London, 20 August 2015
EMA/554401/2015
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

ILARIS

CANAKINUMAB

Procedure no: EMEA/H/C/001109/P46/043

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Administrative information

Rapporteur's contact person:	**Anita Kern** Tel: +49 6103 772004 Email: PEI-FGMono-PolyklonaleAntikoerper@pei.de
Name of the Assessor:	**Anja Schmidt** Tel: +49 6103 772070 Email: Anja.Schmidt@pei.de
EMA Product Lead	**Name: Andras Kouroumalis** Email: Andras.Kouroumalis@ema.europa.eu
Procedure Manager:	**Name: Hector Boix** Email: Hector.Boix@ema.europa.eu

Table of contents

1. Introduction

On 08.06.2015 the MAH submitted a completed paediatric study for Ilaris, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study **CACZ885G2301E1**

An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305; and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever

is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) was submitted by November 2012. A line listing of all the concerned studies is annexed.

ILARIS® 150 mg powder for solution for injection was registered in EU/EEA on 23 October 2009 through the centralized procedure for the following indication:

"Ilaris is indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 4 years and older with bodyweight above 15 kg, including: Muckle-Wells Syndrome (MWS), Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash."

An application (II/21) was submitted in June 2012 to extend the treatment of ILARIS® to the most severe CAPS patients, who include the patients aged 2 to <4 years with body weight 7.5 kg or above. In addition, Novartis proposed in the application to escalate the dose up to a maximum of 600 mg or to 8 mg/kg every 8 weeks for all patients who did not achieve or maintain satisfactory clinical response at the currently approved dose of 300 mg or 4 mg/kg every 8 weeks. Approval was granted in January 2013.

Another pharmaceutical form, ILARIS® 150 mg powder and solvent for solution for injection also referred as injection kit, was registered in EU/EEA on 16 September 2011 to provide the components required for reconstitution and administration of the approved lyophilized powder presentation; i.e., a water for injection vial, an injection syringe, a safety needle, two vial adapters and four cleansing swabs (PSUR11).

On 18 February 2013 and 26 August 2013 approval was granted in EU for Gouty Arthritis (GA) and for Systemic Juvenile Idiopathic Arthritis (SJIA) indications, respectively. In the current EU SmPC (Section 4.1), ILARIS® is currently indicated for:

1. the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) in adults, adolescents and children aged 2 years and older with body weight of 7.5 kg or above, including:

- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
- Severe forms of Familial Cold Autoinflammatory Syndrome (FCAS) / Familial Cold Urticaria (FCU) presenting with signs and symptoms beyond cold-induced urticarial skin rash.

2. the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Ilaris can be given as monotherapy or in combination with methotrexate.

3. the symptomatic treatment of adult patients with frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

2.2. Information on the pharmaceutical formulation used in the study

Canakinumab was supplied as either 150 mg or 25 mg lyophilized cake. The 150 mg canakinumab formulation was used for the 4 mg/kg dose and for the 2 mg/kg dose for patients weighing 15 kg or more. The 25 mg canakinumab formulation was used for the 2 mg/kg dose for patients weighing less than 15 kg. All active drug product batches were produced at the same manufacturing site. Comparability between process D and C has been established. Batch and formulation numbers of the test drug are presented below:

Study drug and strength	Formulation control number	Batch number
Canakinumab 150 mg	7004942.009 (Type C)	Y099ID
	7004637.001 (Type C)	Y099ID
	7004942.012 (Type D)	U015 1208
	7004637.001 (Type D)	U015 1208
	7004942.012 (LYVI)	U003 0409
	7004942.012 (LYVI)	S0035
Canakinumab 25 mg	7006443.006 (Type C)	Y120ID
	7004637.001 (Type C)	Y120ID
	7004637.001 (Type D)	Y120ID
Canakinumab Placebo*	7006443.006 (LYVI)	Y120ID
	7004637.001 (PLB)	Y126 1212
	7001283.008 (PLA LYVI)	Y191 1208
	7001283.009 (PLA LYVI)	Y144 0709
	7001283.009 (PLA LYVI)	Y126 1212

*Placebo powder matching canakinumab, for dilution purposes only

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• CACZ885G2301E1: An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305; and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever

2.3.2. Clinical study

Clinical study number and title

CACZ885G2301E1: An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305; and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever

Description

This was an open-label, non-comparative extension study in which SJIA patients who had participated in studies G2305 or G2301 (Cohort 1) or canakinumab-naïve SJIA patients (Cohort 2) received canakinumab 4 mg/kg by s.c. injection every 4 weeks. The study was designed to run for a set time period, planned to end as late as December 2014.

