International Pemphigus & Pemphigoid Foundation (IPPF) 2021
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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 autoantibodies. PV and PF belong to a heterogenous group of autoimmune blistering diseases and are clinically characterized by mucosal erosions (PV) and cutaneous lesions (PV and PF). In PV, IgG autoantibodies primarily target epidermal desmoglein (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 34 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. Complete clinical remission was achieved with prolonged maintenance therapy in 64% of patients (14/22 total; 5/7, 10 mg/kg; 9/15, 25 mg/kg) after a median time of 92 days in combination with corticosteroids (median daily dose 0.26 mg/kg, range 0.06-0.48 mg/kg).

**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 PH20 SC (i.e. efgartigimod co-formulated with rHuPH20 [recombinant human hyaluronidase PH20], an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously) or placebo PH20 SC, i.e. placebo with rHuPH20 (randomized 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 SC or efgartigimod PH20 SC at a dose of 2,000 mg followed by weekly subcutaneous 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 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 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**

ADDRESS will provide further evidence of the safety and efficacy of efgartigimod in PV and PF patients seen in the phase 2 study. More details on the trials are available on ClinicalTrials.gov (ADDRESS: NCT04598451; ADDRESS+: NCT04598477).