CLINICAL TRIAL

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

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Summary

Background Pemphigus vulgaris and pemphigus foliaceus are potentially life-threatening autoimmune disorders triggered by 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.
Objectives 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 II adaptive trial. In sequential cohorts, efgartigimod was dosed at 10 or 25 mg kg^{-1} intravenously with various dosing frequencies, as monotherapy or as add-on therapy to low-dose oral prednisone. Safety endpoints comprised the primary outcome. The study is registered at ClinicalTrials.gov (identifier NCT03334058).
Results Adverse events were mostly mild and were reported by 16 of 19 (84%) patients receiving efgartigimod 10 mg kg^{-1} and 13 of 15 (87%) patients receiving 25 mg kg^{-1}, with similar adverse event profiles between dose groups. A major decrease in serum total IgG and anti-desmoglein autoantibodies was observed and correlated with improved Pemphigus Disease Area Index scores. Efgartigimod, as monotherapy or combined with prednisone, demonstrated early disease control in 28 of 31 (90%) patients after a median of 17 days. Optimized, prolonged treatment with efgartigimod in combination with a median dose of prednisone 0·26 mg kg^{-1} per day (range 0·06–0·48) led to complete clinical remission in 14 of 22 (64%) patients within 2–41 weeks.
Conclusions 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.

What is already known about this topic?

- Efgartigimod is an Fc fragment engineered for increased affinity for the neonatal Fc receptor (FcRn) to outcompete endogenous IgG binding, thereby preventing recycling and causing increased IgG degradation.

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Conflicts of interest
M.G. has served as a consultant and on advisory boards for argenx, Biotest, Janssen, LEO Pharma, Lilly, Novartis and UCB. Z.B.C. has served on advisory boards for Novartis, Sanofi Genzyme, Ewopharma, AbbVie and argenx. C.D.S. has no disclosures to report. B.D. has no disclosures to report. E.R. has served as a member of advisory boards for Janssen Cilag Hungary, Lilly Hungary and Takeda Pharma. N.R. has no disclosures to report. J.S. has no disclosures to report. E.S.W. is supported in part by a research grant funded by argenx BVBA, Zwijnaarde, Belgium; has a financial interest in argenx BVBA; and may receive royalties from patents owned by the UK Medical Research Council, UT Southwestern Medical Center, and Texas A&M University. W.P., H.H. and P.V. are employed by argenx. P.D. was previously employed by argenx and currently consults for argenx. E.S. has received research grants from argenx, Novartis, UCB, Incyte, Biotest, Dompe, Admirx, Byondis, Fresenius and EUROIMMUN

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Data availability

argenx is committed to responsible data sharing regarding the clinical trials they fund. Included in this commitment is access to anonymized, individual and trial-level data (analysis datasets), and other information (e.g. protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. These clinical trial data can be requested by qualified researchers who engage in rigorous independent scientific research and will only be provided after review and approval of a research proposal and statstical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months. Requests can be submitted to ESR@argenx.com.

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- In previous phase II studies in primary immune thrombocytopenia and myasthenia gravis, as well as in a phase III study in myasthenia gravis, efgartigimod induced reductions in all IgG subclasses with corresponding clinical efficacy and was well tolerated.

What does this study add?

- In this phase II, open-label study of efgartigimod in patients with pemphigus vulgaris and pemphigus foliaceus, efgartigimod induced early decreases in serum total IgG, as well as disease-specific anti-desmoglein 1 and 3 autoantibodies, and was well tolerated.
- The clinical results of this study demonstrate that efgartigimod represents a well-tolerated potential means of achieving early disease control and complete clinical remission of pemphigus while allowing early corticosteroid tapering.

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 IgG autoantibodies targeting desmoglein (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^{-1}) 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 USA 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^{-1} per day. This approach is also associated with a relatively high frequency of relapses, in 25–60% 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 have been implemented such as plasmapheresis, immunoadsorption and intravenous immunoglobulin (IVIg).[5,12,13] However, plasmapheresis and immunoadsorption 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 II 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 II adaptive study to investigate the efficacy and safety of efgartigimod in pemphigus.

