14 February 2023

ADAKVEO ▼ (crizanlizumab): Phase III study (CSEG101A2301) shows no superiority of crizanlizumab over placebo

Dear Healthcare Professional,

Novartis in agreement with the European Medicines Agency (EMA) and <National Competent Authority> would like to inform you of the following:

Summary

- Preliminary results from the phase III study CSEG101A2301 (STAND) did not show a difference between crizanlizumab and placebo in annualized rates of vaso-occlusive crises leading to a healthcare visit over the first-year post randomization.
- The preliminary results do not suggest new safety concerns with crizanlizumab. However, higher rates for grade ≥3 treatment-related adverse events were reported for crizanlizumab compared to placebo.
- Further evaluation of the data from study CSEG101A2301 and their potential impact on the benefit-risk balance of crizanlizumab is currently ongoing by EMA. The final conclusions and recommendations will be communicated as soon as the evaluation has been completed.
- While this evaluation is ongoing, physicians should consider the individual benefit and risks when making therapeutic decisions regarding the use of crizanlizumab.

Background Information

Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOCs) in sickle cell disease (SCD) patients aged 16 years and older. It can be given as an add on therapy to hydroxyurea/hydroxycarbamide (HU/HC) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. Adakveo is currently approved for use at the dose of 5.0 mg/kg.

Crizanlizumab has shown clinical benefit in a randomized phase II trial (CSEG101A2201, SUSTAIN[1]), which led to the conditional marketing authorisation by the European Medicines

[1] SUSTAIN Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (NCT01895361)

Agency. Data from the confirmatory trial CSEG101A2301 (STAND[2]) were requested by EMA as part of the conditions to the marketing authorization.

The initial analysis of the STAND study was conducted on data from 252 participants enrolled in this study from initiation in 2019 to the data cut-off of 31 August 2022. The results did not confirm the statistical superiority of crizanlizumab over placebo in reducing VOCs leading to a healthcare visit over the first year post randomization.

For the primary endpoint, the adjusted annualized rates of VOC leading to healthcare visit over the first year post randomization estimated via negative binomial regression were 2.49, 95% CI: (1.90, 3.26) in the crizanlizumab 5.0 mg/kg arm versus 2.30, 95% CI: (1.75, 3.01) in the placebo arm. Rate ratio was 1.08, 95% CI: (0.76, 1.55) in crizanlizumab 5.0 mg/kg versus placebo.

For the key secondary endpoint, the adjusted annualized rates of VOC leading to healthcare visit and treated at home estimated via negative binomial regression was 4.70, 95% CI: (3.60, 6.14) in crizanlizumab 5.0 mg/kg arm versus 3.87, 95% CI: (3.00, 5.01) in the placebo arm. Rate ratio was 1.21, 95% CI: (0.87, 1.70) in crizanlizumab 5.0 mg/kg versus placebo.

No new safety concerns were identified at this point. However, there were higher rates for grade ≥3 treatment related adverse events for crizanlizumab compared to placebo. Similar results were observed in the 7.5 mg/kg arm. This dose is currently not authorised.

EMA is investigating the impact of these findings for the currently authorised use of crizanlizumab. The final conclusions and recommendations will be communicated as soon as the evaluation has been completed.

While further assessment of the study data is ongoing, physicians should consider the individual benefit and risks when making therapeutic decisions regarding the use of crizanlizumab in SCD.

Company Contact Point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

[2] STAND Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (NCT03814746)