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Treatment of pemphigus vulgaris and foliaceus with efgartigimod, a neonatal Fc receptor inhibitor: a phase 2 multicentre, open-label feasibility trial

Running Title: A phase 2 study of efgartigimod in pemphigus vulgaris and foliaceus

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Matthias Goebeler has served as a consultant and on advisory boards for argenx, Biotest, Janssen, Leo Pharma, Lilly, Novartis, UCB. Zsuzsanna Bata-Csörgő has served on advisory boards for Novartis, Sanofi-Genzyme, Ewopharma, Abbvie, and argenx. Clara De Simone has no disclosures to report. Biagio Didona has no disclosures to report. Eva Remenyik has served as a member of advisory boards of Janssen Cilag Hungary, Lilly Hungary, and Takeda Pharma. Nataliya Reznichenko has no disclosures to report. Johanna Stoevesandt has no disclosures to report. E. Sally Ward is supported in part by a research grant funded by argenx BVBA, Zwijnaarde, Belgium, and has a financial interest in argenx BVBA. E. Sally Ward may receive royalties from patents owned by the UK Medical Research Council, UT Southwestern Medical Center, and Texas A&M University. Wim Parys, Hans de Haard, and Peter Verheesen are employed by argenx. Patrick Dupuy was previously employed by argenx and currently consults for argenx. Enno Schmidt received research grants form argenx, Novartis, UCB, Incyte, Biotest, Dompe, Admirx, Byondis, Fresenius, and Euroimmun and has also received honoraria from argenx, Novartis, UCB, Biotest, Fresenius, Roche, Imevax, Topsa, and Thermo Fisher. Pascal Joly has served as a consultant for Amgen, Principia Biopharma, argenx, Astra Zeneca, Janssen, Thermofisher, Lilly, Sanofi, Akari, Chugai, Novartis, Kezar, Genentech, and Topas.

Summary

Background: Pemphigus vulgaris and pemphigus foliaceus are potentially life-threatening autoimmune disorders triggered by immunoglobulin G (IgG) autoantibodies against mucosal and epidermal desmogleins. There is an unmet need for fast-acting drugs that enable patients to achieve early sustained remission with reduced corticosteroid reliance.

Objective: To investigate efgartigimod, an engineered Fc fragment that inhibits the activity of the neonatal Fc receptor, thereby reducing serum IgG levels, for treating pemphigus.

Methods: Thirty-four patients with mild to moderate pemphigus vulgaris or foliaceus were enrolled in an open-label phase 2 adaptive trial. In sequential cohorts, efgartigimod was dosed at 10 or 25 mg/kg intravenously with various dosing frequencies, as monotherapy or as add-on therapy to low-dose oral prednisone. Safety endpoints comprised the primary outcome.

Results: Adverse events were mostly mild and reported by 16/19 (84%) patients receiving efgartigimod 10 mg/kg and 13/15 (87%) patients receiving the 25 mg/kg dose, with similar adverse event profiles between dose groups. A major decrease in serum total IgG and anti-desmoglein (Dsg) autoantibodies was observed and correlated with improved pemphigus disease area index (PDAI) scores. Efgartigimod, as monotherapy or combined with prednisone, demonstrated early disease control in 28/31 (90%) patients after a median of 17 days. Optimized, prolonged treatment with efgartigimod in combination with a median dose of 0.26 (range 0.06-0.48) mg/kg/day prednisone led to complete clinical remission in 14/22 (64%) patients within 2-41 weeks.

Conclusion: Efgartigimod was well-tolerated and exhibited an early effect on disease activity and outcome parameters, providing support for further evaluation as a therapy for pemphigus. The study is registered at ClinicalTrials.gov (identifier: NCT03334058).

INTRODUCTION

Pemphigus comprises a group of rare autoimmune blistering skin disorders with pemphigus vulgaris (PV) outnumbering pemphigus foliaceus (PF) in most populations. [1] PV is characterized by immunoglobulin G (IgG) autoantibodies targeting desmoglein-3 (Dsg-3), which is associated with mucosal lesions, and in 50% of cases, also with Dsg-1, which is associated with skin lesions. PF involves only anti-Dsg-1 IgG, and lesions are restricted to the skin.[2,3]

Pemphigus is potentially life-threatening, primarily due to secondary infections. Systemic corticosteroids (CS) have dramatically improved the prognosis, reducing mortality to <10%.[1,4,5] CS rapidly improve pemphigus symptoms but must be administered at high daily doses (e.g., oral prednisone 1.0-1.5 mg/kg) to attain efficacy.[6,7] Such high doses and prolonged use are associated with significant side effects, including metabolic complications, broad immunosuppression, and increased risk of infections.[2]

