HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

19 March 2014

ILARIS 150 mg, powder for solution for injection

B/1 bottle (CIP: 34 009 397 457-6 3)

ILARIS 150 mg, powder and solvent for solution for injection

1 vial (powder) + 1 vial (solvent) + 1 injection syringe + 1 needle + 2 vial adapters + 4 cleansing swabs (CIP: 34 009 217 875-9 7)

Applicant: NOVARTIS PHARMA S.A.S.

INN	Canakinumab
ATC code (2013)	L04AC08 (interleukin inhibitor)
Reason for the review	**Extension of indication**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Systemic Juvenile Idiopathic Arthritis (SJIA)"**

Actual Benefit	**Substantial in the treatment of SJIA**
Improvement in Actual Benefit	**Like ROACTEMRA (tocilizumab), ILARIS (canakinumab) provides a moderate improvement in actual benefit (level III) in the management of patients aged 2 years and older, with active systemic juvenile idiopathic arthritis, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.**
Therapeutic use	**ILARIS is a second-line treatment for SJIA in patients who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.**
Target population	**Less than 600 patients**
Recommendations	**The Committee would like to re-assess this medicinal product in one year's time.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (centralised procedure): 23 October 2009 (in CAPS) Marketing Authorisation under exceptional circumstances[1] only in patients with CAPS Extension of indication obtained on 26 August 2013 in SJIA
Prescribing and dispensing conditions/ special status	List I Medicine for hospital prescription only. Initial and repeat prescription reserved for specialists in rheumatology, internal medicine, dermatology or paediatrics. Medicine requiring special monitoring during treatment. Exception drug status

ATC Classification	L	Antineoplastic and immunomodulating agents
	L04	Immunosuppressants
	L04A	Immunosuppressants
	L04AC	Interleukin inhibitors
	L04AC08	canakinumab

02 BACKGROUND

The active ingredient of ILARIS, canakinumab, is a human monoclonal antibody specifically targeted at interleukin-1β (IL-1β).

Since July, 1st 2010, this proprietary medicinal product has been included on the list of proprietary medicinal products refundable by National Health Insurance and on the list of proprietary medicinal products approved for hospital use in the treatment of cryopyrin-associated periodic syndromes (CAPS) in adults, adolescents and children aged 4 years and older and weighing more than 15 kg (Opinion of 10 February 2010). An opinion favourable to the extension of the refundable indication in CAPS to young children (aged 2 years to less than 4 years) was issued by the Committee on 05 February 2014.

In rheumatology, ILARIS has obtained two extensions of indications:

- on 18 February 2013, in hard-to-treat attacks of gouty arthritis; a separate Opinion will be issued by the Committee for this indication.
- on 26 August 2013, in SJIA, the subject of the present assessment.

The indication for ILARIS in SJIA, a rare paediatric disease, is identical to that of ROACTEMRA (tocilizumab), an IL-6 inhibitor recorded in this indication following a Committee opinion of 09 May 2012: 2nd-line treatment (failure of NSAIDs and corticosteroids), from age 2 years. The method of administration of these two proprietary medicinal products differs: ROACTEMRA is administered by IV infusion every 2 weeks, in a dose adapted to the patient's weight. ILARIS is administered subcutaneously, once a month. Since ROACTEMRA is reserved for hospital use, the availability of subcutaneous ILARIS for hospital and outpatient use could have an impact on the organisation of the healthcare system. The long half-life of ILARIS, if poorly tolerated, could be abarrier to its use.

[1]This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency will assess any new information that is available every year and, if necessary, the SPC will be updated.

03 THERAPEUTIC INDICATIONS

Indication concerned by the review:
Systemic juvenile idiopathic arthritis (SJIA)
"ILARIS is indicated for 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."

Other indications not affected by the assessment:
Gouty arthritis*
"ILARIS is indicated for 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 poorly tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate."

"Cryopyrin-Associated Periodic Syndromes*
ILARIS is indicated for 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."

**these indications have been covered in other Opinions*

04 DOSAGE

Treatment should be initiated and supervised by a specialist physician experienced in the diagnosis and treatment of the relevant indication.
After proper training in the correct injection technique, patients or their caregivers may inject ILARIS if the physician determines that it is appropriate.

In SJIA, the recommended dose of ILARIS for patients with body weight ≥ 7.5 kg is 4 mg/kg (up to a maximum of 300 mg), administered every four weeks via subcutaneous injection. Continued treatment with ILARIS in patients without clinical improvement should be reconsidered by the treating physician.

For dosages in the other indications, see the SPC.

05 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections
ILARIS is associated with an increased incidence of serious infections. Therefore patients should be monitored carefully for signs and symptoms of infections during and after treatment with ILARIS. Physicians should exercise caution when administering ILARIS to patients with infections, a history of recurring infections, or underlying conditions which may predispose them to infections.

Treatment of SJIA

Ilaris should not be initiated or continued in patients during an active infection requiring medical intervention. Neutropenia and leukopenia
Neutropenia (absolute neutrophil count [ANC] < 1.5 x 10^9/l) and leukopenia have been observed with medicinal products that inhibit IL-1, including ILARIS. Treatment with ILARIS should not be initiated in patients with neutropenia or leukopenia. It is recommended that white blood cell (WBC) counts including neutrophil counts be assessed prior to initiating treatment and again after 1 to 2 months. For chronic or repeated therapies, it is also recommended to assess WBC counts periodically during treatment. If a patient becomes neutropenic or leukopenic, the WBC counts should be monitored closely and treatment discontinuation should be considered.

Malignancies
Malignancy events have been reported in patients treated with ILARIS. The risk for the development of malignancies with anti-interleukin (IL)-1 therapy is unknown.

