Systemic juvenile idiopathic arthritis (SJIA) is a rare inflammatory disease, affecting approximately 10% of children diagnosed with juvenile idiopathic arthritis in the United States. The classic symptoms of SJIA include pain in the small joints of the hands, wrists, knees, and ankles; rash; and a high, spiking fever of ≥103°F that can last for weeks to months. By definition, SJIA can present at any point until the age of 16 years. However, a long-term outcomes study found that the median age at diagnosis of SJIA was 4 years. The distribution of the disease by sex is roughly equal.

Studies of long-term outcomes of juvenile idiopathic arthritis have demonstrated that disease-related morbidity continues to be evident in adulthood. Among adult patients with SJIA who were evaluated more than 16 years after diagnosis, 66% described joints with limited range of motion, 52% had joint pain, and 30% reported morning stiffness. Adult patients with SJIA also experience impaired quality of life and poor physical functioning, as well as long-term challenges with social functioning and sexual activity.

Although analyses of healthcare costs associated with SJIA are few, it is clear that children with juvenile idiopathic arthritis consume inordinate amounts of healthcare resources. A 2007 study of Canadian children showed that the total annual average direct medical cost for patients with juvenile idiopathic arthritis was almost $1700 higher (2005 Canadian dollars; range, $875-$2500) than for the control patients without juvenile idiopathic arthritis. Higher costs for patients with juvenile idiopathic arthritis were related to specialist visits, diagnostic tests, and medication use. A more recent German study showed that the average total cost of juvenile idiopathic arthritis was highest among patients with seropositive polyarthritis and SJIA. The cost of medications, including biologics, comprised almost 50% of the total healthcare costs for these patients.

Until very recently, the treatment options for patients with SJIA included methotrexate (Trexall); nonsteroidal anti-inflammatory drugs (NSAIDs); systemic corticosteroids; and tocilizumab (Actemra), an interleukin (IL)-6 inhibitor. Tocilizumab is indicated for patients with active SJIA aged ≥2 years and is administered once every 2 weeks as a 1-hour intravenous (IV) infusion. One additional medication was recently added as a new treatment option for this patient population.

FDA Approves Canakinumab for SJIA

In May 2013, the US Food and Drug Administration (FDA) approved a new indication for canakinumab (Ilaris; Novartis) for the treatment of active SJIA in patients aged ≥2 years. Canakinumab is the first IL-1 beta inhibitor approved for the treatment of SJIA, and the only approved SJIA treatment that is given as a subcutaneous (SC) injection once monthly.

The FDA approval of the new indication for canakinumab was based on 2 phase 3 clinical trials of patients with SJIA and demonstrated significant symptom improvement in the majority of patients receiving canakinumab. This drug is already approved by the FDA for the treatment of the rare autoinflammatory diseases that form cryopyrin-associated periodic syndromes.

Canakinumab Fills an Unmet Need

In an interview regarding the treatment of SJIA with canakinumab, Alberto Martini, MD, Professor of Pediatrics, University of Genoa, Italy, stated, “In a sizable proportion of patients [with SJIA], there was a big improvement in symptoms, and there was the possibility to reduce substantially the amount of steroids that these children were receiving….Treatment with this type of cytokine inhibitor could radically change the way we are treating [SJIA].”

The availability of canakinumab for patients with SJIA offers an easier-to-use alternative for children and their families who wish to avoid the logistic and tolerability challenges associated with an IV therapy given every 2 weeks. “The efficacy of Ilaris, along with its monthly subcutaneous dosing, make it an exciting new option for children who are living with this debilitating disease,” said Daniel J. Lovell, MD, MPH, Associate Director, Division of Rheumatology, Cincinnati Children’s Hospital Medical Center, OH.

Mechanism of Action

Canakinumab is a selective fully human monoclonal
antibody that inhibits IL-1 beta, one of the proinflammatory cytokines that comprise the body’s immune system’s defenses. Excess production of IL-1 beta plays a prominent role in inflammatory diseases, including in patients with juvenile rheumatoid arthritis. Canakinumab inhibits inflammation by neutralizing IL-1 beta for a sustained period of time.