Patients and methods

Study design

This phase II, open-label, single-treatment-arm, multicentre trial of efgartigimod dosed at 10 or 25 mg kg^{-1} bodyweight was conducted using an adaptive design with four cohorts involving patients with PV or PF. Participants were sequentially enrolled in each cohort prior to treatment, and a minimum of four 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 the 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 phases) and concomitant prednisone and rescue treatment. Recommendations were driven by safety data, disease activity (Pemphigus Disease Area Index, PDAI), pemphigus disease markers (total serum IgG, anti-Dsg antibodies) and clinical outcome of the disease [disease control (DC), complete clinical response (CR), relapse and concomitant prednisone dose at the outcomes].

The study was conducted in accordance with 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 enzyme-linked immunosorbent assay (ELISA).[9] Patients on oral prednisone (or equivalent) and/or an 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 or immunoadsorption) or if they had undergone treatment with intravenous CS pulse, dapsone, sulfasalazine, tetracyclines, nicotinamide, plasmapheresis or 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 kg^{-1} bodyweight) was administered via intravenous infusion over a period of 2 h if total serum IgG levels were > 1·2 g L^{-1}. Cohorts 1–3 received efgartigimod 10 mg kg^{-1} in weekly infusions for 4 weeks 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 one infusion each at weeks 2 and 6 (as determined a priori), cohort 2 received an infusion every other week for 8 weeks (four doses in total), and cohort 3 received an infusion every other week for 12 weeks (six 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^{-1} each week until achievement of end of consolidation (defined as the time at which no new lesions had developed for a minimum of 2 weeks and approximately 80% of lesions had healed), after which patients received infusions every other week for up to 34 weeks. Newly diagnosed patients and relapsing patients who were off therapy also

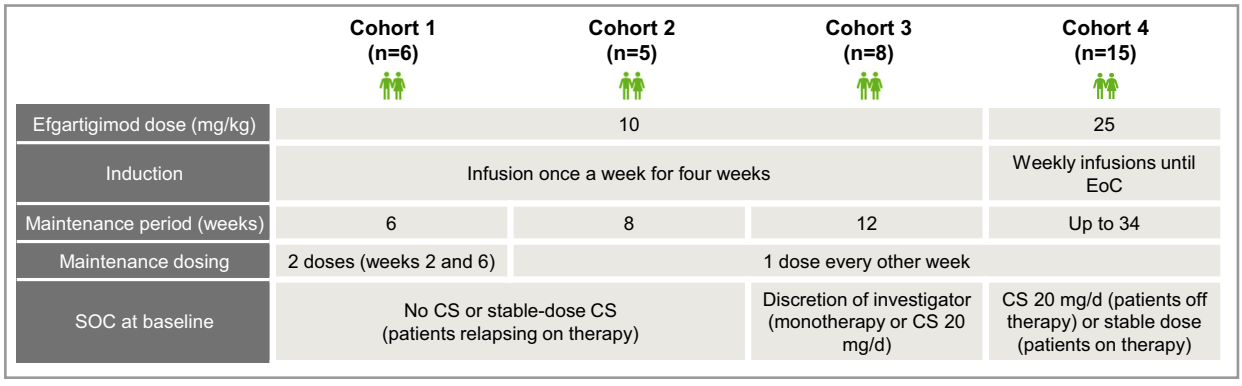

Figure 1 Schematic of the adaptive design of the phase II study. CS, corticosteroids; EoC, end of consolidation; SOC, standard of care.

received prednisone 20 mg per 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. Rescue therapy consisted of prednisone 20 mg per day for patients off therapy and was increased to 40 mg per day in patients already on prednisone. In cohort 3, investigators could start prednisone 20 mg per day at study initiation. Rescue therapy was allowed from the beginning of the maintenance phase in cohort 1 and from any postbaseline visit in cohorts 2–4. In cohort 4, oral prednisone could be tapered from the end of consolidation.