The B cell–targeting monoclonal antibody rituximab was recently approved in the United States and Europe as first-line therapy for moderate to severe PV with a tapered course of glucocorticoids.[8,9] However, rituximab has a relatively slow onset of action that requires concomitant use of CS and is often used in combination with prednisone (or equivalent) at a starting dose of 0.5-1 mg/kg per day. This approach is also associated with a relatively high frequency of relapses in 25% to 60% of cases and severe adverse events in approximately 40% of patients.[8,10,11] These limitations highlight the need for a fast-acting treatment that will permit early CS tapering. A superior safety profile and sustained clinical remission with minimal or no CS therapy are the ultimate goals of an ideal treatment for pemphigus.

Because pathogenic IgGs play a central role in pemphigus pathology, various approaches to reduce pathogenic IgG levels such as plasmapheresis, immunoadsorption, and intravenous immunoglobulins (IVIg) have been implemented.[5,12,13] Plasmapheresis and immunoadsorption, however, are reserved for recalcitrant cases due to high costs and technical requirements. IVIg has proven beneficial as a CS-sparing agent and may as such be considered in refractory cases.[9,14-16]

Efgartigimod is an engineered Fc fragment derived from human IgG1 and equipped with ABDEG mutations that substantially increase its affinity for the neonatal Fc receptor (FcRn).[17] FcRn maintains constant levels of IgG and albumin in the serum by recycling these ligands following uptake into cells.[18-20] Efgartigimod binds to the IgG-binding site of FcRn, thereby reducing the levels of circulating IgG without affecting levels of albumin or other immunoglobulins.[21-23] In healthy volunteers, efgartigimod was well-tolerated and induced an early decline of all IgG subclasses.[23] Similarly, in phase 2 studies in patients with myasthenia gravis and primary immune thrombocytopenia, efgartigimod led to comparable IgG level reductions and was well-tolerated and associated with statistically significant clinical improvement.[21,22] In view of these findings, we have performed a phase 2 adaptive study to investigate the efficacy and safety of efgartigimod in pemphigus.

METHODS

Study design

This phase 2, open-label, single-treatment arm, multicenter trial of efgartigimod dosed at 10 or 25 mg/kg body weight was conducted using an adaptive design with 4 cohorts involving patients with PV or PF. Participants were sequentially enrolled in each cohort prior to treatment, and a minimum of 4 evaluable patients was to be included in each of Cohorts 1-3 and 10 in Cohort 4. The study was conducted at 16 sites in Europe and Israel and comprised a screening period of up to 3 weeks, treatment periods of 9-34 weeks, and a treatment-free, follow-up period of 8 (Cohort 1) or 10 weeks (Cohorts 2-4). An independent data monitoring committee (IDMC) reviewed safety and efficacy data. The IDMC provided recommendations based on the preceding cohort for the maintenance treatment of the subsequent cohort in terms of frequency of administration (to maintain or modify the interval between administration), duration of the maintenance phase (by increasing the number of administrations by a maximum of two per cohort), the dose received (to maintain, increase, or decrease the dose for both the induction and maintenance phase), and concomitant prednisone and rescue treatment. Recommendations were driven by safety data, disease activity (PDAI), PD markers

(total serum IgG, anti-Dsg antibodies), and clinical outcome of the disease (DC, CR, relapse, and concomitant prednisone dose at the outcomes).

The study was conducted in accordance with the Good Clinical Practice guidelines in conformity with the ethical principles of the Declaration of Helsinki and relevant country-specific laws. The study protocol and other appropriate study-related documents were reviewed and approved by the ethics committee or institutional review board of every centre (Table S1; see Supporting Information). All participants provided written, informed consent.

Participants

Eligible patients included those with newly diagnosed or relapsing mild to moderate PV or PF, defined as a PDAI <45 at baseline.[24] Diagnosis of PV and PF was made by positive direct immunofluorescence showing IgG deposits on the keratinocyte cell surface, positive indirect immunofluorescence on monkey oesophagus, and/or positive Dsg-1/3 ELISA.[9] Patients on oral prednisone (or equivalent) and/or immunosuppressant at screening could participate in the study, but the immunosuppressant had to be discontinued before baseline. Patients were excluded if they had a history of pemphigus refractory to second-line therapy (e.g., IVIg, rituximab, plasma exchange/immunoadsorption) or if they had undergone treatment with intravenous CS pulse, dapsone, sulfasalazine, tetracyclines, nicotinamide, plasmapheresis/plasma exchange, immunoadsorption, or IVIg within 2 months prior to baseline or treatment with rituximab or other CD20-targeting therapies within 6 months prior to baseline.