**Dosing and Administration**

The recommended dose and schedule of canakinumab in patients with SJIA is 4 mg/kg, with a maximum of 300 mg for patients with a body weight of ≥7.5 kg. Canakinumab is administered subcutaneously every 4 weeks. There are no contraindications to the use of canakinumab, with the exception of patients who have confirmed hypersensitivity to the active substance of canakinumab or to any of its excipients.

Each monthly SC injection of canakinumab costs $16,000. Canakinumab’s manufacturer offers financial assistance to eligible patients who are unable to afford treatment with canakinumab.

**Phase 3 Clinical Trials**

Canakinumab was approved by the FDA for the treatment of SJIA on the basis of 2 randomized, multicenter, double-blind phase 3 clinical trials. Both trials enrolled patients who had a confirmed diagnosis of SJIA at least 2 months before enrollment in the study (mean disease duration at baseline, 3.5 years); active disease, defined as ≥2 joints with active arthritis (mean number of active joints, 15.4); documented spiking, intermittent fever (>38°C) for at least 1 day within 1 week before study drug administration; and C-reactive protein >30 mg/L. Patients were allowed to continue treatment with stable doses of methotrexate, corticosteroids, and/or NSAIDs. The tapering of corticosteroid doses was allowed according to the design of study 2.

**Trial Design**

In study 1, patients with SJIA received a single dose of canakinumab 4 mg/kg (N = 43) or of placebo (N = 41) via SC injection. Patients were then assessed for efficacy at day 15, and had a safety analysis done up to day 29. The SJIA study 2 had a 2-part design that included an open-label, single-arm, active-treatment period (part 1), followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design (part 2). Overall, 177 patients received canakinumab 4 mg/kg (maximum, 300 mg) in part 1 of study 2, and 100 patients received canakinumab 4 mg/kg (maximum, 300 mg) or placebo every 4 weeks in part 2 of study 2.

The primary objective of study 1 was to demonstrate the superiority of a single dose of canakinumab relative to placebo in the proportion of patients who achieved ≥30% improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion, which included the pediatric ACR core set (ACR 30% criteria for improvement [ACR30] response) and the absence of fever (temperature of ≤38°C in the preceding 7 days) at day 15.

The primary objective of study 2 was to demonstrate the prevention of flare with the use of canakinumab in patients with active SJIA. Flare was defined by a worsening of ≥30% in at least 3 of the 6 core pediatric ACR response variables, combined with an improvement of ≥30% in no more than 1 of the 6 variables, or the reappearance of fever not resulting from infection for at least 2 consecutive days.

**Efficacy: Study 1**

The analysis of study 1 data revealed a significant improvement in patients receiving a single dose of canakinumab versus placebo at day 15. Table 1 presents the percentages of patients by pediatric ACR response rate.
Among patients with SJIA who returned for their day 15 visit, the mean change in patient pain score (0-100 mm visual analog scale) was −50.0 mm with canakinumab (N = 43) compared with +4.5 mm with placebo (N = 25). The mean change in pain score among canakinumab-treated patients was consistent through day 29. All patients treated with canakinumab had no fever at day 3 compared with 87% of patients who received placebo.

### Efficacy: Study 2

**Corticosteroid dose tapering.** A total of 128 patients who entered part 1 (the open-label portion) of study 2, were taking corticosteroids. Of these, 92 patients attempted corticosteroid tapering. Of these 92 patients, 57 (62%) successfully tapered their corticosteroid doses. Almost half (N = 42 [46%]) of the patients discontinued treatment with corticosteroids.

**Time to flare.** In part 2, the probability of having a flare over time was significantly lower for the canakinumab-treated group versus the placebo group. Patients in the canakinumab group had a 64% relative reduction in the risk of flare compared with the patients receiving placebo (hazard ratio, 0.36; 95% confidence interval, 0.17-0.75).