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 AEs. 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 the study investigator at each visit and compared with study baseline; time to DC, defined as no new lesions and established lesions starting to heal; time to end of consolidation (assessed in cohort 4 only); time to relapse (appearance of three 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 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 (total IgG and IgG subclasses and anti-Dsg-1/3 autoantibodies) and pharmacokinetic 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, varicella zoster virus and pneumococcal capsular polysaccharide.

Statistical analyses

Descriptive statistical methods were used to analyse safety and efficacy data. Summaries (mean, SE, median, range) were provided by cohort and/or efgartigimod dose. No formal sample-size calculation was done, but a minimum of four evaluable patients was required in each of cohorts 1–3, 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 three administrations) who had no confounding factors or missing visits that could interfere with the observation of at least one clinical outcome, and did not have a major protocol deviation that affected the efficacy profile.

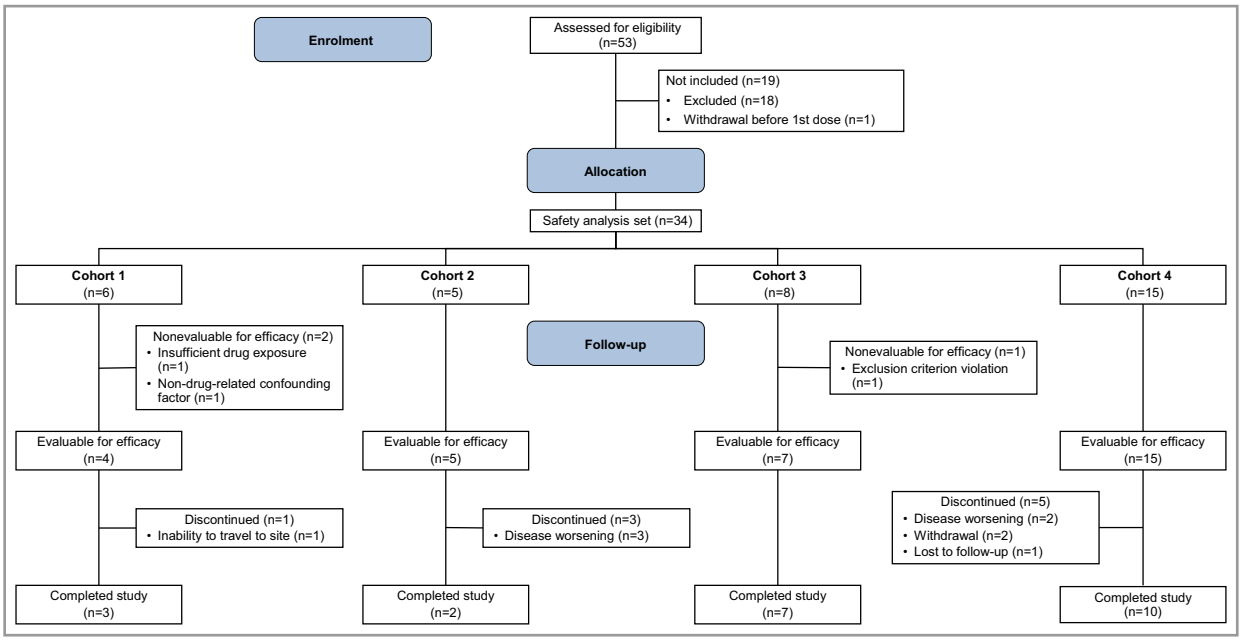

Figure 2 Patient disposition for safety and efficacy analyses.

Table 1 Baseline demographics and characteristics

Baseline characteristics	Safety analysis set (n = 34)	Efficacy analysis set (n = 31)
Age (years), 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 (76)	24 (77)
Mucosal dominant	9 (35)	9 (38)
Mucocutaneous	14 (54)	12 (50)
Cutaneous	3 (12)	3 (13)
Pemphigus foliaceus, n (%)	8 (24)	7 (23)
Anti-Dsg positive, n (%)		
Anti-Dsg-1	9[a] (27)	8[a] (26)
Anti-Dsg-3	11[b] (32)	11[b] (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); median (range)	20·9 ± 2·0; 20·4 (2·0–39·9)	20·1 ± 2·1; 19·0 (2·0–39·9)
Treatment initiated at baseline, n (%)		
Efgartigimod monotherapy	11 (32)	8 (26)
Efgartigimod + prednisone	23 (68)	23 (74)

PDAI, Pemphigus Disease Area Index. [a]Includes one patient positive for only anti-desmoglein (Dsg)-1 at baseline and positive for both anti-Dsg-1 and anti-Dsg-3 later. [b]Includes one patient positive for anti-Dsg-3 at screening but with anti-Dsg-3 < 20 U mL^{-1} at baseline.

