NOVARTIS

NEJM published study shows Novartis compound ACZ885 significantly relieves symptoms in patients with serious form of childhood arthritis

Dec 19, 2012

- - Endpoints met in two Phase III trials, including substantial symptom relief in 84% of systemic juvenile idiopathic arthritis (SJIA) patients treated with ACZ885 in trial-11
- - SJIA patients treated with ACZ885 in trial-2 were nearly three times less likely to suffer a new flare vs. placebo1
- - In trial-2, corticosteroid use substantially reduced in 45% of ACZ885-treated SJIA patients and discontinued completely in one third1
- - ACZ885, a fully human monoclonal antibody, neutralizes interleukin-1 beta (IL-1 beta),1 a key mediator in autoinflammatory diseases such as SJIA1

/* Style Definitions */ span.prnews_span { font-size:8pt; font-family:"Arial"; color:black; } a.prnews_a { color:blue; } li.prnews_li { font-size:8pt; font-family:"Arial"; color:black; } p.prnews_p { font-size:8pt; font-family:"Arial"; color:black; }

EAST HANOVER, N.J., Dec. 19, 2012 /PRNewswire/ -- The New England Journal of Medicine (NEJM) published today the results of two Phase III trials, and both show ACZ885 (canakinumab) provided substantial symptom relief in young patients with systemic juvenile idiopathic arthritis (SJIA).[1] In addition, ACZ885 delayed disease flare recurrence and allowed patients to substantially reduce or discontinue use of corticosteroids.[1] ACZ885 is a Novartis compound being studied for use in SJIA, a rare, disabling and potentially fatal autoinflammatory disease, characterized by spiking fever, rash, and arthritis that may result in joint destruction, functional disability and impaired growth.[1,2]

"Treatment options for SJIA are limited even though it is the most severe subtype of juvenile idiopathic arthritis. By necessity, steroids are commonly used to manage SJIA symptoms despite their known side effects. Long-term use of steroids can negatively impact children's bones and growth," said Daniel Lovell, MD, MPH, study investigator and Joseph E. Levinson Professor of Pediatrics at the Cincinnati Children's Hospital Medical Center. "These data show the potential for ACZ885 to manage SJIA symptoms and reduce the need for high doses of corticosteroids, and that is exciting news."

In beta-SPECIFIC 1 (trial-1), 84% of SJIA patients treated with ACZ885 experienced at least a 30% improvement in symptoms compared to 10% for placebo after 15 days of treatment, which was sustained after 29 days ($p<0.001$).[1] In beta-SPECIFIC 2 (trial-2), 45% of ACZ885-treated patients who were prescribed corticosteroids at study entry were able to substantially reduce their use of steroids, and one third of patients completely discontinued steroids.[1] Additionally, ACZ885-treated patients were nearly three times less likely to experience a new flare, with 74% of ACZ885-treated patients remaining flare-free compared to 25% with placebo ($p=0.003$) (Kaplan-Meier estimate).[1]

"The publication of these data in NEJM highlights the vital need to address the severe burden of disease in children with SJIA," said Tim Wright, MD, Global Head of Development, Novartis Pharmaceuticals. "Novartis is

committed to addressing the unmet medical needs of patients living with rare diseases, and these results underscore the potential of ACZ885 to provide an important new treatment option for children with SJIA."

Data from the Phase III program of ACZ885 in SJIA form the basis for worldwide regulatory submissions. In the EU, regulatory submission was completed in November 2012. US regulatory submission is also on track.

Both studies explored multiple secondary endpoints.[1] During the double-blind, single-dose beta-SPECIFIC 1 study, a third of ACZ885 patients (33%) experienced inactive disease – which includes a complete absence of disease signs and symptoms – vs. 0% for placebo at Day 15.[1] This was sustained until the end of the study (Day 29, 30% of patients for ACZ885 vs. 0% for placebo).[1] At the end of 32 weeks of open-label ACZ885 treatment in beta-SPECIFIC 2, 31% of patients attained inactive disease status, and 62% of patients who continued to receive ACZ885 had inactive disease at the end of the study.[1] In contrast, patients who had received ACZ885 treatment and were then randomized to receive placebo had a 34% rate of inactive disease at this time point.[1] At the end of beta-SPECIFIC 2, 82% of patients met the adapted JIA American College of Rheumatology Pediatric (JIA ACR) 70 response criteria with ACZ885, vs. 62% for placebo-after-ACZ885-treated patients.[1]