Intervention

Efgartigimod (10 or 25 mg per kg body weight) was administered via intravenous infusion over a period of 2 hours if total serum IgG levels were >1.2 g/L. Cohorts 1-3 received efgartigimod 10 mg/kg in 4 weekly infusions during the induction phase (Figure 1). Maintenance dosing regimens were determined by the IDMC based on the preceding cohort. During the maintenance phase, Cohort 1 received 1 infusion each at weeks 2 and 6 (as determined a priori); Cohort 2 received an infusion every other week for 8 weeks (4 doses in total), and Cohort 3 an infusion every other week for 12

weeks (6 doses in total). Efgartigimod was used from baseline as monotherapy in newly diagnosed patients and relapsing patients off therapy. Relapsing patients already taking prednisone continued receiving the tapered dose at which relapse occurred.

During induction, patients in Cohort 4 received efgartigimod 25 mg/kg each week until end of consolidation (EoC; defined as the time at which no new lesions had developed for a minimum of 2 weeks and approximately 80% of lesions had healed) was achieved, after which patients received infusions every other week for up to 34 weeks. Newly diagnosed patients and relapsing patients who were off-therapy also received prednisone 20 mg/day; those already taking prednisone continued receiving the tapered dose at which relapse occurred. In Cohorts 1-3, oral prednisone could be tapered from the beginning of the maintenance phase, and rescue therapy consisted of 20 mg/day of prednisone for patients off-therapy and was increased to 40 mg/day in patients already on prednisone. In Cohort 3, investigators could start 20 mg/day of prednisone at study initiation. Rescue therapy was allowed from the beginning of the maintenance phase in Cohort 1 and from any post-baseline visit in Cohorts 2-4. In Cohort 4, oral prednisone could be tapered from EoC.

No other systemic treatments for pemphigus were permitted during the study. Topical CS, analgesics, and supportive care for CS therapy (e.g., vitamin D, proton-pump inhibitors, specific diets) were allowed.

Outcomes

The primary outcome was safety. Endpoints included the incidence and severity of treatment-emergent adverse events (AEs) and serious adverse events (SAEs). Infections were adverse events of special interest (AESIs) because patients with pemphigus are prone to infections and efgartigimod lowers IgG levels. AEs were summarized by total number of events. In addition, vital signs, electrocardiogram parameters, physical examination abnormalities, and routine clinical laboratory values were assessed. As an additional safety parameter, total serum IgG levels were measured at each visit.

Efficacy endpoints included evolution of the PDAI activity score as assessed by study investigator at each visit and compared to study baseline; time to disease control (DC), defined as no new lesions and established lesions starting to heal; time to EoC (assessed in Cohort 4 only); time to relapse (appearance of 3 or more new lesions per month that do not heal spontaneously within 1 week, or extension of established lesions, evaluated after DC); and time to complete clinical remission (CR), defined as the absence of new lesions and established lesions completely healed by international consensus.[25]

Other secondary endpoints included the evaluation of pharmacodynamic (PD) (total IgG and IgG subclasses and anti-Dsg-1/3 autoantibodies) and pharmacokinetic (PK) parameters, as well as immunogenicity (incidence of antidrug antibodies). Serum anti-Dsg-1 and anti-Dsg-3 IgG were determined by ELISA (Euroimmun, Lübeck, Germany). Exploratory endpoints included serum titres of protective vaccine antibodies against tetanus toxoid (TT), varicella zoster virus (VZV), and pneumococcal capsular polysaccharide (PCP).

Statistical analyses

Descriptive statistical methods were used to analyse safety and efficacy data. Summaries (mean, standard error, median, range) were provided by cohort and/or efgartigimod dose. No formal sample size calculation was done, but a minimum of 4 evaluable patients was required in Cohorts 1-3 each, and 10 in Cohort 4 based on clinical and medical considerations. The safety analysis population was defined as all enrolled patients who received at least one treatment dose. The efficacy analysis population was defined as all patients with a minimum exposure to the investigational product (at least 3 administrations), who had no confounding factors or missing visits which could interfere with the observation of at least one clinical outcome, and did not have a major protocol deviation which affected the efficacy profile. Kaplan Meier methods were used to calculate time to DC, time to EoC, time to relapse, and time to CR.

RESULTS

Study population and patient disposition

From 2 November 2017 to 11 December 2019, 53 patients were screened, 35 of whom were eligible and 34 (26 PV and 8 PF) were enrolled in the trial; one patient withdrew consent before baseline (Figure 2). For the efficacy analysis, 3 patients were excluded by the IDMC for insufficient drug exposure, impetigo as pre-existing non-drug-related confounding factor, and violation of exclusion criteria. Exclusion analysis was performed by the IDMC. Twenty-two patients completed the study. The last patient completed the study on 28 October 2020. Baseline characteristics can be found in Table 1.