Table 2 Summary of treatment-emergent adverse events (AEs)

AEs[a]	Efgartigimod 10 mg kg^{-1} (n = 19)	Efgartigimod 25 mg kg^{-1} (n = 15)	Efgartigimod Overall (n = 34)
Total AEs	60	61	121
Total serious AEs[b]	2	0	2
Details of patients with AEs, n (%)			
≥ 1 AE	16 (84)	13 (87)	29 (85)
≥ 1 serious AE[b]	2 (11)	0	2 (6)
≥ 1 grade 3 severe AE[c]	3 (16)	2 (13)	5 (15)
≥ 1 grade 4 severe AE	0	0	0
≥ 1 treatment-related AE	5 (26)	5 (33)	10 (29)
≥ 1 serious treatment-related AE	0	0	0
≥ 1 AE leading to discontinuation of study drug	1 (5)	0	1 (3)
≥ 1 AE of special interest	11 (58)	10 (67)	21 (62)

[a]Severity and causality of AEs were assessed by the investigator. [b]Two serious AEs reported, which were assessed as unrelated to efgartigimod (pneumonia and tibia fracture). [c]Five grade 3 AEs were reported, three as not related to efgartigimod (syncope, pneumonia and tibia fracture) and two as possibly related to efgartigimod (tooth infection and blood creatine phosphokinase increase).

Kaplan–Meier methods were used to calculate time to DC, time to end of consolidation, 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. Thirty-four (26 with PV and eight with PF) were enrolled in the trial; one patient withdrew consent before baseline (Figure 2). For the efficacy analysis, three patients were excluded by the IDMC for insufficient drug exposure, impetigo as a 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) intravenous infusions of efgartigimod. AE profiles were similar between doses (Tables 2 and 3). At least one treatment-emergent AE was reported by 16 of 19 (84%) patients receiving efgartigimod 10 mg kg^{-1} and 13 of 15 (87%) receiving 25 mg kg^{-1}. The most common AEs were nasopharyngitis, diarrhoea and headache, each reported by four patients (12%) (Table 3); none were considered related to study drug except one event of diarrhoea. All events were of mild or moderate intensity.

In total 32 AESIs were reported in 21 patients (62%), of which seven events in five 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 one of tooth infection, which were grade 3 AESIs (details in Appendix S1; see Supporting Information). 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; see Supporting Information). Total serum cholesterol and low-density lipoprotein cholesterol

Table 3 Grade 1 and 2 adverse events (AEs) occurring in at least two patients (overall) by system organ class and preferred term

	Efgartigimod		
AEs, n (%)	10 mg kg^{-1} (n = 19)	25 mg kg^{-1} (n = 15)	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)
Investigations			
Alanine aminotransferase increased	0	2 (13)	2 (6)
Renal and urinary disorders			
Renal pain	1 (5)	1 (7)	2 (6)

levels remained within normal limits across all timepoints measured in 11 patients from cohort 4 (Figure S1).

Efficacy

Pemphigus Disease Area Index 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^{-1} dose groups (cohorts 1–3). In cohort 4, the 25-mg kg^{-1} 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 seven 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 six patients in cohorts 1–3, with a median 72% reduction after four doses at weekly dosing.

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) (additional details in Appendix S2; see Supporting Information). In cohort 4, end of consolidation was achieved in 11 of 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, seven occurred in the maintenance phase, and seven occurred in the treatment-free, follow-up phase.

