CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

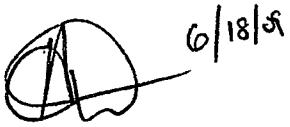
125319

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Supervisory Pharmacologist Memorandum
ADDENDUM - Labeling

BLA NUMBER:	**125,319**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**12/15/2008 (initial receipt)**
PRODUCT:	
(Proposed) Trade Name:	**Ilaris®**
Established Name:	**Canakinumab**
INDICATION:	**Cryopyrin Associated Periodic Syndromes**
INTENDED CLINICAL POPULATION:	**Adults and children ≥ 4 years of age**
SPONSOR:	**Novartis**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)**
PHARM/TOX REVIEWER:	**Kathleen Young, Ph.D.**
PHARM/TOX SUPERVISOR:	**Adam Wasserman, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Ramani Sista, Ph.D.**



Addendum to Supervisory Review Memo - Labeling

This addendum addresses the final label negotiated with the Applicant.

- The Applicant did not contend the removal of an Animal Toxicology section — b(4)
  ——— This section is not to be included according to the CFR unless it communicates important safety data for human use which cannot be otherwise described in other sections.

- The Applicant requested removal of the — section that was b(4)
  proposed in Warnings and Precautions.

b(4)

The PQRI paper which contained Agency representatives from OND and ONDQA recommended toxicologic qualification of leachables was unnecessary below —, total daily intake; therefore, — is a reasonable cut-point for compounds for which we do not have information. Where there is toxicologic information on safety, such as with ———, the recommendation may not be appropriate. Upon evaluation of the toxicologic literature, the only concern is with neonates, and especially pre-term. Although not indicated for this age range as the condition may be identified in neonates it is possible, if not likely, they will be administered the drug product. Neonates will not, however, receive the b(4)
maximum 600 mg dose as described in the worst-case estimate of the Applicant but instead should receive maximally 4 mg/kg. If one were to assume a good sized neonate of 4 kg this would equate to a 16 mg dose which could result in a maximum 540 picogram exposure to —— at the —— maximum. Although there is no information which describes a lower boundary of concern, it appears that morbidity and mortality has only been seen with large intravascular infusions which produce daily —— intake of ~100 mg or greater. I therefore find the removal of this section justified from a toxicologic basis.

- The Applicant did not contend the Pregnancy category C proposal by the Agency [redacted]. This b(4)
  was not accepted; however, the lack of human studies and the uncertainty regarding the predictivity of animal studies for human risk statement required by CFR was moved up to the summary paragraph. Applicant-suggested edits which clarified the specific study methodology in the pregnancy section were retained.

The final recommended wording of the Pregnancy section is reproduced below:

8.1 PREGNANCY

Pregnancy Category C

Canakinumab has been shown to produce delays in fetal skeletal development when evaluated in marmoset monkeys using doses 23-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve [AUC] comparison). Doses producing exposures within the clinical exposure range at the MHRD were not evaluated. Similar delays in fetal skeletal development were observed in mice administered a murine analog of canakinumab. There are no adequate and well-controlled studies of ILARIS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Embryofetal developmental toxicity studies were performed in marmoset monkeys and mice. Pregnant marmoset monkeys were administered canakinumab subcutaneously twice weekly at doses of 15, 50 or 150 mg/kg (representing 23 to 230-fold the human dose based on a plasma AUC comparison at the MRHD) from gestation days 25 to 109 which revealed no evidence of embryotoxicity or fetal malformations. There were increases in the incidence of incomplete ossification of the terminal caudal vertebra and misaligned and/or bipartite vertebra in fetuses at all dose levels when compared to concurrent controls suggestive of delay in skeletal development in the marmoset. Since canakinumab does not cross-react with mouse or rat IL-1β, pregnant mice were subcutaneously administered a murine analog of canakinumab at doses of 15, 50, or 150 mg/kg on gestation days 6, 11 and 17. The incidence of incomplete ossification of the parietal and frontal skull bones of fetuses was increased in a dose-dependent manner at all dose levels tested.

Adam Wasserman, Ph.D.
Supervisory Pharmacologist
Division of Anesthesia, Analgesia and Rheumatology Products

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology
OND IO Paul C. Brown 6-17-09
BLA: 125319
Submission date: December 15, 2008
Drug: canakinumab (Ilaris), fully human monoclonal IgG1/κ antibody against interleukin-1β (IL-1β)
Sponsor: Novartis Pharmaceuticals Corporation
Indication: Adults and Children 4 Years and Older with Cryopyrin Associated Periodic Syndromes (CAPS)

Reviewing Division: Division of Anesthesia, Analgesia and Rheumatology Products

Introductory Comments: The pharm/tox reviewer and supervisor found the nonclinical information submitted to be adequate to support approval of canakinumab for the indication described above. No additional nonclinical studies were recommended.

Reproductive and developmental toxicity:
Embryofetal development:
Embryofetal studies of canakinumab in marmosets and of a murine surrogate antibody in mice showed some delays in ossification that appeared to dose-related and occurred at maternally non-toxic doses. While these findings do not suggest a high risk for irreversible embryo fetal effects, they appear to be related to treatment and should be described in labeling. The sponsor and reviewer originally recommended ——→ b(4)
—— , however, I have further discussed this issue with the supervisor and I believe a pregnancy category of C would be appropriate because of these findings.

Carcinogenicity:
Long term carcinogenicity studies with canakinumab or a surrogate antibody have not been conducted. Such studies are not possible with canakinumab due to its lack of relevance in rodent models and since carcinogenicity studies in nonrodent species are not practical. The sponsor provided a rationale, supported by literature information, suggesting that inhibition of IL-1ß may have limited carcinogenic risk. A theoretical potential for increased risk may be postulated due to perturbation of immune surveillance that may occur with IL-1ß inhibition. However, the data provided to date do not appear to show a particular cause for concern for increased carcinogenic risk.

Conclusions and Recommendations:
I concur that the information provided for canakinumab is adequate to support its approval from a pharm/tox perspective for the indication of CAPS.

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PROJECT MANAGER:	**Ramani Sista**

5/13/09

EXECUTIVE SUMMARY

I. BACKGROUND

The present Biological Licensing Application is submitted by Novartis for canakinumab, a fully human anti-IL-1β IgG1 monoclonal antibody, in the treatment of adults and children ≥ 4 years of age with Cryopyrin Associated Periodic Syndromes (CAPS). CAPS is a spectrum of diseases which includes Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and Neonatal Onset Multisystem Inflammatory Disease (NOMID), which have been determined to be due to a mutation in the NALP3 (also called the CIAS1) gene. This genetic mutation results in the upregulated activity of the Interleukin (IL)-1β converting enzyme caspace-1 (previously referred to as ICE) which cleaves cytosolic pro-IL-1β into the active and secreted form and leads to unrestrained production of the pro-inflammatory cytokine IL-1β underlying the constellation of clinical symptoms characteristic of these conditions.

There are two currently FDA-approved products which target the IL-1 signaling pathway as shown below:

Drug Established Name (Trade Name)	BLA Holder	Date of FDA Approval	Indications Approved (as of 5/2009)	Comments
Anakinra (Kineret®) BLA 103-950	Amgen	11/2001	Rheumatoid Arthritis (≥ 18 y/o)	- Recombinant IL-1Ra - Off-label use in CAPS noted
Rilonacept (Arcalyst®) BLA 125-249	Regeneron Pharmaceuticals	2/2008	CAPS (including FCAS and MWS) in adults and children ≥ 12 y/o	

Anakinra, approved for Rheumatoid Arthritis in 2001, is a recombinant form of the endogenous human IL-1 receptor antagonist (IL-1Ra) which has previously been reported in the published literature to be efficacious in the treatment of all subtypes of CAPS (Hoffman et al., 2004; Ramos et al., 2005; Goldbach-Mansky et al., 2006; Boschan et al., 2006; Thornton et al., 2007; Gattorno et al., 2007; Yamazaki et al., 2008). Rilonacept was recently approved by the Agency for the specific treatment of CAPS in adults and children ≥ 12 years of age.

Canakinumab provides for treatment of CAPS in a patient population (4-11 y/o) which is not currently included in the approved dosing population for Rilonacept and therefore represents an important treatment option for this age group which is a significant portion of the affected CAPS population.

A. Regulatory Summary (Pharmacology/Toxicology)

Several meetings were held with the Applicant during the course of drug development in which general nonclinical issues were discussed and the nonclinical program agreed upon. Significant regulatory agreements were all satisfied in the submitted BLA. A decision to waive the regulatory requirement for a carcinogenicity evaluation will be discussed later in this memo in the face of the apparent ability to conduct a 2-year rodent carcinogenicity bioassay utilizing the surrogate IL-1β mAb in the mouse.

Briefly, canakinumab was demonstrated through — analysis to demonstrate binding affinity solely to human and marmoset IL-1β. No binding to rodent or Macaque (rhesus or cynomolgus) monkey IL-1β was apparent. Therefore, the Applicant conducted the pivotal toxicology studies of canakinumab in the marmoset. In addition to these studies, the Applicant generated a murine surrogate IL-1β mAb (01BSUR) with very similar pharmacodynamic and pharmacokinetic properties compared to canakinumab for testing the effects of IL-1β inhibition in mouse models for reproductive toxicity, juvenile toxicity – critical due to the need to support the juvenile clinical studies and indication proposed, and immunotoxicity. b(4)

Nonclinical Summary

Primary review of the BLA was completed by Dr. Kathleen Young. Based on her review there were no significant issues raised by the nonclinical data with large safety margins above the clinical therapeutic exposure in humans. The Applicant provided nonclinical data indicating canakinumab binds with high (pM) affinity to human and marmoset IL-1β and demonstrated evidence suggestive of nonclinical efficacy in blocking exogenous human IL-1β-mediated effects in both *in vitro* and *in vivo* systems, including inhibition of join inflammation, neutrophil migration and fever in rodent models. Canakinumab does not interact with the IL-1α variant or IL-1Ra variants. Canakinumab showed no ability to generate an ADCC or CDC response despite the presence of the Fc portion of the IgG1 which relates to the absence of significant membrane-bound IL-1β. The Applicant also provided evidence in a mouse model of joint destruction that the surrogate mAb 01BSUR was able to ameliorate damage which has relevance in that it demonstrates the bioactivity of the surrogate used to provide support for reproductive, developmental, and immunologic safety. An evaluation of canakinumab or 01BSUR surrogate absorption (SC route), distribution, and elimination kinetics was provided in the nonclinical models used for evaluation and generally indicated the appropriateness of these species for study. Tissue cross-reactivity studies were conducted for confirmation of appropriate species selection and to bridge three separate formulation changes. In all cases, human and marmoset antigen binding locations were consistent

The principal nonclinical safety dataset provided by the Applicant consists of repeat-dose toxicology and toxicokinetic studies in the marmoset with intravenous (IV) dosing durations up to 6 months and two 13-week bridging toxicology and toxicokinetic studies

to support the subcutaneous (SC) route proposed for approval and to provide an evaluation of toxicologic and pharmacokinetic comparability to support a production cell line switch from the main nonclinical product tested (Process A; ——— and the clinical and to-be-marketed material (represented by Process C; ——— ——— , respectively. Dosing in the marmoset was twice weekly due to the shorter half-life of canakinumab in this species ($t_{1/2}$ ~ 4 days) believed due to reduced affinity for the marmoset FcRn compared to human form. A single injection intra-articular administration to marmoset using Process B material was also included in the safety dataset though the relevance for this indication is unclear. An evaluation of reproductive and developmental safety was addressed through an Embryofetal Developmental Toxicity (i.e. teratogenicity) study with canakinumab in the marmoset as well as the use of the surrogate mAb 01BSUR in a full battery of reproductive toxicity tests comprising evaluations of fertility, embryofetal developmental toxicity, and peri- and postnatal development. Additional support was provided by sperm assessments, testicular histology and FACS analysis, and testosterone analysis in the repeat-dose toxicity studies in the marmoset. Safety support for administration of canakinumab to children was provided by studies of the 01BSUR surrogate in a juvenile mouse model while general immunologic safety was addressed through a dedicated immune study in mice with the 01BSUR surrogate as well as through immunophenotyping of blood and splenic cells collected throughout the major nonclinical toxicity studies with both canakinumab and surrogate.

b(4)

Canakinumab was well tolerated in all nonclinical toxicology studies, including the 6-month IV marmoset study and a 13-week SC bridging toxicity and toxicokinetic study, with generally only injection site effects noted secondary to procedure. Though studies sporadically reported effects suggestive of an altered level of immune activity, this was inconsistent both in observation as well as in direction of effect. Overall, there was no consistent target organs identified with doses up to 150 mg/kg administered twice weekly. Anti-canakinumab antibodies were not detected during the dosing or recovery periods and there was no increase in clearance suggestive of their presence.

Reproductive toxicology studies of offspring exposed to drug indicate the potential for some transient developmental delays with canakinumab in the marmoset as well as in mice using the surrogate 01BSUR. An increased incidence of delayed or incomplete ossification of skull and vertebra was identified in mice while in marmosets vertebral variations were observed as well as an increased incidence of bent/kinked tail; a finding which has little direct clinical relevance. The EFD study in marmoset also demonstrated a small reduction in litter size in the canakinumab-treated group compared with controls but if true this – and there was no evidence of post-implantation loss or fetal death - was represented by a reduced number of multiples (a fairly common reproductive status in the marmoset) and reduced placental weights. While a peri- and postnatal study in mice with the surrogate 01BSUR indicated several parameters to be significantly different in treated offspring compared with controls, these were not outside historical ranges for the conducting laboratory and were considered by both Agency review staff and Applicant to lack biologic or toxicologic significance. No evidence of increased mortality was noted

or developmental issues were found which might be a sequalae of the skeletal ossification delays noted in the embryofetal study in mouse. Prenatal exposure to canakinumab was confirmed by the presence of compound in amniotic fluid as well as in serum obtained from fetus or umbilical cord. Male reproductive toxicity evaluation in repeat-dose toxicology studies in marmoset revealed no drug-induced effects on sperm parameters, testicular structure or cellular composition, and no evidence of altered testosterone levels suggesting minimal potential for transient or permanent reproductive effects in the male.

No consistent or adverse effects on the immune system were observed in repeat-dose toxicology studies conducted in marmosets with examination of standard parameters as well as extensive immunophenotyping of lymphocyte and monocyte subpopulations from blood and spleen. It was noted in the primary review of Dr. Young that septicemia contributing to the death of a marmoset in a 13-week bridging toxicology study may be secondary to interference with immune function of canakinumab but was seen in the context of intestinal ulceration and was observed in an animal treated with the earlier canakinumab process material / —— Notably intestinal inflammation b(4)
and erosive findings were observed in a control animal as well. It is therefore likely that the death represents an extension of a background finding which may have been exacerbated, though not initiated, by drug treatment. The Applicant remarks that the study should be considered not valid due to the high background findings of inflammatory lesions in the GI tract, multi-systemic amyloidosis, and evidence of progressive and chronic nephropathy. The use of an older population of marmosets was believed related to these findings and I note exacerbation of these findings were generally less prominent in the drug material more representative of the final process derived from
— ; marmosets administered —— / canakinumab displayed findings that
were more severe but in the other 13-week SC study or in the 26-week IV study b(4)
conducted in marmoset analogous findings were not observed with material using the
—— process. The surrogate 01BSUR tested in a 4-week immunotoxicity study in mouse did not demonstrate effects on lymphocyte subpopulations (including total, helper, and cytotoxic T lymphocytes, Double positive or negative T lymphocytes in spleen or thymus, and B lymphocytes) or NK cells. T-cell Dependent Antibody Response (TDAR) evaluation of anti-keyhole limpet hemocyanin (KLH) IgM antibody response was unaffected by canakinumab treatment and IgG antibody response, which appeared to be moderately and dose-dependently reduced with canakinumab treatment appears to be an artifact caused by an abnormally high control response.

Examination of the surrogate 01BSUR in a juvenile developmental toxicity study in CD-1 mouse revealed no significant adverse findings. Growth and physical development, reflex development, immune parameters, learning and memory, and reproductive competency in canakinumab-treated juvenile mice was no different from vehicle-treated mice or was well within the range of historical control data from the conducting laboratory with the exception of a higher rate of pre-implanation loss compared to concurrent and historical data. It was noted this was driven by the complete litter loss of a single animal and remaining animals did not differ in the number of offspring produced

per litter and I concur with Dr. Young this does not strongly indicate a reproductive toxicity.

Genetic toxicology studies and nonclinical evaluation of carcinogenicity potential was not conducted by the Applicant. No evidence of hematologic or solid malignancies was observed in the 6 month IV study of canakinumab in marmoset.

Examination of plasma exposure values obtained at the NOAEL level in nonclinical safety evaluation in marmosets indicates sufficient (24 – 287-fold) exposure margins exist for human use at the maximum recommended human dosing proposed for either the weight-based approach in children ≤ 40 kg (2 mg/kg) or in older children and adults with the 150 mg q8 week dosing regimen as described in the primary review of Dr. Young. I note that the final product label may allow dosing up to 4 mg/kg in young children and up to 300 mg q8 weeks in older children and adults. Due to the large safety margins previously described, the nonclinical data would appear to support these levels as well.

II. MAJOR NONCLINICAL ISSUES IDENTIFIED IN PRIMARY REVIEW

Published data developed in knockout models of IL-1 signaling indicate that IL-1β knockouts are viable and thrive (Labow et al., 1997; Glaccum et al., 1997) though the response to infection and the inflammatory response is attenuated (Fantuzzi and Dinarello, 1996; Leon et al., 2006). In addition to the relatively well understood effects of IL-1 on the immune system, several recent publications have examined transgenic models with endogenous or exogenous overexpression of IL-1ra and observed complicated effects on memory (Ben Menachem-Zidon et al., 2008; Spulber et al., 2009). These publications suggest some aspect of IL-1-related signaling, though not necessarily IL-1β, may be implicated in memory.

1. Anti-product antibody response/Antigenicity

Immunogenicity as well as toxicokinetic data provided by the Applicant suggests that the probability of a significant neutralizing anti-product antibody response confounding interpretation of the toxicity data appears limited. The assay format used to detect anti-product antibody was sensitive to prevailing levels of canakinumab in serum such that by the Applicant's own report moderate immunogenicity could not be detected with plasma canakinumab levels above 111 μg/mL while a strong immunogenic reaction would not be detectable above 425 μg/mL. End of treatment period samples could not be utilized as even the low dose groups were associated with Css of >300 μg/mL and data could only be reliably analyzed during the recovery period. No confirmed anti-product antibody responses were reported in any of the marmoset studies though a minority of animals maintained sufficient plasma levels of canakinumab through the recovery period that a negative response could not be made with certainty. Nevertheless, it does not appear that anti-product antibody responses were sufficiently operative in any of the critical supporting studies as to confound study interpretation.

2. Immunosuppression

I concur with Dr. Young that immunotoxicity/immunosupression is a fundamental concern with inhibition of IL-1β. The Applicant has provided evidence of limited effects of canakinumab on measured parameters in general toxicology studies, as well in tests of the 01BSUR surrogate mAb in the peri- and postnatal study, juvenile mouse study, and the dedicated mouse immunotoxicity evaluation in which no apparent changes in lymphocyte subsets were observed and no consistent effects on lymphoid organ size or structure was noted. In addition, the benign TDAR assays conducted as part of the toxicology studies indicate the adaptive/humoral immune system is likely unaffected by exposure as might be expected based on the non-direct effects of IL-1β on Th1 and Th2-type responses. What the Applicant did not provide were assays to evaluate host cell resistance to various pathogens. As IL-1β is prominently involved in the response to pathogens, perturbation of this system will affect pathogen clearance and therefore drug exposure may lead to greater incidence and severity of infections. The Applicant is, however, well aware of this role and provided data from the literature (reviewed in Dinarello 2003) which indicates increased sensitivity to various bacterial and viral infections with IL-1β knockout and blockade in host resistance models. An increased risk of infection (non-opporunistic) was noted in the clinical trials for canakinumab and appropriate language is to be included in the label consistent with other IL-1 blocking agents.

