____

The Patient Information Leaflet will be reviewed by OSE once a working draft label is ready.

DDMAC

DDMAC provided proposed modifications to the label that would remove any promotional tone. These proposed revisions are under consideration by the Division.

RiskMAP

OSE does not consider Regeneron's proposal a formal risk minimization action plan. OSE has not identified any additional safety concerns that warrant consideration of a RiskMAP at this time for the proposed indication. OSE recommends educational materials directed to patients and/or caregivers to provide proper reconstitution and administration instruction. This educational program may occur outside of a formal RiskMAP.

DSI

All sites inspected received either an "NAI" or a "VAP" final classification. Of the four clinical sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled eligibility criteria, received the assigned study medication and had their primary efficacy endpoint captured as specified in the protocol. Data generated at these sites appear acceptable for use in support of BLA 125249.

12. Labeling

- Physician labeling
 - (See above) This is still under review.
 - The applicant has proposed a Pregnancy Category — we are recommending a C with specific language regarding bone and estrogen effects.
 - The following language should be added to the label: Treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.
 - In their proposed physician labeling, the applicant included _____

- The applicant did not address the effects on lipids that were observed in the clinical trial. A description of the effects of Arcalyst treatment on lipid levels should be added to the physician labeling.
 - The pediatric dosing recommendations are too complex and should be simplified.
- Carton and immediate container labels
 - (See above) These are still under review
 - Patient labeling/Medication guide
 - (See above) These are still under review.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action Recommendation:

Approval, pending agreement on labeling and an acceptable educational program for patients/caregivers

- Risk Benefit Assessment

The applicant has provided substantial evidence of efficacy. Arcalyst, as with most immunosuppressants, poses some increased risk for infection, and could pose increased risk for malignancy. Nevertheless, CAPS is a severe and often debilitating condition and there are no approved alternative treatments. The once weekly dosing regimen for Arcalyst also provides some advantage to patients over the daily dosing regimen for the primary product that is currently used in clinical practice to treat CAPS. As per my discussion above under **Pediatrics**, my risk benefit assessment leads me to recommend approval for pediatric patients age 12 and older, as well. This recommendation differs from that of the pharm/tox review team. See my discussion above for why I do not support their recommendation. Further evaluations of the safety in children, and of the safe use by all patients and caregivers will be necessary, however, in the post-marketing period. Further evaluation of the efficacy of lower doses of Arcalyst should also be undertaken post-marketing, if at all possible.

- Recommendation for Postmarketing Risk Management Activities

No specific Risk Management Activities are necessary other than monitoring for problems associated with patient/caregiver reconstitution and administration of the product.

- Recommendation for other Postmarketing Study Commitments

The following are the Regeneron CMC Post-Marketing Commitments:

1. The applicant will assess release and shelf-life specifications for riloncept drug substance, formulated drug substance, and drug product as appropriate. Data and specifications assessment will be provided in 2 years from time of approval and reported in an annual report.
2. The applicant will perform stability testing of one riloncept formulated drug substance lot and one drug product lot annually for each year in which riloncept formulated drug substance or drug product is manufactured. As part of this post approval commitment, the ongoing stability program will continue until testing of all remaining time points from the lots used to support the approved shelf life have been reached. These stability data will be submitted in the annual report. Additionally, lots that are manufactured following significant changes to the approved manufacturing process or facility, and lots that are reprocessed outside of the approved manufacturing process will be placed on stability
3. The applicant will perform validation studies on the modified assay that measures _____ in riloncept drug substance, formulated drug substance, and drug product. Accordingly, Regeneron will establish _____ content specifications for DS, FDS, and DP release and stability, and DS, FDS, DP reference standard qualification and stability. The protocol, final report, and the proposed specification will be submitted as a CBE-30
4. The applicant will conduct a comprehensive validation of _____ for the measurement of _____ for _____ at the concentration of intended use with alternative _____ analytical methods. Methods such as _____ should also address _____. The full validation package will be submitted as _____. In addition, a re-assessment of specifications based on the validated method should be included in the _____
5. The applicant will validate the DS, FDS, and DP riloncept _____ assays for the new proposed acceptance criteria. The validation protocol and report will be submitted to the Agency in the next annual report.
6. The applicant will qualify the additional _____ assays used for _____

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Assay qualifications reports will be submitted in the next annual report

7.

8. The applicant will re-qualify

The qualification procedures and summary data will be submitted in the next annual report.

9.

The following are the Regeneron Nonclinical Pharmacology Toxicology Post-Marketing Commitments:

1. The applicant will conduct a study in the cynomolgus monkey examining the effect of IL-1 Trap exposure of the pregnant female during the third trimester of development.
2. The applicant will conduct a juvenile animal study in the cynomolgus monkey that includes specific assessments of sex hormones and bone development.

The following are the Regeneron Clinical Post-Marketing Commitments:

The following should be required:

1. To assess safety of long-term use of rilonacept in the pediatric patient population establish a pediatric registry. The registry should collect information on growth and development as well as adverse events, particularly serious infections. The duration should be at least 5 years.
2. Conduct a study of pharmacokinetics in the pediatric population.

The following should be recommended:

- To assess whether lower maintenance doses or a longer interval between doses could be equally effective yet potentially safer.

The following is a recommended post-marketing agreement:

- Pharmacovigilance: In addition to standard pharmacovigilance pay particular attention to serious infections, pregnancy outcomes, off-label use and adverse events related to

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problems associated with reconstitution and administration of the product by patients and/or caregivers.

**APPEARS THIS WAY
ON ORIGINAL**

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