Methods

Objective(s)

Study objectives, not designated as primary or secondary objectives, were:

- To assess the long-term safety, tolerability and immunogenicity of canakinumab
- To assess efficacy at an exploratory level by investigating disease control defined by maintenance
- of at least an adapted ACR pediatric 30 during the extension phase
- To introduce Juvenile Arthritis Disease Activity Score (JADAS) and Disease Activity Score (DAS)
- as exploratory assessments of efficacy
- To assess efficacy of canakinumab treatment based on adapted pediatric ACR30 criteria in
- patients who reported previous anakinra, tocilizumab or other biologic treatment

Study design

Open-label, non-comparative extension study

Study population /Sample size

There was no minimum number of patients specified:

patients from Studies G2301 and G2305, as well as canakinumab-naïve patients (following Protocol Amendment 6) who met the entry criteria, could be enrolled. In total, 271 patients were recruited, 147 in Cohort 1 and 124 in Cohort 2. In Cohort 1, all 147 patients were analyzed for both efficacy and safety; in Cohort 2, 123 patients were analyzed for efficacy and safety.

Diagnosis and main criteria for inclusion

The following patients were eligible to enroll in the extension study, and constituted Cohort 1:

- Patients in Study G2305 or G2301 who achieved an adapted ACR pediatric 30 response at Day 15 but who lost response following Day 15.

- Patients in Study G2301 who were not eligible to enter Part II because they were not able to meet the corticosteroid entry criteria of 0.5 mg/kg oral prednisone (or equivalent) or they were not able to taper their steroids by at least 0.3 mg/kg.
- Patients in Study G2301 Part I or Part II who maintained a minimum adapted ACR pediatric 30 response and had not flared when the study stopped.
- Study G2301 patients who were responders in Part I (achieved and maintained a minimum adapted ACR pediatric 30) but experienced a flare in Part II.

For Cohort 2, patients were eligible to enter the study if they were aged ≥ 2 to < 20 years at Screening, with a confirmed diagnosis of SJIA (as per ILAR definition) ≥2 months prior to enrollment with onset of disease at <16 years of age. Patients had to have active systemic disease at baseline, and be willing to discontinue anakinra, rilonacept, tocilizumab or other experimental drug (under close monitoring).

Patients in both cohorts were excluded if they were pregnant of lactating, or had any of the following: active or recurrent bacterial, fungal or viral infection, including HIV, hepatitis B or hepatitis C; risk factors for tuberculosis; underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions; other significant medical conditions; neutropenia; history of malignancy (other than localized basal cell carcinoma of the skin), within the past 5 years; live vaccinations within 3 months; donation or loss of blood within 8 weeks; familial and social conditions rendering regular medical assessment not possible; or a history of drug or alcohol abuse within 12 months.

Additional exclusion criteria for Cohort 2 were moderate to severe impaired renal function; clinical evidence of liver disease or injury; and use of a range of immunosuppressive therapies, including biologics and investigational treatments, within specified time periods prior to the study.

Treatments

Canakinumab 4 mg/kg by s.c. injection every 4 weeks

Outcomes/endpoints

Efficacy: key efficacy variables (which were not specified as primary or secondary) were: proportions of patients who met the adapted pediatric ACR 30/50/70/90/100 response, were able to taper steroids, became steroid-free, had inactive disease or clinical remission, if steroid-free, were able to reduce their canakinumab dose to 2 mg/kg every 4 weeks; and changes over time in JADAS-CRP, DAS28, and SDAI scores. Efficacy was assessed separately for Cohort 1, Cohort 2 and patients from both cohorts who were able to reduce their canakinumab dose to 2 mg/kg. In Cohort 1, efficacy was assessed for 4 groups of patients that were defined based on their outcomes in the previous study:

Group 1 discontinued Study G2301 due to flares, non-response or any other discontinuation; Group 2 patients were responders at the time Study G2301 completed; Group 3 patients entered the extension study after unsuccessfully attempting steroid tapering; and Group 4 was a small, heterogenous group of patients from study G2301 and G2305 who entered the extension study for a variety of reasons.

Safety: Safety was assessed in terms of adverse events, serious adverse events, clinical laboratory assessments, ECG and vital signs. Serious infections, malignancies and cases of macrophage activation syndrome (MAS) were adjudicated by independent committees.

Bioanalytics: Serum canakinumab concentrations and IL-1β concentrations were determined regularly during the study for both cohorts of patients.

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, and safety observations and measurements. Categorical variables were summarized by absolute frequencies and percentages. Continuous variables were summarized by mean, median, standard deviation, lower and upper quartile, minimum and maximum and the number of non-missing data points.