3. Carcinogenicity

The absence of a standard carcinogenicity evaluation from the BLA was agreed upon in consultation with the Agency after internal deliberations between DAARP, DPAP, and DMEP in which canakinumab was under active IND were held. This position was reconfirmed in a Pre-BLA meeting held with the Applicant and is consistent with the ICH S6 Guidance *Preclinical Safety Evaluation of Biologically-Derived Pharmaceuticals*. This decision was due to three factors: 1) Agency Precedent; 2) Feasibility; and, 3) Scientific Rationale. The IL-1-inhibiting drugs Anakinra and Rilonacept were approved for RA and CAPS, respectively, without carcinogenicity evaluation, the latter compound being approved in 2008. While anakinra appears to have been able to neutralize rodent IL-1, both rilonacept and canakinumab represent drug products which did not recognize murine IL-1 and therefore the actual drug product could not be directly tested. As in the rilonacept package, the present Applicant has synthesized a mouse surrogate anti-IL1β mAb used as described previously in several toxicity studies. This surrogate product could be used in a 2-year bioassay, unlike the rilonacept surrogate which could not due to the apparent interference of a significant anti-product antibody response with repeated dosing. Despite the potential for use of the surrogate 01BSUR in a carcinogenicity evaluation, the inability to draw comfort from a negative study due to the difference in the molecule or adequately label and define risk in the setting of a positive carcinogenicity signal both suggest this avenue not be pursued unless a clear risk is apparent from a mechanistic standpoint or the function of the target is considered poorly understood. From a scientific standpoint, canakinumab as a large molecule and IgG structure is not capable of interacting directly with cellular DNA, the function of IL-1 and

Although discussed by Dr. Young in her review, other than as a manufacturing issue there is no toxicologic concern for the presence of —— in the drug product as it is not administered to neonates. b(4)

5. Reproductive Toxicity

Dr. Young has highlighted the effects of canakinumab and 01BSUR in marmoset and mouse embryofetal developmental studies, noting the lack of teratogenicity, and considers the increased incidence of variations and skeletal delays to not be indicative of a significantly adverse finding but suggests inclusion of this data in the label as a precautionary statement. Delays in ossification observed in the marmoset study were not as pronounced or dose-dependent as observed in the mouse study with the surrogate mAb. I note that the mouse may represent the "worst case" estimate of this potential as mAb pass through the placenta throughout the embryofetal period whereas in the non-human primate mAbs begin crossing only later in gestation, generally after the period of major organogenesis. The lack of observable effects in the peri- and postnatal study in the mouse tend to reduce concern over this finding as well.

6. Juvenile toxicity findings

Dr. Young has noted several instances of physical, anatomical and developmental delays in mice administered the surrogate 01BSUR. All statistically significant observations were within the historical control range of data and were not observed at later time-points. I concur with Dr. Young that this does not reflect a significant risk for juvenile development.

7. Comparison with other approved IL-1 products: Rilonacept and Anakinra

Rilonacept, an IL-1-trapping fusion protein, was noted in the nonclinical reviews of Drs. Mamata De and R. Daniel Mellon to generate a confounding anti-product antibody response in the cynomolgus monkey model used and an immunologic response which included renal damage, vascular effects, and possible myocardial damage was described. Reproductive toxicity evaluation conducted in mouse with a surrogate fusion protein as well as in cynomolgus monkey with the clinical product was observed to be potentially associated with a slight increase in gestational abortion and reduction in postnatal viability in mice while in cynomolgus monkey a concern for altered estradiol levels and increased skeletal variations/malformations was raised though the presence of the anti-product antibody response complicated interpretation. The present set of nonclinical studies with canakinumab does not appear to have similar findings. This may be due to a lower immunogenicity potential in the nonclinical model used or the difference in target neutralization (IL-1α and IL-1β for rilonacept; IL-1β only for canakinumab). However, the nonclinical summary of anakinra (recombinant IL-1ra; neutralizes both IL-1α and IL-1β) as reported by Dr. Anne Pilaro indicates anakinra toxicity was largely limited to reversible injection site effects and was without remarkable reproductive toxicity. However, it is unclear if the Applicant utilized models that were responsive to human recombinant IL-1ra and in addition, information on anti-product antibody response, though collected, was not provided. Data addressing the potential anti-product antibody

response was requested by Dr. Pilaro, apparently subsequent to the approval recommendation and action.

III. ADVISORY COMMITTEE ISSUES (*if appropriate*)

N/A

IV. RECOMMENDATIONS

Recommendation on approvability

I concur with the recommendations of Dr. Young that this Biological Licensing Application may be approved pending agreement on labeling.

Recommendation for nonclinical studies

There are no additional nonclinical studies recommended.

Recommendations on labeling

I have the following comments on the proposed Ilaris® (canakinumab) label as well as the recommendations provided by Dr. Young in her review. Final labeling recommendations will be further clarified in an addendum to the review and will be negotiated with the Applicant.

- I do not believe it is necessary to include a SECTION 13.2 ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY section to describe the results of the reproductive and developmental toxicity studies in marmosets and mice. This information will be contained in Section 8.1 PREGNANCY.

b(4)

- Although I agree there is evidence of delayed ossification of various vertebral and cranial bones in the marmoset and mouse, respectively with canakinumab and surrogate 01BSUR, this is only clearly dose-dependent in the mouse and due to the difference in placental transfer of antibodies between the two models as well as the lack of observations of skeletal or functional delays in the peri- and postnatal study in mouse I believe the findings are of limited significance for embryofetal development in humans and a Pregnancy Category — ' as suggested by the Applicant is acceptable.

b(4)

- Section 8.2 NURSING MOTHERS will need revision to include standard 21 CFR201.57 language and the claims of drug product transfer will be removed and consolidated into PREGNANCY 8.1 *non-teratogenic effects*.
- I concur with Dr. Young's recommendation regarding the precautionary statement in the carcinogenicity section of 13.1 CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

BLA NUMBER:	125319
SERIAL NUMBER(S):	000, 014, 015, 017
DATE RECEIVED BY CENTER:	Electronic Submission: 12/15/08 Amendment 014: 3/10/09 Amendment 015: 3/13/09 Amendment 017: 3/16/09
PRODUCT:	ILARIS™ (Canakinumab)
INTENDED CLINICAL POPULATION:	Adults and Children 4 Years and Older with CAPS
APPLICANT:	Novartis Pharmaceuticals Corporation
DOCUMENTS REVIEWED:	NA: electronic submission
REVIEW DIVISION:	Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER:	Kathleen Young, Ph.D. 5/14/09
PHARM/TOX SUPERVISOR:	Adam Wasserman, Ph.D. 5-14-09
DIVISION DIRECTOR:	Bob Rappaport, M.D.
PROJECT MANAGER:	Ramani Sista

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EXECUTIVE SUMMARY

I. Background

Canakinumab, also called NVP-ACZ885-NX-1, ACZ885, ACZ885-NXA, and ACZ885 antibody during product development, is a highly specific, high affinity, fully human monoclonal IgG1/κ antibody against interleukin-1β (IL-1β). The proposed indication is for the treatment of Cryopyrin Associated Periodic Syndromes (CAPS), including Familial Cold-Induced Autoinflammatory Syndrome/Familial Cold-Induced Urticaria (FCAS), Muckle-Wells Syndrome (MWS) ——— b(4)

——— by subcutaneous (SC) injection at the doses of 150 mg in patients weighing more than 40 kg, or 2 mg/kg SC in patients weighing 40 kg or less, once every 8 weeks. The Applicant is proposing titrated increases in the 2 mg/kg dose ——— in pediatric patients weighing ≤ 40 kg, if remission is not observed with the lower dose. The rationale for development of this drug product is the potential neutralization of cytokine activity, believed to underlie symptoms and progression of CAPS, by inhibiting IL-1β activity which has been shown to be upregulated in systemic autoinflammatory disorders (Arend WP. 2002; Agostini L. *et al.* 2004; Dinarello CA. 2005). The Applicant has provided an argument for the rationale that canakinumab may have a lower risk for increased pro-inflammatory reactions and/or immunosuppression-related infections and incidence of malignancies than the potential risk by using other, less specific IL-1 signalling agents such as rilonacept and anakinra (the latter used off label for the treatment of CAPS), and smaller molecule immunosuppressive agents such as methotrexate. This argument is supported by data presented in the published literature that IL-1β may advance tumor development via inflammatory activity, while IL-1α may promote anti-tumor activity (Apte RN, *et al.* 2006). Additionally, canakinumab half-life is longer than that of rilonacept and anakinra currently used in the treatment of CAPS, and therefore is proposed to provide a longer duration of action will allow less frequent administration.

Canakinumab, derived using hybridoma technology was developed using ——— immunized with recombinant human IL-1β alone or conjugated to keyhole limpet hemocyanine (KLH). The ——— carry part of the human IgG repertoire, and the hybridomas derived from the ——— express fully human antibodies. ———

——— Product A (lyophilisate formulation for the drug substance produced by the ——— was evaluated in the early clinical trials in CAPS patients and in the general toxicology, embryo-fetal development (Segment II Reproductive Toxicology) and tissue cross-reactivity studies in marmosets. Product B (lyophilisate formulation for the drug substance produced by the ———, also referred to as ——— was used in the study to investigate single dose, local intra-articular toxicity and pharmacokinetics in marmosets, and in the Phase 3 clinical studies in CAPS patients. Product C (lyophilisate formulation b(4)

b(4)

were used in the later clinical trials in CAPS patients and to evaluate comparative tissue cross-reactivity in humans and marmosets. Product D (lyophilisate formulation is the substance intended for marketing. Products A-D are considered to be comparable by Product reviewer, based on structural characterizations identified by physiochemical and biological testing. Products A-C were shown to be comparable in *in vitro* and *in vivo* bridging pharmacokinetics (PK) studies in marmosets and in the tissue cross-reactivity studies in humans and marmosets, and in the clinical PK and pharmacodynamic (PD) studies conducted during product development. Although no nonclinical bridging studies were conducted specifically using Product D, comparability of Product D with Products A-C was supported based on manufacturing and structural characterizations, biological testing, immunotoxicity and potential formation of anti-drug antibody. The manufacturing changes were conducted in agreement with European regulatory authorities and with FDA Agency recommendations during development, including pre-IND (January 2006) and pre-BLA (October 2008) meeting discussions.

II. Recommendations

A. Recommendation on approvability

The appropriate nonclinical studies were conducted, using adequate and well-validated methodology in support of the safety and labeling of canakinumab for the clinical indication as proposed. Canakinumab can be approved under BLA 125319 from a pharmacology and toxicology perspective.

B. Recommendation for nonclinical studies

No further nonclinical studies are needed for marketing approval.

C. Recommendations on labeling

The following revisions to the Proposed Labeling are recommended:

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

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1 Page(s) Withheld

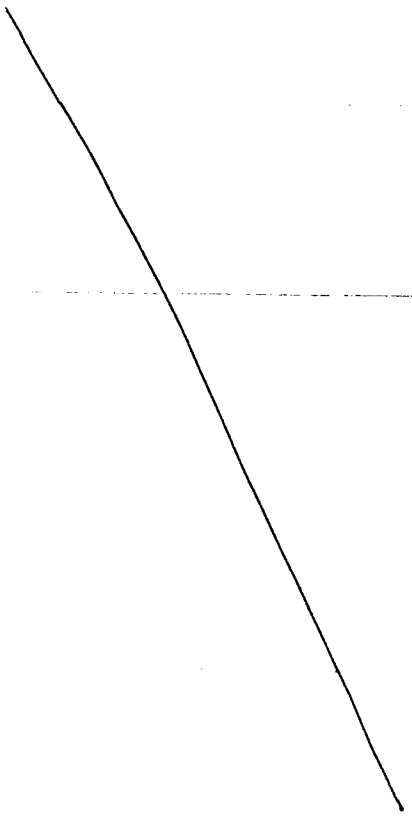
_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Pharm/Tox- 1



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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The nonclinical studies conducted in support of the clinical safety of canakinumab administration were appropriate and adequate according to the general recommendations in the ICH Guidance for Industry (S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) and in agreement with Agency recommendations and concurrence, provided during drug development. As recommended in the ICH Guidelines, the Applicant assessed the relative sensitivity of marmoset, mouse and human IL-1β to ACZ885 *in vitro*, and determined affinity and pharmacological effects for selection of the most appropriate species for the toxicology studies and to support extrapolation of the results of the toxicology studies to findings in the clinical studies. The methodology used in the nonclinical studies was appropriate, using adequate recovery period evaluations of sufficient duration, the same subcutaneous (SC) route of administration intended for clinical use, as well as evaluation of chronic toxicity using the intravenous route. The indication for treatment of pediatric patients with CAPS ages 4 years and older was supported by the results of a well-designed juvenile toxicity study in CD-1 mice, using a properly validated mouse anti-mouse ACZ885 surrogate, 01BSUR.

The studies in mice used the mouse anti-mouse ACZ885 surrogate antibody 01BSUR, because ACZ885 does not cross-react with any of the recombinant murine IL-1β isoforms due to differences in the amino acid position 64 of IL-1β , composed of glutamic acid in humans and marmoset monkeys and alanine in the other mammalian species. Immunogenicity assessments were included in the toxicology studies, and in the batch comparison studies conducted during product development in support of the interpretation of study results. No concerns were raised based on the data and understanding of the mechanism of action, with the exception of the potential for immunosuppressive effects that may increase the potential risks for infection and malignancies.

Marmosets were determined to be the most relevant species for toxicologic evaluation, based on fully comparable ACZ885 binding to marmoset IL-1β with that in humans.

ACZ885 showed approximately dose-proportional increases in exposure, without gender differences. Peak plasma levels (C_{max}) were observed at approximately 12-120 hours (T_{max}) after subcutaneous administration, suggesting slow absorption. Plasma concentrations were 2-3 times higher after repeated administration twice weekly for 14 weeks than after a single dose. The accumulation half-life was approximately 24-40 hours. Exposure values (AUC and Cmax) were similar in marmosets for SC ACZ885 batches manufactured using the ——— in several bridging PK studies including a 13-Week Batch Comparison Study. Additionally, bridging PK assessments to investigate potential changes in elimination rates after IV administration of the IgG1 antibodies ———— result of manufacturing changes during product development, found no differences in the pharmacokinetic parameters, including elimination. Overall, SC ACZ885 bioavailability was determined to be approximately 60% in marmoset, comparable to human bioavailability of approximately 67%. b(4)

The results of 01BSUR PK and TK assessments in CD-1 mice demonstrated exposure and kinetics values similar to those of ACZ885, with peak serum levels at approximately 24 hours (T_{max}) after SC injection. In the bridging PK comparison studies on 01BSUR and ACZ885, the results showed mean maximum plasma levels of approximately 70 mcg/ml 01BSUR, compared to 98-167 mcg/ml following IV injection at the same 10 mg/kg dose of ACZ885. Mean $AUC_{0\text{-}inf}$ values were approximately 40,070 mcg.h/ml for 01BSUR and 12,413-43,622 mcg.h/ml for ACZ885, and the half-life values were approximately 319 h for 01BSUR and 300-347 h for ACZ885 at the same 10 mg/kg IV dose. ACZ885 placental transfer was demonstrated in the Embryo-Fetal Development (Segment II) study TK assessments in marmosets, which showed mean fetal serum and amnionic fluid concentrations of 7.0%-8.7% and 1.8%-2.0% the mean concentration in the maternal serum, respectively, at doses from 15-150 mg/kg SC. Placental transfer was also demonstrated for 01BSUR given by SC injection in the Embryo-Fetal Development and Pre- and Post-natal Development studies in mice, with fetal exposure 9-26 times higher in the first, and 4-6 times higher than in maternal mice in the second study.

The results of TK analyses in an IV toxicity study in marmosets at the dose of 5 mg/kg showed total systemic serum clearance of 0.45 ml/h/kg, a mean distribution half-life of 10.8 hours, and terminal phase half-life of 104 hours (approximately 4 days), compared to 6.5-8 days across toxicology studies in marmosets given SC ACZ885 at the same dose. No increases in clearance were observed with increased duration of treatment in marmosets, suggesting absence of anti-drug antibody formation under the conditions of those studies. The mean terminal half-life of 01BSUR was 13-17 days and CL/F was 6 ml/kg/d after a single 10 mg/kg IV injection in mice. 01BSUR clearance was estimated at 3.66 ml/kg/d. The results of PK and TK analyses in the clinical trials showed comparable, low ACZ885 clearance and long half-life profiles to those by ACZ885 in marmosets and 01BSUR in mice, although the half-life was considerably longer at approximately 21-30 days in the human studies. Twice-weekly dosing was used in the marmoset studies to support comparative exposure with that in humans, due to the difference in half-lives. No studies were conducted to explore potential pharmacokinetic drug interactions with ACZ885.

Repeated-dose toxicology studies were conducted in marmosets using the intravenous (IV) route for 4 and 26 weeks at doses of up to 100 mg/kg/twice weekly, and by subcutaneous injection for 43 days and 13 weeks at doses of up to 150 mg/kg twice weekly. Two 13-week SC toxicity studies were performed; one to investigate ACZ885 toxicity using the original drug substance produced by the ——— and one to compare the toxicokinetic (TK) and toxicity profiles of the drug produced using the original ——— with the TK and toxicity profiles of the drug substance produced using the ———. Appropriate recovery period evaluations were included in each study. Repeated-dose toxicology studies of up to 6 months duration by the IV route and 13 weeks by the SC route included the standard toxicology parameters (e.g., clinical signs, clinical pathology, electrocardiography, ophthalmoscopy, necroscopic gross and microscopic organ and tissue examinations and organ weights, and toxicokinetics (TK)). Assessments were conducted for presence of anti-ACZ885 antibodies and lymphocyte subpopulation (CD3, CD4, CD8, CD14, CD16, CD20, CD56) and monocyte immunophenotyping and gene expression analysis in peripheral blood leukocytes, monocytes and splenic nucleated cell suspensions. Gene expression was also analyzed in tissue samples from liver, kidney, spleen, lung, and mesenteric lymph nodes in the 13-week SC bridging study. Additionally, male reproductive parameters, including semen sperm evaluation (motility, number, morphology), and testicular size and histopathology, including testicular cell population quantitation, and serum testosterone were evaluated in the 6-month IV toxicity study.

b(4)

No target organs of canakinumab toxicity were conclusively and consistently identified across studies (see discussion of specific findings, below). There were no adverse ACZ885-induced effects on male reproductive measures, or anti-ACZ885 antibodies detected in the general toxicology studies.

The potential for immunotoxicity by biotechnology-derived pharmaceutical products is a concern, although there was no compelling evidence that was consistent across nonclinical SC toxicology studies for ACZ885-induced alteration of immune function.

The results of the 4-week SC tolerability study in female marmosets showed slight intestinal hyperplasia (epithelial and Peyer's patch) with marked lymphocytic infiltrate and minimal abscess in one of four high-dose (150 mg/kg/twice weekly) females, slight leukocytic infiltrate in the gall bladder in one of four mid-dose (50 mg/kg/twice weekly) and one of four high-dose females, and anemia and inflammatory leukocytosis with increased lymphocytes, monocytes and eosinophils in one mid-dose female, possibly secondary to ACZ885-induced immunosuppression. In the 13-week SC toxicology investigation in marmosets given 15-150 mg/kg/twice weekly ACZ885 there was an increase in minimal lymphoid hyperplasia of the spleen (large active follicles) in the main study and recovery male marmosets, in the absence of treatment-related effects on lymphocyte phenotype of splenic suspensions and blood samples, changes in anti-drug antibody levels and without findings in the female animals. No treatment-related effects in spleen were observed in the other general toxicology studies in marmosets, including the 6-month IV toxicity study of longer duration. Spleen enlargement was found in the F_0 dams including the controls in the Segment I study on male and female fertility in CD-1 mice given 01BSUR, suggesting a possible vehicle effect. However, a different vehicle composition was used in the 13-week toxicity study in marmosets, casting some doubt that the effects in spleen in that study were vehicle-related.

In a 13-week comparative SC toxicity study in marmosets given ACZ885 produced by different cell lines ——— at the single dose level of 150 mg/kg twice weekly (vs. control vehicle), there were several findings that may be secondary to treatment-related effects on immune function. Septicemia with inflammatory cell infiltration in the intestinal mucosa, intestinal mucosal ulceration with neutrophil loss and neutrophilic inflammation with bacteria present throughout the body were found in one of four male marmosets given ACZ885 produced by the ——— that died during the treatment period, but there was no other evidence of immunosuppression in that study. No increase in the incidence of infection was seen in the marmosets given ACZ885 produced using the ——— in that study, nor in the other 4-13 week SC and 26 week IV toxicology studies, and in the embryo-fetal toxicity study (Segment II) study in marmosets. A very slight decrease in lymphocytes and increase in neutrophils, with low WBC, anemia and increased reticulocytes were observed in one of three female marmosets given 10 mg/kg single intra-articular injection (only dose tested). Enlarged adrenals and kidneys with histological evidence of cortical hypertrophy and inflammatory cell foci with fibrosis and atrophic tubuli were found in one of the marmosets, and swollen finger with abscesses and acute inflammation of the bladder in another marmoset in that study. Systemic exposure was verified by TK analyses. The findings were within the historical background range of incidence.

