Direct Healthcare Professional Communication (DHPC)

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 Medicines and Healthcare products Regulatory Agency (MHRA) 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 annualised rates of vaso-occlusive crises leading to a healthcare visit over the first-year post randomisation.
- 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 randomised phase II trial (CSEG101A2201, SUSTAIN[1]), which led to the conditional marketing authorisation. Data from the

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

confirmatory trial CSEG101A2301 (STAND[2]) were requested as part of the conditions to the marketing authorisation.

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 randomisation.

For the primary endpoint, the adjusted annualised rates of VOC leading to healthcare visit over the first year post randomisation 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 annualised 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.

Call for reporting

Adakveo (Crizanlizumab)▼ is subject to additional monitoring. This will allow quick identification of new safety information. Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme.

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason

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

- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Card website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Suspected side effects can also be reported by calling 0800 731 6789 for free.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, investigation results, treatment dates, and product brand name.

Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.report.novartis.com.

Company contact point

If you have any questions or require further information, please contact Novartis Medical Information department on 01276 698370 or email medinfo.uk@novartis.com.

Yours faithfully,

Geritt Zijlstra
Chief Medical Officer
Novartis Pharmaceuticals UK Ltd

In accordance with our Privacy Notices (novartis.com/uk-en/privacy-policy). Novartis is providing you with this letter to provide you with updated information about the preliminary results from the phase III study CSEG101A2301 (STAND).