Cohort 1 and Cohort 2 were analyzed separately.

For minimum adapted ACR Pediatric scores, the last measurement recorded from the patient's previous study was considered baseline for the current study. Patients were classified in the following non-mutually exclusive categories: Non-Responder, minimum achieved adapted ACR Pediatric 30, minimum achieved adapted ACR Pediatric 50, minimum achieved adapted ACR Pediatric 70, minimum achieved adapted ACR Pediatric 90, achieved adapted ACR Pediatric 100. Frequencies and percentages of patients in each category were presented by visit, corresponding ACR status at baseline, and subgroup. The frequency and percentage of patients who were able to taper oral steroids (both successfully and unsuccessfully) and of patients who reached steroid-free regimen was presented. A patient was considered to have tapered steroids successfully if their steroid dose was reduced from baseline and the patient did not flare and maintained a minimum adapted ACR Pediatric 30 at the last measurement. A patient was considered to have unsuccessfully tapered steroids if their steroid dose was reduced during the study but dose at end of study was greater than or equal their dose at baseline or if steroid dose was reduced but the patient did not maintain a minimum adapted ACR Pediatric 30 at the last measurement. Inactive disease was defined as no joints with active arthritis; no fever (body temperature ≤ 38°C), no rheumatoid rash, serositis, splenomegaly, hepatomegaly or generalized lymphadenopathy attributable to JIA; normal CRP; a Physician's Global Assessment of disease activity indicating no disease activity (i.e. best possible score ≤10mm), Clinical remission was defined as at least 12 months of inactive disease on medication during the extension trial.

Adverse events were coded using MedDRA Version 17.1, that provides the primary system organ class and preferred terms. Adverse events were summarized by presenting the number and percentage of patients having any AE, having any AE in each primary system organ class and having each individual AE based on the preferred term. A table of AEs by maximum severity was also produced. All other information collected (e.g. severity, relationship to study drug) was listed as appropriate. Deaths, serious adverse events, and AEs leading to discontinuation of study drug were summarized by primary system organ class and preferred term and listed. Primary system organ class infections and infestations were also listed separately.

Results

Recruitment / Number analysed

There was no minimum number of patients specified: patients from Studies G2301 and G2305, as well as canakinumab-naïve patients (following Protocol Amendment 6) who met the entry criteria, could be enrolled.
In total, 271 patients were recruited, 147 in Cohort 1 and 124 in Cohort 2. In Cohort 1, all 147 patients were analyzed for both efficacy and safety; in Cohort 2, 123 patients were analyzed for efficacy and safety.

Baseline data

Cohort 1 patients had a median age of 9 years (range 2-20 years). The majority of patients (55%) were female and Caucasian (85%). Baseline disease characteristics varied between efficacy analysis

groups. Group 2 reflected a more stable disease state on entry to the extension study, with median numbers of active joints and joints with limitation of motion of zero, and a low CRP level; most patients were steroid-free and NSAID-free, and half were methotrexate-free. Groups 1, 3 and 4 had more active disease, particularly Groups 3 and 4.

Cohort 2 patients had a median age of 8 years (range 2-19 years); 61% of patients were female and 90% were Caucasian. Patients in Cohort 2 had active SJIA at baseline; approximately 58% of patients were using steroids and 43% methotrexate, and 40% NSAIDs. Median numbers of active joints and joints with limitation of motion were both 5.0. Approximately 57% of patients had fever at baseline.

Efficacy results

ACR pediatric response in each efficacy analysis group in Cohort 1 was sustained or improved from the response on entry to the extension study. Most ACR non-responders on entry in Groups 1, 3 and 4 (there were no non-responders in Group 2) showed ACR ≥30 responses at Month 3 (82.4%, 58.8% and 66.7% in each group, respectively), and these responses were sustained until last assessment in most patients. ACR ≥30 responders at baseline in all groups tended to sustain their responses through the extension study. At last assessment, Group 2 showed higher rates of higher level ACR responses than the other groups, and had a lower rate of non-response than Groups 1 or 3 (there were only 5 baseline ACR ≥30 responders in Group 4, making comparisons difficult). Group 3 (patients who failed to taper their steroid dose in Part I of Study G2301) showed the highest rate of loss of response at last assessment.

Cohort 2 showed a rapid response to treatment, with over 50% of patients having ACR ≥70 responses at Day 15, and 24% having ACR 100 responses. By Day 57, 75% of patient had ACR ≥70 responses, and 8.3% were non-responders. At last assessment, 67% of patients had ACR ≥70 responses, and 77% had ACR ≥30 responses, with 23% being non-responders. In Cohort 2, ACR responses were also assessed by prior use of anakinra, tocilizumab, or other biologics; no major differences in response were observed.