Safety and tolerability

The 34 patients comprising the safety population received a median of 10 (range 2, 24) IV infusions of efgartigimod. AE profiles were similar between doses (Tables 2 and 3). At least one treatment-emergent AE was reported by 16/19 (84%) patients receiving efgartigimod 10 mg/kg and 13/15 (87%) receiving 25 mg/kg. The most common AEs were nasopharyngitis, diarrhoea, and headache, each reported by 4 patients (12%) (Table 3); none were considered related to study drug except one event of diarrhoea. All events were of mild or moderate intensity.

A total of 32 AESIs were reported in 21 patients (62%), of which 7 events in 5 patients (15%) were considered related to study treatment. None led to study discontinuation, and all were mild to moderate except a case of pneumonia and tooth infection, which were grade 3 AESIs (see Appendix S1 for details). No abnormal infection patterns were observed.

No clinically significant changes in vital signs, electrocardiograms, physical examinations, or clinical laboratory assessments were observed. Albumin was modestly and transiently increased (Figure S1). Total serum cholesterol and low-density lipoprotein (LDL) cholesterol levels remained within normal limits across all time points measured in 11 patients from Cohort 4 (Figure S1).

Efficacy

PDAI score

At the end of the induction phase, PDAI activity scores decreased by a median of 75% to a mean of 7.7 ± 3.5 (median 2.0; range 0.0-46.0) in the 10 mg/kg dose groups (Cohorts 1-3). In Cohort 4, the 25 mg/kg dose was associated with a 52% median PDAI reduction to a mean of 9.4 ± 1.9 (median 5.0; range 1.0-20.8) (Figure 3). The 7 patients from Cohort 3 completed the study with a median 78% PDAI activity score reduction. The 10 patients from Cohort 4 who completed the study had a median >99% reduction. Efgartigimod monotherapy improved PDAI activity scores in 6 patients in Cohorts 1-3, with a median 72% reduction after 4 weekly doses.

Disease control endpoints

As shown in Table 4, efgartigimod treatment achieved DC in 28 of 31 patients (90%) after a median time of 17 days (range 6-92) (see Appendix S2 for additional details). In Cohort 4, EoC was achieved in 11/15 patients (73%) after a median time of 43 days (range 34-99). Among the 28 patients achieving DC, 14 relapses were reported in 11 patients (39%), with a median time to first relapse of 211 days (range 10-211). No relapses occurred in the induction phase, 7 occurred in the maintenance phase, and 7 occurred in the treatment-free, follow-up phase.

In Cohorts 3 and 4, 64% of patients (14/22; 5/7 from Cohort 3 and 9/15 from Cohort 4) achieved CR after a median time of 92 days (range 13-287) on maintenance therapy consisting of efgartigimod plus prednisone (median daily dose, 0.26 mg/kg [range 0.06-0.48]).

IgG and anti-Dsg antibody levels

After the first infusion, serum IgG decreased by 40% to 45% (Figure S2). On Day 29, the median reduction in IgG level was 62% (range 54% to 74%) with efgartigimod 10 mg/kg and 66% (24% to 75%) with efgartigimod 25 mg/kg. Serum levels of IgG subclasses (IgG1 through IgG4) generally followed total IgG level reductions (Figure S3).

Serum levels of anti-Dsg-1 and anti-Dsg-3 IgG decreased over time (Figure 4), reaching a median 61% reduction from baseline for anti-Dsg-1 and 49% for anti-Dsg-3 antibodies at the end of the induction phase. Patients in Cohort 4 who achieved EoC and were switched to biweekly dosing of efgartigimod had a sustained IgG level reduction of approximately 50-60% for as long as biweekly infusions were maintained. Similarly, the suppression of anti-Dsg-1/3 antibodies could be maintained, albeit more heterogeneously for anti-Dsg-3 antibodies. At the end of the treatment-free follow-up (week 8 or week 10 post last drug administration), IgG levels rose back to normal. For anti-Dsg-1 IgG the median change from baseline was 70% reduction, and 42% reduction for anti-Dsg-3 IgG, indicating more prolonged suppression of pathogenic antibodies compared with total IgG levels. Detailed information on pharmacokinetics, are provided in Appendix S3 and Figure S4.

