ACZ885: An Investigational Treatment in Systemic Juvenile Idiopathic Arthritis (SJIA)

What is ACZ885?
ACZ885 (canakinumab) is a selective, fully human anti-IL-1 beta monoclonal antibody being investigated to treat systemic juvenile idiopathic arthritis (SJIA). SJIA is a rare systemic interleukin-1 beta (IL-1 beta)-mediated autoinflammatory disease characterized by daily spiking fevers, rash, chronic pain, arthritis that may result in joint destruction, functional disability and impaired growth\(^1\,\text{,}^2\). Patients can also suffer enlargement of their liver and spleen, as well as inflammation of the lining of their organs\(^1\). SJIA affects less than one child per 100,000\(^3\).

Under the brand name Ilaris\(^\circ\), ACZ885 is approved in more than 60 countries, including in the EU, US, Switzerland and Japan for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), a rare, life-long, genetic, autoinflammatory disease with debilitating symptoms\(^4\). CAPS is a disease that comprises three different phenotypes sharing a number of common symptoms, such as chronic recurrent fever, urticaria, occasional arthritis, deafness and potentially life threatening amyloidosis\(^4\):
- Familial Cold Autoinflammatory Syndrome (FCAS)
- Muckle-Wells Syndrome (MWS)
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID).

Worldwide regulatory submissions for ACZ885 in SJIA are planned for 2012.

ACZ885 as a potential treatment for SJIA
The aim of SJIA therapy is to suppress systemic inflammation and induce disease inactivity\(^5\). Long-term corticosteroid use in children is associated with potentially serious adverse effects, including Cushing syndrome, growth suppression and osteoporosis\(^5\).

ACZ885 inhibits interleukin-1 beta (IL-1 beta) signaling, which is an important part of the body’s immune system defenses\(^4,6\). IL-1 beta plays a prominent role in certain inflammatory diseases, including SJIA\(^7\).

The inflammation that causes the symptoms of SJIA is thought to be due to activation of the innate immune system, which is normally responsible for the initial response to infection. During periods of active inflammation in SJIA, white blood cells (neutrophils and pro-inflammatory activated monocytes) are recruited and activated, causing further inflammation through release of signalling molecules called cytokines\(^8\).

IL-1 beta is a cytokine that is produced excessively in patients with SJIA – monocytes from SJIA patients produce high levels of this cytokine\(^9\). ACZ885 provides selective and sustained inhibition of IL-1 beta, which is a scientifically recognized driver of inflammation in SJIA\(^10\).

Key clinical ACZ885 data
There are two completed Phase III pivotal studies of ACZ885 in SJIA (ClinicalTrials.gov identifiers: NCT00886769 and NCT00889863). An extension study is also ongoing (ClinicalTrials.gov identifier NCT00891046).
ACZ885 in Systemic Juvenile Idiopathic Arthritis (SJIA) Media Backgrounder

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The first of the two pivotal Phase III studies involved 84 patients with active SJIA between the ages of 2 and 19 years and showed that ACZ885 provided significant and substantial symptom relief compared with placebo. The study met all primary and secondary endpoints.\(^{11}\)

In this study, most ACZ885-treated patients (83.7\%) responded to treatment, defined as having a minimum 30\% improvement in their symptoms vs. 9.8\% for placebo (p<0.0001), within 15 days after a single subcutaneous (s.c.) injection. The majority of patients (67.4\%) achieved at least a 50\% improvement vs. 4.9\% for placebo (p<0.0001), while a third of patients (32.6\%) achieved a 100\% improvement vs. 0\% for placebo (p<0.0001)\(^{11}\). Patients were evaluated using the American College of Rheumatology (ACR) Pediatric criteria, adapted to include the absence of fever – a key systemic feature of SJIA.