Hypersensitivity reactions
Hypersensitivity reactions with ILARIS therapy have been reported. The majority of these events were mild in severity. During clinical development of ILARIS in over 2300 patients, no anaphylactoid or anaphylactic reactions were reported. However, the risk of severe hypersensitivity reactions, which is not uncommon for injectable proteins, cannot be excluded.

Macrophage activation syndrome in SJIA patients
Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions, in particular SJIA. If MAS occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians have to be attentive to symptoms of infection or worsening of SJIA, as these are known triggers for MAS. Based on clinical trial experience, ILARIS does not appear to increase the incidence of MAS in SJIA patients, but no definitive conclusion can be drawn at present.

06 THERAPEUTIC NEED[2,3,]

The aim of treating systemic JIA is to control the articular and systemic manifestations (fever, asthenia, anaemia). There is no curative treatment.

Immediate-acting symptomatic treatments (NSAIDs, corticosteroids) are the first line of treatment.

NSAIDs are used as first-line treatment if there are no contraindications or severity criteria, but their efficacy is variable. Systemic corticosteroid therapy is indicated, after receiving the opinion of a specialist, for the treatment of the systemic manifestations, in the event of NSAID hepato toxicity, insufficient efficacy or intolerance of NSAIDs, the presence of signs of severity (substantial impairment of general condition, weight loss, systemic toxicity, severe anaemia, significant symptomatic serositis) or the onset of macrophage activation syndrome. When the disease is under control, the dose of corticosteroids can be gradually reduced in line with the change in the systemic, clinical and laboratory manifestations (chronic condition guide prepared by HAS).

In the event of arthritis-related pain, analgesic treatment with non-opioid products, weak opioids or strong opioids can also be given. Symptomatic systemic treatments can be combined with intra-articular injections of corticosteroids if arthritis persists in one or more locations. The long-term use of corticosteroids in children is associated with numerous adverse effects, particularly growth retardation and bone demineralisation.

Immunosuppressant treatments such as methotrexate and anti-TNFs have Marketing Authorisation only in polyarticular JIA. According to the experts and the chronic condition guide prepared by

[2]Job Deslandre et al. Arthrites Juvéniles idiopathiques. Orphanet encyclopaedia. September 2003
[3]HAS. Protocole National de Diagnostic de Soin (PNDS) pour les arthrites juvéniles idiopathiques [National diagnosis and healthcare protocol (PNDS) for juvenile idiopathic arthritis]. July 2009.

HAS, they can be used in systemic JIA in minimally inflammatory and polyarticular forms but their efficacy is variable. Anakinra (KINERET, an IL1 receptor antagonist, does not have Marketing Authorisation in JIA but is offered (off-label in the National diagnosis and healthcare protocol (PNDS)) on the advice of experts in forms of JIA that have persistent systemic signs, in the same way as tocilizumab (ROACTEMRA, IL6 inhibitor)[8] which has Marketing Authorisation in this indication.

In the light of this information, the therapeutic alternatives in the basic treatment of systemic JIA that have Marketing Authorisation are few in number, and there is thus a therapeutic need.

07 CLINICALLY RELEVANT COMPARATORS

The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of therapeutic use and intended for the same population of patients, on the date of the assessment.

07.1 Medicinal products

Another proprietary medicinal product is authorised in this indication.
It is ROACTEMRA (tocilizumab, an interleukin 6 inhibitor, administered by IV infusion), marketed by ROCHE. Its indication is strictly identical to that of ILARIS: "Treatment of active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. ROACTEMRA can be given as monotherapy (in case of intolerance of MTX or when treatment with MTX is inappropriate) or in combination with MTX)"
It was assessed by the Committee which, on May 9th 2012, allocated it a substantial AB and a moderate IAB (level III), with the following wording:
"Taking into account:
- the important size effect versus placebo in one clinical study;
- the absence of therapeutic alternatives with specific marketing authorisation for this condition;
- but the risks, especially from infections, linked to biological therapies to be monitored in this paediatric population
the Transparency Committee considers that ROACTEMRA (tocilizumab) provides a moderate improvement in actual benefit (level III) in the treatment of active systemic juvenile idiopathic arthritis in children aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids."

07.2 Other health technologies

Not applicable

Conclusion
ROACTEMRA (tocilizumab) is the only clinically relevant comparator refunded by National Health Insurance.

08 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

ILARIS has Marketing Authorisation in SJIA in all countries of the European Union and in the USA. On the date on which this document was prepared, ILARIS was refundable in Germany only, in its indication in the Marketing Authorisation. An assessment of its refundability was in progress in Italy. Its refundability is not recommended by NICE (United Kingdom) because no data have been supplied by the company.

09 ANALYSIS OF AVAILABLE DATA

Two clinical studies versus placebo (2305 and 2301) and their open extension phase (2301 E1) have been supplied.
Patients from a phase II dose-finding study (2203) were taken into account in the evaluation of safety.

09.1 Efficacy

The efficacy data for canakinumab (ILARIS) in the treatment of systemic JIA are based on the results of two phase III placebo-controlled studies:[4]
- study 2305 (β-SPECIFIC 1) lasting 1 month (n = 84), and
- study 2301 (β-SPECIFIC 2) which comprised an open part and a double-blind part.

The company has also supplied the interim results for the open extension phase (still in progress) of the two studies versus placebo (study 2301 E1).

Because it was developed in parallel, comparison with tocilizumab was not possible. In fact, the patients were included in the two studies evaluating canakinumab between July 2009 and December 2010, whereas tocilizumab has had Marketing Authorisation in Europe[5] in SJIA only since August 1st 2011.

