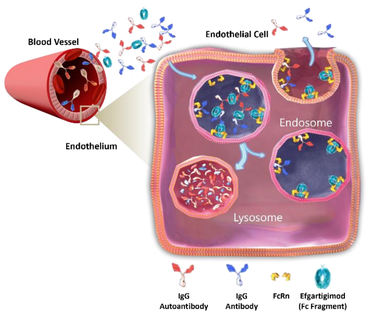
Treating Bullous Pemphigoid by Inhibiting FcRn: Pre-registration Report of a Phase 2/3 Trial With Efgartigimod

Donna A. Culton,[1] Hideyuki Ujiie,[2] Enno Schmidt,[3] Dedee F. Murrell,[4] Ivaylo Stoykov,[5] Peter Verheesen,[5] Luca Borradori,[6] Russell Hall,[7] Pascal Joly[8]

[1]Department of Dermatology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, United States; [2]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; [3]Department of Dermatology, University of Lubeck, Lubeck, Germany; [4]Department of Dermatology, St George Hospital and University of New South Wales, Sydney, Australia; [5]argenx, Ghent, Belgium; [6]Department of Dermatology, University Hospital Inselspital, Bern, University of Bern, Bern, Switzerland; [7]Department of Dermatology, Duke University School of Medicine, Durham, North Carolina, United States; [8]Department of Dermatology, Rouen University Hospital, Rouen, France.

BACKGROUND

EFGARTIGIMOD: Engineered IgG1 Fc Fragment [1-5]



- The neonatal Fc receptor, FcRn, recycles immunoglobulin (Ig)G, extending its half-life and serum concentration[1]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity for FcRn[2]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling, and promoting lysosomal degradation of IgG, without impacting its production leading to[2-5]
  - Targeted reduction of all IgG subtypes
  - No impact on IgM or IgA
  - No reduction in albumin levels
  - No increase in cholesterol
- Efgartigimod is approved for the treatment of generalized myasthenia gravis (gMG) in patients positive for anti-acetylcholine receptor (AChR) antibodies in the US and in patients with an insufficient response to steroids or non-steroid immunosuppressive therapies in Japan

BULLOUS PEMPHIGOID: An IgG-Mediated Autoimmune Disease[6]

- Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin
  - It typically presents with highly pruritic eruptions with widespread blister formation, eczematous and/or urticarial lesions, and has a high morbidity
- It primarily affects the elderly over 70 years of age and has an estimated annual incidence between 10 to 40 new cases per million individuals
- BP is mediated by IgG and IgE autoantibodies against BP180 (BPAG2, type XVII collagen) and BP230 (BPAG1e), two components of the dermal-epidermal junction
- These autoantibodies are pathogenic and cause inflammation by triggering an inflammatory cascade and directly impairing dermal-epidermal adhesion

EFGARTIGIMOD IS CLINICALLY EFFECTIVE AND WELL TOLERATED IN PHASE 2 AND 3 TRIALS IN IMMUNE-MEDIATED DISORDERS[4,7-9]

- In an open-label phase 2 trial in participants with **pemphigus**, disease control was achieved in **90%** of cases (median time: **17 days**). Complete remission was achieved in **64%** of participants (median time: **92 days**) in combination with a low prednisone dose.
- In a phase 3 trial in participants with **gMG**, **68%** of participants responded to efgartigimod (MG-ADL responders*) compared with 30% of those in the placebo group.
  - In a study comparing efgartigimod administered intravenously or subcutaneously in participants with gMG, consistent clinical efficacy and safety was observed in both groups (MG-ADL responders: 69.1% IV vs 69.1% SC; n=110).
- In a phase 2 trial in participants with **primary immune thrombocytopenia** (**ITP**), **46.2%** of participants showed a platelet count of ≥50×10^9/L for at least 10 days.
- Efgartigimod treatment is associated with a decrease in serum levels of total IgG (including pathogenic autoantibodies) and was **generally well tolerated** in trials in participants with gMG, primary ITP, and pemphigus (open-label study).
- Efgartigimod is also being evaluated in phase 3 trials in pemphigus, primary ITP, chronic inflammatory demyelinating polyneuropathy, and idiopathic inflammatory myositis.

