

Novartis drug crizanlizumab shown to prolong time to patients' first sickle cell pain crisis in subgroup analysis of SUSTAIN study

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- - Investigational therapy crizanlizumab (SEG101, formerly SelG1) approximately doubled the time to first on-treatment sickle cell pain crisis, according to new subgroup analysis of Phase II SUSTAIN data
- - Results were consistent across patient subgroups despite differences in disease severity, genotype or background therapy
- - New findings for crizanlizumab, a potential disease-modifying, preventive treatment option for patients with sickle cell disease, presented at ASH 2017
- - Discussions with health authorities continue; FDA filing anticipated by end of 2018 pending outcome of ongoing healthy volunteer bridging study

EAST HANOVER, N.J., Dec. 11, 2017 /PRNewswire/ -- Results from a post hoc subgroup analysis of the Phase II SUSTAIN study show that crizanlizumab, an investigational humanized anti-P-selectin monoclonal antibody, delayed the time to first sickle cell pain crisis (SCPC) in patients vs. placebo in key subgroups of adult patients with sickle cell disease¹. Findings were featured during an oral session at the 59th American Society of Hematology (ASH) Annual Meeting (Abstract #613; Monday, December 11, 10:30 AM ET).

Acute sickle cell pain crises, also referred to as vaso-occlusive crises, are a common painful complication of the disease and the main reason that patients seek medical care in hospitals.² Currently, treatment options are limited. The data from a subgroup analysis of the Phase II SUSTAIN study showed that crizanlizumab, at 5.0 mg/kg per month increased the time to SCPC in patients on treatment, including those in high-risk subpopulations and with hydroxyurea use¹.

"Pain is the primary cause of suffering in sickle cell disease," said Julie Kanter, M.D., Division of Pediatrics, Medical University of South Carolina, a study investigator. "What this new analysis of the SUSTAIN data suggests is that once patients start crizanlizumab, they are likely to have a longer time before experiencing another pain crisis. These findings are consistent regardless of the severity of disease, genotype, or the use of background therapy. That is a potentially promising new development for patients. Fewer pain crises mean less organ damage long term."

The analysis looked at the following subgroups of patients with sickle cell disease:

- Patients with 2-4 or 5-10 SCPC events in the year before the study
- Patients with the HbSS genotype, and non-HbSS genotypes
- Patients who were or were not taking hydroxyurea

In all of these subpopulations, crizanlizumab at 5.0 mg/kg per month increased the estimated median time to first SCPC vs. placebo by approximately two-fold or more.

In patients taking crizanlizumab who experienced 2-4 SCPCs in the prior year, time to first on-treatment pain crisis was 4.8 vs 1.6 months with placebo (HR 0.53 with 95% CI [0.31, 0.90]). For patients with 5-10 SCPCs in

the prior year, time to first on-treatment pain crisis was 2.4 vs 1.0 months (HR 0.47 with a 95% CI [0.25, 0.89]).

In patients with the HbSS genotype, there was a 3.7-fold increase in estimated median time to first SCPC in those taking crizanlizumab vs. placebo (4.1 vs 1.1 months; HR 0.50 with 95% CI [0.31, 0.80]). In patients taking hydroxyurea, the time to first on-study SCPC was longer with crizanlizumab vs placebo (2.4 vs 1.2 months; HR 0.58 with 95% CI [0.35, 0.96]), suggesting its potential as an additive therapy¹.

"This analysis from SUSTAIN is another important step to bringing what we hope will be a new disease-modifying therapy to patients with sickle cell disease," said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. "The results are consistent among different groups of patients, which gives us even more confidence in our development program for this promising medicine."

About the Subgroup Analysis and the SUSTAIN trial

The heterogeneity in severity of sickle cell disease and various other factors make it important to understand differences in response of various subgroups of patients in order to increase understanding of crizanlizumab and the role of P-selectin in SCD. This post hoc analysis evaluated the time to first SCPC among subgroups of the SUSTAIN study population – those who had 2-4 or 5-10 SCPCs within the prior year; patients with HbSS or non-HbSS genotypes; and patients with or without concomitant treatment with hydroxyurea. The goal was to further assess the efficacy of crizanlizumab at 5.0 mg/kg per month vs placebo, and identify differences in treatment response among those subgroups¹.

The SUSTAIN trial was a multicenter, multinational, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of the anti-P-selectin antibody crizanlizumab with or without concomitant use of hydroxyurea therapy in sickle cell disease patients with sickle cell-related pain crises. Results, which were published in The New England Journal of Medicine, showed that crizanlizumab reduced the median annual rate of SCPCs by 45% compared to placebo (1.6 vs 3.0, p=0.01) in patients with or without hydroxyurea therapy.³ These data will help support discussions with regulatory agencies, with filing anticipated in the U.S. by the end of 2018.

Adverse events that occurred in 10% or more of the patients in either active-treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia, diarrhea, pruritus, vomiting, and chest pain. There were no apparent increases in infections with crizanlizumab treatment.³

About crizanlizumab (SEG101)

Crizanlizumab (SEG101) is an investigational humanized anti-P-selectin monoclonal antibody that binds a molecule called P-selectin on the surface of endothelial cells and platelets in the blood vessels, causing a blockade of P-selectin^{3,4}. P-selectin is a driver^{3,5} of the vaso-occlusive process^{3,5}. Vaso-occlusive crises, also known as SCPCs, occur episodically when sickle-shaped red blood cells block blood flow through blood vessels⁶. The therapeutic blockade of P-selectin can prevent painful vaso-occlusion in small blood vessels and maintain blood flow^{3,6}.

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