DISCUSSION

Given the direct association of pathogenic autoantibody titres with pemphigus activity,[2] we investigated whether efgartigimod, an FcRn inhibitor, would rapidly improve the condition of patients with pemphigus by reducing serum anti-Dsg autoantibody levels in this phase 2 study. The primary outcome was safety, and efgartigimod was well-tolerated, with few adverse events (predominantly infections) occurring at similar rates in the 10 and 25 mg/kg dose groups. As infections are a well-known side effect of CS treatment, the respective contributions of efgartigimod and CS to the incidence of these infections is difficult to determine. Most resolved spontaneously or rapidly upon treatment without the need to discontinue efgartigimod. One case of pneumonia required hospitalization and interruption of efgartigimod therapy. This patient (29-year-old female, body weight 35 kg, BMI, 15.0 kg/m^2) was enrolled as a relapsing PV patient and had been receiving prednisone at a stable dose of 0.3 mg/kg/day before and during the trial participation and fully recovered following treatment with antibiotics and supportive care. The patient's pneumonia was assessed by the treating investigator as being not related to efgartigimod, however, a potential effect of efgartigimod cannot be ruled out. No IgG reductions necessitated efgartigimod discontinuation for any patient, and only modest, stable, transient increases in serum albumin levels were observed, all of which remained within normal limits.

PK parameters were in line with data obtained from healthy volunteers receiving 10 or 25 mg/kg as well as with PK data from other studies using 10 mg/kg.[21-23] Serum levels of anti-vaccine antibodies (VZV, TT, PCP) decreased along with total IgG during efgartigimod treatment, with full recovery after treatment cessation. Surprisingly, a rise in vaccine antibody levels was observed in some patients during efgartigimod treatment, although exposure to the respective vaccines could be excluded, and there was no clinical evidence of infectious disease. These findings demonstrate that efgartigimod did not inhibit production of protective IgG. This observation, together with the benign evolution of infections during the trial, suggests the risk of infections is unaltered during efgartigimod treatment. An ongoing phase 3, randomized controlled trial will provide further data to answer this question.

During the efgartigimod induction phase, early reductions in total serum IgG, IgG subclasses, and anti-Dsg-1/3 autoantibodies by about 70% were observed after a weekly treatment course of 2-3 weeks. In contrast, the B-cell depleting antibody rituximab demonstrates a slow and progressive decline in autoantibody levels within months,[8,26] illustrating the critical difference in the modes of action between these treatments. Blockade of FcRn causes rapid degradation of circulating IgG, including autoantibodies, while removal of autoantibody-producing B cells has no immediate impact on circulating autoantibodies, which typically have a half-life of about 3-4 weeks. The rationale for this approach was established in a randomized trial showing that IVIg saturates FcRn and thereby eliminates pathogenic antibodies.[27] Interestingly, FcRn-deficient mice are resistant to experimental pemphigus,[28] and expression of FcRn in keratinocytes has been documented.[29] It is, thus, plausible that protection from pathogenic autoantibodies via FcRn inhibition is mediated not only through induction of autoantibody degradation but also via blockade of FcRn in keratinocytes. Additionally, the involvement of FcRn in other aspects of the immune system such as phagocytosis and antigen presentation has recently gained considerable attention.[30-32] While the beneficial effect of FcRn antagonism in pemphigus may be attributed to a combination of mechanisms, study data confirm that strategies to deplete pathogenic antibodies have a profound impact on patients' response to therapy. Consistent with this, in all cohorts of our study DC was achieved within 1-4 weeks in the vast majority of patients. DC was similarly observed in patients with PV and PF, newly diagnosed and relapsing, and mild and moderate pemphigus. Furthermore, concomitant initial doses of prednisone

were low (median 0.28 mg/kg/day), suggesting a contribution of efgartigimod to clinical efficacy. Optimal rates of CR were achieved with concomitant prednisone treatment, indicating an additive effect of prednisone to efgartigimod. Of note, CR was achieved at much lower doses of prednisone than usual, ranging from 0.06 to 0.48 mg/kg/day (median, 0.26). Besides its well-known anti-inflammatory effects, prednisone has been shown to up-regulate expression of genes encoding keratinocyte adhesion molecules such as E-cadherin and desmogleins.[33,34]

The adaptive nature of the trial permitted us to observe that the lowering of serum IgG was controlled with alternate-week dosing of efgartigimod during the maintenance phase, whereas the dosing every 4 weeks was insufficient to maintain suppression. In Cohorts 3 and 4 with prolonged efgartigimod treatment (15 and 34 weeks, respectively), patients had sustained PDAI activity reductions, and CR was reached within a median of 13 weeks (range 2-41 weeks). Recently, the results of a phase 1b/2 trial with an anti-FcRn monoclonal antibody, ALXN1830 (NCT03075904) were published confirming the rapid improvement in PDAI scores in pemphigus patients.[35]

In the present trial, relapses occurred in 39% of patients. These primarily occurred early, before CR, and were observed during prolonged administration intervals of 2 or more weeks. Late relapses, i.e., after CR, occurred during alternate-week dosing or during treatment-free follow-up. In contrast, no relapses occurred when patients were maintained at weekly efgartigimod dosing, suggesting that a weekly administration of efgartigimod beyond reaching CR may help to prevent relapses.

