NOVARTIS

FDA accepts file and accelerates review of Novartis sickle cell disease medicine crizanlizumab (SEG101)

Jul 16, 2019

- - FDA grants crizanlizumab Priority Review based on Phase II data showing prevention of vaso-occlusive crises (VOCs) in patients with sickle cell disease, shortening FDA review to six months from standard ten months
- - Vaso-occlusive crises (also called sickle cell pain crises) are unpredictable and extremely painful events that can lead to serious life-threatening complications and death(1)

EAST HANOVER, N.J., July 16, 2019 /PRNewswire/ -- Novartis today announced the US Food and Drug Administration (FDA) accepted the company's Biologics License Application (BLA) and has granted Priority Review for its investigational sickle cell medicine crizanlizumab (SEG101). If FDA-approved, crizanlizumab is expected to represent the first monoclonal antibody targeting the P-selectin mediated multi-cellular adhesion in sickle cell disease.

Novartis submitted the application for crizanlizumab for the prevention of vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD) and was granted Breakthrough Therapy designation in December 2018. VOCs are unpredictable and extremely painful events that can lead to serious acute and chronic life-threatening complications and death. VOCs also lead to significant health care utilization. They are the most common cause of emergency room visits and hospital admissions for SCD patients, with total medical costs exceeding $1.1 billion annually in the United States[2].

Priority Review is granted to therapies that the FDA determines have the potential to provide significant improvements in the treatment, diagnosis, or prevention of serious conditions. The designation is intended to shorten the FDA review period to six months from the standard ten months.

"The FDA's decision to give crizanlizumab priority review reflects the impact that this medicine could have for the many thousands of US sickle cell adult patients who experience painful vaso-occlusive crises," said John Tsai, MD, Head of Global Drug Development and Chief Medical Officer, Novartis. "We are looking forward to the opportunity, if crizanlizumab is approved, to reimagine medicine in sickle cell disease for patients who live with this condition every day of their lives."

The FDA submission is supported by Phase II results from the SUSTAIN study, which showed that crizanlizumab (5 mg/kg) reduced the median annual rate of VOCs leading to health care visits by 45.3% compared with placebo (1.63 vs 2.98, P=0.010) in patients with or without hydroxyurea. Clinically significant reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype or hydroxyurea use.

The study also demonstrated that crizanlizumab (5 mg/kg) showed:

- A greater than two-fold increase in the percentage of patients who did not experience any VOCs vs placebo (36% vs 17%, P=0.010)[3]
- A three-fold longer median time to first VOC vs placebo (4.07 vs 1.38 months, P< 0.001)
- A 42% reduction in median annual rate of days hospitalized vs placebo (4.00 vs 6.87 P=0.45)

The most frequently reported adverse reactions (≥10%) in patients (N=111) treated with 5 mg/kg crizanlizumab were back pain, nausea, pyrexia, and arthralgia. The majority of adverse reactions were mild to moderate (Grade 1 or 2). Severe (Grade 3) events were observed for arthralgia and pyrexia 0.9% [1 case] each. No patients discontinued treatment due to adverse reactions based on the analysis. In the SUSTAIN trial, there were no apparent increases in reported overall infections (53.0% vs 53.2%) or neutropenia (3.1% vs 6.5%) adverse events with crizanlizumab treatment compared to placebo.

About Sickle Cell Disease

Sickle cell disease is a debilitating inherited genetic blood disorder that affects the shape of the red blood cells and can make blood cells and blood vessels stickier than usual[4,5]. When blood cells stick to one another, they can form multicellular adhesion clusters in the bloodstream. These clusters can reduce and block the flow of blood and oxygen, which can cause damage to the blood vessels and lead to acute and chronic complications[4,6]. These blockages also can lead to painful crises called VOCs, which are considered the clinical hallmark of the disease and the main reason why patients seek medical care in hospitals[4]. The average sickle cell patient in the United States is estimated to face nearly $1 million in total lifetime health care costs[7].

About crizanlizumab (SEG101)

Crizanlizumab (SEG101) is an investigational humanized monoclonal antibody blocking P-selectin mediated multicellular adhesion that is in late-stage development for the prevention of vaso-occlusive crises (VOCs), also known as pain crises, in patients with sickle cell disease (SCD). Crizanlizumab binds to a molecule called P-selectin on the surface of platelets and endothelium in the blood vessels, and has been shown to inhibit interactions between endothelial cells, platelets, red blood cells, sickled red blood cells, and leukocytes. P-selectin is one of the major drivers of the vaso-occlusive process. Our goal is to deepen understanding of the true impact of VOCs on patients' bodies and lives and to explore how crizanlizumab can help to achieve more pain-crisis-free days for patients with SCD[4].

The SUSTAIN clinical study is one of the clinical studies in the SENTRY clinical trial program for crizanlizumab. Major active trials in the SENTRY program include:

- SOLACE-adults (A2202) Phase II study investigating the pharmacological properties and safety of crizanlizumab in patients with sickle cell disease aged 16 and above
- SOLACE-kids (B2201) Phase II study investigating the appropriate dosing, safety, and efficacy of crizanlizumab in pediatric patients with sickle cell disease
- STAND (A2301) Phase III study investigating the efficacy and safety of crizanlizumab in sickle cell disease patients aged 12 and above
- SUCCESSOR retrospective cohort study among adult sickle cell disease patients in the US

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and

economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. 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 is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 105 000 people of nearly 140 nationalities work at Novartis around the world. Novartis Pharmaceuticals Corporation, a US affiliate of Novartis, is located in East Hanover, NJ. Find out more at www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References

1. Yale SH. Approach to the vaso-occlusive crisis in adults with sickle cell. Am Fam Physician. 2000;61(5):1349-1356.
2. Kauf TL, Coates TD, Huazhi L, et al. The cost of health care for children and adults with sickle cell disease. Am Hematol. 2009;84(6):323-327.
3. Ataga KI, Kutlar A, Kanter J et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017; 376(5):429-439.
4. Gutsaeva D, Parkerson J, Yerigenahally S, et al. Inhibition of cell adhesion by anti–P-selectin aptamer: a new potential therapeutic agent for sickle cell disease. Blood. 2011;117(2):727-735.
5. Sparkenbaugh E, Pawlinski R. Interplay between coagulation and vascular inflammation in sickle cell disease. J Haematol. 2013;162(1):1-22.
6. Steinberg M. Management of sickle cell disease. N Engl J Med. 1999;340(13):1021-1030.
7. American Society of Hematology. State of sickle cell disease 2016 report. http://www.scdcoalition.org/pdfs/ASH%20State%20of%20Sickle%20Cell%20Disease%202016%20Report.pdf. Accessed July 17, 2018.

SOURCE Novartis Pharmaceuticals Corporation