In beta-SPECIFIC 1, 56% of patients experienced adverse events (AEs) with ACZ885 vs. 39% with placebo.[1] In Part I of beta-SPECIFIC 2, 78% of patients had a reported AE and during Part II, AEs were reported for 80% of ACZ885-treated patients (vs. 70% of placebo-after-ACZ885-treated patients).[1] Serious adverse events (SAEs) that were most frequently reported were flares of SJIA, infections and macrophage activation syndrome (MAS).[1] MAS occurred in seven patients across beta-SPECIFIC 1 and beta-SPECIFIC 2, and infections were more frequent with ACZ885 than placebo.[1]

About the studies

Beta-SPECIFIC 1
The Phase III, 4-week, randomized, double-blind, placebo-controlled study involved 84 patients between the ages of 2 and 19 years with active SJIA.[1] Patients were treated with either a single subcutaneous (s.c.) dose of ACZ885 (4 mg/kg, up to 300 mg) or placebo.[1]

The primary endpoint was the proportion of patients achieving the JIA ACR 30 response criteria, defined as 30% improvement in at least three of the six variables, worsening of more than 30% in no more than one of the criteria, and resolution of fever, from baseline at Day 15.[1] The six variables included physician's assessment of disease activity, parent's or patient's assessment of overall well-being, functional ability (assessed by an adapted version of the Childhood Health Assessment Questionnaire-Disability Index [CHAQ-DI]), number of joints with active arthritis, number of joints with limitation of motion and C-reactive protein, a laboratory measure of inflammation.[1]

Other evaluations included an adapted JIA ACR 50, 70 and 100 response criteria (representing a 50%, 70% and 100% improvement, respectively), and disease inactivity.[1] 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).

The most common AEs were abdominal pain and nasopharyngitis.[1] SAEs, including infections, were reported for two patients for ACZ885 vs. two for placebo.[1] These did not lead to discontinuation.[1]

Beta-SPECIFIC 2

The Phase III, two-part study had an open-label, single-arm active treatment in Part I followed by a randomized, double-blind, placebo-controlled, event-driven withdrawal design in Part II.[1] A total of 177 patients between the ages of 2 and 19 years with active SJIA were enrolled in the study.[1] Some of these patients had previously participated in the beta-SPECIFIC 1 trial. In Part I, patients received a s.c. dose of ACZ885 (4 mg/kg, up to 300 mg) every 4 weeks. After 8 weeks, patients using corticosteroids who met the adapted JIA ACR 50 response criteria began tapering (reducing) their corticosteroid use until either: a) the corticosteroid dose had been decreased while maintaining the JIA ACR 30 criteria; or b) a maximum of 20 weeks passed without reaching the tapering goal.[1] In Part II of the study, patients were randomized to either continue receiving ACZ885, or to receive placebo every 4 weeks ("placebo-after-ACZ885 group"), 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 corticosteroids in at least 25% of SJIA patients (Part I); and b) demonstrate that time to flare is extended with ACZ885 vs. placebo (Part II).[1] The adapted JIA ACR 30, 50, 70 and 100 were evaluated, in addition to disease inactivity.[1]

In Part I of the study, the most common AEs were nasopharyngitis, abdominal pain and headache.[1] SAEs were reported in 15 patients, and included seven patients with infections and four patients with MAS.[1] Five SAEs led to discontinuation and one patient died of MAS.[1]

In Part II, the most common AEs were abdominal pain, cough and nasopharyngitis.[1] Six patients in each treatment group experienced one or more SAE, which included two infections in each group, and one case of MAS in the placebo-after-ACZ885 group.[1] Six patients, all in the placebo-after-ACZ885 group, discontinued the study due to AEs or SAEs, and one patient died from MAS.[1]

MAS is a known, potentially fatal condition associated with SJIA that may include liver abnormalities, bleeding disorders, central nervous system dysfunction and multiple organ failure.[3] Approximately 7% of SJIA patients are diagnosed with MAS.[3]

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.[4] Excessive production of IL-1 beta plays a major role in certain inflammatory diseases, including SJIA.[5] ACZ885 works by attaching itself to IL-1 beta for a sustained period of time, neutralizing its activity and inhibiting IL-1 beta-mediated inflammation.[4]

ACZ885 is currently approved in the US and other countries for a different disease state. ACZ885 is also being studied in other diseases in which IL-1 beta plays a key role in causing inflammation, such as TNF-receptor associated periodic syndrome, Familial Mediterranean Fever, gouty arthritis and cardiovascular disease. ACZ885 is not approved for the treatment of SJIA. Not all potential patients with these diseases would be eligible for treatment with ACZ885, if approved for the applicable disease.