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A 28-day SC 01BSUR injection study with 28-day recovery period was conducted in CD-1 mice specifically to explore potential immunosuppression by ACZ885, using the murine ACZ885 surrogate 01BSUR. The results showed a 10% and 61% inhibition of anti-KLH IgG response with 50 and 150 mg/kg/week in the males only, but there was an abnormally high response in the controls used for comparison. In contrast, the anti-KLH IgG response was increased in the treated females, but in the context of extremely high variability within groups, and there were no differences from controls in anti-KLH IgG

response in the recovery animals. There were no effects in the immunophenotyping assays, including relative proportions and absolute numbers of Total ($CD3e^+$), Helper ($CDe3^+/CD4^+$), and Cytotoxic ($CDe3^+/CD8a^+$) T lymphocytes, Double positive T lymphocytes (spleen and thymus, $CD3e^+/CD4^+/CD8a^+$), Double negative T lymphocytes (spleen and thymus, $CD3e^+/CD4^-/CD8a^-$), B lymphocytes ($CD19^+$), and Natural Killer lymphocytes ($CDe3^-/NK1.1^+$). There were no treatment-related immunogenicity/anti-01BSUR antibody responses, and no interference with the T-cell dependent anti-KLH IgM response (TDAR). In the necropsy examinations, there were no changes in gross pathology, organ weights and histophathology findings, particularly in lymph node tissues that could be conclusively attributed to treatment.

A full battery of reproductive toxicology studies were conducted by the Applicant, including evaluations of male and female fertility (Segment I) in mice, embryo-fetal development (Segment II) in mice and marmosets, and pre- and post-natal development (Segment III) in CD-1 mice.

No major 01BSUR-related effects were observed in CD-1 mice on male and female fertility, major fetal malformations or teratogenicity, and post-natal neurobehavioral and reproductive development. There were no ACZ885-related effects on major fetal malformations or teratogenicity in marmosets. Additionally, there were no effects in the immunology assessments conducted in adult (F_1) offspring of treated mice, including blood, thymus and spleen immunophenotyping using determination of total, absolute and percent differential counts for T, Helper T, Cytotoxic T, B, and Natural Killer lymphocytes, and organ weights, and no anti-ACZ885 antibody formation was detected. However there were several minor treatment-related effects found in the embryo-fetal development studies, incomplete ossification suggestive of slight developmental delay was observed in both species that are considered unlikely to affect the survival and function of the offspring.

The results of the embryo-fetal development study in marmosets administered ACZ885 at doses of 15, 50, and 150 mg/kg/twice weekly on GD 25-109 SC, showed a slight decrease in mean placental weights at the HD compared to controls, that was possibly related to lower litter size (mean 1.86 vs. 2.45 in the controls) at this dose. There was a slight increase in numbers of fetuses with kinked (3/26 HD vs. 1/27 control) and/or bent (1/26 at the HD vs. 0 in the controls) tail in the external examination. No treatment-related visceral variations or malformations were found. The skeletal examination revealed a slight increase in effects on the terminal caudal vertebra, with incomplete vertebral ossification in 1/27, 4/30, 10/32, and 2/26 fetuses in the control, LD, MD, and HD groups, respectively, suggestive of transient developmental delay. Misaligned and/or bipartite vertebrae were revealed in 5, 17, 16, and 12 in the control, LD, MD, and HD groups, respectively. No treatment-related effects were found in the fetal histopathology examination. The results of the TK analyses in the marmosets showed adequate maternal exposure to test article that increased with dosing duration. All fetuses of treated dams were exposed to ACZ885, in a dose-proportional manner; test article was found in fetal serum and amniotic fluid at concentrations of 7.0%-8.7% and 1.8%-2.0%, respectively,

the concentrations in maternal serum. No anti-ACZ885 antibody formation was detected in the maternal and fetal marmosets.

The results of the embryo-fetal toxicity study in CD-1 mice exposed to 01BSUR on Gestation Days (GD) 6, 11, and 17 showed increased incidence of incomplete ossification of the parietal bones at 50 mg/kg (11.3%, 14/124 fetuses in 9/20 litters) and 150 mg/kg (24%, 25/104 fetuses in 8/18 litters) when compared to the concurrent control incidence of 2.8% (3/106 fetuses in 1/17 litters) and historical control incidence for the laboratory (0%-4.2%), in the absence of maternal toxicity. Additionally, the fetal examinations revealed incomplete ossification of the frontal bones at 150 mg/kg (18.3% [19/104 fetuses in 9/18 litters] compared to 5.7% [6/106 fetuses in 3/17 litters] in the concurrent controls and 0%-4.2% in the historical controls for the laboratory). There were no other treatment-related skeletal effects or findings in the fetuses at the LD of 15 mg/kg SC. The results of the TK analyses showed adequate 01BSUR exposure in the dams (serum concentration at the HD = 321 mcg/ml) and evidence of placental transfer with adequate exposure in the fetuses (serum concentration at the HD = 136 mcg/ml) on Day 17.

The Applicant conducted a SC juvenile development study in CD-1 mice administered 01BSUR at doses of 0, 15, 50 or150 mg/kg once weekly from post-partum (PP) days 7-70, in support of the proposed SC canakinumab indication for the treatment of CAPS in pediatric patients ages 4 and above. In the pre-weaning physical development evaluation, a slight increase was observed in the mean day of auricular startle at the mid-dose (50 mg/kg/week) in the male pups and high-dose male and female pups compared to control pups before post-partum day 21. The post-weaning physical development assessments found a slight but statistically significant increase in the mean number of days to vaginal opening in the adult high dose (150 mg/kg/week) females compared to concurrent controls. Also, there was a statistically significant increase in pre-implantation loss (group mean 20.38%) at the high dose compared to concurrent (4.26%) and historical (7%-12.8%) controls, in the fertility assessment of dams that had received treatment as juveniles. There were no treatment-related effects in the immunogenicity assessments and in the immunophenotyping in blood, spleen and thymus, nor on lymphocyte and lymphocyte subset counts.

Studies to evaluate genetic toxicology and carcinogenicity are commonly not required for biologic drugs unless there are special concerns based on mechanism of action or findings in the general toxicology studies, and these studies were not requested or conducted on ACZ885 in prior agreement with the Agency. ACZ885 does not cause signal transduction, is not a growth factor or hormone, contains no non-peptide chemical linker molecules, and produced no cell toxicity *in vitro*. Although ACZ885 is not expected to directly cause cell proliferation or DNA damage for the reason that no interactions with DNA and chromosomal material are likely, the potential for increased incidence of malignancy secondary to immunomodulation is of concern. The large ACZ885 protein requires endocytosis by active transport, complexed to FcRn for cellular uptake, a mechanism that is not available at the nucleus. No direct DNA binding is anticipated, ACZ885 is not electrophilic and has no active metabolites. No tumors were found in the histopathology examinations of a 6-month intravenous toxicology study in

marmosets, and there was no evidence of chronic inflammation in the nonclinical studies *in vivo*.

In summary, the appropriate nonclinical studies were conducted in support of clinical administration and were adequate according to the general recommendations in the ICH Guidance for Industry (S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) and in agreement with Agency recommendations and concurrence, provided during drug development. Safety pharmacology and pharmacodynamic drug interaction studies are generally not required for investigation and registration of biologic agents, and were not conducted on ACZ885 by the Applicant. No primary drug effects are expected in the central nervous, cardiovascular, pulmonary, renal, and gastrointestinal systems due to absence of non-specific tissue binding, although toxicity secondary to inflammatory changes and/or infection remain a theoretical concern and have been observed in nonclinical studies on other agents that inhibit IL-1β. There were no treatment-related adverse neurobehavioral effects or changes in cardiovascular (including QT interval and heart rate), pulmonary, renal and gastrointestinal function and morphology. ACZ885 binding in heart tissue was weak in the tissue cross reactivity studies in human and marmoset tissues. Due to the highly selective binding to the IL-1β receptor, little or no interaction with hERG channels is expected. Renal toxicity by canakinumab is unlikely due to the large molecular size of the protein, preventing glomerular filtration. No adverse pharmacodynamic drug interactions with canakinumab are expected.

Discussion

ACZ885 and 01BSUR PK/TK profiles were fully characterized in marmosets and mice, respectively, using single and repeated dose intravenous (IV) and subcutaneous (SC) administration. Additionally, six exploratory PK studies were conducted to optimally determine and validate the analytical (ELISA) and immunogenicity (surface plasmon resonance spectroscopy) methodology used in the ACZ885 and 01BSUR PK/TK assessments. Comparative PK/PD evaluation of drug substance produced by different cell-lines with manufacturing changes during the course of drug development was performed, to bridge the canakinumab lyophilisates produced by the ——— and used in the marmoset toxicology and early clinical studies, to the to-be-marketed drug substance produced in the ——— Additional evaluations compared human and marmoset PK/TK parameters. b(4)

Absorption was slow by the SC route, with high T_{max} values, characteristic of SC administered high molecular weight monoclonal antibody proteins. ACZ885 showed approximately dose-proportional increases in exposure, without gender differences. The primary systemic absorption pathways following extravascular administration of the high molecular weight monoclonal antibody proteins are generally by convective transport through lymphatic vessels into circulating blood, and to a lesser extent by diffusion across blood vessels near the site of administration. Accumulation was observed with increased duration of treatment, that may be related to FcRn receptor saturation. In contrast, accumulation with repeated administration was not consistently reported in the

clinical trials. The Applicant provided adequate evidence of PK comparability in marmosets for SC ACZ885 batches manufactured using the ——— ; in several bridging PK studies. Additionally, bridging PK evaluation was conducted to investigate potential changes in elimination rates after IV administration of the IgG1 antibodies with ——— b(4)

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. The PK/TK assessments on 01BSUR in mice showed similar exposures and kinetics to those of ACZ9885 in marmosets. Low, but nearly equivalent steady state volume of distribution (Vss) values were observed after IV and SC injection of ACZ885 in marmosets and following ACZ885 and 01BSUR injection in CD-1 mice. Low volume of distribution (Vd) values were also similar to the findings in clinical PK/TK evaluations on ACZ885, and approximated plasma volume in both the nonclinical and clinical studies, suggesting little distribution into other tissues and organs outside of the circulatory system. No studies were conducted specifically to address ACZ885 metabolism and excretion. Canakinumab is expected to be metabolized and cleared by proteolytic degradation, consistent with the pathway observed for the immunoglobulins and other large protein molecules. No active canakinumab metabolites are predicted. Renal clearance is unlikely, due to the large size of the canakinumab protein molecule, preventing glomerular filtration. Canakinumab is slowly cleared from circulation by FcRn receptor binding, upon which the antibody-FcRn complex is transported across the cell membrane into cytoplasm and is degraded by endosomal catabolism or recycled to cell surface, to be released back into circulation. No drug interactions are expected, as canakinumab does not interact with cytochrome P450 enzymes.

The 6-month IV toxicology study in marmosets at doses of up to 100 mg/kg/twice weekly is considered to be acceptable for the evaluation of chronic toxicity by ACZ885 in the absence of any concerns raised with respect to the mechanism of action and the results of the toxicology studies of shorter duration, as per ICH Guidance to Industry (S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) and in agreement with Agency recommendations and concurrence provided during drug development. The Applicant also performed two 13-week SC toxicology studies in marmosets, bridging the chronic IV study to the proposed SC route of administration and to bridge the drug substance that was originally produced using the ——— , to the substance produced using the ——— that is intended for the marketed product, with respect to toxicokinetic and toxicity profiles. The selection of marmosets as the most relevant species was well-supported, based on the results of ACZ885 PK and bioactivity profiles in marmosets, other mammalian species (e.g., rodents), and humans. In addition to the standard toxicology parameters, the Applicant also evaluated potential ACZ885 effects on presence of anti-drug antibody formation, lymphocyte subpopulation and monocyte immunophenotyping, and gene expression in peripheral blood leukocytes, monocytes and splenic nucleated cell suspensions, gene expression in liver, kidney, spleen, lung and lymph node tissues, and male reproductive parameters. The results of the chronic IV and 13-week subchronic toxicology studies in marmosets identified no clear, conclusive, and repeatable target organ toxicity at doses up to that limited by b(4)

feasibility in terms of solubility, dosing volumes and frequency. In contrast, the results of the SC and IV toxicology studies conducted on Rilonacept (Interleukin-1 Trap [IL-1 Trap], approved for the Treatment of CAPS, BLA 125249, Pharmacology Toxicology Reviewer Mamata De, Ph.D.), conducted in cynomolgus monkeys for durations of up to 6 months, showed treatment-related deaths, clinical signs (e.g., lethargy, emesis), and target organ toxicity in the injection site, heart, kidney, lung, reproductive organs and immune system. Rilonacept administration resulted in histopathologic findings of mono/polymorphonuclear cell tissue infiltration (macrophages, eosinophil, plasmocytes and lymphocytes), arteritis, cellular degeneration, granuloma formation, and mineralization. These findings were attributed by Dr. De to possible proinflammatory reaction due to immune complex deposition or hypersensitivity vasculitis associated with mono and polymorphonuclear cell infiltration (e.g., eosinophil), to increased infection due to immunosuppression, or to exaggerated pharmacology of IL-1 Trap.

The potential for immunotoxicity is a concern for canakinumab as for most biotechnology-derived pharmaceuticals, although there was no compelling evidence that was consistent across nonclinical SC toxicology studies for ACZ885-induced alteration of immune function. The main concern from a nonclinical pharmacology and toxicology perspective based on the canakinumab mechanism and action is the potential for immunosuppression leading to increased risk of infection and malignancies. Additionally, the biologic drugs are generally considered to present increased risk of hypersentivity reactions. Treatment-related effects on IgG response has been associated with hypersensitivity reactions and complement activation that could neutralize drug activity and the corresponding endogenous protein via development of anti-product antibodies. However, no decreases in test article exposure was found at any dose in the Immunotoxicity study conducted in CD-1 mice using 01BSUR, or in the TK assessments in the other toxicology study in mice administered 01BSUR and marmosets given ACZ885. The absence of other indices of immunotoxicity and the equivocal results for an IgG response in the Immunotoxicity study provide weak evidence suggestive of potential immunotoxicity by ACZ885.

Increased incidence of malignancies and infection and anti-drug antibody formation have been demonstrated in nonclinical and clinical studies on several other immunosuppressive products, monoclonal antibodies and Fc fusion proteins. The potential for formation of anti-drug antibodies in the nonclinical studies on ACZ885 was minimized by appropriate species selection using marmosets, which showed identical three-dimensional structure, sequence homology, and glycosylation to those in humans, for evaluation of general toxicology and embryo-fetal development, and by using an appropriate surrogate model with CD-1 mice administered 01BSUR, that shows identical biologic effects to those by canakinumab in humans. Although there was equivocal evidence of toxicity that could have been related to ACZ885-related immunotoxic effects, the findings were sporadic and/or inconsistent in terms of cross-gender, cross-species, or cross-study repeatability, were observed without corresponding changes in corresponding clinical pathology and histopathology parameters, and/or were within historical control range for the laboratories. However, the potential for immunotoxicity, particularly for toxicity related to immunosuppressive effects and/or hypersensitivity reactions in clinical

treatment cannot be entirely ruled out, and should be described in the product label. Adequate monitoring during treatment is warranted. Spleen size was monitored in clinical study CACZ8852201, with no treatment-related findings in human patients.

While the results of the embryofetal toxicity study in marmosets showed no evidence of teratogenicity with exposure to ACZ885, there was some suggestion of slight treatment-related developmental delay, indicated by increased incidence of incomplete caudal vertebral ossification at all ACZ885 doses (1/27, 4/30, 10/32, and 2/26 fetuses in the control, LD, MD, and HD groups, respectively). A lower incidence of treatment-related toxicity in the higher than in lower doses could be observed for biologic drugs if anti-drug antibodies are induced at higher dose levels, but no anti-ACZ885 antibodies were found in this study. Therefore, in the absence of neutralization of ACZ885, the high dose incidence is comparable to that in the control group, and this finding is considered to be equivocal. Additionally, bent/kinked tail was observed with increased incidence at the HD in several fetuses, compared to controls. The results also suggested a slight treatment-related reduction in reproductive performance indicated by slight reductions in the number of fetuses per litter and reduced placental weights at the HD, which likely reflects fewer triplets and more singlets and twin pregnancies at the HD than in the controls and other groups. There were no late resorptions found in the ultrasonography, as there were no differences in the numbers of fetuses vs. the numbers of embryos present at the Day 50 ultrasonography. The possibility that the reduction in numbers of fetuses per litter and reduced placental weights at the HD could have been due to early resorptions could not be assessed, because uterine scars are not formed in the marmoset upon early abortion. Results suggestive of treatment-related fetal developmental delay were also found in the embryo-fetal toxicity study in CD-1 mice given 01BSUR. The incidence of incomplete ossification of the parietal and frontal bones at the MD and/or HD exceeded the concurrent and historical control incidences.

In comparison to the results of the reproductive toxicity studies conducted on ACZ885 and 01BSUR, there were multiple treatment-related findings in the reproductive toxicity studies conducted on Rilonacept (IL-1 Trap, BLA 125249, refer to Pharmacology Toxicology review by Mamata De, Ph.D.) in mice given a surrogate IL-1 Trap molecule (Segments I and III) and cynomogus monkeys administered human IL-1 Trap (Segment II). The results included treatment-related decreased fertility index in male and female mice, early resorptions at all doses, post implantation loss, increased abortion and still born pups, presence of IL-1 Trap antibodies in F_0 males, and in the Segment III study, an 8-fold increase in F_1 pup and F_2 litter deaths. Increased skeletal variation in lumbar vertebrae and late pregnancy spontaneous abortions were noted at all doses in the monkeys. Most of the findings in the reproductive toxicity battery of studies were observed in all dose groups, providing either very low or no safety margins for potential adverse effects on fertility, embryofetal development and pre- and postnatal development in clinical use.

The 01BSUR-related effects were noted in the SC juvenile development study in CD-1 mice, including a slight increase in the mean day of auricular startle, an increase in the mean number of days to vaginal opening, and an increase in pre-implantation loss in the

adult F_1 generation. However, the increases in day of auricular startle were similar to control values in another study, were within historical range for the laboratory and there were no treatment-related effects seen in the post-weaning evaluation of auditory startle habituation. The slight increase in mean number of days to vaginal opening in the adult high dose females (150 mg/kg/week) compared to concurrent controls, was within control range for the performing laboratory. The increase in pre-implantation loss at the high dose compared to current and historical control juvenile mice can be attributed to a 74% loss in one of the 20 female mice evaluated, and the mean number of live embryos in the HD group was within the historical range for the laboratory. Therefore the pre-implantation loss noted in this study did not provide a strong signal for reproductive toxicity by 01BSUR in juvenile mice in the absence of other treatment-related effects on reproductive function and in the offspring (F_2 generation) of the treated pups. For these reasons, the findings in this study are considered to be equivocal, as they uncovered no compelling evidence for serious adverse ACZ885-related effects on behavioral, developmental, learning, and memory and reproductive parameters in juvenile mice, and are considered to be equivocal for treatment-related effects on juvenile development.