### Safety Profile of Canakinumab in SJIA

The most common (≥10%) adverse drug reactions in patients with SJIA who received canakinumab were infections (ie, nasopharyngitis, upper respiratory tract infections), abdominal pain, and mild-to-moderate injection-site reactions (Table 2).

#### Infections

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Study 1</th>
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<tbody>
<tr>
<td>Canakinumab (N = 177) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Canakinumab (N = 50) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Infection (eg, nasopharyngitis, [viral] upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)</td>
<td>97 (54.8); 0.91</td>
</tr>
<tr>
<td>Placebo (N = 41) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 (30.2); 1.26</td>
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#### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Study 2</th>
<th>Study 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canakinumab (N = 50) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Canakinumab (N = 43) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>25 (14.1); 0.16</td>
</tr>
<tr>
<td>Skin reactions</td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction, mild&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (10.7)</td>
</tr>
<tr>
<td>Injection-site reaction, moderate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (1.1)</td>
</tr>
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</table>

<sup>a</sup>Incidence rate represents the exposure-adjusted incidence rate per 100 patient-days.

<sup>b</sup>No injection-site reaction led to study discontinuation.

IR indicates incidence rate; SJIA, systemic juvenile idiopathic arthritis.

Source: Ilaris (canakinumab) injection prescribing information; 2013.

### Table 2  Adverse Reactions from 2 Pivotal Clinical Trials of Canakinumab in Patients with SJIA

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
<th>Study 1</th>
</tr>
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<tbody>
<tr>
<td>Canakinumab (N = 177) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Canakinumab (N = 50) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Placebo (N = 41) N (%); IR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 (30.2); 1.26</td>
<td>5 (12.2); 1.37</td>
</tr>
<tr>
<td>Infection (eg, nasopharyngitis, [viral] upper respiratory tract infection, pneumonia, rhinitis, pharyngitis, tonsillitis, sinusitis, urinary tract infection, gastroenteritis, viral infection)</td>
<td>97 (54.8); 0.91</td>
<td>27 (54); 0.59</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>25 (14.1); 0.16</td>
<td>8 (16); 0.15</td>
</tr>
<tr>
<td>Skin reactions</td>
<td></td>
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</tr>
<tr>
<td>Injection-site reaction, mild&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (10.7)</td>
<td>6 (12.0)</td>
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<sup>a</sup>Incidence rate represents the exposure-adjusted incidence rate per 100 patient-days.

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Source: Ilaris (canakinumab) injection prescribing information; 2013.
Experts suggest that biologics, including canakinumab, are effective alternatives for children with SJIA who wish to avoid the potentially devastating toxicities of treatment with high-dose corticosteroids.

**Macrophage activation syndrome.** Macrophage activation syndrome is a life-threatening disorder that can develop in patients with rheumatic conditions, in particular in patients with SJIA. Physicians should be attentive to any symptoms of infection or worsening of SJIA, because these are known triggers for macrophage activation syndrome. Of 201 patients with SJIA who were treated with canakinumab in clinical trials, 11 cases of macrophage activation syndrome were observed. In clinical trials, canakinumab did not increase the incidence of macrophage activation syndrome in patients with SJIA, but no definitive conclusion can be made at this point.  

**Immunosuppression.** The impact of treatment with anti-IL-1 therapy on the development of malignancies is not known. However, treatment with immunosuppressants, including canakinumab, may result in an increase in the risk of malignancies.  

**Conclusion**

For children and adolescents with SJIA, canakinumab offers clinically and statistically significant efficacy benefits, a favorable tolerability profile, and a convenient schedule and route of administration. Experts suggest that biologics, including canakinumab, are effective alternatives for children with SJIA who wish to avoid the potentially devastating toxicities of treatment with high-dose corticosteroids. Clinical studies are under way to assess the safety and efficacy of the prolonged use of various canakinumab doses, as well as to elucidate the role of canakinumab and other biologics relative to corticosteroids in patients with SJIA.  

**References**