***MG-ADL responders** = ≥2-point Myasthenia Gravis Activities of Daily Living score improvement sustained for ≥4 weeks

PHASE 2/3 BALLAD KEY ELIGIBILITY CRITERIA

Key inclusion criteria

- Male or female adults ≥18 years of age
- Clinical diagnosis of BP confirmed by histology, positive direct immunofluorescence (IF), and positive serology (indirect IF, enzyme-linked immunosorbent assay, or chemiluminescence enzyme immunoassay)
- Investigator Global Assessment of Bullous Pemphigoid (IGA-BP) score of 3 or 4 at screening and baseline
- Karnofsky performance status of at least 60% at screening

Key exclusion criteria

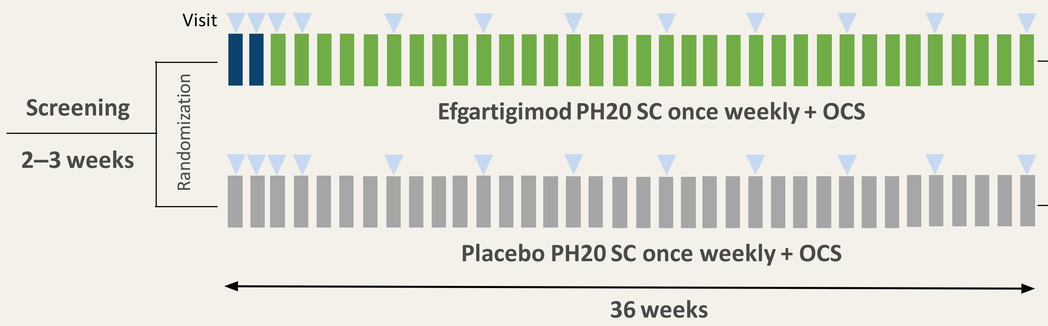
- Any other form of pemphigoid or autoimmune blistering disease
- Received unstable dose of treatments known to cause or exacerbate BP for ≥4 weeks prior to baseline
- Use of other BP treatments other than oral corticosteroids:
  - Conventional immunosuppressants including azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil or dapsone must be discontinued before baseline
  - Sulfasalazine, intravenous Ig, subcutaneous Ig, immunoadsorption, or plasma exchange within 8 weeks of baseline visit
  - Tetracycline ± nicotinamide within 2 weeks of baseline visit
  - Any monoclonal antibody (including rituximab) within 6 months of baseline visit
- Clinically significant uncontrolled active or chronic, bacterial, viral, or fungal infection at screening

Phase 2/3 BALLAD (ARGX-113-2009) Trial Design

ballad Bullous Pemphigoid Study

Efgartigimod PH20 SC Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Trial in Bullous Pemphigoid

Study Population: 160 patients (40 for Part A: Proof of Concept and 120 for Part B: Confirmatory)
Parts A and B are identical in schedule, structure, assessments, and conduct



ARGX-113-2010 open-label extension (OLE)
- 52-week study with the primary endpoint of safety
- Efgartigimod PH20 SC 1000 mg once weekly + OCS tapering
- Endpoint - CR or PR for ≥8 weeks

Complete 7-week treatment-free follow-up period
Visits at week 39 and week 43

Efgartigimod 2000 mg
Efgartigimod 1000 mg

Concomitant oral corticosteroid treatment

- Prednisolone (or equivalent) starting dose **0.5 mg/kg/day**
- Dosage will be **adjusted** (tapered, increased, stopped, or reinitiated) according to each participant's BP disease status
  - Once CDA has been sustained for ≥2 weeks, **dose tapering will begin** and continue biweekly until the participant is off OCS
  - If CDA is not achieved within 1–3 weeks, then **dosage may be increased to 0.75 mg/kg/day** for up to an additional 3 weeks
  - If a participant experiences a relapse, OCS dose will be increased based on the clinical judgement of the investigator
- A participant will be considered as a **treatment failure if CDA is not achieved** with the above dosage and **rescue therapy may be initiated***

Efgartigimod co-formulated with hyaluronidase PH20 for convenient SC administration in <2 min
HCP-supported administration at home
Self-administration in OLE

US sites now recruiting.

BP: bullous pemphigoid; **CDA:** control of disease activity; **CR:** complete remission; **EFG:** efgartigimod; **HCP:** health care provider; **OCS:** oral corticosteroids; **PR:** partial remission; **SC:** subcutaneous.
***Rescue therapy** may also be initiated if the participant relapses twice or presents with steroid toxicity, or any severe adverse event deemed by the investigator to be related to OCS therapy. These participants will stop efgartigimod therapy but will continue attending study visits through the 36-week treatment period while receiving rescue therapy.