Approximate exposure margins for the human antibody ACZ885 relative to the recommended human dose of 150 mg or 2 mg/kg in patients ≤ 40 kg in weight are presented in the following table (by the reviewer):

Exposure Margins in the Nonclinical Studies on ACZ885 and 01BSUR

Species	Study	Doses (all w/ vehicle controls)	Target Organ Findings	Dose at NOAEL	AUC_{0-t} (mcg.h/ml) mean♂+♀	Multiple of Clinical AUC[b]
Marmoset	26-wk IV Toxicity	10, 30, 100 mg/kg ACZ885 2X weekly	None	100 mg/kg	86,978 (0.083-24h, Wk 23) Equiv. AUC over 0-8 wks = 4,872,000[b]	(5X) 287X
Marmoset	13-week SC Toxicity	15, 50, 150 mg/kg ACZ885 2X weekly	-Dose-related spleen hyperplasia ♂s no findings in phenotyping, ♀s or other gen. tox. & clin. studies, probably 2° to possible immunosuppression	-If treatment related: none -w/o spleen effects: 150 mg/kg	(Wk 14) 402430 (0-1368h)	24X
Mouse	Fertility	15, 50, 150 mg/kg SC 01BSUR 1X weekly[e]	None	150 mg/kg	95585 (0-120h, 1st dose)[f]	NA[g]
Mouse	EFT	15, 50, 150 mg/kg/wk SC 01BSUR (GD 6,11, 17)[e]	-No major malformations. -Developmental delay: incompl. ossification parietal (at 50 & 100 mg/kg) and frontal (100 mg/kg) bones	EF toxicity: 15 mg/kg Teratogenicity: 150 mg/kg	Dev. Delay: 6436: (0-120h) Teratogenicity: 95585 (0-120h)[b]	NA[g]
Marmoset	EFT	15, 50, 150 mg/kg/2X weekly SC ACZ885 (GD25-109)	-No maj. malformations -↑Bent/kinked tail at 150 -↑Developmental delay: incompl. vertebral ossification in all treated	Embryotoxicity: not identified Major malformations: 150 mg/kg	(Day 109) 141,000 (0-48h) Equivalent AUC over 0-8 wks = 3,950,000[b]	Major malformation: 232X
Mouse	PPD	15, 50, 150 mg/kg/wk SC 01BSUR (GD6-PPD 21)	-Slight ↑histiocytosis mandibular,mesenteric lymph nodes in F_1 adult ♂ at 50 and 150, without lesions	For pre- and post-natal development 150 mg/kg	95585 (0-120h, 1st dose)[f]	NA[g]

Species	Study	Doses (all w/ vehicle controls)	Target Organ Findings	Dose at NOAEL	AUC_{0-t} (mcg.h/ml) mean♂+♀	Multiple of Clinical AUC[b]
Juvenile Mouse	SC Juvenile Toxicity	15, 50, 150 mg/kg/wk SC 01BSUR (PPD 7-70)	-Slight delay day of vaginal opening at 150 (w/in historical range) -Slight ↑day auricular startle development at 50&150 (w/in historical range) -↑pre-implantation loss at 150 (due to loss in 1 dam), w/in historical range)	For major behavior, developmental, learning, memory, reprod. effects: 150 mg/kg	(Day 63) 154,000 (0-72h)	NA[g]
Mouse	28-Day SC Immunoto.	10, 50, 150 mg/kg/wk SC 01BSUR	None	150 mg/kg	(Day 25-57) 1,406,520 (D28-57)	NA[g]

[a] For detailed description of the TK analyses, refer to the original study review, above under Section 2.6 Pharmacology Toxicology Review

[b] Relative to approximately equivalent AUC_{0-inf} values of approximately 17,000 mcg/h/ml in adult CAPS patients treated by SC injection at 150 mg/once every 8 weeks, and AUC_{0-inf} value of approximately 14,400 mcg.h/ml in pediatric patients at 2 mg/once every 8 weeks; AUC values for the nonclinical exposures at the NOAEL were extrapolated to reflect approximate values over 0-8 weeks, compared with the values provided for clinical exposure

[c] Based on proposed clinical dose 150 mg in a 70 kg patient and 2 mg/kg in patients ≤ 40 kg in weight

b(4)

[e] For detailed methodology, refer to the original study review, above, under Section 2.6.6.6 Reproductive and Developmental Toxicology

[f] Based on results of EFT study TK analyses in maternal mice administered 0, 15, 50, and 150 mg/kg 01BSUR on gestation days 6, 11, and 17

[g] NA = not applicable: surrogate

B. Pharmacologic activity

ACZ885 binds with high potency (association rate constants of 1.37-1.57 M^{-1} x sec^{-1} x 10^6 and dissociation rate constants of 3.70-8.19 sec^{-1} x 10^{-5}) and high affinity to human (K_D = 26.5-60 pM) and marmoset (K_D = 22.8 pM) IL-1β. IL-1β is a cytokine produced by mononuclear phagocytes in response to injury and infection. ACZ885 does not cross-react with any other IL-1 human antibodies (e.g., IL-1α, IL-1Ra, IL-18, IL-33), nor with recombinant IL-1 β from the other mamalian species tested, including mice, rats, rabbits, and cynomolgus and rhesus monkeys, due to differences in the amino acid position 64 of IL-1β (glutamic acid in humans and marmoset monkeys vs. alanine in the other species). Upon binding, the interaction of IL-1β with the IL-1 type I and II receptors is prevented (IC50 = 40 pM in human and approximately 1/2 the potency in marmoset).

IL-1β receptor activation leads to signal transduction related to that by the Toll-like receptors in the immune response to infection. Upon signal transduction to intracellular machinery (pathways include NFkB, Erk1/2, p38, Jnk1/2/3, and pI3 kinase pathways) via receptor activation, intracellular adapter molecules and IRAK protein kinases are activated, releasing cytokines, chemokines, and pro-inflammatory mediators. The main signaling pathways are similar in all mammals. IL-1β is proposed by the Applicant to be involved in the pathobiology of autoinflammatory syndromes

b(4)

b(4)

The results of *in vitro* mechanism of action studies demonstrated that upon binding to and inactivation of the IL-1 receptor IL-1RI and IL-1RII, ACZ885 effectively prevented the interaction of IL-1β with these receptors, and subsequent production of interleukin 6 (IL-6) in human primary fibroblasts, in a dose dependent manner. Comparative evaluation showed similar neutralizing activity of IL-1β by canakinumab in human (IC_{50} = 35 ± 13 pM) and ACZ885 in marmoset (IC_{50} = 95 ± 14 pM).

Three studies were conducted to compare the cross-reactivity profiles of ACZ885 produced using the ——— b(4)
——— in normal and human tissues. The results of these studies showed qualitatively similar cross reactivity in human and marmoset tissues (cell types, stain intensity, frequency and subcellular localization) that are consistent with known distribution of IL-1β expressing cells, although the cross-reactivity profile in the marmoset tissues was slightly less, quantitatively than in human tissues. Minor, qualitative binding differences were observed, including ACZ885 staining in marmoset but not in human follicular and germinal cells in the ovary, and in Leydig, Sertoli and gametogenic precursors in the testis. There were several differences noted in distribution of low-grade cytoplasmic staining in epithelial tissues at high concentrations of ACZ885-FITC, with staining observed in human, but not marmoset prostate and thyroid, and in marmoset, but not human parathyroid and vas deferens. The results of these studies support the biocomparability of ACZ885 produced by the ——— , and b(4)
the similar cross-reactivity in human and marmoset tisseus, with the observation of nearly identical IL-1β bioactivity in marmoset and human responses support the selection marmoset for evaluation of ACZ885 toxicology.

A mouse anti-mouse ACZ885 surrogate, 01BSUR was developed for the evaluation of reproductive toxicity, juvenile toxicity and immunotoxicity in the mouse, due to the absence of cross-reactivity by ACZ885 with murine IL-1β. The surrogate antibody was produced in mice that were immunized with recombinant mouse IL-1β. In this procedure, the mouse IgG1/κ isotype, which has no interaction with Fcγ receptors was converted to the IgG2a/κ isotype which is functionally equivalent to the human IgG1 isotype with regard to Fcγ receptor binding. 01BSUR binds to IgG1 and IgG2a isotypes of mouse IL-1β with K_D values of 284 and 302 pM, respectively. Both the parent (IgG1) and the isotype IgG2a inhibit mouse IL-1β activity via inhibition of IL-6 production in b(4)
——— fibroblasts (IgG1 IC_{50} = 31.3 pM, 01BSUR IC_{50} = 24.0 pM).

Animal models of inflammation and neutrophil migration were used to investigate ACZ885 activity related to the proposed indication *in vivo*. Joint inflammation and b(4)
architectural destruction induced in response to articular injection of ——— expressing human IL-1β was attenuated in a dose-dependent manner in mice given intraperitoneal (IP) ACZ885 2 hours before the articular injection. In that study,

proteoglycan synthesis in the cartilage was normalized, and ACZ885 reduced ——— — engineered human IL-1β -induced neutrophil migration in the mouse airpouch. In the rat, IV pre-treatment with ACZ885 blocked fever induced by IV injection of human IL-1β. No enhancement of human IL-1β pharmacodynamic activity by ACZ885 was observed in the rodent models. b(4)

Several *in vivo* studies in mouse models of arthritis were used to evaluate the pharmacologic activity of 01BSUR with that of ACZ885. The surrogate antibody, given by intraperitoneal (IP) injection after induction of collagen injection-induced paw swelling, significantly reduced the swelling. Paw swelling was prevented in that model by prior 01BSUR injection.

Studies to investigate secondary pharmacodynamic effects ACZ885 were not conducted because no non-specific tissue binding was found in the earlier *in vitro* binding and cross-reactivity studies. No treatment-related effects were observed in the toxicology studies on ACZ885 and 01BSUR that would suggest secondary pharmacologic activity. Although ACZ885 demonstrated Fcγ receptor binding *in vitro*, no cell surface-bound antigen binding, which is required for antibody dependent cellular toxicity was found. ACZ885 did not bind IL-1β producing human CD14+ monocytes, nor was found to recruit human monocytic cells of the C1q component pathway. Therefore, no effects on antibody dependent cellular cytotoxicity and complement-dependent cytotoxicity is expected. Furthermore, no immunosuppressive properties by ACZ885 were found in IL-1 receptor deficient mice *in vivo*, although IL-1β is involved in enhancement of immune function of the Th2 T-cell subset. No inhibition of human mixed lymphocyte reaction was found, and therefore no T-cell-related immunosuppression is anticipated.

C. Nonclinical safety issues relevant to clinical use

Nonclinical safety issues relevant to clinical use that were identified in the studies using ACZ885 in marmosets and the mouse anti-mouse ACZ885 surrogate 01BSUR in CD-1 mice include potential risks related to immuotoxicity, skeletal developmental delay in the unborn fetus, and slightly delayed juvenile physical and reflex development (discussed below). Additionally, a residual solvent, ——— used during manufacturing that is known to present a serious risk to newborn and infant human patients was identified in the drug product intended for clinical treatment; however, there is no concern for administration as proposed for children ages 4 years and older. The nonclinical safety issues warrant clear and adequate precautionary statements in the product label, and appropriate clinical monitoring and/or preventative measures. b(4)

Immunogenicity study methodology is still under development and not yet fully understood or established from a commercial and a regulatory point of view. It is generally accepted that the results of nonclinical immunogenicity evaluation do not always predict the occurrence of immunogenic effects by biological agents in humans. Regarding immunotoxicity, there was equivocal evidence for ACZ885-induced suppression of immune function in the nonclinical studies, but the findings were not

consistent across studies, and were without correlative within-study indices of quantitative and qualitative immune cell alterations. As ACZ885 targets IL-1β, a critical cytokine in the regulation of the immune response, a risk of toxicity secondary to immunosuppression, such as infection and/or malignancy may be increased. Increased incidence of malignancies and infection, and anti-drug antibody formation have been demonstrated in nonclinical and clinical studies on several other, less selective immunosuppressive products (such as the IL-1 inhibiting agents rilonacept and anakinra), monoclonal antibodies and Fc fusion proteins. Patients were monitored for potential immunosuppression and/or infection in the clinical studies on canakinumab during product development. Refer to the Clinical Review for BLA 125319 for detailed review of the clinical study findings.

Slight developmental delay was suggested by findings of treatment-related increases in incidence of incomplete ossification of the parietal and frontal bones in mice compared to concurrent and historical control incidence, and slight treatment-related increases in incidence of incomplete caudal vertebral ossification, misaligned and/or bipartite vertebral centrum compared to concurrent control findings (historical control data for the laboratory unavailable) in the marmosets. There were treatment-related effects in the Embryo-Fetal Development studies in mice given 01BSUR and in marmosets administered ACZ885 that point to a potential for adverse effects on the unborn human fetus, although there were no major malformations were observed in these studies which would be likely to adversely affect function or survival.

The results of the juvenile development study in CD-1 mice administered 01BSUR showed no major, adverse treatment-related effects on neurobehavioral measures, learning and memory. However, there were minor, but statistically significant treatment-related changes in some measures of pre-weaning and post-weaning physical development, and in reproductive performance of adult mice that were administered 01BSUR as juveniles (from age 7-70 days), that should be noted. Slight, but statistically significant increases were observed in the mean day of auricular startle in the pre-weaning evaluation, and in the mean number of days to vaginal opening and pre-implantation loss in the adult females given 01BSUR as juveniles. The increase in mean day of auricular startle was similar to controls in another study in CD-1 mice, within historical control range for the laboratory, and without a corresponding effect in the post-weaning evaluation of auditory startle habituation. The mean day of vaginal opening was within historical control range for the performing laboratory, and there were no treatment-related effects on preputial separation. Increased pre-implantation loss was significantly increased compared to both concurrent and historical control range, although there was a 74% loss in one of the females in the affected group that probably biased the assessment. Therefore, these effects did not provide a strong signal for juvenile toxicity, but do suggest a need for appropriate assessment of risk-benefit and adequate monitoring for signs of delays in physical and/or reflex development in the treatment of pediatric patients with canakinumab.

The manufacturing residual solvent, [redacted] was found in the clinical b(4)

formulation at the concentration of [redacted] is contraindicated in solutions for administration to neonates, due to an increased incidence of hypersensitivity reactions and in severe cases, respiratory failure, neutotoxicity with flaccid areflexic paraplegia. Increased mortality as a result of metabolic acidosis, CNS depression, respiratory distress, hypotension and renal failure has occurred in premature infants exposed to this agent. However, in older patients (≥ 4 years of age) with more maturely developed metabolic pathways, [redacted] that has been [redacted]

b(4)

b(4)

The Applicant will be asked to remove the solvent from the final batch during production, or to include an adequate precautionary statement in the product label, regarding the risks to neonates.

References

Agostini L. *et al.* (2004) NALP3 forms an IL-1beta-processing inflammasome with increased activity in Mucle-Wells autoinflammatory disorder. Imunity 20(2):319-1359.

Apte RN, *et al.* (2006) The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. Cancer Metastasis Rev. 25(3):387-408

Arend WP. (2002) The balance between IL-1 and IL-1Ra in disease. Cytokine Growth Factor Rev. 13(405):323-349.

Dinarello CA. (2005) Blocking IL-1 in systemic inflammation. J. Exp. Med. 201(9):1355-1359.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

BLA number: 125319
Review number: 1
Sequence number 000/December 17, 2008/Biologics License Application
Information to Applicant: Yes () No (x)
Applicant and/or agent: Novartis Pharmaceuticals Corporation
Manufacturer for drug substance: Novartis Pharma Stein AG, Stein, Switzerland

Reviewer name: Kathleen Young, Ph.D.
Division name: Division of Anesthesia, Analgesia and Rheumatology Products
HFD #: 170
Review completion date: May 14, 2009

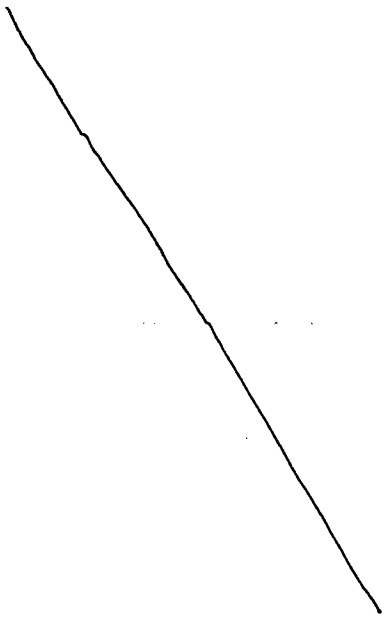
Drug:

Trade name: ILARIS™
Generic name: Canakinumab
Code name: ACZ885
Chemical name: Immunoglobulin G1, anti-(human interleukin-1beta ($IL\text{-}1_B$)) human monoclonal ACZ885; (1 Glu>Glp)-γ1 heavy chain (221-214')-disulfide with kappa light chain, dimmer (227-227":230-230")-bisulfide
CAS registry number: 402710-25-2 (variable heavy γ1 chain); 402710-27-4 (variable light κ chain)
Molecular formula/molecular weight: $C_{6452}H_{9958}N_{1722}S_{42}$/145,157 Dalton
WHO number: 8836
Identification number of the production strain: b(4)

Other names and laboratory codes: NVP-ACZ885-NX-1; ACZ885; ACZ885-NXA; ACZ885 antibody
Structure: (from the original BLA submission)

Canakinumab (ACZ885) is a high-affinity fully human anti-human-interleukin (IL)-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine (Mouse Myeloma) SP2/0-Ag14 cells and comprised of two 447-(or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons. Both heavy chains of ACZ885 contain N-linked oligosaccharide chains attached to the protein backbone at Asn(298). b(4)

Figure 1-1 Amino acid sequence of the ACZ885 drug substance



b(4)

Relevant INDs/NDAs/DMFs: IND 100,040

Drug class: Human anti-IL-1β monoclonal antibody (IgG1/κ isotype)/immunomodulator

Intended clinical population: Adults and children ages 4 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS)

b(4)

Clinical formulation: (reproduced from the original BLA submission)

The quantitative composition of ACZ885 150 mg Powder for solution for injection is outlined in Table 1-1.

Table 1-1 Quantitative composition of ACZ885 150 mg Powder for solution for injection

Ingredient	Bulk drug product solution[1] (mg/ml)	Total amount of drug product per vial (mg)[2]	Declared content of one vial (mg)	Function	Reference to standards
ACZ885	[redacted]	180.0	150.0	Drug substance	Novartis monograph
Sucrose					
L-histidine					
L-histidine hydrochloride monohydrate					
[redacted]					
Polysorbate 80					
Water for injection					

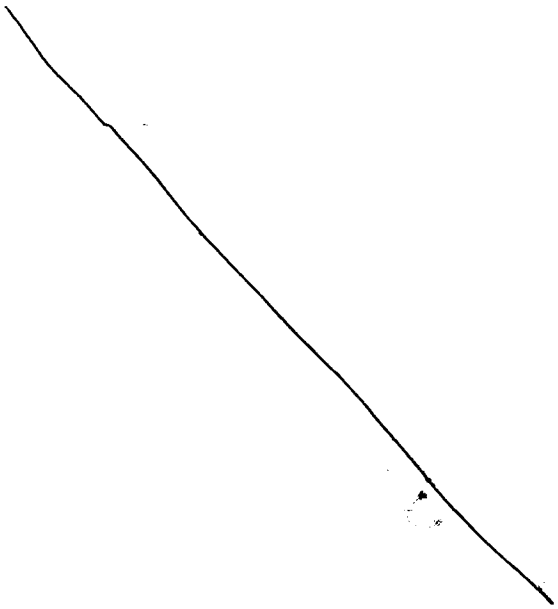
b(4)

2.6.7.4 Drug Substance / Impurities in toxicology studies

DP batch No.	DS Batch No.	Cell line, process	Strength form	Composition	Title of study Study number	Manufacturing site (DS and DP)	By- and degradation products by SEC (a)	

b(4)

DP batch No.	DS Batch No.	Cell line, process	Strength form	Composition	Title of study Study number	Manufacturing site (DS and DP)	By- and degradation products by SEC (a)



b(4)

The manufacturing residual solvent, —— was found at the concentration of —— his solvent is contraindicated in solutions for administration to neonates, although this is of less concern in patients ages ≥ 4 years old (see discussion under Executive Summary, above). b(4)

Route of administration: Subcutaneous

Disclaimer: ***Tabular and graphical information are reproduced from the original BLA submission, unless cited otherwise.***

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of BLA 125319 are owned by Novartis Pharmaceutical Corporation or are data for which Novartis Pharmaceutical Corporation has obtained a written right of reference. Any information or data necessary for approval of BLA 125319 that Novartis Pharmaceutical Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Novartis Pharmaceutical Corporation does not own

(or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA 125319.

Studies reviewed within this submission:

Cross Reactivity of ACZ885, a Human Monoclonal IgG1/k Antibody Against Human IL-1β, with Normal Human Tissues and Normal Marmoset Tissues —— —— Study IM782, Novartis Study 0180142) b(4)

Cross-Reactivity Study of ACZ885-FITC with Normal Human and Marmoset Tissues —— Study IM1364, Novartis Study 0680267) b(4)

Cross-Reactivity Study of FITC-Labeled ACZ885 (HAS-) with Normal Human and Marmoset Tissues — Study IM1496, Novartis Study 0770362) b(4)

28-Day Intravenous Administration Toxicity Study with a 2-Month Recovery Period in the Marmoset (Novartis Study 0280160. —— Study 1939-003) b(4)

26-Week Intravenous Administration Toxicity Study with a 6-Week Recovery Period in the Marmoset (Novartis Study 0380070. —— Study 1939-004) b(4)

Subcutaneous Tolerability Study in Female Marmosets with Toxicokinetics (Novartis Study 0370163)

13-Week Subcutaneous Toxicity Study in Marmosets with an 8-Week Recovery Period (Novartis Study 0470033)

13-Week, Twice Weekly Subcutaneous Batch Comparison Study in Marmosets (Novartis Study 0770370)

ACZ885 Surrogate (01BSUR): A Once Weekly Subcutaneous Injection Fertility Study in the Mouse —— Study 901096, Novartis Reverence 0680149) b(4)

ACZ885 Surrogate (01BSUR): A Weekly Subcutaneous Injection Embryo-Fetal Development Study in the Mouse —— Study 901097, Novartis Study 0680148) b(4)

A Subcutaneous Embryo-Fetal Development Study in the Marmoset Monkey —— Study 1939-005, Novartis Study 0480152) b(4)

ACZ885 Surrogate (01BSUR): A Weekly Subcutaneous Injection Pre and Postnatal Study in the Mouse —— Study 901098, Novartis Study 0680150) b(4)

ACZ885 Surrogate (01BSUR): A Weekly Subcutaneous Injection Juvenile Toxicology Study in the Mouse —— Study 901383, Novartis Study 0770274) b(4)

ACZ885 Surrogate (01BSUR): A 28-Day (Weekly Dosing) Subcutaneous Injection Immunotoxicity Study in the Albino Mouse with a 28 Day Recovery Period (— — Study 301461, Novartis Study 0670570) b(4)

Single Dose Intra-Articular Administration Study in the Marmose (— — Study 1939-018, Novartis Study 0670425) b(4)

Studies not reviewed within this submission:

The nonclinical studies conducted to investigate the primary and secondary pharmacology and pharmacokinetics of ACZ885 are summarized in this review.

