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Novartis Phase III study showed 62% of patients with most severe form of childhood arthritis were symptom-free with ACZ885 treatment

- *Data also showed one third of patients became steroid-free within five months with ACZ885[1], a fully human monoclonal antibody that inhibits IL-1 beta[2]*
- *ACZ885 regulatory submissions on track for 2012 in systemic juvenile idiopathic arthritis (SJIA), a rare, disabling and potentially fatal autoinflammatory disease[3]*
- *A Phase II study of ACZ885 in TNF-receptor associated periodic syndrome (TRAPS) showed substantial symptom relief in this rare, periodic fever syndrome[4]*

Basel, 6 June 2012 – Novartis announced today new data from two trials with ACZ885 (canakinumab); a pivotal Phase III study in patients with systemic juvenile idiopathic arthritis (SJIA), and a Phase II study in patients with tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). SJIA and TRAPS are both rare and serious autoinflammatory diseases that usually start in childhood[4-6].

Both studies met their primary endpoints, and the results will be presented on 7 June at the annual congress of the European League Against Rheumatism (EULAR 2012), in Berlin, Germany[1,4].

In the Phase III study, 62% of SJIA patients treated with ACZ885 had inactive disease status at the end of the placebo-controlled period. In contrast, patients who had received ACZ885 treatment and were then randomized to receive placebo had a 32% rate of inactive disease at this time point. 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). In addition, one third (33%) of SJIA patients treated with ACZ885 were able to completely discontinue corticosteroids[1].

The aim of SJIA therapy is to suppress systemic inflammation and induce disease inactivity[7]. Long-term corticosteroid use in children is associated with potentially serious adverse effects, including Cushing syndrome, growth suppression, and osteoporosis[7].

Data from this Phase III study support the safety and efficacy profile of ACZ885 in the study population. Side effects observed in this study were similar to those already seen for ACZ885's approved indication in CAPS (Cryopyrin-Associated Periodic Syndromes), including infections and neutropenia[1]. Infections were the most common category of adverse event (AE) in both parts of the study. Cases of macrophage activation syndrome (MAS) were also reported[1].

"In clinical practice, our aim is to help children with SJIA lead a normal life. It is encouraging to see many patients become free of SJIA symptoms in this trial," said Prof Alberto Martini, Professor of Pediatrics at the University of Genoa and Head of Pediatric Rheumatology at the G. Gaslini Research Institute, Italy. "It is also positive that a third of

patients achieved sufficient symptom control with ACZ885 to allow them to completely discontinue corticosteroid therapy."

In the Phase II study, 90% of TRAPS patients treated with ACZ885 experienced clinical remission after only one week of treatment. Clinical remission included a clinically significant improvement of disease symptoms, as assessed by the treating physician. After two weeks of treatment, 95% of patients with TRAPS treated with ACZ885 had achieved a complete or almost complete response (clinical remission as well as reduced levels of CRP and/or serum amyloid A [SAA], a protein associated with acute inflammation), which was maintained until the end of treatment with monthly dosing[4].

Side effects observed in this study were similar to those already seen for ACZ885's approved indication in CAPS. Infections, mostly upper respiratory tract infections (URIs), were the most commonly reported category of AE[4].

"It is encouraging to witness that targeting interleukin-1 beta with ACZ885 can result in such marked improvement of symptoms in patients with these rare and debilitating conditions, such as SJIA and TRAPS", said John Hohneker, Head of Development for Integrated Hospital Care for the Pharmaceuticals Division of Novartis. "We are committed to investigating new treatments that can address the existing unmet medical need in immune-mediated diseases, no matter how rare some of these conditions may be."

SJIA is a rare systemic interleukin-1 beta (IL-1 beta)-mediated autoinflammatory disease characterized by daily spiking fevers, rash, chronic pain, and arthritis that may result in joint destruction, functional disability and impaired growth[3,8]. Patients can also suffer enlargement of their liver and spleen, as well as inflammation of the lining of their organs[3]. SJIA affects less than one child per 100,000[9].

MAS is a known, potentially fatal condition associated with SJIA that is characterized by liver abnormalities, bleeding disorders, central nervous system dysfunction and multiple organ failure[10,11]. Approximately 10% of SJIA patients are diagnosed with MAS, some of whom suffer repeated episodes[8].

TRAPS is a rare auto-inflammatory disease that can affect both children and adults[12-14]. This genetically inherited disease is characterized by long and intermittent attacks that can involve fever, rash, abdominal pain, conjunctivitis, severe skin infection, inflammation around the eyes and severe joint pain[12-14].

Amyloidosis is a serious complication of TRAPS and is estimated to occur in 25% of patients[15]. This long-term complication involves the production of SAA during inflammation, and can lead to liver and/or kidney failure. In some instances, amyloidosis can be fatal[16].

There are currently no approved treatments for TRAPS. While nonsteroidal anti-inflammatory drugs, steroids and colchicine have been shown to relieve some symptoms, there can be problems with limited and intermittent efficacy, in addition to the side-effects of long-term steroid use, particularly in children[12,17].