During the study, 55.8\% of patients experienced adverse events (AEs), including infections, with ACZ885 vs. 39\% with placebo. However, a direct comparison of AEs between the ACZ885 and placebo treatment groups is difficult because most patients discontinued from the placebo arm due to lack of efficacy (~2.7 times greater observation period in the ACZ885 group)\(^{12}\). No serious local injection site reactions were reported\(^{12}\). Serious adverse events (SAEs), including infections, were reported for two patients in the ACZ885 group vs. two in the placebo group\(^{11}\). Two patients (one in each treatment group) had a reported event of macrophage activation syndrome (MAS) and three patients had serious infections (two in the ACZ885 group and one in the placebo group)\(^{11}\). No SAEs led to discontinuation and all resolved without complications\(^{11}\).

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The second pivotal Phase III study had two parts and included 177 patients between the ages of \(\geq 2\) and \(<20\) years with active SJIA. Both primary endpoints were met. Data from the open-label Part 1 of this study showed that 45\% of patients with active SJIA who entered the trial using an oral corticosteroid (often described as steroids) were able to substantially reduce their corticosteroid dose within 28 weeks of commencing treatment with ACZ885 (p<0.0001), during a maximum 20 week tapering period\(^{13}\). These patients also maintained a minimum adapted ACR Pediatric 30 criteria response\(^{13}\). In addition, one third (33\%) of SJIA patients treated with ACZ885 who entered the trial using an oral corticosteroid were able to completely discontinue their corticosteroids\(^{13}\).

Within the placebo-controlled phase (Part 2), patients who had a minimum adapted ACR Pediatric 30 criteria at the end of Part 1 were randomized to either continue receiving ACZ885, or to receive placebo every 4 weeks, until a pre-specified number (37) of flare-events (“flares”) had occurred.

In Part 2, patients using ACZ885 were nearly three times (0.37 hazard ratio) less likely to suffer a new flare\(^{13}\). Only 22\% of ACZ885-treated patients experienced a new flare, vs. 52\% of patients on placebo during the study (p=0.0043)\(^{13}\). At the end of the study, 62\% of SJIA patients treated with ACZ885 had inactive disease status\(^{13}\). In contrast, patients who received placebo in Part 2 after previous ACZ885 treatment had a 32\% rate of inactive disease at this time point\(^{13}\). Disease inactivity is a rigorous definition of improvement, comprising absence of symptoms including: no active arthritis, no fever, no rheumatoid rash, as well as normalized blood markers normally associated with inflammation, such as ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein)\(^{14}\).
In Part 1 of the study, when all patients received open-label ACZ885 (representing 58 patient years), 138 of 177 patients (78%) reported an AE, with the most common being nasopharyngitis, headache and cough. SAEs were reported in 15 patients, with the most common being infections, MAS (four cases) or flare-associated events. Five SAEs led to discontinuation and one patient died of MAS. During Part 2, when patients received either ACZ885 or placebo in a blinded fashion, AEs (the most common being arthralgia, cough, nasopharyngitis and pyrexia) were reported by 40 of 50 (80%) ACZ885-treated patients vs. 35 of 50 (70%) placebo-after-ACZ885-treated patients. Six patients in each treatment group experienced one or more SAE, which mainly included infections, MAS and flare-associated events. Six patients, all in the placebo arm, discontinued the study due to AEs or SAEs during Part 2. One patient died from MAS two days after study discontinuation in the placebo-after-ACZ885 group.

**Development of ACZ885 in other areas**

ACZ885 is being studied in other diseases in which IL-1 beta plays a prominent role in inflammation, such as Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), gouty arthritis and cardiovascular disease. Not all patients with these diseases would be eligible for treatment with ACZ885, if approved.

**References**

4. Ilaris [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2009.
13. Ruperto N, Brunner H, Horneff G. Efficacy and safety of canakinumab, a long acting fully human anti-interleukin-1β antibody, in systemic juvenile idiopathic arthritis with active systemic features: results from a phase III study. Oral presentation at: The 2011 ACR Annual Scientific Meeting; 2011 November 5-9; Chicago, US.

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