2.6.2 PHARMACOLOGY

2.6.2.2 Primary pharmacodynamics

Mechanism of action:

ACZ885 is a highly specific, high affinity fully human anti-IL-1β IgG1/κ antibody, and is produced by mice that are genetically engineered to express a segment of human immunoglobulin inventory. IL-1β is a cytokine produced by mononuclear phagocytes in response to injury and infection. IL-1β receptor activation leads to signal transduction related to that by the Toll-like receptors in the immune response to infection. Upon signal transduction to intracellular machinery (pathways include NFkB, Erk1/2, p38, Jnk1/2/3, and pI3 kinase pathways) via receptor activation, intracellular adapter molecules and IRAK protein kinases are activated, releasing cytokines, chemokines, and pro-inflammatory mediators. The main signaling pathways are similar in all mammals. IL-1β is proposed by the Applicant to be involved in the pathobiology of autoinflammatory syndromes (— — Possible involvement with — — b(4)

The results of the *in vitro* primary mechanism of action and binding studies showed that ACZ885 is specific for human and marmoset IL-1β only, amongst the vertebrate species tested, including mouse, rat, rabbit, rhesus and cynomolgus monkey. The results of an *in vitro* study using ELISA methodology showed no cross-reactivity of ACZ885 with IL-1 proteins with similar 3-dimensional structure but lacking primary sequence homology, including IL-1F1 (IL-1α), IL-1F3 (IL-1Ra), IL-1F4 (IL-18), IL-1F5, IL-1F6, IL-1F7, IL-1F8, IL-1F9, and IL-1F11 (IL-33) (Study RD-2008-00922). Additionally, no cross-reactivity was found to IL-1β from mouse, rat, rabbit, rhesus and cynomolgus monkey, as IL-1β from these species lack homology with that in human and marmoset (Studies RD-2000-02340, RD-2000-02157, RD-2008-00535). The critical residues of the antibody

that interact or bind with ACZ885 have been identified only in human and marmoset, in *in vitro* investigations. Therefore, the pivotal toxicology studies conducted in support of the safety of canakinumab clinical administration were performed in the marmoset.

Tissue Cross Reactivity Studies in Normal Human and Marmoset Tissues

Three studies were conducted to compare cross-reactivity profiles of ACZ885 produced by ——— ——— in normal and human tissues. b(4)
The results of the first study on the ——— antibody (Study # 0180142) showed qualitatively similar cross reactivity in human and marmoset tissues, that are consistent with known distribution of IL-1β expressing cells, although the cross-reactivity profile in the marmoset tissues was quantitatively less than in human tissues. The second study (Study # 0680267) on the ——— antibody (HAS+) (FITC-conjugated ACZ885) showed overall positive staining consistent with known human and marmoset tissue IL-1β expression, with similar cross-reactivity across tissues, cell types, stain intensity, frequency and subcellular localization. Minor differences were observed, however, with ACZ885 staining found in marmoset but not in human follicular and germinal cells in the ovary and in Leydig, Sertoli and gametogenic precursors in the testis. The third study (Study # 0770362), conducted using the ——— staining in normal tissue cryosections, also showed similar staining in human and marmoset tissues with respect to cell types stained and to subcellular localization, intensity and frequency, particularly those with known IL-1β expressed sites. There were several differences noted in distribution of low-grade cytoplasmic staining in epithelial tissues at high concentrations of ACZ885-FITC, with staining observed in human but not marmoset prostate and thyroid, and in marmoset but not human parathyroid and vas deferens. The overall comparability of ACZ885 binding and IL-1β bioactivity in marmoset and human responses support the selection marmoset for evaluation of ACZ885 toxicology.

b(4)

b(4)

A mouse anti-mouse ACZ885 surrogate, 01BSUR was developed for the evaluation of reproductive toxicity, juvenile toxicity and immunotoxicity in the mouse, due to the absence of cross-reactivity by ACZ885 with murine IL-1β. The surrogate antibody was produced in mice immunized with recombinant mouse IL-1β (mouse IgG1/κ isotype which has no interaction with Fcγ receptors, converted to IgG2a/κ isotype which is functionally equivalent to the human IgG1 isotype in binding to Fcγ receptors). 01BSUR binds IgG1 and IgG2a isotypes of mouse IL-1β with K_D values of 284 and 302 pM, respectively (Study RD-2008-00482). Both the parent (IgG1) and the isotype IgG2a inhibition mouse IL-1β activity via inhibition of IL-6 production in ——— fibroblasts (IgG1 IC_{50} = 31.3 pM, 01BSUR IC_{50} = 24.0 pM) (Study RD-2008-00482).

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Animal models of inflammation and neutrophil migration were used to investigate ACZ885 activity related to the proposed indication *in vivo*. Joint inflammation and architecture destruction induced in response to articular injection of ——— expressed human IL-1β was attenuated in a dose-dependent manner in mice given

b(4)

intraperitoneal (IP) ACZ885 2 hours before the articular injection (ED_{50} = 0.06 mg/kg at 72 hours, Study RD-2001-000743). In that study, proteoglycan synthesis in the cartilage was normalized by ACZ885 (ED_{50} = 0.53 mg/kg IP). ACZ885 also reduced —— cell engineered human IL-1β -induced neutrophil migration in the mouse airpouch (ED_{50} = 0.65 mg/kg IP, Study RD-2001-03103). In the rat, pre-treatment (0.5 h) with ACZ885 at the doses of 1 and 3 mcg/kg IV blocked fever induced by IV injection of human IL-1β (0.5 mcg/kg) (Study RD-2001-00777). No enhancement of human IL-1β pharmacodynamic activity by ACZ885 was observed in the rodent models. b(4)

Several *in vivo* studies in mouse models of arthritis were used to evaluate the pharmacologic activity of 01BSUR with that of ACZ885. The surrogate antibody, given twice weekly at 2-10 mg/kg by intraperitoneal injection (IP) after induction of paw swelling in response to collagen injection, significantly reduced the swelling. Paw swelling was prevented in that model by prior 01BSUR injection at 7.5 mg/kg IP twice weekly (Study RD-2008-00611). Based on the results, the maximum effective dose of 10 mg/kg once weekly 01BSUR was selected for administration in the subsequent reproductive toxicity studies in mice.

Study title: ***Cross Reactivity of ACZ885, a Human Monoclonal IgG1/κ Antibody Against Human IL-1β, with Normal Human Tissues and Normal Marmoset Tissues***

Key study findings:

- Cross-reactivity profile in marmoset tissues quantitatively less than but qualitatively similar to profile in human tissues
    - Cross reactivity in human tissues with mononuclear cells, mast cells, selected epithelial, neural, endocrine, and mesenchymal tissues was consistent with known distribution of IL-1β expressing cells
    - High affinity staining (at low concentrations) in human and marmoset
        - Mononuclear cell membrane and cytoplasm in multiple tissues and alveolar macrophages in lung
    - Low affinity staining (requiring high concentrations) in human and marmoset
        - Mast cell cytoplasmic granules in multiple tissues
        - Mesenchymal tissues (stroma, vascular and/or intrinsic smooth muscle cytoplasm)
        - Purkinje cells and/or glial cells in CNS
        - Glandular and ductular epithelium cytoplasm in human mammary gland and prostate, and in marmoset salivary gland, and epithelium in pancreas and salivary gland
        - Stratified squamous epithelium cytoplasm in human mammary gland, eye, skin, and thymus, and in marmoset eye and skin
        - Epithelium and granulose cell cytoplasm in ovary and testes in human, in Leydig cells in testis in marmoset
        - Mesangial cell cytoplasm in human and marmoset kidney glomerulus

- Reagents: Avidin-biotin-horseradish peroxidase complex (ABC) 3,3-diaminobenzidine HCl (DAB)

Satellite groups used for toxicokinetics or recovery: Not applicable
Age: Available for human and marmoset tissue donors, not provided
Weight: Not applicable
Unique study design or methodology:

- Biotinylated tertiary antibody procedure: endogenous peroxidase activity blocked using sodium azide (1 mM), glucose (10 mM) and glucose oxidase (1 U/mL) for 60 min at 35 deg.C to block endogenous peroxidase activity
- Avadin and biotin solutions changed sequentially (15 min each) with PBS protein solution (0.5% casein and 1 mg/ml heat aggregated rabbit IgG (5 mg/ml stock solution diluted in PBS) used to block non-specific antibody binding
- Tissues incubated for 60 minutes with antibody (ACZ885 or control articles) and then rinsed
- Secondary and biotinylated tertiary antibodies applied for 30 minutes
- Slides washed and DAB reacted
- Slides washed again and stained counterstained with hemotoxylin, dehydrated and covereslipped

Observations: Tests and Measurements

- Tissue or cell type identified by Pathologist
- Intensity of staining graded as follows: ± = equivocal, 1+ = weak, 2+ = moderate, 3+ = strong, 4+ = intense, and Neg = negative
- Slides stained for B2-microglobulin interpreted Positive or Negative

Results

- Intense staining of ACZ885 to positive control (Affi-Gel 10-IL-1B) bound with recombinant IL-1β at 100 and 10 mcg/ml, strong to intense staining at 1 mcg/ml: validation of study methodology
- No staining by negative control antibody to positive control (Affi-Gel 10-IL-1β at any concentration tested
- No staining under assay control conditions
- No staining in negative control tissue (human brain stem)
- No staining by other cellular elements with negative control antibody and under any assay control conditions
- Binding considered to be high-affinity, highly specific

- ACZ885 binding was identified in the following tissues:

Mononuclear Cells, Macrophages, Hofbauer Cells in Placenta: (High affinity binding)

- Human:

- Membrane and cytoplasm of mononuclear cells in interstitium, vessels, parenchyma in lung, lymph node (paracortex), spleen (periarteriolar lymphoid sheath and cords of Billroth [red pulp in spleen])
- Cytoplasm of alveolar macrophages in lung, macrophages and dendritic cells in tonsil and Hofbauer placental cells
- (placental tissue not studied)

- Marmoset:
  - Membrane of mononuclear cells in adrenal, kidney, liver, lung, lymph node paracortex, and periarteriolar lymphoid sheath and cords of Billroth
  - Cytoplasm of alveolar macrophages in lung

Mast Cells: Relatively low-affinity binding in human and marmoset, requiring high concentrations

- Human:
  - Cytoplasmic granules in mammary gland, eye, gastrointestinal tract (colon), esophagus, stomach, heart, lymph node, Fallopian tube, pancreas, pituitary, prostate, skin, striated muscle, testis, thymus, ureter, urinary bladder, and uterus
- Marmoset:
  - Intracytoplasmic granules in adrenal, eye, gastrointestinal tract (esophagus), lymph node, pancreas, peripheral nerve, pituitary, striated muscle and uterus

Mesenchymal Tissues (Stroma, vascular and/or intrinsic smooth muscle): Low affinity (requiring high test article concentrations)

- Human:
  - Cytoplasm of placental stroma, testis, thyroid, meningeal stroma in brain and spinal cord
  - Cytoplasm of vascular smooth muscle in brain, gastrointestinal tract (small intestine, stomach), heart, placenta, prostate, salivary gland, spinal cord, spleen, testis, thymus, thyroid, and tonsil
  - Cytoplasm of intrinsic smooth muscle in mammary gland, gastrointestinal tract (small intestine), skin, spleen and stomach
- Marmoset:
  - Cytoplasm of stroma in thyroid and meningeal stroma surrounding brain and spinal cord
  - Cytoplasm of vascular smooth muscle in brain (cerebellum)
- Qualitatively similar binding in human and marmoset smooth muscle, but quantitatively less (in frequency and intensity) binding in the marmoset

Purkinje Cells and/or Glial Cells: Low affinity binding, at high concentrations only

- Human:
  - Cytoplasm of Purkinje (cerebellum) and glial cells (cerebellum), glial cells in spinal cord, neurons in spinal cord
- Marmoset:
  - Cytoplasm of Purkinje (cerebellum) and glial cells (cerebellum, cerebrum-cortex) and glial cells in spinal cord

Glandular and Ductular Epithelium: Low affinity binding, requiring high concentrations

- Human:
  - Cytoplasm of acinal epithelium in mammary gland, prostate
- Marmoset:
  - Cytoplasm of salivary gland
  - Cytoplasm of ductular epithelium in pancreas and salivary gland

Stratified Squamous Epithelium: Low affinity binding

- Human:
  - Cytoplasm of stratified squamous epithelium in mammary gland, eye (cornea), skin (epidermis, adnexa, eccrine glands), and thymus (Hassall's corpuscles)
- Marmoset:
  - Eye (cornea) and skin (epidermis and adnexa)

Ovary, Testis: Low affinity binding requiring high concentrations

- Human:
  - Cytoplasm of epithelium and granulose (thecal/luteal) ovarian cells, Leydig cells, Sertoli cells and gametogenic precursors in testis
- Marmoset:
  - Leydig cells in testis
- Differences in binding patterns in human and marmoset ovary and testis likely due to species differences in maturity of tissue donors and related cyclicity in those tissues (IL-1β expression dependent on luteal phase in humans)

Mesangial Cells: Low affinity binding, at high concentrations only

- Human:
  - Cytoplasm of mesangial cells in kidney glomerulus
- Marmoset:
  - Cytoplasm of mesangial cells in kidney glomerulus
- IL-1β expression rare in normal human tissues, and therefore ACZ885 binding in the kidney likely due to increased expression caused by disease

Endocrine Tissues:

- Human:
  - Cytoplasm of follicular epithelial cells (low affinity) and/or C cells (higher intensity of reactivity)
- Marmoset:
  - Cytoplasm of follicular epithelial cells (low affinity) and/or C cells (higher intensity of reactivity)

Study title: ***Cross-Reactivity Study of ACZ885-FITC with Normal Human and Marmoset Tissues***

Key study findings:

- Positive staining consistent with known human and marmoset tissue IL-1β expression
- ACZ885-FITC staining similar in human and marmoset tissues, in cell type stained, intensity, frequency, and subcellular localization
- Equivocal to weak staining (low affinity, at high concentrations only) in human and equivocal to moderate staining in marmoset stromal cell interstitial fluid and cytoplasm in most tissues
- Intermediate to low affinity staining in marmoset cerebellar Purkinje cell cytoplasm
- Low affinity staining in both human and marmoset
    - Mononuclear cell (macrophages, mast cells) cytoplasm and/or cytoplasmic granules in interstitium and vessels, and in parenchyma in several tissues
        - Human small intestine, stomach, Kupffer cells in liver, lung, fallopian tube, parathyroid, peripheral nerve, placenta (Hofbauer cells), skin, spleen (periarteriolar lymphoid sheath and cords of Billroth), thymus, tonsil
        - Marmoset colon, esophagus, small intestine, kidney, liver Kupffer cells, lung, lymph node, placenta (Hofbauer cells), spleen (periarteriolar lymphoid sheath and cords of Billroth) and thymus
- Low to very low affinity staining (at high concentrations only) in human and marmoset:
    - Glial cell cytoplasm and/or cytoplasmic granules in cerebrum in human, cerebellum in marmoset, and in both human and marmoset retina, pituitary pituicytes (modified glial cells), spinal cord
    - Epithelial cytoplasm and/or cytoplasmic granules in human and marmoset: hepatocytes, fallopian tube, pituitary, placenta trophoblasts, prostate, salivary gland thymus, follicular and parafollicular cells in thyroid, ureter, and uterus
        - Additionally, in mammary gland ducts in human, and esophagus, biliary duct, ovary follicular cells and granulosa (thecal/luteal cell cytoplasm, germinal epithelium, pancreas, parathyroid, urinary bladder, cervix, and in marmoset
    - Hematopoietic progenitor cell cytoplasm in bone marrow of one human donor only, and in marmoset
- Staining also observed in human and marmoset eye lens and luminal proteinic material in placenta and prostate
- Staining observed in marmoset Leydig and Sertoli cell, and gametogenic precursor cell cytoplasm in testis
- Cross-reactivity differences: staining in ovarian follicular and germinal cells, Leydig, Sertoli and gametogenic precursors in testis in marmoset but not human

using ACZ885-FITC and therefore, the EnVision with rabbit anti-FITC secondary antibody procedure was used in the present study

Satellite groups used for toxicokinetics or recovery: Not applicable

Unique study design or methodology: Unfixed tissue samples placed in molds, frozen in OCT embedding medium, sectioned (5 mcm), and fixed in acetone. Prior to staining slides were fixed in 10% neutral buffered formalin. ACZ885-FITC and the negative control HuIgG1-FITC were used to stain full panel of tissues from normal human and marmoset donors. Antibody dilutions compared to positive control to determine minimal specific staining concentration, with minimum set at 1:2400 mcg/ml. Indirect immunoperoxidase procedure performed, with procedures (staining, antibody dilutions and controls) qualified in preliminary staining runs. Fixed cryosections were rinsed in phosphate-buffered saline, 0.3M NaCl, pH 7.2, and endogenous peroxidase blocked using incubation with peroxides solution. Protein block used to decrease nonspecific binding, followed by application of unconjugated secondary antibody (rabbit anti-fluorescein), double rinse, and treatment with peroxidase-labeled goat anti-rabbit IgG polymer. Polymer was rinsed twice and the slides were counterstained with hematoxylin, blued in saturated lithium carbonate, dehydrated, cleared (xylene) and coverslipped.

Observations by the Study Pathologist:

- Tissue or cell type identified by Pathologist
- Intensity of staining graded as follows: ± = equivocal, 1+ = weak, 2+ = moderate, 3+ = strong, 4+ = intense, and Neg = negative
- Staining frequency of cell type identified as very rare (<1% cells of the specific type), rare (1-5%), rare to occasional (>5-25%), occasional (>25-50%), occasional to frequent (>50-75%), frequent (>75-100%)
- Slides stained for B2-microglobulin interpreted Positive or Negative
- Reactivity judged as high-affinity if tissue stained by 2 lower test article concentrations, and low-affinity if reactivity only at highest 2 concentrations tested, very low affinity if staining only at the highest concentration, and intermediate-affinity in tissues in which intensity or frequency of staining was decreased at low concentrations when compared to high concentration staining

Results: Positive ACZ885-FITC staining observed in the following tissues:

Human:

- Stromal cell interstitial fluid and cytoplasm in most tissues (equivocal to weak suggesting low affinity, only at high concentration)
- Cerebrum glial cell cytoplasm and/or cytoplasmic granules, retina (eye), pituitary pituicytes (modified glial cells), spinal cord (low affinity)
- Mononuclear cells (macrophages and mast cells) cytoplasm and/or cytoplasmic granules in interstitium, vessels or parenchyma of small intestine, stomach, Kupffer cells in liver, lung, fallopian tube, parathyroid, peripheral nerve, placenta (Hofbauer cells), skin, spleen (periarteriolar lymphoid sheath and cords of Billroth), thymus, tonsil (low-affinity)

- Epithelial cytoplasm and/or cytoplasmic granules in mammary gland ducts, hepatocytes, fallopian tube, pituitary, placenta (trophoblasts), prostate, salivary gland, thymus, follicular and parafollicular cells in thyroid, ureter, uterus (very low affinity)
- Hematopoietic progenitor cell cytoplasm in bone marrow (one donor, very low affinity)
- Eye lens
- Luminal proteinic material in prostate and placenta

Marmoset:

- Stromal cell interstitial fluid and cytoplasm in most tissues (equivocal to moderate staining with very low affinity)
- Glial cell cytoplasm and/or cytoplasmic granules in cerebellum, cerebrum, retina, pituicytes (pituitary modified glial cells), spinal cord (Low affinity)
- Cerebellum Purkinje cell cytoplasm (intermediate to low affinity)
- Spinal cord neuronal cytoplasm and/or cytoplasmic granules (very low affinity)
- Mononuclear cell (macrophage, mast cell) cytoplasm and/or cytoplasmic granules in interstitium, vessels, parenchyma in several tissues (colon, esophagus, small intestine, kidney, liver Kupffer cells, lung, lymph node, placenta (Hofbauer cells), spleen (periarteriolar lymphoid sheath and cords of Billroth), thymus) (low affinity)
- Epithelium cytoplasm and/or cytoplasmic granules in esophagus, hepatocytes, biliary duct, ovary follicular cells and germinal epithelium, fallopian tube, pancreas, parathyroid, pituitary, placent (trophoblasts), prostate, salivary gland, thymus, follicular and parafollicular cells in thyroid, ureter, urinary bladder, uterus, cervix (very low affinity)
- Epithelium and granulosa (thecal/luteal) cell cytoplasm in ovary
- Leydig and Sertoli cell, and gametogenic precursor cell cytoplasm in testis
- Hematopoietic progenitor cell cytoplasm in bone marrow (very low affinity)
- Lens of eye
- Placenta and prostate luminal proteinic material

Conclusions:

- Positive staining consistent with known human and marmoset tissue IL-1β expression
- ACZ885-FITC staining staining similar in human and marmoset tissues, in cell type stained, intensity, frequency, and subcellular localization
- Differences in staining in ovary follicular and germinal cells, Leydig, Sertoli and gametogenic precursors in testis in marmoset but not human

Study title: ***Cross-Reactivity Study of FITC-Labeled ACZ885 (HAS-) with Normal Human and Marmoset Tissues***

Key study findings:

- Positive staining consistent with known human and marmoset tissue IL-1β expression
- Equivocal to moderate staining in stromal cell interstitial fluid and stromal cell cytoplasm in most tissues, similar in human and marmoset
- Equivocal (human) or weak (marmoset) to moderate staining in intravascular fluid in brain and esophagus, and in
  - Human bone marrow and lymph node
  - Marmoset pancreas
- Equivocal to weak (both human and marmoset) staining in glial cell cytoplasm and/or cytoplasmic granules in spinal cord
- Equivocal (human) or weak (marmoset) to moderate (marmoset) or strong (human) staining in mononuclear cell (macrophages, mast cells) cytoplasm and/or cytoplasmic granules in interstitium, vessels, or parenchyma in multiple tissues, including colon, lung, lymph node, salivary gland, spleen (periarteriolar lymphoid sheath, cords of Billroth), thymus, and tonsil, and in
  - Human brain, ovary, thyroid
  - Marmoset esophagus, small intestine, stomach, kidney
- Equivocal to weak (marmoset) or moderate (human) staining in epithelial cytoplasm and/or cytoplasmic granules in salivary gland, thymus, and in
  - Human pituitary, prostate, thyroid follicular and parafoolicular cells
  - Marmoset parathyroid, vas deferens
- Equivocal to weak (human, in one donor only) or moderate (marmoset) staining in hematopoietic progenitor cell cytoplasm in bone marrow
- ACZ885-FITC staining staining similar in human and marmoset tissues, in cell type stained, intensity, frequency, and subcellular localization
- Differences in staining distribution of low-grade cytoplasmic staining in epithelial tissues (low affinity):
  - Prostate, thyroid in human but not marmoset
  - Parathyroid and vas deferens in marmoset but not human

Study no.: [redacted] Study # IM1496, Novartis Study # 0770362 b(4)

Conducting laboratory and location: [redacted]

Date of study initiation: September 20, 2007
GLP compliance: Yes
QA report: yes (x) no ( )
Drug FITC-labeled ACZ885 (ACZ885-FITC HAS-), **lot #** E-35126/110, **and % purity:** >95%

anti-fluorescein), double rinse, and treatment with peroxidase-labeled goat anti-rabbit IgG polymer. Polymer was rinsed twice and the slides were counterstained with hematoxylin, blued in saturated lithium carbonate, dehydrated, cleared (xylene) and coverslipped.