About the studies

ACZ885 in SJIA

The pivotal Phase III study in patients with SJIA comprised of an open-label, single-arm active treatment period (Part 1) followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design period (Part 2)[1]. A total of 177 patients between the ages of ≥2 and <20 years with active SJIA were enrolled in the study[1]. In Part 1, patients received a subcutaneous (s.c.) dose of ACZ885 (4 mg/kg, up to 300 mg) every 4 weeks. After 8 weeks, patients who entered the trial using a corticosteroid and who had a minimum adapted American College of Rheumatology (ACR) Pediatric 50

criteria began tapering (reducing) their steroid use until either: **a)** the dose had been tapered by a pre-specified amount depending on the baseline corticosteroid dose[18] while maintaining the adapted ACR Pediatric 30 criteria (successful tapering of steroids); or **b)** a maximum of 20 weeks passed without reaching this goal (unsuccessful tapering of steroids)[1]. In Part 2 of the study, 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[1].

The primary endpoints were to: **a)** assess if ACZ885 allows tapering of steroids in at least 25% of SJIA patients (Part 1); and **b)** demonstrate that time to flare is extended with ACZ885 vs. placebo (Part 2)[1].

Both primary endpoints were met, with 45% of patients successfully reducing their use of steroids within 28 weeks of commencing treatment with ACZ885 ($p<0.0001$)[1]. At this time point (end of Part 1), 31% of patients had inactive disease. Patients using ACZ885 were nearly three times (0.37 hazard ratio) less likely to suffer a new flare in Part 2. Only 22% of ACZ885-treated patients experienced a new flare, vs. 52% of patients on placebo during the study ($p=0.0043$)[1]. In Part 1 of the study (representing 58 patient years), 138 of 177 patients (78%) reported an AE, with the most common being nasopharyngitis, headache and cough. Serious adverse events (SAEs) were reported in 15 patients, with the most common being infections, MAS (four cases) or flare-associated events[1]. Five SAEs led to discontinuation and one patient died of MAS[1]. During Part 2, 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)[1]; and six patients in each arm experienced one or more SAE, which mainly included infections, MAS and flare-associated events[1]. Six patients, all in the placebo arm, discontinued the study due to AEs or SAEs during Part 2[1]. One patient died from MAS after study discontinuation in the placebo group.

ACZ885 in TRAPS

The ongoing Phase II, open-label, multicenter study investigating the efficacy and safety of ACZ885 in patients with active TRAPS involves 20 patients with a median age of 39 years (range, 7–78 years), who receive ACZ885 150 mg (or 300 mg) every four weeks. The primary endpoint of the study, is complete or almost complete response at Day 15.

Complete response was defined as clinical remission and normal CRP and/or SAA levels. Almost complete response was defined as clinical remission and elevated but ≥70% reduction of baseline CRP and/or SAA[4]. Clinical remission was maintained for all patients from Day 15 onwards in the four month treatment period, except for one patient with a relapse at Day 85 who subsequently responded to the scheduled ACZ885 dose[4].

At least one AE was reported for 95% of patients, and most AEs were mild in severity. One SAE, a URI that lasted two days, was reported[4].

About ACZ885

ACZ885 is a fully human monoclonal antibody that inhibits IL-1 beta, which is an important part of the body's immune system defenses[2]. Excessive production of IL-1 beta plays a major role in certain inflammatory diseases, including SJIA[19] and TRAPS[4]. ACZ885 works by neutralizing IL-1 beta for a sustained period of time, thereby inhibiting inflammation[2].

Under the brand name Ilaris®, ACZ885 is approved in more than 60 countries, including the EU, US and Switzerland for the treatment of adults and children as young as four years with CAPS, a rare, lifelong, inflammatory disorder with debilitating symptoms[2]. ACZ885 is also being studied in other diseases in which IL-1 beta plays a key role in causing inflammation, such as gouty arthritis and cardiovascular disease. ACZ885 is not

approved for the treatment of SJIA or TRAPS. Not all potential patients with these diseases would be eligible for treatment with ACZ885, if approved.

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The foregoing release contains forward-looking statements that can be identified by terminology such as “on track,” “potentially,” “will,” “encouraging,” “committed,” “being studied,” “potential,” or similar expressions, or by express or implied discussions regarding potential submissions or approvals of new indications or labeling for ACZ885 or the timing of any such submissions or approvals, or regarding potential future revenues from ACZ885. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with ACZ885 to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that ACZ885 will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that ACZ885 will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding ACZ885 could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; competition in general; government, industry and general public pricing pressures; unexpected manufacturing issues; the company’s ability to obtain or maintain patent or other proprietary intellectual property protection; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2011, the Group’s continuing operations achieved net sales of USD 58.6 billion, while approximately USD 9.6 billion (USD 9.2 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Novartis Group companies employ approximately 124,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

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