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Title: Efficacy and Safety of Efgartigimod PH20 Subcutaneous in Adult Patients with Pemphigus Vulgaris (PV) and Pemphigus Foliaceus (PF): ADDRESS, a Global Phase 3 Clinical Trial in Progress

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Introduction

Efgartigimod is an engineered Fc fragment that inhibits the activity of the neonatal Fc receptor (FcRn), thereby reducing the levels of circulating IgG including pathogenic IgG autoantibody levels. PV and PF belong to a heterogenous group of autoimmune blistering diseases and are clinically characterized by mucosal erosions (PV) and cutaneous blisters (PV and PF). In PV, IgG autoantibodies primarily target epidermal desmoglein 3 (Dsg-3) and, in the case of mucocutaneous PV, also Dsg-1, while PF is attributed to the presence of IgG autoantibodies directed against Dsg-1. In a phase 2 trial in mild to-moderate PV and PF patients (NCT03334058), efgartigimod was found to rapidly decrease the serum levels of anti-Dsg-3 and Dsg-1 IgG. Decreases in these autoantibodies were associated with clinical improvement and reduction in disease activity and progression, as shown by the validated clinical scoring system, the Pemphigus Disease Area Index (PDAI). Efgartigimod, as monotherapy and combined with prednisone, demonstrated a rapid onset of action with disease control (DC) in 90% (28/31) of patients with a median time of 17 days. Fourteen of 22 (64%) of patients on efgartigimod treatment with prednisone 0.1–0.5 mg/kg/d achieved complete clinical remission (CR; efgartigimod doses: 10 mg/kg: median 36 days, range 13–93; 25 mg/kg: 92 days, range 41–287).

Materials and methods

ADDRESS is a global, multicenter, phase 3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of efgartigimod in patients with PV or PF. Eligible patients are over 18 years old with moderate to severe PV or PF (PDAI activity score ≥15) and are newly diagnosed or relapsing. A total of 150 patients (126 PV and 24 PF) will be randomized and enter a 30-week treatment period to receive either efgartigimod SC co-formulated with PH20 (recombinant human hyaluronidase PH20, an enzyme used to increase the dispersion and absorption of co-administered substances when administered SC) or placebo/PH20 (randomization 2:1). All patients, regardless of treatment assignment, will concomitantly receive oral prednisone (or equivalent) at a starting dose of 0.5 mg/kg daily. On days 1 and 8, patients will receive placebo/PH20 or efgartigimod PH20 SC at a dose of 2,000 mg followed by weekly SC injections of 1,000 mg until complete remission on minimal therapy (CRmin), defined by absence of new

lesions and complete healing of established lesions while the patient is receiving minimal prednisone therapy of ≤10 mg/day for at least 2 months (8 weeks), is achieved. The primary endpoint is the proportion of PV patients who achieve CRmin within 30 weeks. Key secondary endpoints include the proportion of PV and PF patients who achieve CRmin within 30 weeks, cumulative prednisone dose over the trial in PV patients, time to CR in PV patients, and time to disease control (DC) in PV patients. Safety, tolerability, and quality of life will also be assessed during the study. Trial patients will be eligible for continuation into ADDRESS+, a long-term open-label extension trial.

Results

ADDRESS recruitment is ongoing with a target of 150 patients with PV or PF across approximately 100 sites in 20 countries.

Conclusions

More details on the trials are available on ClinicalTrials.gov (ADDRESSS: NCT04598451; ADDRESS+: NCT04598477).