Observations

- Tissue or cell type identified by Pathologist
- Intensity of staining graded as follows: ± = equivocal, 1+ = weak, 2+ = moderate, 3+ = strong, 4+ = intense, and Neg = negative
- Staining frequency of cell type identified as very rare (<1% cells of the specific type), rare (1-5%), rare to occasional (>5-25%), occasional (>25-50%), occasional to frequent (>50-75%), frequent (>75-100%)
- Slides stained for B2-microglobulin interpreted Positive or Negative
- Reactivity judged as high-affinity if tissue stained by 2 lower test article concentrations, and low-affinity if reactivity only at highest 2 concentrations tested, very low affinity if staining only at the highest concentration, and intermediate-affinity in tissues in which intensity or frequency of staining was decreased at low concentrations when compared to high concentration staining

Results:

Human

- Stromal cell interstitial fluid and stromal cell cytoplasm in most tissues (equivocal to moderate staining)
- Intravascular fluid in bone marrow, brain (cerebrum [cortex], esophagus, lymph node (equivocal to moderate staining)
- Glial cell cytoplasm and/or cytoplasmic granules in spinal cord (equivocal to weak staining)
- Mononuclear cell (macrophage, mast cell) cytoplasm and/or cytoplasmic granules in interstitium, vessels, parenchyma in several tissues (brain, colon, lung, lymph node, ovary, salivary gland, spleen (periarteriolar lymphoid sheath, cords of Billroth), thyroid, thymus, tonsil (equivocal to strong staining)
- Epithelial cytoplasm and/or cytoplasmic granules of pituitary, prostate, salivary gland, thymus, thyroid follicular and parafollicular cells (equivocal to moderate staining)
- Hematopoietic progenitor cell cytoplasm in bone marrow (one donor, equivocal to weak staining)

Marmoset

- Stromal cell interstitial fluid and cytoplasm in most tissues (equivocal to moderate staining)
- Intravascular fluid in brain, esophagus, pancreas (weak to moderate)
- Glial cell cytoplasm and/or cytoplasmic granules in spinal cord (equivocal to weak)
- Mononuclear cells (macrophages, mast cells) cytoplasm and/or cytoplasmic granules in intersitium, vessels, or parenchyma in multiple tissues: colon,

esophagus, small intestine, stomach, kidney, lung, lymph node, salivary gland, spleen (periarteriolar lymphoid sheath and cords of Billroth), thymus, tonsil (weak to moderate)
- Epithelial cytoplasmic and/or cytoplasmic granules of parathyroid, salivary gland, vas deferens (adjacent to testis), thymus (equivocal to weak)
- Hematopoietic progenitor cell cytoplasm in bone marrow (equivocal to moderate)

Conclusions:
- Positive staining consistent with known human and marmoset tissue IL-1β expression
- ACZ885-FITC staining staining similar in human and marmoset tissues, in cell type stained, intensity, frequency, and subcellular localization
- Differences in staining distribution of low-grade cytoplasmic staining in epithelial tissues (low affinity):
  - Prostate, thyroid in human but not marmoset
  - Parathyroid and vas deferens in marmoset but not human

Mouse anti-mouse IL-1β antibody surrogate 01BSUR

The mouse anti-mouse IL-1β surrogate 01BSUR was developed for evaluation of reproductive toxicity, juvenile toxicity and immunotoxicity in the CD-1 mice, due to the absence of cross-reactivity by ACZ885 with murine IL-1β. The surrogate antibody was produced in mice immunized with recombinant mouse IL-1β (mouse IgG1/κ isotype which has no interaction with Fcγ receptors, converted to IgG2a/κ isotype which is functionally equivalent to the human IgG1 isotype in binding to Fcγ receptors). IgG1 and IgG2a (01BSUR) mAb isotypes bind mouse IL-1β with K_D values of 284 and 302 pM, respectively (Study RD-2008-00482). Both the parent (IgG1) and the isotype IgG2a inhibits mouse IL-1β activity as indicated by inhibition of IL-1β-induced production in —— fibroblasts (IgG1 IC_{50} = 31.3 pM, 01BSUR IC_{50} = 24.0 pM) (Study RD-2008-00482). b(4)

The proposed mechanism of action by ACZ885 is via high affinity binding with human IL-1 with association rate constants of 1.37-1.57 $M^{-1} \times sec^{-1} \times 10^6$ and dissociation rate constants of 3.70-8.19 $sec^{-1} \times 10^{-5}$. The results of studies RD-200-02340 and RD-2006-01434 demonstrated equilibrium binding constants (K_D) from 26.5-60 pM in human and 22.8 pM in marmoset (Study RD-2001-00650)). Upon binding to and inactivation of the IL-1 receptor IL-1RI and IL-1RII, ACZ885 effectively prevents the interaction of IL-1β with these receptors, and subsequent production of interleukin 6 (IL-6) in human primary fibroblasts in a dose dependent manner (IC_{50} = 30.7-63.0 pM (Studies RD-2000-02423, RD-2000-02423, RD-2006-01434, RD-2008-00863). Comparative evaluation (Study RD-2001-00650) showed similar neutralizing activity of IL-1β by ACZ885 in human (IC_{50} = 35 ± 13 pM) and marmoset (IC_{50} = 95 ± 14 pM).

Drug activity related to proposed indication: *In vivo* studies

There are no nonclinical models available for the proposed indication CAPS, though several experiments were done to evaluate the ability of ACZ885 to attenuate inflammation induced by IL-1β. Several animal models of inflammation and neutrophil migration were tested, for ACZ885 blockade of IL-1β -induced cytokine activity. In one pharmacodynamic activity study in mice, joint inflammation and architecture destruction were induced using articular injection of a mouse —— cell line engineered to express and secrete human IL-1β. The results of the study showed intraperitoneal (IP) ACZ885 dose-dependently attenuated the joint inflammation and destruction when administered 2 hours before articular injection of the human IL-1β (ED50 = 0.06 mg/kg at 72 hours after articular IL-1β). Further, proteoglycan synthesis in the cartilage was normalized by the ACZ885 (ED_{50} = 0.53 mg/kg (Study RD-2001-000743). There was a dose-related reduction of —— cell engineered human IL-1β -induced neutrophil migration into the mouse airpouch by ACZ885 (ED_{50} = 0.65 mg/kg IP) following the airpouch IL-1β -injections (Study RD-2001-03103). The results of one study in rat showed intravenous (IV, administered at 1 and 3 mcg/kg, 0.5 hours before fever induction) ACZ885 blockade of fever induced by IV injection of human IL-1β (0.5 mcg/kg) (Study RD-2001-00777). The results of the pharmacodynamic activity studies in rodent models demonstrated inhibition of human IL-1β activity by ACZ885 by the IP and IV routes, without enhancing human IL-1β pharmacodynamic activity.

b(4)

b(4)

The pharmacologic activity by 01BSUR was shown to be comparable to that of ACZ885 on human IL-1β in several *in vivo* studies in mouse models of arthritis. There was a statistically significant reduction in paw swelling in response to collagen injection by 01BSUR at 2-10 mg/kg IP twice weekly, and 01BSUR was further shown to prevent the development of the paw swelling when given prior to the collagen injections at 7.5 mg/kg IP twice weekly. The results of the murine inflammation model studies suggested a maximum effective dose of 10 mg/kg once weekly 01BSUR in mice (Study RD-2008-00611).

2.6.2.3 Secondary pharmacodynamics

No studies were conducted to investigate secondary pharmacodynamic effects by canakinumanb. No non-specific tissue binding was found in the *in vitro* binding and cross-reactivity studies, and there were no clear treatment-related effects in the toxicology studies that would indicate secondary pharmacologic activity by this agent. There is a potential for Fcγ receptor binding that was demonstrated *in vitro* (Studies RP00471A and RD-2008-01113), although no binding by ACZ885 to cell surface-bound antigen, which is required for antibody dependent cellular cytotoxicity was found. No binding of ACZ885 to IL-1β -producing human CD14+ monocytes was found and there was no recruitment to human monocytic cells of the C1q complement pathway.

Therefore, no antibody dependent cellular cytotoxicity or complement dependent cytotoxicity is expected to be associated with ACZ885.

Additionally, there was no clear and compelling evidence of immunosuppression with ACZ885 in IL-1R-deficient mice *in vivo*, although IL-1 $_{B}$ is involved in enhancement of immune function of the Th2 T cell subset. No inhibition of human mixed lymphocyte reaction was observed, and therefore, no suppression of T cell function is anticipated.

2.6.2.4 Safety pharmacology

No studies were conducted by the Applicant on ACZ885 specifically to address safety pharmacology parameters; safety pharmacology studies are generally not required for investigation and registration of biologic agents. Primary drug effects on the central nervous, cardiovascular, pulmonary, renal, and gastrointestinal systems, are not expected, although toxicity in these systems that is secondary to inflammatory changes (e.g. inflammatory cell infiltration) and/or infection remain a theoretical concern and have been noted in the results of nonclinical studies on other agents that inhibit IL-1β. Standard Safety Pharmacology parameters were included in the 43-day and 13-week subcutaneous (SC) toxicology studies, and in the 4- and 26-week intravenous (IV) toxicology evaluations in marmoset, and are summarized below (refer to **Section 2.6.6.3 Repeated Dose Toxicity** under **Toxicology** below, for specific methods used in the toxicology studies in marmoset).

Neurological effects: No treatment-related effects on central nervous system function or structure were found in the toxicology studies in marmoset in the evaluations of clinical signs and in the histopathology examinations.

Cardiovascular effects: There were no treatment-related effects on blood pressure and on the cardiovascular system, including QT interval changes in the toxicology study assessments in marmoset using standard measurements of blood pressure, electrocardiography and histopathology examination. The results of the cross-reactivitiy studies showed very weak binding in human cardiac tissue, and therefore no hERG channel interaction is anticipated. However, toxicity secondary to inflammatory changes and/or infection remain a theoretical concern and have been observed in nonclinical studies on other agents that inhibit IL-1$_{B}$.

Pulmonary effects: No adverse treatment-related effects were found on pulmonary function and morphology in the standard evaluations performed in the toxicology studies in marmoset.

Renal effects: There were no treatment-related effects on renal function and morphology in the clinical pathology and histopathology evaluations in the toxicology studies in marmoset.

Gastrointestinal effects: There were no treatment-related gastrointestinal effects in the clinical signs and histopathology examinations included in the toxicology studies in marmoset.

Abuse liability: The potential for canakinumab abuse is considered to be negligible, due to the absence of CNS effects or expected penetration of the blood-brain barrier. No studies were conducted on ACZ885 to evaluate abuse liability.

2.6.2.5 Pharmacodynamic drug interactions

Studies to investigate potential drug interactions are not generally required for biologic agents, and were not conducted for ACZ885. No adverse pharmacodynamic drug interactions with canakinumab are expected (see discussion under **OVERALL SUMMARY, CONCLUSIONS AND RECOMMENDATIONS**).

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

The results of the pharmacokinetic and toxicokinetic analyses discussed in this section are presented in tabular form for reference, under **2.6.4.10 Tables and Figures to Include Comparative TK summary**, below.

2.6.4.3 Absorption

ACZ885 pharmacokinetic parameters were assessed in CD-1 mice using 01BSUR and in marmosets using ACZ885 single and repeated dose intravenous (IV) and subcutaneous (SC) administration in specific pharmacokinetic studies and as part of the toxicokinetic assessments in the toxicology studies. Additionally, six studies were conducted to investigate and validate the analytical (ELISA) and immunogenicity (surface plasmon resonance spectroscopy) methodology used in these studies for both ACZ885 and 01BSUR. Comparative pharmacokinetics studies were conducted in marmosets, to bridge the drug substances produced by manufacturing changes using different cell lines during the course of product development, from the ACZ885 lyophilisates produced using the ——— in the toxicology studies and clinical trials, to the current to-be-marketed drug product produced by the ——— Comparative pharmacokinetics was examined in marmoset monkey and human. b(4)

ACZ885 toxicokinetic parameters by the SC route in the marmoset were examined in general toxicology (13-week SC Toxicity Study # 0470033, 13-week SC Batch Comparison Study # 0770373) and embryo-fetal development (Study #480152) studies. These evaluations demonstrated approximately dose-proportional increases in exposure in the the dose range of 5-150 mg/kg, without gender differences. Peak plasma levels (Cmax) occured approximately 12-120 hours after administration. The Cmax values were 22-35 mcg/ml at 5 mg/kg single dose, and approximately 488 mcg/ml at the highest SC dose tested of 150 mg/kg given twice weekly. Plasma exposures were 2-3 times

higher after repeated administration for 13 weeks than the observed concentrations after single doses, suggesting accumulation. The accumulation half-life was 24-40 hours. The Day 1 and Week 14 AUC values in the 13-week SC Toxicity Study are presented in the following table, for comparison (from the original BLA submission):

ACZ885 AUC Values (±SD) in the 13-Week SC Toxicity Study in the Marmoset (Study #0470033)

AUC (mcg.h/ml)		15 mg/kg twice weekly		50 mg/kg twice weekly		150 mg/kg twice weekly	
		Males	Females	Males	Females	Males	Females
$AUC_{0\text{-}96h}$	Day 1	8344 (1345)	6890 (1053)	31726 (5118)	26823 (2153)	76591 (8961)	75422 (17299)
$AUC_{0\text{-}1368h}$	Week 14	Not available	Not available	Not available	Not available	462113 (7659)	342748 (142962)
$AUC_{0\text{-}24}$	Day1	1873 (436)	1485 (379)	6344 (789)	5487 (887)	13197 (1748)	14306 (3464)
$AUC_{0\text{-}24}$	Week 14	7144 (2574)	5151 (891)	24673 (7350)	20930 (6218)	46954 (6933)	50170 (10867)

$AUC_{0\text{-}72h}$ exposure values were similar in the 13-Week Batch Comparison Study, comparing exposure to ACZ885 manufactured using the ——— , at the dose of 150 mg/kg twice weekly, and when comparing the AUC values at 150 mg/kg twice weekly in the SC toxicity study in marmoset in the table above. Additionally, exposure increased with repeated administration, demonstrating accumulation and/or FcRn receptor saturation by both process materials. $AUC_{0\text{-}72h}$ (mcg.h/ml) values (± CV%, coefficient of variation) were 57487.9 (± 34.2) mcg.h/ml in males and 62102.6 (± 21.4) mcg.h/ml in females given Formulation A (———), and 61656.1 (±15.8) mcg.h/ml in males and 60075.2 (±38.4) mcg.h/ml in females given Formulation B (———) on Day 1. The AUC analyses in Week 13 of dosing showed $AUC_{0\text{-}72h}$ values of 172815 (±18.4) mcg.h/ml in the males and 179980 (±21.9) mcg.h/ml in the females given Formulation A, and 143097 (-) mcg.h/ml in the males and 174530 (±16.9) mcg.h/ml in the females administered Formulation B.

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SC ACZ885 bioavailability was approximately 60% in marmoset, determined by plasma concentration comparison to that by the IV administration at the same doses.

01BSUR pharmacokinetic parameters were evaluated in a separate pharmacokinetic study and in the toxicokinetic assessments in the immunotoxicity study in CD-1 mouse. The results, comparing values determined at the single IV 01BSUR doses of 10 (LD), 50 (MD) and 150 (HD) mg/kg (Study # 0500653) and single SC ACZ885 dose of 10 mg/kg (Studies 0430015, 0430016, and 0310114) showed peak serum concentrations (Cmax) of 69.2 mcg/ml after SC and 124.4, 97.8, and 167.7 mcg/ml after IV 01BSUR at the LD, MD, and HD, respectively. Peak serum 01BSUR levels were observed at 24 hours (Tmax) after the SC injection. The results of the toxicokinetic assessments in the immunotoxicity study in CD-1 mice administered 01BSUR weekly for 28 days at 10, 50, and 150 mg/kg SC showed peak serum levels at 24 hours (Tmax) across doses except for the LD females, which showed a Tmax of 168 hours. The peak plasma concentrations were 329 (males) and 408 (females) mcg/ml, 1810 (males) and 1990 (females), and 3880 (males) and 4610 (females) at 10, 50, and 150 mg/kg, respectively.

The canakinumab pharmacokinetic profile demonstrated in the clinical studies was shown to be similar to that in marmosets. In the clinical studies, canakinumab showed SC

bioavailability of approximately 66.6%, approximately dose-linear increases in exposure, low volume of distribution and low clearance, and a long half life of approximately 21-30 days. However, accumulation with repeated administration was not observed in the clinical studies.

2.6.4.4 Distribution

Low steady state volume of distribution (Vss) values were observed after intravenous (IV) and subcutaneous (SC) ACZ885 and 01BSUR administration in the pharmacokinetic and toxicokinetic assessments in mice and marmosets. The mean Vss values approximated serum volume, indicating minimal distribution outside of circulation.

The mean Vss ranged from 58.5 ml/kg after single IV administration at 5 mg/kg, comparable to serum volume of 60 ml/kg in the marmoset. In comparison, mean volume of distribution (Vss) in rhesus monkey administered single 2 mg/kg IV injections was 87.4 ml/kg (Study # R01-1005).

The mean volume of distribution (Vd) in CD-1 mice administered 01BSUR at doses of 10, 50, and 150 mg/kg weekly for 28 days was 89.4 ml/kg across dose levels (Study #0500653).

ACZ885 placental transfer was demonstrated in the Embryo-Fetal Development study (#480152) in marmosets. The results of the toxicokinetic evaluations (presented below, from the original BLA submission) showed fetal serum concentrations of 7.0%-8.7% and amnionic fluid concentrations of 1.8%-2.0% the mean concentration in maternal serum, at the doses of 15, 50 and 150 mg/kg SC. Maternal and fetal serum and amnionic fluid concentrations increased in a dose-proportional manner.

