Efficacy of divozilimab in the treatment of systemic sclerosis: results of the randomized phase III clinical trial BCD-132-5/LIBERIUS

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The search for new therapeutic options for the treatment of systemic sclerosis (SSc) is an urgent issue in rheumatology. The article presents the results of the double-blind, randomized, placebo-controlled phase III clinical trial BCD-132-5/LIBERIUS on the efficacy and safety of divozilimab (BCD-132) in the treatment of SSc.

Objective: *to investigate the efficacy and safety of divozilimab in patients with SSc compared to placebo.*

Material and methods. *After enrolment in the study, patients received divozilimab or placebo for 48 weeks, after which they were switched to an open-label divozilimab therapy until week 96.*

Results and discussion. *Divozilimab was superior to placebo regarding the primary endpoint change in mRSS at week 48 compared to baseline, and the therapy had a positive effect on respiratory function parameters. Divozilimab treatment was well tolerated.*

Conclusion. *Thus, divosilimab may represent a new therapeutic option for patients with SSc.*

Keywords: *divozilimab; systemic sclerosis; systemic scleroderma.*
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Systemic scleroderma (systemic sclerosis, SSc) is a progressive immunoinflammatory rheumatic disease. The pathogenesis of SSc is based on immune disorders that initiate inflammation, as well as vasculopathy with severe microcirculation disorders and generalized fibrosis leading to severe damage to vital organs [1]. The disease worsens the quality of life and has an unfavorable prognosis [2, 3]. The heterogeneity of clinical manifestations interferes with timely diagnosis and routing of patients for appropriate treatment [4].

Treatment of SSc is carried out taking into account the dominant clinical manifestations of the disease and includes vascular, anti-inflammatory, immunosuppressive and antifibrotic drugs, including genetically engineered biological drugs (GEBDs). The principles of organ-specific SSc therapy are described in detail in the guidelines of the European League Against Rheumatism (EULAR), in a number of national guidelines, including those of the Russian Association of Rheumatologists, as well as in more recent international expert recommendations [5–7].

The value of biological therapy and targeted drugs in the treatment of SSc is being extensively studied. TNF-α blockers (infliximab, etanercept), rituximab, tocilizumab, antithymocyte immunoglobulin, interferons (α and γ), imatinib, antibodies to the transforming growth factor β1, etc. have been used for the treatment of SSc [8]. Available data on the involvement of B cells in the pathogenesis of SSc [9] justify the use of rituximab in the treatment of this disease. In two small randomized clinical studies, the efficacy of anti-CD20 therapy was confirmed in patients with limited and diffuse forms of SSc [10], as well as in interstitial lung disease caused by SSc [11]. Based on the results obtained, rituximab was approved for treatment of SSc in Japan [12] and included in international clinical guidelines for this disease [6, 7].

BCD-132 (divozilimab) is a humanized monoclonal antibody against CD20. Divozilimab selectively interacts with the extracellular part of the CD20 transmembrane antigen located on the surface of normal and malignant mature B cells and their precursors without binding to hematopoietic stem cells, pro-B cells, plasma cells, or other normal tissues. Previously, divozilimab was studied in patients with multiple sclerosis [13–15], and based on the results of clinical studies, it was approved for this indication in the Russian Federation in 2023.

BCD-132-5/LIBERIUS is a Phase III randomized, double-blind, placebo-controlled clinical study of the efficacy and safety of divozilimab in patients with systemic scleroderma (ClinicalTrials.gov code NCT05726630).

This publication presents the results of the primary and secondary efficacy endpoints within the main study period in adult patients.

Aim. The aim of the study was to assess the efficacy and safety of divozilimab in patients with systemic scleroderma versus placebo.

Material and Methods. The study included patients over 14 years of age with a diagnosis of systemic scleroderma and a modified Rodnan skin score (mRSS) ≥10 and ≤20. Upon confirmation of eligibility, adult subjects were randomly assigned at a 1:1 ratio to receive either divozilimab or placebo for 48 weeks. After evaluating the primary endpoint at Week 48, all patients were switched to open-label divozilimab therapy until Week 96. Participants under 18 years old received only divozilimab.

Results. The analysis included 151 patients over 18 years of age (76 patients in the divozilimab group, 75 patients in the placebo group). The groups were balanced in terms of age, gender, race, baseline anthropometric characteristics, and had comparable baseline characteristics of the underlying disease, such as duration of SSc, form of SSc (limited/diffuse/sine), baseline mRSS, and respiratory parameters.

The primary efficacy endpoint in the study was the change in the modified Rodnan skin score (mRSS) from baseline to Week 48. The adjusted mean mRSS change was -5.8 (95% CI: -7.9; -3.8) in the divozilimab group and -2.7 (95% CI: -4.8; -0.7) in the placebo group. The difference in the adjusted mean values was -3.1 (95% CI: -4.5; -1.7), $p<0.0001$, which indicates the superiority of divozilimab over placebo in respect of skin manifestations of the disease.

The secondary efficacy endpoint was change from baseline in forced vital capacity (FVC) at week 48. Both groups showed an increase in FVC from baseline at week 48. Moreover, the mean increase in FVC was higher in the divozilimab group compared to placebo group: 0.148 L (95% CI: -0.003; 0.298) versus 0.094 L (95% CI: -0.065; 0.253), $p=0.5017$.

The treatment was well tolerated, and the safety profile was consistent with that of anti-CD20 monoclonal antibodies.

Discussion. The study proved the superiority of divozilimab over placebo in patients with SSc. Divozilimab significantly improves skin manifestations of the disease and has a positive impact on the respiratory function.

Conclusion. Thus, divozilimab can present a new therapeutic option for patients with SSc.

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