In patients who reduced their canakinumab dose to 2 mg/kg, all patients for whom assessments were available had ACR ≥90 responses, and 96.6% had ACR 100 responses on starting the 2 mg/kg dose. At subsequent visits, responses appeared to be sustained, with over 85% of patients having ACR 100 response at each time point, and over 90% having ACR ≥90 responses at all time points other than

Month 36 (87.5%).

In Cohort 1, of 66 patients on steroids on entry to the extension study, 30.3% became steroid-free and successful steroid tapering (but not becoming steroid-free) was achieved by 19.7%. The proportions of patients who became steroid-free were broadly similar in each of Groups 1, 3 and 4, and higher in Group 2, although most Group 2 patients were already steroid-free on entry to the extension. In Cohort 2, of 71 patients using steroids at baseline, 33.8% became steroid-free, and 23.9% were able to taper steroids but not to zero.

In Cohort 1, Groups 1, 3 and 4 had 3.0%, zero and 9.1% of patients with inactive disease on entry to the extension; at last assessment the corresponding figures were 39.4%, 12.5% and 36.4%. In Group 2, 73.0% of patients had inactive disease on entry; this increased to 79.4% at last assessment. In Cohort 2, 23.9% of patients had inactive disease by Day 15, as did 50.8% at last assessment. For patients who were able to reduce their canakinumab dose to 2 mg/kg, 88.9% of patients had inactive disease on starting treatment with 2 mg/kg, and overall, 93.3% of patients had inactive disease on at least 1 visit, and 73.3% at their last assessment in the study.

In Cohort 1, JADAS10-CRP scores reflected the patients' disease status on entry to the extension study. Groups 1, 3 and 4 had much higher baseline scores than Group 2 (medians 16.4, 17.85, and 21.1, all indicating high disease activity, compared with 0.2, indicating inactive disease, in Group 2), but showed decreases over the course of the extension study (changes from baseline to last assessment of -9.2, -0.95, and -1.4, respectively, with median last assessment values indicating moderate disease activity in Groups 1 and 4). In Group 2, the very low JADAS10-CRP score remained unchanged during the extension study. In Cohort 2, baseline median JADAS10-CRP score was 22.3 (indicating high disease activity), with median changes from baseline of -12.0 at Day 15 and -16.8 at last assessment; median scores at these time points indicated moderate and low disease activity, respectively. JADAS27-CRP and JADAS71-CRP scores were consistent with JADAS10-CRP scores in both cohorts, as were DAS28-CRP and SDAI scores.

Safety results

Safety was summarized separately for Cohort 1 and Cohort 2. There were no deaths during the study, although 1 patient died due to disease progression 3 months after discontinuing from the study for lack of therapeutic effect. In both cohorts, approximately 30% of patients had at least 1 SAE. The most common SAEs in both cohorts mainly appeared to be related to SJIA. The most frequent were flares or worsening of SJIA (preferred term 'juvenile idiopathic arthritis', in 9.5% of Cohort 1 patients and 10.6% of Cohort 2 patients), macrophage activation syndrome (MAS: preferred term histiocytosis haematophagic, in 6.8% and 4.9%, respectively), and pyrexia (in 3.4% and 3.3%, respectively). Infection SAEs were reported in a total of 17.7% of patients in Cohort 1 and 10.6% in Cohort 2. The most common infection SAEs were gastroenteritis (2.7% in Cohort 1 and 1.6% in Cohort 2), pneumonia (1.4% and 2.4%, respectively), and varicella (2.0% and 0.8%, respectively). A wide range of bacterial and viral infections (and one case of toxoplasmosis) were reported as SAEs, but in most cases each occurred in only 1 patient in each cohort. MAS SAEs occurred in 10 patients (12 events) in Cohort 1, and in 6 patients (8 events) in Cohort 2. All but 1 event were reported as resolved, but 3 patients discontinued due to MAS SAEs. One patient had a malignancy during the study (anaplastic large cell lymphoma), which in retrospect had probably been present prior to study entry.

Laboratory assessments revealed changes consistent with the known pharmacological activity of canakinumab, with SJIA, its complications, and its response to treatment. Hematology parameters generally tended to shift towards normal, particularly in Cohort 2 (where patients had more active disease than those in Cohort 1 and had not previously been treated with canakinumab). Most clinical chemistry parameters tended to remain unchanged, other than those that reflected the anti-inflammatory effects of canakinumab (decreases in CRP and fibrinogen were observed). Clinically notable abnormalities of laboratory parameters were observed in both cohorts. There were few significant hematology abnormalities in either cohort: the most common involved hemoglobin or neutrophils. These abnormalities tended to be isolated and not associated with AEs (the one exception for hemoglobin was the patient noted previously with lymphoma); of note there were no unusual, severe or serious infections that were clearly associated with the cases of low neutrophil counts.