Table 5-1 Mean toxicokinetic parameters of ACZ885 in marmoset maternal serum on Day 109

Dose	15 mg/kg			50 mg/kg			150 mg/kg		
TK parameters	mean	CV%	n	mean	CV%	N	mean	CV%	n
T_{max}	25.7	44.3	14	27.4	31.8	14	30.9	36.5	14
C_{max}	322	19	14	1220	21.5	14	3560	32.6	14
C_{max}/Dose	21.5	19.1	14	24.5	21.5	14	23.7	32.5	14
AUC(0-48h)	13900	20.8	14	52200	22.5	14	141000	26.9	14
AUC(0-48h)/Dose	929	20.8	14	1040	22.4	14	939	26.8	14

Units: T_{max} (h), C_{max} (µg/mL), C_{max}/Dose ((µg/mL)/(mg/kg)), AUC(0-48) (h*µg/mL), AUC(0-48)/Dose ((h*µg/mL)/(mg/kg)).

n = number of determinations

Table 5-2 Mean ACZ885 concentrations in marmoset amniotic fluid and fetal serum

Dose	0 mg/kg			15 mg/kg			50 mg/kg			150 mg/kg		
	mean	CV%	n	mean	CV%	n	mean	CV%	n	mean	CV%	n
Fetal serum	0.000	-	20	29.1	38.8	22	110	30	23	246	36.4	18
Fetal amniotic fluid	0.000	-	11	6.14	57	14	27.7	31.2	14	62.6	34.3	14

Mean concentration expressed in µg/mL

n = number of determinations

01BSUR placental transfer was demonstrated in the Embryo-Fetal Development study in mice dosed by SC injection (Study # 0680148). The surrogate antibody was used in the mouse studies because the fully human monoclonal anti-human IL-1β antibody, ACZ885 demonstrated cross-reactivity with the marmoset IL-1 $_B$ only; 01BSUR demonstrated similar *in vivo* biologic activity and *in vitro* potency on mouse IL-1 $_B$ to that by ACZ885 on human IL-1 $_B$. In the embryo-fetal study, maternal serum 01BSUR concentrations increased in a dose-proportional manner across the dose range of 15-150 mg/kg SC following 3 injections on days 6, 11, and 17. However, the mean serum levels were lower after the 2nd and 3rd doses than after the 1st dose. The fetal serum levels were 24.9, 67.3, and 136 mcg/ml at the maternal doses of 15, 50, and 150 mg/kg/week, respectively) and maternal serum levels were 2.29, 2.56, and 15.4 mcg/ml across the same dose range, respectively after two weeks of 01BSUR administration, demonstrating 9-26 times higher fetal than maternal exposure.

01BSUR showed placental and possibly lactational transfer in the Peri- and Postnatal Development study in mice (Study # 068150), although pup exposure may have been due to the long half life of placentally transferred drug substance. The maternal serum concentrations on post-partum day (PPD) 49 were 7.57, 23.6, and 85 mcg/ml at the doses of 15, 50, and 150 mg/kg SC, respectively, administered on gestation days (GD) 6 and 13 and on PPD 2. The F1 pups showed serum concentrations of 44.2, 142, and 490 mcg/ml in the males and 39.2, 142, and 300 mcg/ml in the females on the same sampling day, demonstrating 4-6 times higher concentrations in the pups than in the maternal mice.

2.6.4.5 Metabolism

No studies on ACZ885 metabolism were conducted. Canakinumab is expected to be metabolized by proteolytic degradation, known to be the predominant mechanism of elimination of immunoglobulins in general. No active canakinumab metabolites are predicted.

2.6.4.6 Excretion

No studies were conducted to examine canakinumab excretion. However, it is expected that elimination is predominantly via proteolytic catabolism within cytoplasmic endosomes. Canakinumab is cleared from circulation slowly due to FcRn receptor binding which protects the protein from proteolysis, and recycles antibody from endosome to cell surface (Wang W, *et al.* Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin. Pharmacol. Ther. 84(5):548-558, 2008). Total systemic serum clearance was 0.45 ml/h/kg in marmoset at 5 mg/kg IV (Study # R01-957). In that study, the distribution half-life was 10.8 hours, and terminal phase half-life was 104 hours. The mean terminal half-life was approximately 6.5-8 days in marmosets across studies, and 15-17.4 days in rhesus monkeys (Study # R01-1005). No increases in clearance were observed with increased duration of treatment in the toxicology studies, suggesting no anti-ACZ885 antibody formation.

The mean terminal half-life of 01BSUR was 319 hours (13 days) and CL/F was 6 ml/kg/d after a single 10 mg/kg IV injection in the pharmacokinetics study in mice (Study #0500563). Clearance of 01BSUR was estimated at 3.66 ml/kg/d and the terminal half-life was 17 days in the immunotoxicity study in CD-1 mice (Study # 0500653) administered 10, 50, and 150 mg/kg weekly by SC injection for 28 days, comparable to the observed half-life of 13 days in Study #0500563.

2.6.4.7 Pharmacokinetic drug interactions

No studies were conducted to explore potential pharmacokinetic drug interactions with canakinumab. No interactions are expected, as canakinumab does not interact with nor is metabolized with cytochrome P450 isoenzymes.

2.6.4.8 Other Pharmacokinetic Studies

Pharmacokinetic bridging studies were conducted in marmosets to compare ACZ885 produced by different manufacturing cell lines during product development. The manufacturing changes during development, and clinical and nonclinical studies using the series of products produced are presented in the following table (from the original BLA submission):

Table 3-3 Summary of the main manufacturing changes for drug substance and drug product during development, the corresponding comparability exercises and the material used per clinical study or program

Item	
Production cell line	
Drug substance concentration	
Drug product strength	
Drug substance manufacturing site	
Drug product manufacturing site	
Drug substance scale (approximate working volume)	
Drug substance manufacturing change	
Comparability exercise	
PKPD Comparison in Humans	
Toxicology Test	
Material per clinical study	
Use of ACZ885 batches	

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In Study DMPK R0600200, the marmosets received single dose (5 mg/kg SC) ACZ885 from Process A (———) or from Process B (———), with a 43-day PK evaluation period after dosing. The results of the Process A and Process B substance comparisons are presented in the following table (from the original BLA submission):

b(4)

Table 3-4 Arithmetic Mean (SD) ACZ885 Plasma Pharmacokinetic Parameters Following a Single Subcutaneous Dose of 5 mg/kg — derived ACZ885 or a Single Subcutaneous Dose of — derived ACZ885

b(4)

	5 mg/kg — derived ACZ885	5 mg/kg — derived ACZ885
Parameters	(N=14)	(N=16)
C_{max} (ng/mL)	29,607 (10717)	31,863 (8573)
t_{max}[3] (day)	3.00 (0.33-14.0)	3.00 (0.33-5.00)
AUC_{last} (ng.day/mL)	279,798 (85879)	302,841 (85844)
AUC_{∞} (ng.day/mL)	289,403 (86046)	312,818 (92040)
CL/F (L/day/kg)	0.0189 (0.0061)	0.0173 (0.0048)
$t_{1/2}$ (day)	7.07 (1.83)	6.33 (1.91)

[3]Representative of median (range)
Source: [DMPK R0600200]

Study DMPK R0700526 compared pharmacokinetic parameters of ACZ885 — manufactured using Process B — with 2 ACZ885 formulations using ACZ885 manufactured under Process C (— in marmosets given single dose 5 mg/kg injections. Blood samples were collected for analysis for 43 days after dosing. The results of this study are presented in the following table (from the original BLA submission):

b(4)

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Table 3-6 **Arithmetic Mean (SD) ACZ885 Serum Pharmacokinetic Parameters Following a Single Subcutaneous Dose of 5 mg/kg Product type C or a Single Subcutaneous Dose of liquid formulation of Product type C or a Single Subcutaneous Dose of Product type B**

Parameters	Product type B [redacted] (N=14)	Product type C (N=13)	Liquid from of Product type C drug substance [redacted] (N=14)
C_{max} (µg/mL)	39.8 (6.59)	35.1 (6.26)	35.5 (5.59)
T_{max}[a] (day)	2.00 (1.00-4.00)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
AUC_{last} (µg.day/mL)	379 (74.6)	340 (79.4)	324 (71.7)[b]
AUC_{∞} (µg.day/mL)	383 (74.5)	347 (79.5)	333 (78.7)[b]
CL/F (L/day/kg)	0.0135 (0.0025)	0.0151 (0.00348)	0.0158 (0.0036)[b]
$t_{1/2}$ (day)	4.57 (0.942)	4.67 (1.10)	4.51 (0.730)[b]

[a] median (range); [b] n=13

Source: [DMPK R0700526-1]

b(4)

The ratios of geometric means of test and reference and their associated 90% confidence intervals for the pharmacokinetic parameters of ACZ885 following a single s.c. dose of 5 mg/kg ACZ885 [redacted] with reference to a single s.c. dose of 5 mg/kg [redacted] are summarized in Table 3-7.

b(4)

Table 3-7 **Ratios of Geometric Means and 90% Confidence Intervals for the Pharmacokinetic Parameters of ACZ885 Following a Single Subcutaneous Dose of 5 mg/kg of [redacted] With Reference to a Single Subcutaneous Dose of 5 mg/kg of [redacted]**

Parameter	Test[a]	Test[b]	Ref[c]	Ratio (%) Test[a]/ Ref[c]	90% CI for Ratio (Test[a]/ Ref[c])	Ratio (%) Test[b]/ Ref[c]	90% CI for Ratio (Test[b]/ Ref[c])
C_{max} (µg/mL) (n=12)	35.2	35.3	40.0	88.00	81.47 - 95.06	88.43	81.93 - 95.45
AUC_{last} (µg.day/mL) (n=12)	338	326	379	89.36	84.20 - 94.83	86.08	81.11 - 91.36
AUC_{∞} (µg.day/mL) (n=12)	344	334	382	90.07	84.60 - 95.90	87.43	82.12 - 93.08

[redacted]

b(4)

Source: [DMPK R0700526-1]

No differences in ACZ885 pharmacokinetic parameters were found in the studies comparing the test article produced by the [redacted] used in the early clinical trials and nonclinical toxicology studies (Product A, also defined by the Applicant as Process A) to [redacted] used in the later Phase III clinical studies to produce Product B (Process B) and subsequently the [redacted], Product C (Process C) and Product D (Process D) that is intended for marketing.

b(4)

Additional bridging studies were conducted in the mouse to evaluate potential changes in elimination rates after IV administration of the IgG1 antibodies with [redacted],

b(4)

[redacted]

Dose (mg/kg)	Gender	T_{max}(h)	C_{max} (µg/mL)	C_{max}/D (µg/mL)/(mg/kg)	$AUC_{432-457}$ (µg.hr/mL)	$AUC_{432-457}$/D (µg.hr/mL)/(mg/kg)
10	Female	168	329	33	184164	18416
	Male	24	408	41	205956	20596
50	Female	24	1810	36	591588	11832
	Male	24	1990	40	696816	13936
150	Female	24	3880	26	1304400	8696
	Male	24	4610	31	1508640	10058

01BSUR compartmental pharmacokinetic parameters in albino mice after repeat subcutaneous injection of ACZ885 surrogate (01BSUR)

Model	Parameter	Value
1 compartment	CL (mL/kg/day)	3.66
	V (mL/kg)	89.4
	Ka (1/day)	0.976 (fixed)

2.6.5.3B Pharmacokinetics: Pharmacokinetics of ACZ885 in serum following a single intravenous dose in the marmoset

Species / strain	Marmosets	
Report number:	[DMPK(US) R01-967]	
Location in CTD:		
Gender(M/F) / Number of animals:	Male / 3 marmosets	
Feeding condition:	Fasted	
Vehicle / Formulation:	A solution at concentration 4.9 mg/mL ACZ885 in a 50 mM citric acid buffer containing 140 mM sodium chloride (pH 7.0). After receipt, the frozen solution was stored at −80°C for a week. Prior to dosing, the solution was thawed and centrifuged at 1000 x g for 10 minutes	
Method of Administration:	I.v..	
Dose (mg/kg):	5 mg/kg single	
Sample:	Serum	
Analyte / Assay:	ACZ885 / competitive ELISA (LOQ = 50 ng/mL) [Report DMPK(CH) R00-1915]	
PK parameters	C_0 [µg/mL]	177 (21.6)
	AUC(0-∞) [(µg/mL)-h)]	11600 (3470)
	AUC(0-∞)/dose [(µg/mL)-h)/(mg/kg)]	2330 (694)
	$t_{\frac{1}{2},\alpha}$ [h]	10.8 (5.61)
	$t_{\frac{1}{2},\beta}$ [h]	104 (13.2)
	MRT [h]	131 (16.8)
	V_{ss} [mL/kg]	58.5 (12.7)
	CL [mL/h/kg]	0.45 (0.12)

2.6.5.3e Pharmacokinetics: Single intravenous dose (bolus injection) placental transfer study in marmoset monkeys

Species / strain	Marmosets		
Report number:	[BAPK(EU) R0320070]		
Location in CTD:			
Gender(M/F) / Number of animals:	Female / 5 marmosets		
Feeding condition:	Fasted		
Vehicle / Formulation:	Liquid solution in vials		
Method of Administration:	i.v.		
Dose (mg/kg):	100 mg/kg single		
Sample:	Serum		
Analyte / Assay:	ACZ885 / competitive ELISA (LOQ = 100.5 ng/mL) [Report ICPP(EU) R0250521] and [Report ICPP(EU) R0250522].		
AZC885 distribution	Maternal serum	Fetal serum	Amniotic fluid
Concentration range [µg/mL]	1650-2000	10-71	1.2-2.5

2.6.5.3f Pharmacokinetics: Single intravenous dose (bolus injection) study in Rhesus monkeys

Species / strain	Rhesus Monkey	
Report number:	[DMPK(EU) R01 1005]	
Location in CTD:		
Gender(M/F) / Number of animals:	male / 4 rhesus monkeys	
Feeding condition:	fed	
Vehicle / Formulation:	Liquid solution in vials	
Method of Administration:	i.v.	
Dose (mg/kg):	2 mg/kg single	
Sample:	Serum	
Analyte / Assay:	ELISA (LOQ = 50 ng/mL)	
Serum Pharmacokinetic Parameters		
Arithmetic Mean (SD)	T_{max} (days)	1.00
(Noncompartmental)	C_0 (µg/mL)	37.4 (7.78)
	AUClast (day*µg/mL)	417 (79.6)
	AUCINF_obs (day*µg/mL)	518 (81.9)
	$t_{1/2}$ (day)	17.4 (5.24)
	Vz_obs (mL/kg)	101 (40.8)
	Cl_obs (mL/day/kg)	3.92 (0.56)

The results of the toxicokinetic evaluation in the Subcutaneous Tolerability Study in Female marmosets (Novartis Study 0370163) are presented in the following tables (from the original BLA submission):

Table 4-1 Mean toxicokinetic parameters of ACZ885 in marmoset serum

	5 mg/kg		50 mg/kg		150 mg/kg	
	Females	SD	Females	SD	Females	SD
t_{max}	24 to 120	n. a.	24 to 72	n. a.	24 to 72	n. a.
C_{max}	33.07	7.16	307.86	85.31	488.34	165.55
C_{max}/dose	6.61	1.43	6.16	1.71	3.26	1.10
AUC(0-1008h)	8120	3396	59772	22091	97684	37847
AUC(0-1008h)/dose	1624	679	1195	442	651	252
$t_{1/2}$ (672 to 1008h)	108	4	131	14	135.3	56.4

Units: t [h]. C [µg/mL]. C/dose [(µg/mL)/(mg/kg)]. AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].
n. a.: not applicable

Repeated dose pharmacokinetics were not evaluated separately. Absorption kinetics information for repeated dose ACZ885 and 01BSUR administration in mice and marmosets were collected in the toxicokinetics evaluations for the toxicology studies.

The results of the toxicokinetic evaluation in the 28-day Intravenous Administration Toxicity Study in marmoset —— Study 1939-003, Novartis Study 0280160) in Weeks 1 and 4 are presented in the following tables (from the original BLA submission): b(4)

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on Week 1, administration on Day 1

	10 mg/kg				30 mg/kg				100 mg/kg			
	Males**	SD	Female***	SD	Males**	SD	Female***	SD	Males****	SD	Female****	SD
t_{max}	0.083	*	1	*	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*
C_{max}	272.28	3.30	167.86	18.12	647.27	70.47	606.70	64.35	2184.66	277.63	2346.51	47.27
C_{max}/dose	27.23	0.33	16.8	1.8	21.58	2.35	20.22	2.15	21.85	2.78	23.47	0.47
AUC(0.083-24h)	3688	319	2942	147	10447	2224	9979	2037	35166	3770	37668	2665
AUC(0.083-24h)/dose	368.8	31.9	294	15	348.2	74.1	332.6	67.9	351.7	37.7	376.7	26.6

Units: t [h]. C [µg/mL]. C/dose [(µg/mL)/(mg/kg)]. AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].
*: not available or applicable.
**: n=2
***: n=3
****: n=5

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on Week 4, administration on Day 26

	10 mg/kg				30 mg/kg				100 mg/kg			
	Males**	SD	Female**	SD	Males**	SD	Female**	SD	Males***	SD	Female***	SD
t_{max}	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083	*	0.083 to 8	*	0.083 to 1	*
C_{max}	240.68	113.84	276.01	27.18	862.23	185.14	978.37	130.89	2963.03	743.59	2901.58	351.68
C_{max}/dose	24.1	11.4	27.6	2.7	28.7	6.2	32.5	4.4	29.6	7.4	29.0	3.5
AUC(0.083-24h)	4392	1902	5001	584	15477	3868	14480	1074	54553	11925	52718	4607
AUC(0.083-24h)/dose	439	190	500	58	516	129	483	36	546	119	527	46
									Males from recovery period, n=2	SD	Females from recovery period, n=2	SD
$t_{1/2}$									7.9	0.1	6.5	0.1

Units: t_{max} [h].$t_{1/2}$ [days]. C [µg/mL]. C/dose [(µg/mL)/(mg/kg)].
AUC(0.083-24h) [h·µg/mL]. AUC(0.083-24h)/dose [(h·µg/mL)/(mg/kg)].
*: not available or applicable.
**: n=3
***: n=5

The results of the toxicokinetic evaluation in the 26-Week Intravenous Administration Toxicity Study in marmoset —— Study 1939-004, Novartis Study 0380070) in Weeks 1, 11, and 23 are presented in the following tables (from the original BLA submission): b(4)

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets Day 1 of administration

Administration Day 1	10 mg/kg Males**	SD	Females**	SD	30 mg/kg Males***	SD	Females***	SD	100 mg/kg Males****	SD	Females****	SD
t_{max}	0.083	*	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*
C_{max}	284.2	34.0	183.6	27.2	686.3	20.7	637.7	115.8	2417.4	306.2	1835.1	364.4
C_{max}/dose	28.4	3.4	18.4	2.7	22.9	0.7	21.3	3.9	24.2	3.1	18.4	3.6
AUC(0.083-96h)	9412	272	6845	814	26519	1785	24589	4688	89116	9616	83413	16328
AUC(0.083-96h)/dose	941	27	685	81	884	59	820	156	891	98	834	163
AUC(0.083-24h)	3566	348	2597	359	10107	253	9857	2148	34644	4243	31039	5469
AUC(0.083-24h)/dose	357	35	260	36	337	8	329	72	346	42	310	55

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=3, results from one animal were not included due to an atypical profile

***: n=4

****: n=8

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets in Week 11 of administration

Administration Week 11	10 mg/kg Males**	SD	Females**	SD	30 mg/kg Males**	SD	Females**	SD	100 mg/kg Males***	SD	Females***	SD
t_{max}	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 8	*	0.083 to 1	*
C_{max}	469.8	107.6	375.8	53.8	1387.1	236.9	1240.5	113.7	3900.3	643.6	3646.7	739.1
C_{max}/dose	47.0	10.8	37.6	5.4	46.2	7.9	41.3	3.8	39.0	6.4	36.5	7.4
AUC(0.083-96h)	25788	5908	16823	1885	72741	19597	55132	6882	208838	49548	163321	30113
AUC(0.083-96h)/dose	2577	591	1682	189	2425	653	1838	229	2089	495	1633	301
AUC(0.083-24h)	8065	1352	6120	762	24474	5064	20077	2219	70589	14744	58475	9838
AUC(0.083-24h)/dose	806	135	612	76	816	169	669	74	707	147	585	98

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=4

***: n=6

Table 2-3 Mean toxicokinetic parameters of ACZ885 in serum of marmosets in Week 23 of administration

Administration Week 23	10 mg/kg Males**	SD	Females**	SD	30 mg/kg Males**	SD	Females**	SD	100 mg/kg Males***	SD	Females***	SD
t_{max}	0.083	*	0.083 to 1	*	0.083	*	0.083 to 24	*	0.083 to 1	*	0.083 to 1	*
C_{max}	738.1	178.0	536.0	55.5	2102.2	267.2	1635.7	573.9	5740.9	1397.5	4957.4	584.3
C_{max}/dose	73.8	17.8	53.6	5.6	70.1	8.9	54.5	19.1	57.4	14.0	49.6	5.6
AUC(0.083-96h)	36900	7818	23682	3859	95486	18644	78822	19174	268334	49763	226800	16925
AUC(0.083-96h)/dose	3690	782	2368	386	3183	621	2627	639	2683	498	2268	169
AUC(0.083-24h)	11630	1911	8393	1379	31587	5228	25562	6425	92493	13675	81484	9878
AUC(0.083-24h)/dose	1163	191	839	138	1053	174	852	214	925	137	815	99