Study 2305

Primary objective:
To demonstrate the superiority in terms of efficacy (assessed using the ACR paediatric 30 response[6] adapted to day 15) of a single subcutaneous injection of canakinumab by comparison with placebo.

Methodology:
Placebo-controlled, randomised, double-blind.

Inclusion criteria:
Patients aged 2 to 19 years, with confirmed SJIA (2004 ILAR criteria) that is active (defined by the presence of fever > 38° for at least 24 hours, at least two inflamed joints and a plasma CRP > 30 mg/l) were included. Patients receiving concomitant treatments in a stable dose could be included (prednisolone in a dose < 1 mg/kg/day for at least 3 days, methotrexate in stable doses for least 8 weeks, NSAIDs in stable doses for at least 2 weeks before entering the study).
Patients previously treated with anakinra, TNF-α or IL-6 inhibitors could be included on condition that they observed a weaning period based on the half-life of these biological therapies.

Treatments received:
Patients were randomised to receive either a single subcutaneous injection of canakinumab 4 mg/kg (maximum 300 mg) or placebo on day 1. Randomisation was stratified by the number of active joints (≤ 26 / > 26), the response to prior treatment with anakinra (yes/no) and the dose level of prednisolone (≤ 0.4 mg/kg/> 0.4 mg/kg).
The doses of corticosteroids and methotrexate remained constant throughout the study.

Primary efficacy endpoint:

[4]Ruperto N, Brunner HI, Quartier P et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012; 367: 2396-2405.
[5]It should be noted that it has had Marketing Authorisation in Japan since April 2008.
[6]ACR (American College of Rheumatology) criteria, adapted in clinical studies, to take account of the presence of systemic signs characteristic of SJIA, particularly fever.

Proportion of patients with an ACR paediatric 30 response (ACRpedi30) adapted to Day 15.

The ACRpedi30 response adapted by the addition of the absence of fever endpoint is a validated composite endpoint that has been used to evaluate the efficacy of other biological therapies, particularly tocilizumab, in JIA.

The adapted ACRpedi30 response was defined as:
- an improvement by comparison with baseline of at least 30% for at least 3 of variables 1 to 6 in the ACR paediatric score, with no worsening of >30% in more than one variable from 1 to 6 in this score and
- no intermittent fever (≤ 38°) in the previous week (variable 7).

The ACR paediatric score is a composite endpoint which comprises the following seven variables:
- the global assessment of the disease activity by the investigator on a 100 mm visual analogue scale (VAS)
- the global assessment by the parents or the patient (age permitting) of the subject's overall well-being on a 100 mm VAS
- a questionnaire assessing the child's state of health (CHAQ disability scale (0 to 3))
- the number of joints affected by arthritis
- the number of joints with restricted mobility
- a laboratory measure of inflammation: serum CRP (mg/l)
- the absence of intermittent fever associated with SJIA during the previous week.

Calculation of the population:
A total of 122 patients had to be randomised to show a difference of 30% in ACRpedi30 responders between the two groups at Day 15 with a significance level of 0.025 and a statistical power of 90%.

Results

- Characteristics of the patients included, see Table 1:

The demographic characteristics of the patients were comparable in the two groups.
A total of 84 patients (41 in the canakinumab group and 43 in the placebo group) were included, the mean age was 9 years on inclusion (with 43% of children between 6 and 11 years and 28.5% under 6 years); 63% were girls. The mean duration of the disease was 3.4 years; about 70% of the patients were receiving corticosteroid therapy and 63% were being treated with methotrexate.
In fact, following an interim analysis of 80 patients (66% of the theoretical population), the study was discontinued early on the recommendation of the study's Monitoring Committee because of a lower level of responses in the placebo group compared with the initial hypotheses and a very significant difference in the ACR paediatric response rates between the two groups.

As regards previous treatments with biological therapies, the proportion of patients previously treated with:
- anakinra was 37%, comparable between the two groups. Half the patients previously treated with anakinra (16 out of 31) stopped the treatment for a reason other than efficacy or safety;
- etanercept was 33%, lack of efficacy was the reason for stopping treatment;
- adalimumab was 8.3%, lack of efficacy was the reason for stopping treatment, and
- tocilizumab was 3.5%, lack of efficacy or intolerance was the reason for stopping treatment;
- no patient had been treated with abatacept.

Table 1.Characteristics of the patients on inclusion in study 2305

	Canakinumab N=41	Placebo N=43	Total N=84
Age (years)			
mean (SD)	8.3 (5.1)	9.7 (4.3)	9.0 (4.8)
Age range n (%)			
≥ 2 - < 4 years	9 (20.9)	0 (00.0)	9 (10.7)
4 - < 6 years	8 (18.6)	7 (17.9)	15 (17.9)
≥ 6 - < 12 years	14 (32.6)	22 (42.9)	36 (42.9)
≥ 12 - < 20 years	12 (27.9)	12 (28.6)	24 (28.6)
Duration of disease (days)			
Mean (SD)	1146	1309	1225
Number of active joints			
Mean (SD)	15.8 (15.3)	12.4 (12.2)	14.1 (13.9)
Median	10	7	8
CRP mg/ml			
Mean (SD)	193 (157)	157 (123)	175 (142)
Median	141	137	141
Previous treatment (%)			
Anakinra	37.2	36.6	37
Etanercept	30.2	36.6	33.3
Adalimumab	7.0	9.8	8.3
Tocilizumab	2.3	4.9	3.5
Number of patients with and without corticosteroids (%) on inclusion			
With	72.1	68.3	70.2
Without	27.9	31.7	29.8
Doses of corticosteroids (mg/kg/j)			
Mean (SD)	0.38 (0.24)	0.87 (2.8)	0.61 (1.9)
Min – max	0.02-1.00	0.09-15.0	0.02-15.0
Median	0.34	0.21	0.27

- Results

After 15 days the proportion of patients with a ACR paediatric 30 response on day 15 was 83.7% in the group treated with canakinumab versus 9.8% in the placebo group, i.e. an absolute difference in terms of the proportion of responders of 73.9% in favour of canakinumab p<0.0001.