In cohorts 3 and 4, 64% of patients (14 of 22; five of seven in cohort 3, and nine of 15 in 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^{-1}, range 0·06–0·48).

IgG and anti-desmoglein antibody levels

After the first infusion, serum IgG decreased by 40–45% (Figure S2; see Supporting Information). On day 29, the median reduction in IgG level was 62% (range 54–74%) with efgartigimod 10 mg kg^{-1} and 66% (range 24–75%) with efgartigimod 25 mg kg^{-1}. Serum levels of IgG subclasses (IgG1–IgG4) generally followed total IgG level reductions (Figure S3; see Supporting Information).

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 end of consolidation 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 after the 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 is provided in Appendix S3 and Figure S4 (see Supporting Information).

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 II study. The primary outcome was safety, and efgartigimod was well tolerated, with

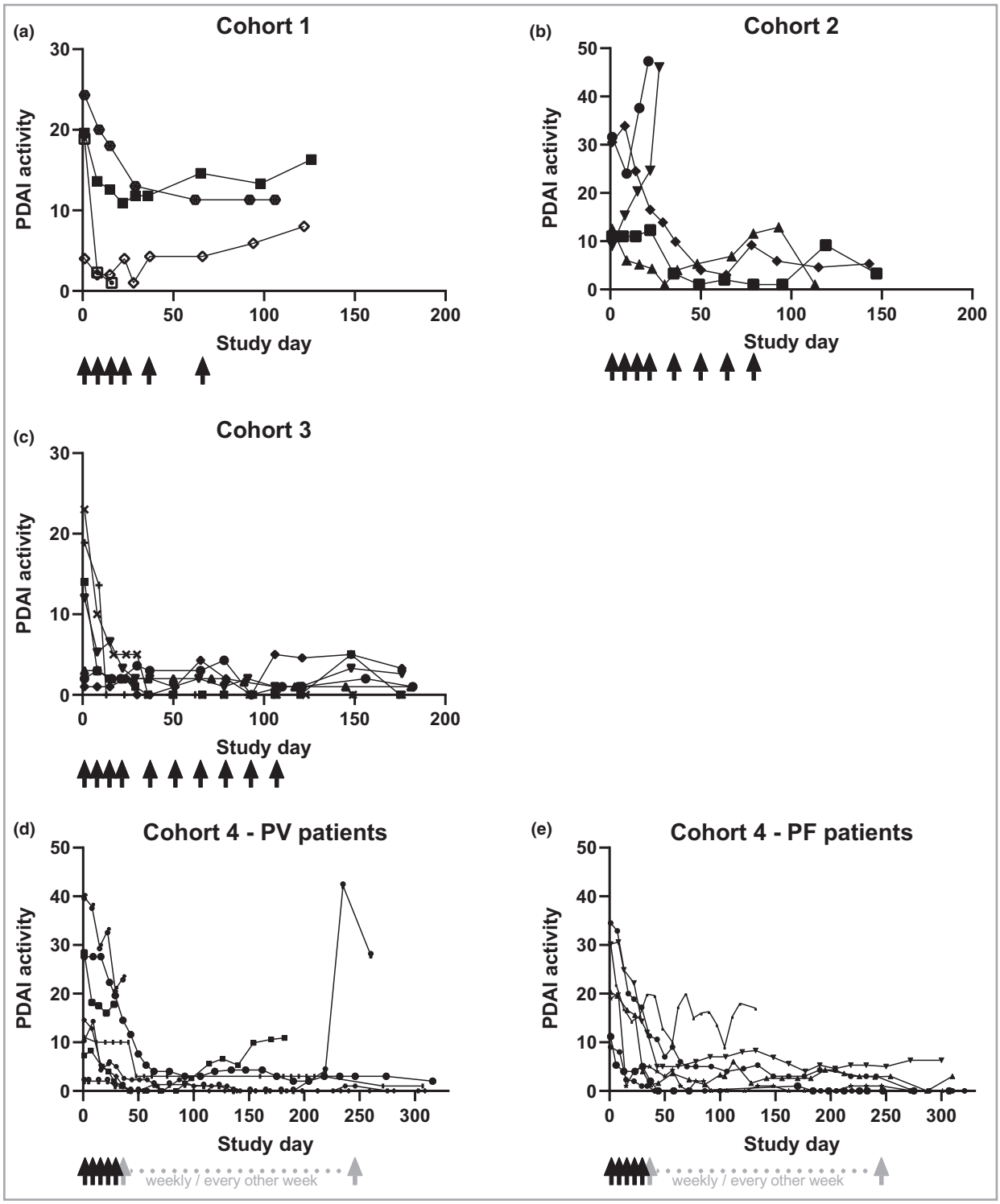

Figure 3 Individual patients' Pemphigus Disease Area Index (PDAI) activity scores over time in cohorts 1–4. Cohort 4 includes patients with pemphigus vulgaris (PV) and pemphigus foliaceus (PF).

few AEs (predominantly infections) occurring at similar rates in the 10- and 25-mg kg^{-1} 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 are 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 woman, bodyweight 35 kg, body mass index 15·0 kg m^{-2}) was enrolled as a patient with relapsing

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