Study limitations included those associated with open-label, single-arm designs lacking a randomized, double-blind control group as well as the comparably short treatment periods and follow-up after treatment. Additionally, the varying use of prednisone amongst study participants and exclusion of severe manifestations of pemphigus from the study may limit the generalizability of the results.

In summary, this proof-of-concept study of efgartigimod in pemphigus provides evidence that efgartigimod meets current medical needs of patients suffering from PV or PF by demonstrating a favourable safety profile, early onset of action in reaching DC and CR in newly diagnosed and

relapsing patients, and a potential to use lower initial doses of CS and early CS tapering. Based on these data, a phase 3 randomized, controlled trial was initiated to further study the efficacy and safety of efgartigimod in PV and PF (NCT04598451).

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Figure Legends

Figure 1. Schematic of the adaptive design of the phase 2 study. EoC, end of consolidation; SOC, standard of care; CS, corticosteroid.

Figure 2. Patient disposition for safety and efficacy analyses.

Figure 3. Individual patients' pemphigus disease area index (PDAI) activity scores over time in Cohorts 1-4. Cohort 4 includes patients with pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

Figure 4. Mean serum levels over time of anti-Dsg-1 autoantibodies in Cohorts 1-3 (*A*) and Cohort 4 (*C*), and anti-Dsg-3 autoantibodies in Cohorts 1-3 (*B*) and Cohort 4 (*D*). Error bars represent standard error of the mean (SEM).

Table 1. Baseline demographics and characteristics.

Baseline characteristics	**Safety analysis set (n=34)**	**Efficacy analysis set (n=31)**
Age, mean ± SE	51.5 ± 2.6	52.4 ± 2.8
Sex, n (%)		
Male	12 (35)	10 (32)
Female	22 (65)	21 (68)
Pemphigus vulgaris, n (%)	26 (77)	24 (77)
Mucosal-dominant	9 (35)	9 (38)
Mucocutaneous	14 (54)	12 (50)
Cutaneous	3 (11)	3 (12)
Pemphigus foliaceus, n (%)	8 (24)	7 (23)
Anti-desmoglein positive, n (%)		
Anti-Dsg-1	9* (27)	8* (26)
Anti-Dsg-3	11† (32)	11† (35)
Anti-Dsg-1 and anti-Dsg-3	14 (41)	12 (39)
Disease history, n (%)		
Newly diagnosed	14 (41)	12 (39)
Relapsing	20 (59)	19 (61)
Baseline severity, n (%)		
Mild (PDAI <15)	12 (35)	12 (39)
Moderate (PDAI 15-44)	22 (65)	19 (61)
Baseline PDAI score, mean ± SE (min, median, max score)	20.9 ± 2.0 (2.0, 20.4, 39.9)	20.1 ± 2.1 (2.0, 19.0, 39.9)
Treatment initiated at baseline, n (%)		
Efgartigimod monotherapy	11 (32)	8 (26)
Efgartigimod + prednisone	23 (68)	23 (74)

*Includes 1 patient positive for anti-Dsg-1 only at baseline and positive for anti-Dsg-1 and anti-Dsg-3 later.

†Includes 1 patient positive for anti-Dsg-3 at screening but with anti-Dsg-3 <20 U/mL at baseline.

Abbreviation: Dsg, desmoglein.

Table 2. Summary of treatment-emergent adverse events.

Adverse events (AEs)*	**Efgartigimod 10 mg/kg (n=19)**	**Efgartigimod 25 mg/kg (n=15)**	**Efgartigimod Overall (n=34)**
Total no. of AEs	60	61	121
Total no. of serious AEs†	2	0	2
Patients with			
≥1 AE, n (%)	16 (84)	13 (87)	29 (85)
≥1 Serious AE,† n (%)	2 (11)	0	2 (6)
≥1 Grade 3 severe AE,‡ n (%)	3 (16)	2 (13)	5 (15)
≥1 Grade 4 severe AE, n (%)	0	0	0
≥1 Treatment-related AEs, n (%)	5 (26)	5 (33)	10 (29)
≥1 Serious treatment-related AEs, n (%)	0	0	0
≥1 AE leading to discontinuation of study drug, n (%)	1 (5)	0	1 (3)
≥1 AEs of special interest, n (%)	11 (58)	10 (67)	21 (62)

*Severity and causality of AEs were assessed by the investigator.