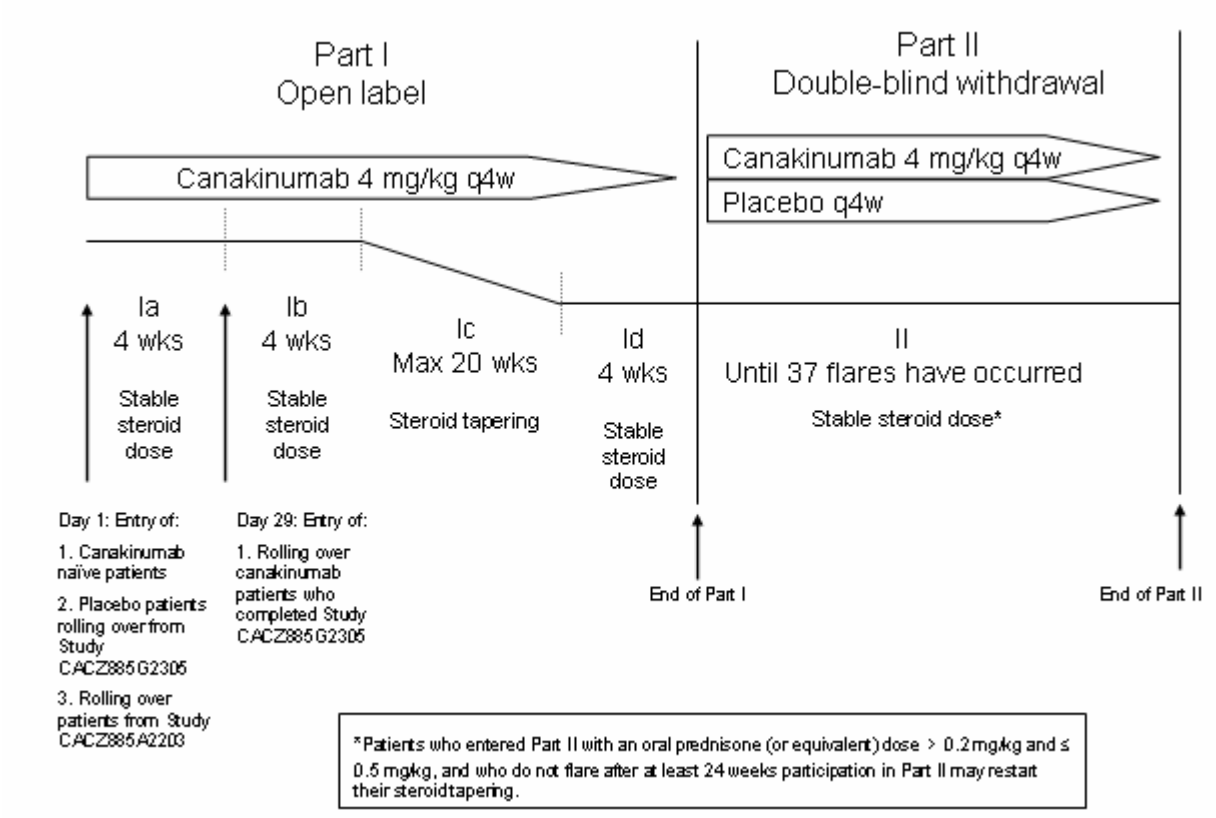
The analyses of predefined subgroups, particularly use or non-use of corticosteroids on inclusion, confirmed the robustness of this result; they did not show any influence of the use of cortico-steroids on inclusion on the efficacy of canakinumab. The superiority of canakinumab on all secondary endpoints, particularly the percentages of ACRpedi50/70/90/100 response, was also demonstrated.

The percentage of discontinuations of treatment was 14% (6/43) in the canakinumab group and 90.2% (37/41) in the placebo group on account of “unsatisfactory therapeutic efficacy”. No discontinuation on account of adverse effects was reported.

Study 2301

Objectives and methods:
Given the rarity of the disease and the desire to avoid giving a placebo for more than 4 weeks, this phase III study with a complex methodology included patients from two studies that evaluated canakinumab (study 2305 described earlier and a phase II dose-finding study, A2203) and some new patients.
Its primary objective was to evaluate the efficacy and safety of repeated doses of canakinumab in preventing flare-ups of inflammation.
It consisted of two parts, an open part 1 during which all patients were treated with canakinumab followed by a part 2 in which patients selected as responders to canakinumab were randomised double-blind to receive either canakinumab or placebo.