	DC	CR	Relapse
All patients	31	22	28
Yes, n (%)	28 (90)	14 (64)	11 (39)
No, n (%)	3 (10)	8 (36)	17 (61)
Time to DC, CR or relapse (days), median (range)	17 (6–92)	92 (13–287)	211 (10–211)
Patients by cohort, n/N (%)			
Cohort 1	4/4 (100)	–	2/4 (50)
Cohort 2	3/5 (60)	–	2/3 (67)
Cohort 3	7/7 (100)	5/7 (71)	3/7 (43)
Cohort 4	14/15 (93)	9/15 (60)	4/14 (29)
Patients on efgartigimod monotherapy	8	–	–
Yes, n (%)	6 (75)	–	–
No, n (%)	2 (25)	–	–
Time to DC, CR or relapse (days), median (range), n/N (%)	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)	7/8 (88)	6/11 (55)
Moderate (PDAI 15–44)	17/19 (89)	7/14 (50)	5/17 (29)

PDAI, Pemphigus Disease Area Index.

PV. She had been receiving prednisone at a stable dose of 0·3 mg kg^{-1} per day before and during the trial 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.

Pharmacokinetic parameters were in line with data obtained from healthy volunteers receiving doses of 10 or 25 mg kg^{-1}, as well as with pharmacokinetic data from other studies using 10 mg kg^{-1}.[21–23] Serum levels of antivaccine antibodies (tetanus toxoid, varicella zoster virus and pneumococcal capsular polysaccharide) 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 III, 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' responses 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 with mild and moderate pemphigus. Furthermore, concomitant initial doses of prednisone were low (median 0·28 mg kg^{-1} per day), suggesting a contribution of efgartigimod to clinical efficacy. Optimal rates of