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=4

***: n=6

The results of the toxicokinetic evaluation in the 13-Week Subcutaneous Administration Toxicity Study in marmoset (Novartis Study 0470033) on Day 1 and in Week 14 are presented in the following tables (from the original BLA submission):

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on day 1-3 of administration

	15 mg/kg				50 mg/kg				150 mg/kg			
Administration Day 1	Males*	SD	Female*	SD	Males*	SD	Female*	SD	Males*	SD	Female*	SD
t_{max}	12 to 24	**	24 to 96	**	12 to 96	**	12 to 48	**	24 to 96	**	48 to 96	**
C_{max}	112.8	19.9	88.9	18.2	401.1	48.8	355.7	20.4	990.2	116.6	925.7	230.0
C_{max}/dose	7.5	1.3	5.9	1.2	8.0	1.0	7.1	0.4	6.6	0.8	6.2	1.5
AUC(0-96h)	8344	1345	6890	1053	31726	5118	26823	2153	78591	8981	75422	17299
AUC(0-96h)/dose	556	90	459	70	635	102	536	43	511	60	503	115
AUC(0-24h)	1873	436	1485	379	6344	789	5487	887	13197	1748	14306	3464
AUC(0-24h)/dose	125	29	99	25	127	16	110	18	88	12	95	23

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].
AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].
*: n=4
**: not applicable

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on week 14 of administration

	15 mg/kg				50 mg/kg				150 mg/kg			
Administration Week 14	Males*	SD	Female*	SD	Males*	SD	Female*	SD	Males**	SD	Female**	SD
t_{max}	12 to 24	****	12 to 24	****	12 to 24	****	12	****	0 to 24	****	0.083 to 24	****
C_{max}	342.0	112.1	241.6	36.0	1170.3	381.8	1001.3	318.7	2210.1	257.1	2336.2	582.2
C_{max}/dose	22.8	7.5	16.1	2.4	23.4	7.6	20.0	6.4	14.7	1.7	15.6	3.7
AUC(0-1368h)***	****	****	****	****	****	****	****	****	462113	7659	342748	142962
AUC(0-1368h)/dose***	****	****	****	****	****	****	****	****	3081	51	2285	953
AUC(0-24h)	7144	2574	5151	891	24873	7350	20930	6218	46954	6933	50170	10887
AUC(0-24h)/dose	476	172	343	59	493	147	419	124	313	46	334	72
$t_{1/2}$(504-1368h) ***									143	15	127	9

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].
AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].
*: n=4
**: n=6, main study and recovery animals
***: n=2, only recovery animals
****: not applicable or available

The results of the toxicokinetic evaluation in the 13-Week Twice Weekly Subcutaneous Batch Comparison Study in marmosets (Novartis Study 0770373) on Day 1 and in Week 13 are presented in the following tables (from the original BLA submission):

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Table 2-1 Mean concentrations and toxicokinetic parameters of ACZ885 in marmoset serum on week 1/Day 1

Formulation	Group 2 Formulation A (150mg/kg/day)				Group 3 Formulation B(150mg/kg/day)			
Day 1 Time (h)	M*	CV%	F*	CV%	M*	CV%	F*	CV%
0	0.000	-	0.000	-	0.000	-	0.000	-
7	241	70.1	257	54.1	328	46.3	356	83.7
24	748	45.3	887	42.2	826	20.3	815	66.6
48	1080	35.0	1180	15.7	1100	2.3	1080	27.3
72	1110	24.6	1040	25.1	1210	51.7	1100	22.8
TK parameters on Day 1								
t_{max}	60	23.1	48	40.8	54	22.2	48	40.8
C_{max}	1200.25	28.6	1190	14.8	1355	38.7	1208	17.6
C_{max}/Dose	8.00175	28.6	7.933	14.8	9.0335	38.7	8.05325	17.6
$AUC_{(0\text{-}72h)}$	57487.9	34.2	62102.6	21.4	61656.1	15.8	60075.2	38.4
$AUC_{(0\text{-}72h)}$/Dose	383.253	34.2	414.018	21.4	411.041	15.8	400.502	38.4

M: male, F: female, *: n=4,

CV%: coefficient of variation expressed in %

Units : ACZ885 concentrations [µg/mL]. t_{max} [h]. C_{max} [µg/mL]. C_{max}/dose [(µg/mL)/(mg/kg/day)]. $AUC_{(0\text{-}72h)}$ [h·µg/mL]. $AUC_{(0\text{-}72h)}$/dose [(h·µg/mL)/(mg/kg/day)].

Table 2-2 Mean concentrations and toxicokinetic parameters of ACZ885 in marmoset serum on week 13/ Day85

Formulation	Group 2 Formulation A(150mg/kg/day)				Group 3 Formulation B(150mg/kg/day)			
Day 85 Time (h)	M*	CV%	F*	CV%	M**	CV%	F*	CV%
0	2400	16.9	2560	40.6	1620	69.8	2150	39.1
7	2400	11.3	2600	34.0	1950	70.8	2350	30.4
24	2730	23.7	2720	14.3	2260	53.5	2530	9.8
48	2320	20.6	2460	24.8	2010	58.7	2600	17.2
72	2000	13.5	2090	31.0	1640	83.5	2070	18.6
TK parameters on Day 85								
t_{max}	19.75	43	13.75	88.6	24	-	19.75	108.2
C_{max}	2785	20.5	3050	11.3	2255	-	2717.5	13.9
C_{max}/Dose	18.5665	20.5	20.3333	11.3	15.033	-	18.1168	13.9
$AUC_{(0\text{-}72h)}$	172815	18.4	179980	21.9	143097	-	174530	16.9
$AUC_{(0\text{-}72h)}$/Dose	1152.1	18.4	1199.87	21.9	953.977	-	1163.53	16.9

M: male, F: female, *: n=4,**:n=2

CV%: coefficient of variation expressed in %

Units : ACZ885 concentrations [µg/mL]. t_{max} [h]. C_{max} [µg/mL]. C_{max}/dose [(µg/mL)/(mg/kg/day)]. $AUC_{(0\text{-}72h)}$ [h·µg/mL]. $AUC_{(0\text{-}72h)}$/dose [(h·µg/mL)/(mg/kg/day)].

The following table presents the results of the pharmacokinetic evaluation (Study comparing ACZ885 lyophilisate produced using the original [redacted] for the nonclinical toxicology studies and clinical trials vs. [redacted] for production of the marketed drug substance, as a result of manufacturing changes during product development (from the original BLA submission):

b(4)

2.6.5.3D Single dose cross-over pharmacokinetic study comparing ACZ885 versus [redacted] derived ACZ885 lyophilisate following a subcutaneous dose in the marmoset

Species / strain	Marmoset /			
Report number:	[R0600200]			
Location in CTD:				
Gender(M/F) / Number of animals:	M / 8 per treatment group (cross-over design)			
Feeding condition:	Fed			
Vehicle / Formulation:	[redacted]derived ACZ885 and [redacted]erived ACZ885 as aqueous solution in vials containing 1 mL of 5 mg/mL ACZ855 in a buffer solution. Other ingredients in the formulation include, sucrose (270 mM), histidine (30 mM pH 6.0) and Tween 80 (0.06 % (m/v)). The vials were stored at ~20°C and allowed to equilibrate to room temperature before dosing.			
Method of Administration:	s.c.			
Dose (mg/kg):	5 mg/kg single			
Sample:	Serial blood samples were collected at specified times for at least 31 days after dosing for determination of plasma concentrations of ACZ885 during each of the dosing periods.			
Analyte / Assay:	ACZ885 / in plasma by a validated competitive ELISA [ICPP(EU) R0250521-02] and [ICPP(EU) R0250522].			
PK parameters: Arithmetics Mean (SD) (Noncompartmental analysis, WinNonlin®)	5 mg/kg [redacted]derived ACZ885 (Reference) (N=14) *	5 mg/kg [redacted]erived ACZ885 (Test) (N=16)	Ratio Test / Reference	90% CI for Ratio
C_{max} (ng/mL)	29,607 (10717)	31,863 (8573)	1.0656	0.90 -1.26
t_{max} [d]	3.00 (0.33-14.0)	3.00 (0.33-5.00)		
AUC(0-last) [(ng/mL)*d)]	279,798 (85879)	302,841 (85844)	1.0448	0.90 - 1.21
AUC(0-∞) [(ng/mL)*d)]	289,403 (86046)	312,818 (92040)	1.0435	0.91 - 1.20
CL/F (L/day/kg)	0.0189 (0.0061)	0.0173 (0.0048)		
$t_{1/2}$ (day)	7.07 (1.83)	6.33 (1.91)		
	* PK data from two animals were excluded from the analysis due to insufficient data set			

b(4)

The results of pharmacokinetic analyses comparing the lyophilized forms with human serum albumin/transferrin (LYO/HAS+) and without human serum albumin/transferring (LYO/HAS-), and the liquid form free of human serum albumin/transferring (PFS/HAS-) are presented in the following table (from the original BLA submission):

2.6.5.3E Single dose cross-over pharmacokinetic study comparing subcutaneous pharmacokinetics of three ACZ885 products in marmosets: (i) the lyophilized form containing human serum albumin/transferrin (LYO/HSA+), (ii) the lyophilized form free of human serum albumin/transferrin (LYO/HSA-), and (iii) the liquid form free of human serum albumin/transferrin (PFS/HSA-)

Species / strain	Marmoset /
Report number:	[R0700526]
Location in CTD:	
Gender(M/F) / Number of animals:	M / 15 per treatment group in three way cross-over design
Feeding condition:	Animals were not fasted overnight; food was presented approximately 2 hours post-dose.
Vehicle / Formulation:	(i) ACZ885 lyophilisate containing human serum albumin/transferrin (LYO/HSA+) (ii) ACZ885 lyophilisate free of human serum albumin/transferrin (LYO/HSA-) (iii) ACZ885 liquid form free of human serum albumin/transferrin Each vial contained 1.2 mL of 5 mg/mL ACZ855 in a buffered excipient solution. The vials were stored at < -80°C. Before dosing, the vials were removed from the freezer, allowed to equilibrate to room temperature and swirled gently for 10 seconds to ensure homogeneity of the solution).
Method of Administration:	s.c.
Dose (mg/kg):	5 mg/kg single
Sample:	Serial blood samples were collected at specified times for up to 43 days after dosing for determination of serum concentrations of ACZ885
Analyte / Assay:	/
Objetive of the study	[redacted]

b(4)

Serum Pharmacokinetic Parameters Arithmetic Mean (SD) (Noncompartmental)	LYO/HSA+ (N=14)	LYO/HSA- (N=13)	PFS/HSA- (N=14)
C_{max} (µg/mL)	39.8 (6.59)	35.1 (6.26)	35.5 (5.59)
t_{max}[a] (day)	2.00 (1.00-4.00)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
AUC(0-last) [(µg/mL)-d)]	379 (74.6)	340 (79.4)	324 (71.7)[b]
AUC(0-∞) [(µg/mL)-d)]	383 (74.5)	347 (79.5)	333 (78.7)[b]
CL/F (L/day/kg)	0.0135 (0.0025)	0.0151 (0.00348)	0.0158 (0.0036)[b]
$t_{1/2}$ (day)	4.57 (0.942)	4.67 (1.10)	4.51 (0.730)[b]

[a] median (range); [b] n=13

Ratios of Geometric Means and 90% Confidence Intervals for the Pharmacokinetic Parameters (n=12)	Test[a]	Test[b]	Reference[c]	Ratio (%) Test[a]/ Reference[c]	90% CI for Ratio (Test[a]/ Reference[c])	Ratio (%) Test[b]/ Reference[c]	90% CI for Ratio (Test[b]/ Reference[c]
C_{max} (µg/mL)	35.2	35.3	40.0	88.0	81.5-95.1	88.4	81.9-95.5
AUC(0-last) [(µg/mL)-d)]	338	326	379	89.4	84.2-94.8	86.1	81.1-91.4
AUC(0-∞) [(µg/mL)-d)]	344	334	382	90.1	84.6-95.9	87.4	82.1-93.1

[a] Test: LYO/HSA- ([redacted]-derived lyophilized form of ACZ885 free of human serum albumin/transferrin)
[b] PFS/HSA- ([redacted]-derived liquid form of ACZ885 free of human serum albumin/transferrin)
[c] LYO/HSA+ ([redacted]-derived lyophilized form of ACZ885containing human serum albumin/transferrin)

b(4)

Clinical PK parameters for the single SC dose of 150 mg in adult patients with CAPS (Study cacz885a2102) are presented in the following table, for comparison with the results of the TK assessements in the nonclinical studies (from the original BLA submission)*:

Title of study: An open-label, phase II dose titration study of ACZ885 (human anti-IL-1β monoclonal antibody) to assess the clinical efficacy, safety, pharmacokinetics and pharmacodynamics in patients with NALP3 mutations

PK/PD results: Non compartmental serum PK parameters of canakinumab after an initial s.c. dose of 150 mg in adult patient are shown in the table below.

	Cmax [µg/mL]	tmax [d]	AUClast [µg*d/mL]	AUC0-∞ [µg*d/mL]	F (%)	t½ [d]	CL/F [L/d]	Vz/F [L]
n	25	25	22	22	4	22	22	22
Mean	15.9		674	708	66.5	26.1	0.228	8.33
SD	3.52		189	206	22.2	7.31	0.0597	2.62
Median	16.2	6.98	634	656	69.7	25.6	0.229	7.97
Min	10.4	1.92	387	405	37.3	13.1	0.125	4.38
Max	21.7	14.0	1124	1204	89.3	39.2	0.370	13.9
CV%	22.2		28.0	29.1	33.5	28.0	26.2	31.4

Peak serum levels were reached by approximately 7 days. Maximum serum concentrations were on average 15.9 (± 3.52) µg/mL. Apparent half-life following the single s.c. dose administration was 26.1 (± 7.31) days. Moderate inter-subject variability with a coefficient of variation of approximately 22.2% and 29.1% was observed in Cmax and AUC-∞ values. Correcting for bioavailability of ~67%, the PK of canakinumab was in line with the expected PK characteristics of a human IgG molecule, i.e. low apparent clearance (average CL/F was 0.228 ± 0.0597 L/d) and a low apparent volume of distribution (Vz/F was 8.33 ± 2.62 L). In pediatric patients enrolled only in Stage 2, PK inference using non-compartmental analysis could not be drawn from 2 subjects as the length of PK assessment from their first s.c. dose was very short (10 days or shorter). Peak concentrations of canakinumab occurred between 2 to 7 days following s.c. administration of 150 mg or 2 mg/kg s.c. dose of canakinumab. Apparent half-lives ranged from 22.9 to 25.7 days, in line with the PK properties seen in adults. CL/F and Vz/F values were 0.131 and 0.0621 L/d, and 4.48 and 2.30 L, respectively, for the 2 subjects given 2 mg/kg dose. These parameter estimates are consistent with the relatively smaller body weight of pediatric patients. The older child, subject 5131, had CL/F and Vz/F values of 0.232 L/day and 7.67 L respectively, more in line with the PK characteristics observed in adults.

*Note that the AUC_{last} values were provided in units of mcg.d/ml. These values were multiplied by 24 for comparison with the AUC values calculated as mcg.h/ml for the nonclinical study data, by the reviewer.

Comparative ACZ885 pharmacokinetics in marmosets and humans are presented in the following table (from the original BLA submission):

Table 4-1 Comparative pharmacokinetics (Mean (SD)) of ACZ885

Parameters	Rhesus Monkey[e]	Marmoset Monkey[a,b]		Human		
				Healthy Adults[c]	MWS[d]	
Dose	2 mg/kg i.v.	5 mg/kg i.v.	5 mg/kg s.c.[b]	10 mg/kg i.v.	10 mg/kg i.v.	150 mg s.c.
CL(L/day)	0.0012 (0.002)	0.004 (0.0008)	0.007 (0.002)	0.1367 (0.0351)	0.182 (0.05)	0.228 (0.06)
Vz(L)	0.3 (0.12)	n.a	n.a	5.07 (0.99)	8.19 (2.42)	8.33 (2.62)
Vss (L)	0.26 (0.07)	0.02 (0.004)	n.a	n.a	7.08 (2.12)	n.a
$T_{1/2,terminal}$ (day)	17.4 (5.2)	4.33 (0.548)	7.07 (1.83)	26.4 (5.70)	31.2 (3.39)	26.1 (7.31)
F % (s.c bioavailability)	n.a	n.a	80	n.a	n.a	86.5

[a] Parameters presented are based on results obtained from [Study DMPK(US) R01-957] and adjusted for a marmoset weighing 350 g

[b] Parameters presented are based on results obtained from [Study DMPK R0600200] for — -derived ACZ885 and adjusted for a marmoset weighing 350 g b(4)

[c] Results from [Study CACZ885B2101]

[d] Results from [Study CACZ88A2102]

[e] Parameters presented are based on results obtained from [Study R001-1005] and adjusted for rhesus monkey weighing 3 kg.

n.a. not available or not applicable

Comparative systemic exposure in marmosets administered 100 mg/kg IV twice weekly (96-hour dosing interval) ACZ885 in the 26-week toxicity study (#0380070) and 150 mg/kg SC twice weekly (24-hour dosing interval) in the 13-week toxicity study (#0470033) with systemic exposure in human CAPS patients receiving the recommended clinical dose of 150 mg SC every 8 weeks and a maximum potential dose of 600 mg/kg SC (56-day dosing interval) is presented in the following table (from the original BLA submission):

Table 10-1 Comparative pharmacokinetics in marmosets and humans (CAPS patients)

CAPS Patients			Exposure Multiple		
Dose	[a]$AUC_{0-\tau,ss}/_{\tau}$ (Cavg) (µg /mL)	[a]$C_{max,ss}$	[b]Based on $AUC_{0-24h,ss}/_{24h}$ (Cavg) of 2023 µg/mL at 150 mg/kg s.c.	[b]Based on $C_{max,ss}$ of 2273 µg/mL at 150 mg/kg s.c.	[c]Based on $AUC_{0-96h,ss}/_{96h}$ (Cavg) of 2579 µg/mL at 100 mg/kg i.v.
150 mg s.c. q8 weeks.	9.59	17.5	211	130	269
600 mg s.c. q8 weeks.	38.4	70.1	52.6	32.4	67.2

[a] 150 mg s.c. is recommended clinical dose. AUC and C_{max} obtained from population PK model, based on data at 150 mg s.c. and simulated PK data for a potential 600 mg s.c. clinical dose. (ACZ885 CAPS Modeling report)

[b] $AUC_{0-tau,ss}/_{\tau}$ and $C_{max,ss}$ in CAPS patients simulated from the PK-based binding model were compared with highest mean (male and female) $AUC_{0-24h,ss}/_{24h}$ and $C_{max,ss}$, respectively, observed at 150 mg/kg s.c. in 13 week study in marmosets [study 0470033] to calculate the exposure multiple; τ (tau or dosing interval) is approximately 24h in marmosets administered ACZ885 s.c. twice weekly, and τ is 56 days in patients administered ACZ885 q8 weeks.

[c] $AUC_{0-tau,ss}/_{\tau}$ in CAPS patients estimated from the PK-based binding model were compared with highest mean (male and female) $AUC_{0-96h,ss}/_{96h}$, observed at 100 mg/kg i.v. in 26 week study in marmosets [study 0380070] to calculate the exposure multiple; τ (tau or dosing interval) is approximately 96h in marmosets administered ACZ885 twice weekly, and τ is 56 days in patients administered ACZ885 q8 weeks.

Comparison based on observed C_{max} are given in Figure 10-1 below.

The relative exposures (AUC and Cmax) in marmosets at the IV dose of 100 mg/kg IV for 26 weeks to exposures in human rheumatoid arthritis patients are presented in the following table (from the original BLA submission):

RA Patients			Exposure Multiple	
Dose (mg/kg)	AUC_{0-inf} (mg.h/ml)	Cmax (mcg/ml)	Based on AUC_{0-96h} of 268 mg.h/ml at NTEL	Based on C_{max} of 5741 mcg/ml at NTEL
0.3	5.4	10.8	50	532
1	36	40.6	7.4	141
3	65.3	113.4	4.1	51
10	278	400	0.96	14

Maximum AUC_{0-inf} observed in RA patients compared with highest AUC_{0-96h} at NTEL in 26-wk IV toxicity study in marmosets to calculate exposure multiple. Parameters assumed comparable to multiple clinical dosing, with AUC0-inf after single dose equal to AUC0-t at steady state (t = dosing interval) = approximately 96 hr in twice weekly studies in marmoset.