About SJIA

SJIA is a rare systemic interleukin-1 beta (IL-1 beta)-mediated autoinflammatory disease characterized by spiking fever, rash, and arthritis that may result in joint destruction, functional disability and impaired growth.[1,2] Patients can also suffer enlargement of their liver and spleen, as well as inflammation of the lining of their organs.[1,2] SJIA affects less than one child per 100,000.[6]

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.[1,8,9]

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "potential," "committed," "on track," or similar expressions, or by express or implied discussions regarding potential new indications or labeling for ACZ885 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. 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 regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; 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 Pharmaceuticals Corporation researches, develops, manufactures and markets innovative prescription drugs used to treat a number of diseases and conditions, including cardiovascular, dermatological, central nervous system, bone disease, cancer, organ transplantation, psychiatry, infectious disease and respiratory. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which 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 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 127,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis.

References

1. Ruperto N, Brunner H, Quartier P, et al. Canakinumab in Systemic Juvenile Idiopathic Arthritis: 2 randomized trials. N Engl J Med 2012; e-pub ahead of print.
2. Pascual V, Allantaz F, Arce E. Role of Interleukin-1 (IL-1) In the Pathogenesis of Systemic Onset Juvenile Idiopathic Arthritis and Clinical Response to IL-1 Blockade. The Journal of Experimental Medicine 2005; 201(9):1479-1486

3. Behrens EM, Beukelman T, et al. Occult Macrophage Activation Syndrome in Patients with Systemic Juvenile Idiopathic Arthritis. J Rheumatol 2007;34;1133-1138
4. Ilaris [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2012
5. Martinon F, Petrilli V. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 2006; 440(9): 237-241
6. Ramanan AV, Grom AA. Does systemic-onset juvenile idiopathic arthritis belong under juvenile idiopathic arthritis? Rheumatology (Oxford) 2005; 44(11):1350-3.
7. Wallace CA. Current Management Of Juvenile Idiopathic Arthritis. Best Practice & Research Clinical Rheumatology Vol. 20, No. 2, pp. 279–300, 2006
8. U.S. National Library of Medicine (NLM), National Institutes of Health (NIH). Cushing Syndrome. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000389.htm. Last accessed: 12/12/12
9. Teitelbaum SL, et al. Should Bisphosphonates be Used for Long-Term Treatment of Glucocorticoid-Induced Osteoporosis? Arthritis Rheum. 2011 February 63(2): 325–328. doi:10.1002/art.30135

Novartis Media Relations

Julie Masow	Lucia Aurello
Novartis US Communications	Novartis US Pharma Communications
+1 212 830 2465 (direct)	+1 862 778 0788 (direct)
+1 862 579 8456 (mobile)	+1 862 368 5044 (mobile)
julie.masow@novartis.com	lucia.aurello@novartis.com

e-mail: us.mediarelations@novartis.com

For Novartis multimedia content, please visit www.thenewsmarket.com/Novartis
For questions about the site or required registration, please contact: journalisthelp@thenewsmarket.com.

SOURCE Novartis Pharmaceuticals Corporation

Source URL: *https://qa1.novartis.us/us-en/news/media-releases/nejm-published-study-shows-novartis-compound-acz885-significantly-relieves-symptoms-patients-serious-form-childhood-arthritis*

List of links present in page

1. https://qa1.novartis.us/us-en/us-en/news/media-releases/nejm-published-study-shows-novartis-compound-acz885-significantly-relieves-symptoms-patients-serious-form-childhood-arthritis
2. http://www.novartis.com/
3. http://twitter.com/novartis
4. http://www.nlm.nih.gov/medlineplus/ency/article/000389.htm
5. mailto:julie.masow@novartis.com
6. mailto:lucia.aurello@novartis.com
7. mailto:us.mediarelations@novartis.com
8. http://www.thenewsmarket.com/Novartis
9. mailto:journalisthelp@thenewsmarket.com