†Two serious AEs reported which were assessed as unrelated to efgartigimod (pneumonia and tibia fracture).

‡Five grade 3 AEs were reported, 3 as not related to efgartigimod (syncope, pneumonia, and tibia fracture), and 2 as possibly related to efgartigimod (tooth infection and blood creatine phosphokinase [CPK] increase).

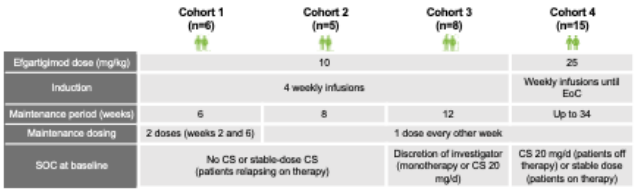
Table 3. Grade 1 and 2 AEs occurring in ≥2 patients (overall) by system organ class and preferred term

Adverse events (AEs), n (%)	**Efgartigimod 10 mg/kg (n=19)**	**Efgartigimod 25 mg/kg (n=15)**	**Efgartigimod Overall (n=34)**
Infections and infestations			
Nasopharyngitis	0	4 (27)	4 (12)
Urinary tract infection	1 (5)	2 (13)	3 (9)
Rhinitis	0	2 (13)	2 (6)
Bronchitis	2 (11)	0	2 (6)
Gastroenteritis	1 (5)	1 (7)	2 (6)
Respiratory tract infection	1 (5)	1 (7)	2 (6)
Impetigo	1 (5)	1 (7)	2 (6)
Gastrointestinal disorders			
Diarrhoea	2 (11)	2 (13)	4 (12)
Abdominal pain	1 (5)	2 (13)	3 (9)
Vomiting	2 (11)	1 (7)	3 (9)
General disorders and administration site conditions			
Influenza-like illness	1 (5)	2 (13)	3 (9)
Fatigue	1 (5)	1 (7)	2 (6)
Skin and subcutaneous tissue disorders			
Dry skin	1 (5)	1 (7)	2 (6)
Nervous system disorders			
Headache	1 (5)	3 (20)	4 (12)
Dizziness	2 (11)	1 (7)	3 (9)
Blood and lymphatic system disorders			
Anaemia	1 (5)	2 (13)	3 (9)
Respiratory, thoracic, and mediastinal disorders			
Cough	1 (5)	1 (7)	2 (6)

Adverse events (AEs), n (%)	Efgartigimod 10 mg/kg (n=19)	Efgartigimod 25 mg/kg (n=15)	Efgartigimod Overall (n=34)
Investigations			
Alanine aminotransferase increased	0	2 (13)	2 (6)
Renal and urinary disorders			
Renal pain	1 (5)	1 (7)	2 (6)

Table 4. Incidence of disease control (DC), clinical remission (CR), and relapse from DC in overall population and by subgroups from the efficacy analysis set.

	Disease control	**Complete clinical remission**	**Relapse**
Overall, n	31	22	28
Yes, n (%)	28 (90)	14 (64)	11 (39)
No, n (%)	3 (10)	8 (36)	17 (61)
Median time to DC, CR, or relapse, days (range)	17 (6-92)	92 (13–287)	211 (10-211)
Cohort 1, n/N (%)	4/4 (100)	-	2/4 (50)
Cohort 2, n/N (%)	3/5 (60)	-	2/3 (67)
Cohort 3, n/N (%)	7/7 (100)	5/7 (71)	3/7 (43)
Cohort 4, n/N (%)	14/15 (93)	9/15 (60)	4/14 (29)
On efgartigimod monotherapy, n	8	-	-
Yes, n (%)	6 (75)	-	-
No, n (%)	2 (25)	-	-
Median time to DC, CR, or relapse, days (range)	16 (8-30)	-	-
Pemphigus vulgaris, n/N (%)	22/24 (92)	9/15 (60)	9/22 (41)
Pemphigus foliaceus, n/N (%)	6/7 (86)	5/7 (71)	2/6 (33)
Disease history, n/N (%)			
Relapsing patients	18/19 (95)	7/13 (54)	7/18 (39)
Newly diagnosed patients	10/12 (83)	7/9 (78)	4/10 (40)
Disease severity at baseline, n/N (%)			
Mild (PDAI < 15)	11/12 (92)	7/12 (58)	6/11 (55)
Moderate (PDAI 15-44)	17/19 (89)	7/19 (37)	5/17 (29)