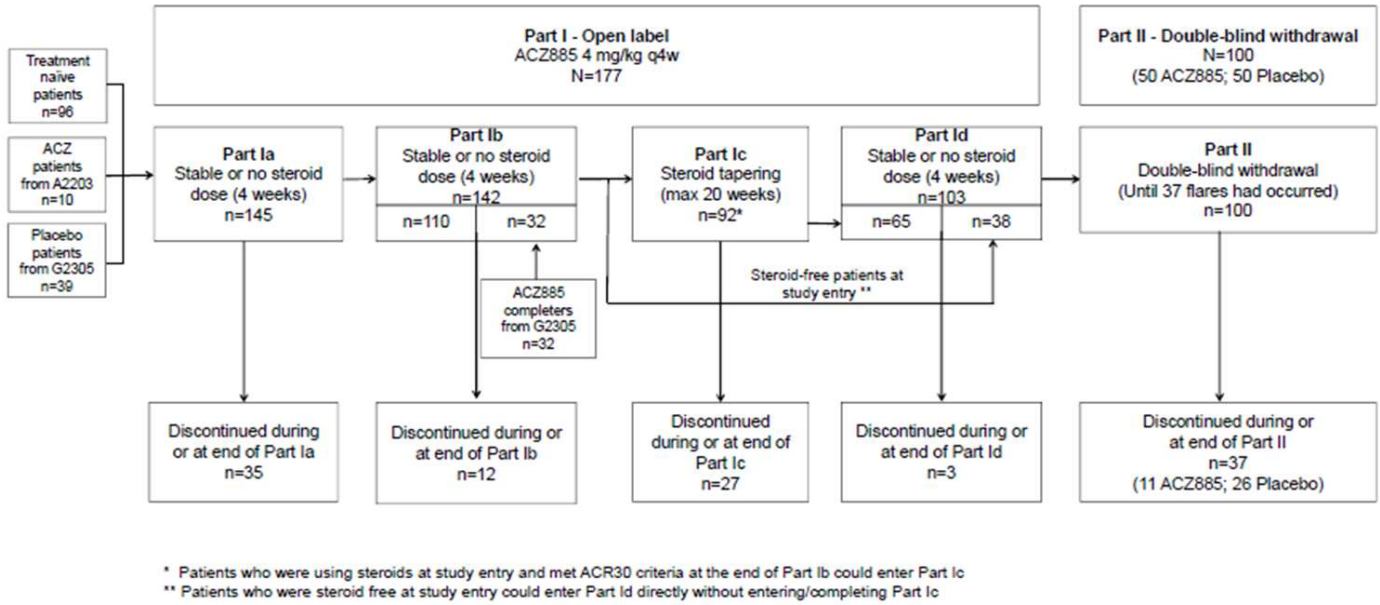
Figure 1. Diagram from the EPAR summarizing study 2301



- Part 1

The primary objective of part 1 was to evaluate whether treatment with canakinumab allowed a reduction in the corticosteroid therapy in at least 25% of the patients. It was made up of four sub-parts (1a, 1b, 1c and 1d) and lasted up to 32 weeks (corresponding to eight injections of canakinumab).

Figure 2. Diagram from the EPAR summarizing part 2 of study 2301



Parts 1a and 1b, each of 4 weeks' duration (corresponding to one subcutaneous injection of canakinumab), had as their objective the induction and maintenance of an ACR 30 response without adjusting the dose of corticosteroids.

The following patients could be included in part 1a:
- those naive to canakinumab because they had never participated in a study evaluating it,
- those from study 2305 who received the placebo,
- those from study 2305 who were treated with canakinumab but did not complete the study (discontinued treatment before the evaluation on Day 15) or who were not responders on Day 15,
- those from the phase II study A2203 who had a relapse within 6 months or more after the last injection of canakinumab.

These patients received an injection of canakinumab without adjustment of their dose of cortico-steroid if they were taking one.
At the end of part 1a, i.e. on Day 29, only responders to ACR paediatric 30 (among those included in 1a) could continue the study and be included in part 1b. In addition to these patients, patients who could be included in 1b were patients who had received an injection of canakinumab during study 2305 and had an ACR paediatric 30 response.
In part 1b, as in part 1a, patients had an injection of canakinumab without adjustment of their dose of corticosteroid.

At the end of periods 1a and 1b, all patients, whatever their time of inclusion, had received two injections of canakinumab.
At the end of part 1b, only patients who on inclusion in the study were being treated with oral corticosteroid and who were ACR paediatric 50 responders with a CRP ≤ 10 mg/l and without fever were included in part 1c.
Part 1c lasted up to 20 weeks and its objective was to reduce the doses of corticosteroids in accordance with the regimen predefined in the study protocol (see Table 2).

Table 2. Regimen with reducing the doses of corticosteroids during part 1c

Initial dose of prednisolone (or equivalent)	Reduction scheme specified in the protocol
> 0.1 mg/kg/day	Reduction of 0.1 mg/kg a week to reach a level of 0.1 mg/kg/day
< 0.1 mg/kg/day	Reduction to 0.05 mg/kg/day, every day for 1 week
≤ 0.05 mg/kg/day	Alternately level (e.g. every 48 h) for 2 weeks then stop

Patients from part 1b who had not been treated with corticosteroids did not participate in part 1c but went straight into part 1d.

The aim of part 1d was to administer a stable dose of corticosteroids for 4 weeks before randomisation to part 2 of the study. Part 1d served to ensure that patients had received at least 12 weeks of treatment with canakinumab before they entered randomised part 2.

- Part 2

Patients who were ACR paediatric 30 responders at least at the end of part 1 were randomised to the 2nd part to receive canakimumab 4 mg/kg every 4 weeks or placebo. The doses of corticosteroids had to remain stable. The main aim of this 2nd part was to demonstrate that the time to relapse was longer with canakinumab than with placebo.

Primary efficacy endpoint:
- Part 1: percentage of patients treated with corticosteroids at the start of part 1 who managed to reduce the doses of corticosteroids as specified in the protocol by the end of part 1c.
- Part 2: time to relapse

Results

- Part 1

Assignment of patients

A total of 177 patients were included in part 1, of which:
- 145 in part 1a (135 naive to canakinumab including 96 patients who had not participated in an earlier study, 39 who received placebo in study 2305) and 10 patients from the phase II study A2203).
- 142 in part 1b of which 32 included patients who had previously received canakinumab and had completed study 2305 who entered part 1b directly.
- 92 patients in part 1c
- 103 in part 1d including patients who had successfully reduced their doses of corticosteroids in accordance with the criteria stipulated in the protocol (n = 65) and patients who were not being treated with corticosteroids on entering the study and who went directly from part 1b to 1d (n = 38)

Seventy seven patients out of 177 (43.5%) prematurely discontinued their treatment in part 1, mainly on account of insufficient efficacy (72/77).