Abnormalities of liver function tests were the most noteworthy clinical chemistry abnormalities. These most commonly occurred in association with MAS or flares or worsening of SJIA. Two patients in Cohort 2 had notably elevated transaminases combined with elevated bilirubin and/or alkaline phosphatase levels: both patients had concurrent MAS SAEs.

Adverse events and SAEs were also summarized for patients who were able to reduce their canakinumab doses to 2 mg/kg. The profile of AEs was broadly similar [G2301E1-Section 12.2.1], as were rates of some AEs (many infections, for example), to Cohorts 1 and 2 as a whole, but the total

rate of AEs was lower, as were rates of musculoskeletal AEs, particularly those reflecting signs and symptoms of SJIA. The exposure-adjusted rate of juvenile idiopathic arthritis in patients who reduced their doses was 0.024 events per 100 patient-days, compared with 0.053 and 0.121 events per 100 patient-days in Cohorts 1 and 2, respectively.

The rate of SAEs [G2301E1-Section 12.3.2] was much lower in patients who had reduced their canakinumab dose (overall rate 0.040 SAEs per 100 patient-days, compared with 0.089 for Cohort 1 and 0.154 for Cohort 2). Of note, patients who had reduced their doses had no SAEs of juvenile idiopathic arthritis (i.e. SJIA flares/worsening) and the rate of MAS SAEs (0.005 events per 100 patient-days) was lower than in Cohort 1 (0.009) or Cohort 2 (0.012). Given the nature of the differences between patients who reduced their doses and Cohorts 1 and 2 as a whole, these differences may be due to the lower disease activity in this subset of patients.

This extension study provides a further 365 patient-years from Cohort 1 and 184 patient-years from Cohort 2. The safety profile of canakinumab in SJIA patients in this extension did not appear to be substantially different to that observed in previous studies and represented in the SmPC.

2.3.3. Discussion on clinical aspects

In patients who had previously been treated with canakinumab in other studies (Cohort 1), the response to treatment was sustained or improved during long-term treatment in the extension study. In canakinumab-naïve patients with highly active SJIA (Cohort 2), including patients who had previously been treated with other biologics, canakinumab treatment was associated with a rapid response and sustained therapeutic effect, according to a range of efficacy parameters. In both previously-treated and canakinumab-naïve patients, the observed efficacy was consistent across a range of efficacy assessments, including ACR paediatric scores, JADAS-CRP, DAS-CRP and SDAI scores. Prior use of anakinra, tocilizumab, or other biologics did not appear to affect ACR paediatric response in canakinumab-naïve patients. Patients with well-controlled disease who were steroid-free were able to reduce their canakinumab dose from 4 mg/kg to 2 mg/kg without loss of efficacy.

The long-term safety data from this study did not show notable differences to the known safety profile of canakinumab.

3. Rapporteur's overall conclusion and recommendation

Canakinumab treatment in patients with sJIA provided a sustained long term response also in patients who were already second line (had other biological treatment previously). The efficacy was shown with accepted and validated endpoints like ACR, DAS, JADAS-CRP as well as with quality of life questionnaires. The result that patients with stable steroid free disease were able to reduce the canakinumab dose is of high importance especially in view of the long term safety profile and is already reflected in the SmPC.

The safety profile was consistent with previous canakinumab studies in other indications. The slightly better safety profile of the reduced 2mg/kg dose is important. The rates of SAEs was lower in the reduced dose, steroid free, cohort with otherwise sustained efficacy.

The report does not provide any evidence that further actions are required.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Ilaris Active substance: Canakinumab

Study title	Study number	Date of completion	Date of submission of final study report
A multi-centre, open label, repeated dose range finding study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics and efficacy of an anti-IL-1beta monoclonal antibody (ACZ885) given subcutaneously in pediatric subjects with active systemic juvenile idiopathic arthritis	CACZ885A2203	LPLV: 9-Mar-2010 DBL: 2-Jul-2010	4-Mar-2011
A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations	CACZ885G2305	LPLV: 2-Dec-2010 DBL: 9-Feb-2011	10-Jun-2011
A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations	CACZ885G2301	LPLV:12-Sep-2011 DBL: 3-Oct-2011	12-Mar-2012
An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations	CACZ885G2301E1	LPLV:10-Dec-2014 DBL: 18-Feb-2015	Current submission