	Cohort 1 (n=6)	Cohort 2 (n=5)	Cohort 3 (n=8)	Cohort 4 (n=15)
Efgartigimod dose (mg/kg)	10			25
Induction	4 weekly infusions			Weekly infusions until EoC
Maintenance period (weeks)	6	8	12	Up to 34
Maintenance dosing	2 doses (weeks 2 and 6)	1 dose every other week		
SOC at baseline	No CS or stable-dose CS (patients relapsing on therapy)		Discretion of investigator (monotherapy or CS 20 mg/d)	CS 20 mg/d (patients off therapy) or stable dose (patients on therapy)

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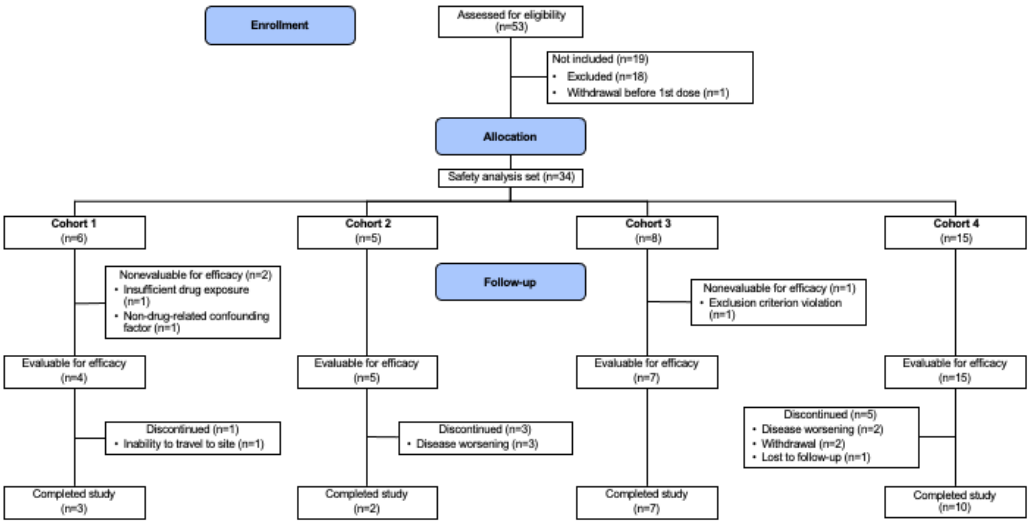

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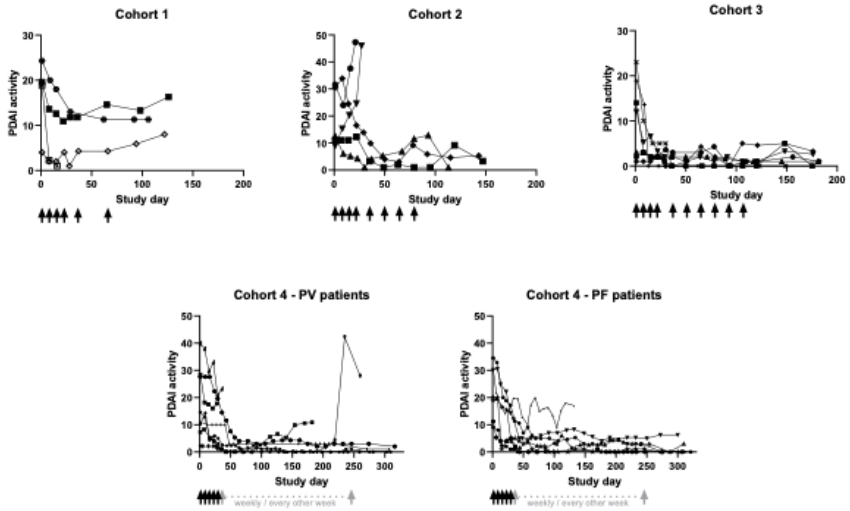

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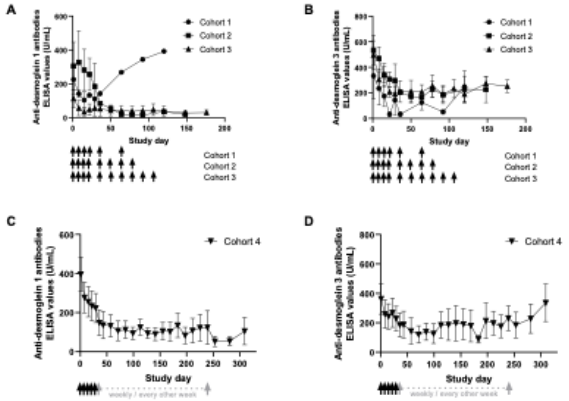

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