PRIMARY ENDPOINT (PARTS A & B)

Proportion of participants in complete remission on minimal oral corticosteroid therapy (≤0.1 mg/kg/day) for ≥8 weeks at week 26

KEY SECONDARY AND ADDITIONAL ENDPOINTS (PART B)

- Cumulative dose of OCS from baseline to week 36
- Proportion of participants who achieve IGA-BP score of 0 while off OCS for ≥8 weeks at week 36
- Change in BPDAI score
- Incidence and severity of AEs, AESIs, and SAEs
- Quality-of-life scores
- Time to achieve:
  - Control of disease activity (CDA)*
  - Complete remission (CR)**
  - CR** on minimal OCS therapy (≤0.1 mg/kg/day) for ≥8 weeks
  - CR** off OCS therapy for ≥8 weeks
- PK/PD of efgartigimod

AE: adverse event; **AESI:** adverse event of special interest; **BPDAI:** Bullous Pemphigoid Disease Area Index; **OCS:** oral corticosteroid; **PD:** pharmacodynamics; **PK:** pharmacokinetics; **SAE:** serious adverse event.

***CDA** = no new lesions, established lesions starting to heal, and pruritic symptoms start to abate. ****CR** = absence of new lesions, established lesions completely healed, and absence of pruritis.
Minimal therapy is defined as ≤0.1 mg/kg/day of OCS with efgartigimod PH20 SC or placebo PH20 SC.

We gratefully acknowledge the clinicians, patient organizations, and scientists who have collaborated on the design of this trial

DISCLOSURES AND ACKNOWLEDGEMENTS

DAC: Consultant: argenx; Research Funding: Principia Biopharma, Cabaletta Bio. **HU:** Consultant: argenx, Ono, Nihon-Pharmaceutical, Sun Pharma, and Ishin Pharma; Research Funding: JB, Otsuka, Taiho, Boehringer Ingelheim, Kyowa Kirin, Kaken, Sun Pharma, Shionogi, Teijin, Mitsubishi Tanabe, Nihon Zoki, Eisai, Torii, and Tokiwa. **ES:** Consultant: argenx, UCB, Roche, Thermo Fisher, AstraZeneca, Topas; Research Funding: Novartis, UCB, Incyte, Biotest, argenx, Dompe, Admirx, Synthon/Byondis, Fresenius Medical Care, AstraZeneca. **DFM**: argenx, Principia Bio, Sanofi-Regeneron, Roche, AstraZeneca, UCB, Amgen, Janssen, Novartis. **IS, PV:** Employees of argenx. **LB:** consultant for argenx. **RH:** Consultant: argenx, Cabaletta Bio, Akari Therapeutics, Seal Rock Therapeutics. **PJ:** Consultant: Roche, Amgen, Principia Biopharma, argenx, AstraZeneca, Thermo Fisher, Sanofi, Akari Therapeutics, Janssen, Novartis, Servier, Chugai, Kezar Life Science, Regeneron, UCB.

The phase 2/3 BALLAD trial is funded by argenx. Medical writing and editorial support for this presentation was provided by Eloquent Medical Affairs and funded by argenx.

REFERENCES

1. Sesarman A, et al. *Cell Mol Life Sci.* 2010;67(15):2533-2550.
2. Ulrichts P, et al. *J Clin Invest.* 2018;128(10):4372-4386.
3. Vaccaro C, et al. *Nat Biotech.* 2005;23(10):1283-1288.
4. Howard JF Jr, et al. *Lancet Neurol.* 2021;20(7):526-536.
5. Nixon AE, et al. *Front Immunol.* 2015;6:176.
6. Kridin K, et al. *Front Med (Laussane).* 2018;5:220.
7. Newland AC, et al. *Am J Hematol.* 2020;95(2):178–187.
8. Goebeler M, et al. *Br J Dermatol.* 2021;10.1111. **9.** argenx, Inc. (March 22, 2022). Topline Results: ADAPT-SC Bridging Study in gMG.

Presented at the Annual Meeting of the Society for Investigative Dermatology (SID) in Portland, Oregon from 18–21 May 2022.