Characteristics of the patients (see Table 3)

The patients included in part 1 had a mean age of 8.7 years (43% of patients were between 6 and 11 years of age), the mean duration of the disease was 3.2 years, 84% of patients had systemic signs. The proportion of patients receiving treatment on inclusion was 72% for corticosteroid therapy, 54% for methotrexate, 60% for NSAIDs.

Prior treatments with biological therapies were reported for:
- 83 patients (46.9%) with anakinra (the reasons for stopping treatment were lack of efficacy 20.9%, safety 11.3% or other reason).
- 58 patients (32.8%) with etanercept (n = 56), 31.6% due to lack of efficacy,
- 10 patients (5.6%) with tocilizumab (treatment stopped both for lack of efficacy and for safety reasons)
- 9 patients (5.1%) with adalimumab, all due to lack of efficacy.

No patient had been treated with abatacept.

The median duration of treatment in this part 1 was 113 days (4 to 233 days), i.e. 3.8 months with a median number of four injections of canakinumab.

Table 3. Characteristics of the patients on inclusion in part 1 and on inclusion in part 2 of study 2301

	Part 1	**On inclusion in part 2 as per randomisation**		
	Canakinumab n = 177	Canakinumab n = 50	Placebo n = 50	Total n = 100
Age (years)				
mean (SD)	8.7 (4.5)	9.1 (4.2)	9.0 (4.8)	9.1 (4.5)
Age range n (%)				
≥ 2 - < 4 years	21 (11.9)	5 (10.0)	5 (10.0)	10 (10.0)
≥ 4 - < 6 years	32 (18.1)	5 (10.0)	11 (22.0)	16 (16.0)
≥ 6 - < 12 years	76 (42.9)	24 (48.0)	18 (36.0)	42 (42.0)
≥ 12 - < 20 years	48 (27.1)	16 (32.0)	16 (32.0)	32 (32.0)
Sex				
male (%)	44.6	44.0	46.0	45.7
female (%)	55.4	56.0	54.0	55.0
Duration of the disease (days)				
mean (SD)	1123 (1098)	1350 (1102)	973 (1110)	1154 (1115)
median	757	1000	658	806
min - max	56-5367	136-4517	56-5367	56-5367
Number of active joints (n)				
mean (SD)	14.9	10.5	11.6	11.1
median	10	7.0	7.5	7.0
CRP mg/ml				
mean (SD)	198 (147)	183 (161)	182 (141)	182 (153)
median	160	121	149	138
Prior treatment (%)				
with MTX	53	56	52	54
with biological therapy (%)	66	66	54	
- anakinra	46.9	50.0	40.0	45.0
- etanercept	32.8	26.0	22.0	24.0
- adalimumab	5.1	8.0	4.0	6.0
- tocilizumab	5.6	8.0	2.0	5.0
Number of patients with and without corticosteroids on inclusion (%)				
With	72.3	64	60	62
Without	27.7	36	40	38
Doses of prednisolone or equivalent (mg/kg/day)				
mean (SD)	0.37 (0.28)	0.29 (0.25)	0.35 (0.35)	0.32 (0.26)
median	0.27	0.2	0.27	0.26
min - max	0.02-1	0.02-1	0.03-0.97	0.02-1

Result of open part 1 on the primary endpoint relating to the reduction in the dose of corticosteroids

Given the non-comparative nature of this part, the results from it are purely descriptive and consequently their level of evidence is very low.

Out of the 128 patients included in part 1 who were receiving corticosteroids on inclusion, 92 tried, in part 1c, to progressively reduce their corticosteroids. The proportion of patients who had successfully reduced their doses of corticosteroids by the end of part 1c in accordance with the regimen given in the protocol was 44.5% (57/128) versus 55.5% (71/128) who did not manage to do so. The aim of achieving 25% of patients reducing their dose of corticosteroid was thus achieved. The mean dose of corticosteroids was reduced from 0.34 mg/kg/day on inclusion to 0.05 mg/kg/day.

- Part 2 (randomised)

Assignment of patients
A total of 100 patients identified as ACRpedi30 responders during part 1 were randomised to part 2, 50 patients per group.

Characteristics of the patients (see Table 3)
The demographic and medical characteristics were comparable between the two treatment groups, even though it should be noted that:
- fewer patients were aged 4-5 years in the canakinumab group (10%) compared with placebo (22%) and more patients were aged 6-11 in the canakinumab group (48%) compared with placebo (36%).
- the median time since diagnosis of the disease was about 2.7 years in the canakinumab group versus 1.8 years in the placebo group
- the proportion of patients who had had two or more flare-ups of inflammation within 12 months before entering the study was 58% in the canakinumab group versus 40% in the placebo group
- the proportion of patients who had systemic signs in the 6 months of the disease was 90% in the canakinumab group versus 72% in the placebo group.

However, no statistical difference in these parameters was demonstrated between the two groups:

Thirty seven (37) patients stopped treatment during part 2 (canakinumab: 11, placebo: 26), mainly on account of inadequate efficacy or a relapse (canakinumab: 11/50, placebo: 20/50). Four (4) patients stopped treatment on account of an adverse effect (all in the placebo group).

The median duration of treatment in part 2 was 221 days (i.e. 7.4 months) in the canakinumab group and 181 days (i.e. 6 months) in the placebo group.
Thus, the patients were treated in study 2301 (part 1 + part 2) for 1 year (mean).