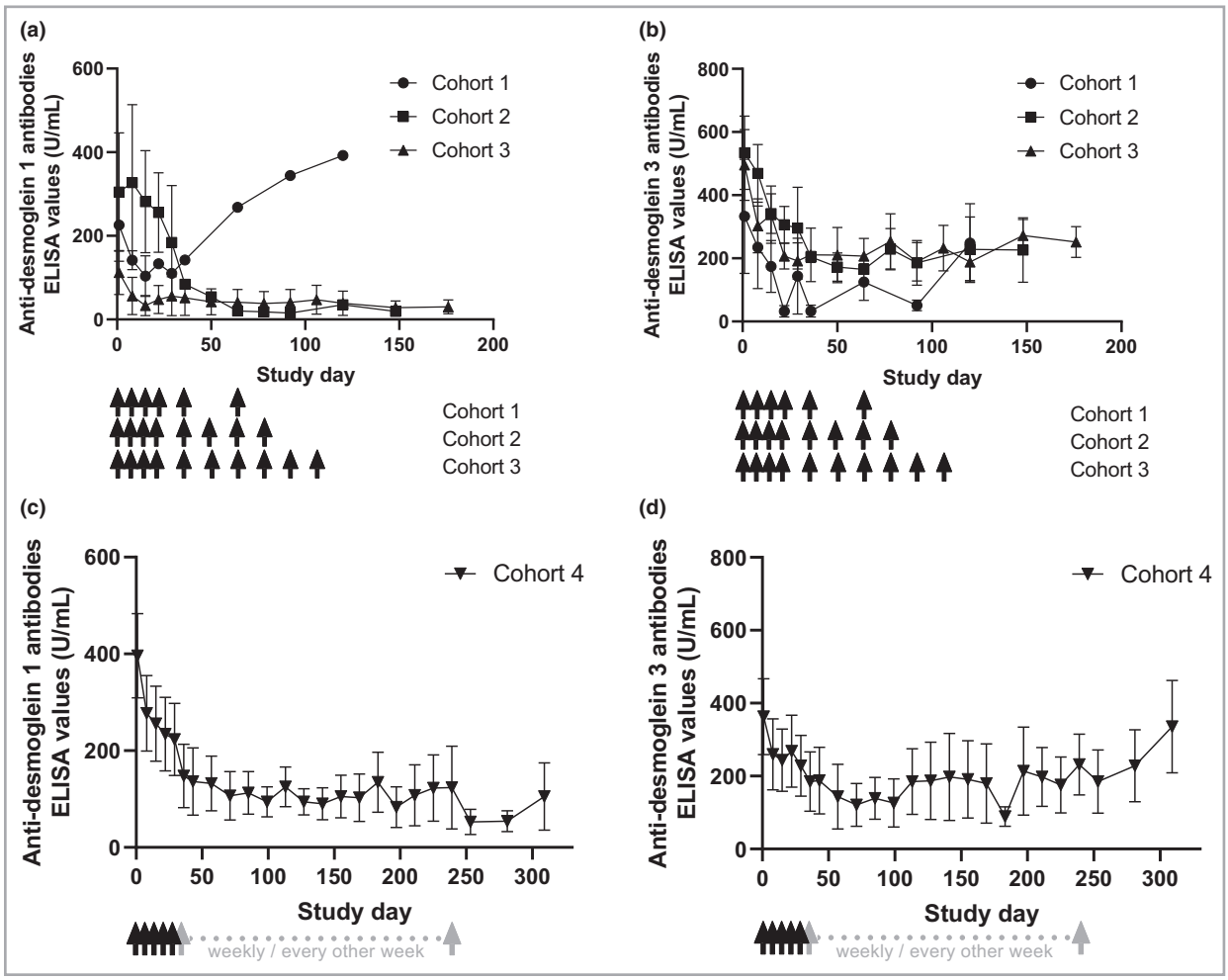

Figure 4 Mean serum levels over time of anti-desmoglein (Dsg)-1 autoantibodies in cohorts 1–3 (a) and cohort 4 (c), and anti-Dsg-3 autoantibodies in cohorts 1–3 (b) and cohort 4 (d). Error bars represent the standard error of the mean (SEM). ELISA, enzyme-linked immunosorbent assay.

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^{-1} per day (median 0·26). Besides its well-known anti-inflammatory effects, prednisone has been shown to upregulate 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). Recently, the results of a phase Ib/II trial with an anti-FcRn monoclonal antibody, ALXN1830 (NCT03075904), were published, confirming the rapid improvement in PDAI scores in patients with pemphigus.[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 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 weekly administration of efgartigimod after 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 among 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 the current medical needs of patients with 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 III randomized controlled trial was initiated to further study the efficacy and safety of efgartigimod in PV and PF (NCT04598451).

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Severe adverse events.
Appendix S2. Disease control endpoints.
Appendix S3. Pharmacokinetics.
Figure S1. Serum levels of albumin.
Figure S2. Serum levels of total IgG.
Figure S3. Mean serum levels of IgG subclasses IgG1, IgG2, IgG3 and IgG4.
Figure S4. Mean serum levels of anti-tetanus toxoid, anti-varicella zoster virus and anti-pneumococcal capsular polysaccharide antibodies over time in patients treated up to 238 days (34 weeks) in cohort 4.
Table S1. List of investigators and sites.