Primary efficacy endpoint = time to relapse
For the placebo group, the median time to relapse was 236 days, i.e. about 8 months (95% CI: 141-449 days). This could not be estimated in the canakinumab group because of the small number of relapses observed (< 50%, p = 0.0043).
The reduction in the relative risk of occurrence of a flare-up was estimated by the Kaplan-Meier method with canakinumab, by comparison with placebo, as 64% (HR 0.36; 95% CI: 0.17 to 0.75; p = 0.0032).

Data from the extension of the two aforementioned studies
This phase is ongoing; only interim data have been presented. The median period of exposure was 49 weeks (3-144). Almost one third (42/147) of patients were treated during more than 96 weeks (2 years). These data suggest that the efficacy of canakinumab is maintained.

09.2 Safety/Adverse effects

The safety data for canakinumab in SJIA are from four studies, including two phase III studies (2301, 2305), the interim results of their open extension phase (2301 E1) and one phase II study (2203). In total, 201 patients with SJIA aged from 2 to less than 20 years were treated with canakinumab in these clinical studies. The median duration of exposure was 617 days (4-1829) and the median number of injections was 22 (1-49).
The proportion of patients who had an adverse event (AE) during the studies was 85.1% (171 out of 200). Infections were the most common AEs. The following were reported: nasopharyngitis (29.4%), cough (25.9%), fever (25.9%), vomiting (22.9%), diarrhoea 22.4%, upper respiratory infections (22.4%) and headaches (20.9%). The majority of these AEs were mild to moderate in severity. Serious AEs were reported in 16.9% of the patients.

Four deaths were reported during the studies, two of which were linked to an infection and two following a macrophage activation syndrome (MAS). None of these deaths was attributed by the investigator to the canakinumab.

MAS is a serious complication and the main cause of mortality from SJIA. During the studies, 12 cases of MAS were reported (10 in the canakinumab group and 2 in the placebo group); 2 of the cases had a fatal outcome (1 in each group). Out of the 10 cases reported in the canakinumab group, 7 were considered by the investigators to be probably attributable to the treatment.
The EMA considered that no conclusion could be drawn on a possible increased risk of MAS in patients with SJIA who were treated with canakinumab. It asked that a registry be set up to monitor MAS as part of the RMP.

Thirty patients (15%) had infections which were considered serious; two of these patients (1%) had stopped the treatment following the infection.

The incidence of discontinuations of treatment with canakinumab on account of AEs was 9.5%, mainly on account of a flare-up of juvenile arthritis (4%), MAS (2.5%), fever (1%) and pneumonia (1%).

No severe local reaction to the injection was reported during the studies.

Overall, the median period of patient follow-up is short (600 days) when assessing the medium- to long-term safety of ILARIS (particularly as regards MAS), hence the need for post-marketing surveillance requested as part of the RMP.

09.3 Summary & discussion

Efficacy
In one study, the efficacy and safety of a single dose of canakinumab was evaluated versus placebo. Forty-three (43) patients who had active systemic arthritis with fever, at least two active joints and C-reactive protein above 30 mg/l, received a subcutaneous injection of 4 mg/kg canakinumab and 41 received a placebo. These patients had a mean age of 9 years, most (63%) were girls, the disease had lasted for more than 2 years, 63% were being treated with methotrexate and 70% were receiving corticosteroid therapy.
After 2 weeks, 84% of the patients treated with canakinumab had an adapted ACR paediatric 30 response (primary endpoint), as did 10% with placebo, an absolute difference in terms of the proportion of responders of 73.9% in favour of canakinumab, $p<0.0001$.
In this study, 14% (6/43) of the patients in the canakinumab group and 90.2% (37/41) of those in the placebo group stopped treatment on account of “unsatisfactory therapeutic efficacy”. No discontinuation on account of adverse effects was reported.

In a second study, out of 128 patients selected as responders to canakinumab (ACR paediatric 30 response) who were being treated with corticosteroids at the time of their inclusion in the study, 92 tried to progressively reduce their corticosteroids. Of these, 44.5% (57/128) successfully reduced their doses of corticosteroids. The mean dose of corticosteroids was reduced from 0.34 mg/kg/day on inclusion to 0.05 mg/kg/day; because of the noncomparative nature of this phase, the level of evidence of these results is very low.

In the second part of the study, 100 patients were randomised to receive treatment with either canakinumab or placebo. The median time to relapse (primary endpoint) was 236 days, i.e. 7.9 months (95% CI: 141–449 days) with placebo and could not be estimated in the canakinumab group because of the small number of relapses observed (< 50%), p = 0.0043). The reduction in the relative risk of occurrence of a flare-up was estimated by the Kaplan-Meier method with canakinumab by comparison with placebo at 64% (HR 0.36; 95% CI: 0.17 to 0.75; p = 0.0032).
During this part, 37 patients stopped treatment (canakinumab: 11, placebo: 26), mainly on account of inadequate efficacy/relapse (canakinumab: 11/50, placebo: 20/50). Four (4) patients stopped treatment on account of an adverse effect (all in the placebo group).

Data from the open follow-up phase of these two studies are currently limited (median duration of exposure of 49 weeks); they suggest that the efficacy of canakinumab is maintained.

Adverse effects
The commonest adverse events were infections (nasopharyngitis and infections of the upper airways). The majority of these AEs were mild to moderate in severity. Serious AEs were reported in 16.9% of the patients. Four deaths unrelated to canakinumab were reported during the studies. Twelve (12) cases of macrophage activation syndrome (MAS) were reported (10 with canakinumab and 2 with placebo), of which 2 cases with a fatal outcome (canakinumab: 1; placebo: 1). An MAS follow-up registry is provided for as part of the RMP. No severe local reaction to the injection was reported during the studies.

Overall, the median period of patient follow-up is short (600 days) when assessing the medium- to long-term safety of ILARIS (particularly as regards MAS), hence the need for post-marketing surveillance requested as part of the RMP.

09.4 Planned studies

A follow-up registry is provided for as part of the risk management plan for ILARIS.
The RMP also provides for the initiation of a phase IV study and continuation of the ongoing extension phase:

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
CACZ885 G2301E1	To provide further long term efficacy and safety data of canakinumab in SJIA patients treated with canakinumab in SJIA pivotal trials.	Long term efficacy, Long term safety, Immunogenicity/ allergenicity, Macrophage Activation Syndrome (for SJIA)	On-going	Dec 2014

Phase IV Study (under development): Canakinumab (ACZ885) dose reduction or dose interval prolongation in active Systemic Juvenile Idiopathic Arthritis (SJIA): efficacy and safety study	To explore the efficacy and safety of canakinumab dose reduction or dose interval prolongation in canakinumab treatment-naïve patients who are both responders and who satisfy pre-defined criteria for inclusion	Long term safety and efficacy of reduced dosing regimen or reduced dosing frequency in patients reaching inactive disease status for 18 months	Planned	TBD
SJIA Pharmachild registry	To collect prospective safety, tolerability, efficacy, and treatment adherence information on juvenile idiopathic arthritis (JIA) subjects exposed to any biological agents and methotrexate (MTX), according to local standard practice	Infections, Neutropenia, Thrombocytopenia, Opportunistic infections, Severe injection site reactions, Malignancy, Canakinumab – immunosuppressant, combination therapy toxicity (for CAPS and SJIA), Macrophage activation syndrome (for SJIA), Missing information: Pregnancy	Under discussion	

010 THE MEDICINE'S THERAPEUTIC USE

Canakinumab is the first IL-1 inhibitor to have Marketing Authorisation in patients aged 2 years and older with systematic JIA who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

It is administered by SC injection once a month, which should, unlike the other biological therapy currently available in this indication (tocilizumab, IL-6 inhibitor, IV infusion twice a month, reserved for hospital use), allow outpatient management of certain patients.
Given its long half-life, its use must be considered by taking account of infection risks, and special attention must be paid to the possible occurrence of macrophage activation syndrome, which has been reported in clinical studies with canakinumab, even though it has not so far been formally established that ILARIS increases the incidence of this syndrome (see SPC).

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual Benefit

◗ Juvenile idiopathic arthritis is the term used for all inflammatory conditions of the joints without an identified cause, starting before the age of 16 years and with a duration of more than 6 weeks.[7] The systemic form of JIA (Still disease) preferentially occurs between the age of 1 and 5 years. It is characterised by the presence at least arthritis lasting at least 6 weeks and extra-articular signs dominated mainly by fever and a cutaneous disorder.[8]

◗ ILARIS is intended as a symptomatic treatment.

◗ Its efficacy/adverse effects ratio is high.

◗ Public health benefit

The public health burden of JIA, a rare disease, is small because of the small number of patients affected by this condition. The burden represented by the indication for ILARIS, which is indicated in patients aged 2 years and older who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids is therefore at best low.

Since improving the management of orphan diseases is an identified priority (GTNDO [National group of experts defining French public health objectives],[1] Rare Disease Plan), the treatment of this condition is a public health need.

In view of the available data, and in the absence of any study versus an active comparator, a moderate impact on morbidity is expected in the patients treated. The additional impact of ILARIS by comparison with the usual management cannot be determined. An impact on the quality of life due to the functional improvement can be expected; however, the data presented (CHQ-PF50 questionnaires) are fragmentary in nature and cannot be used to determine that impact.

The transferability of the data to current clinical practice is acceptable.

ILARIS therefore provides a partial response to the identified public health need.

Consequently, at best a low public health benefit is expected for ILARIS in this indication.

◗ This proprietary medicinal product is indicated as second-line treatment of systemic JIA in patients who have responded inadequately to previous therapy with NSAIDs and corticosteroids.

◗ There is just one treatment alternative; a single proprietary medicinal product with Marketing Authorisation in this indication (ROACTEMRA/tocilizumab).

Consequently, the Committee considers that the actual benefit of ILARIS is substantial.

[7] Job Deslandre et al. Arthrites Juvéniles idiopathiques. Orphanet encyclopaedia. September 2003.
[8] Heyman R, Prieur AM. Systemic forms of juvenile idiopathic arthritis: diagnosis and prognosis. Med Ther Pediatr 2006; 9(1): 16-22.

011.2 Improvement in Actual benefit

Like ROACTEMRA (tocilizumab), ILARIS (canakinumab) provides a moderate improvement in Actual benefit (level III) in the management of patients aged 2 years and older with active systemic juvenile idiopathic arthritis who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

012 TARGET POPULATION

On the basis of the wording of its Marketing Authorisation, the target population of ILARIS is made up of patients aged 2 years and older with active systemic JIA who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. It is of the same order as that of tocilizumab (ROACTEMRA).
According to data from the National Institute for Demographic Studies (INED), as ofJanuary, 1st 2013 there are about 12,522,000 children aged 2 to 17 years in France.
According to ORPHANET,[9] the prevalence of systemic JIA in France is estimated to be about 5/100,000 or about 600 patients.
There are no epidemiological data that can be used to estimate the proportion of patients with an inadequate response to NSAIDS and to corticosteroids.

013 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

◗ Specific requests inherent to reimbursement

The Committee reiterates that ILARIS has exception drug status.

◗ Request for data

The Committee wishes to re-assess ILARIS in a period of 1 year, mainly on the basis of the data from the registry requested as part of the RMP.

[9]The Orphanet reports, rare diseases series. Prevalence of rare diseases, June 2013.