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# Safety, Tolerability, and Activity of ALXN1830 Targeting the Neonatal Fc Receptor in Chronic Pemphigus

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Pemphigus is a debilitating IgG-mediated autoimmune disease requiring better tolerated, more targeted, and rapid onset therapies. ALXN1830 is a humanized IgG4 antibody that blocks neonatal Fc receptor interactions with IgG. A multicenter, open-label safety and tolerability phase 1b/2 trial (NCT03075904) was conducted in North America from July 2017 to January 2019 and included patients aged  $\geq 18$  years with a confirmed diagnosis of pemphigus (vulgaris or foliaceus) and active disease. Dosing included five weekly intravenous doses of ALXN1830 (10 mg/kg) and follow-up through day 112 (study termination). Pharmacokinetics, pharmacodynamics, safety, and efficacy, as evaluated by determining the change in the median pemphigus disease area index, were determined. In this pilot study of eight patients, five weekly infusions of ALXN1830 produced a rapid improvement in the pemphigus disease area index score within 14 days of the first dose. Pemphigus disease area index improvement increased further together with reductions in IgG, circulating immune complexes of IgG, and anti-desmoglein antibodies without affecting albumin, IgM, IgA, or C-reactive protein levels. ALXN1830 was well-tolerated, with headache as the most common adverse event. This study reveals the importance of neonatal Fc receptor in the biology of pemphigus and the potential for use of ALXN1830 in pemphigus treatment.

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## INTRODUCTION

IgG antibodies and their associated immune complexes (ICs) can be pathogenic in a range of autoimmune diseases (Ludwig et al., 2017; Suurmond and Diamond, 2015). Pemphigus (vulgaris and foliaceus) is a debilitating disease with painful blisters of the skin and mucosal surfaces that can cause severe and fatal complications. The disease is characterized by IgG autoantibodies directed at the desmosomal cadherins desmogleins (DSGs) 1 and 3, important for keratinocyte cell adhesion in tissues subjected to mechanical stress (Amagai et al., 1999; Huijbers et al., 2018). Disease activity is associated with the levels of anti-DSG1 and anti-DSG3 autoantibodies in the circulation, and their reduction

has been shown to correlate with clinical response (Joly et al., 2017; Yeoh et al., 2019). Current treatment approaches involve general suppression of the immune system, removal of the autoantibodies, or elimination of antibody production through the use of glucocorticoids, immunosuppressive treatments, intravenous (i.v.) Ig, immunoadsorption, or anti-CD20 antibodies, which have unique limitations, including delayed or limited clinical efficacy or concerning side effects (Kasperkiewicz et al., 2017; Paran et al., 2005; Prins et al., 2007; Sekul et al., 1994).

The neonatal Fc receptor (FcRn) is a key determinant of IgG levels and function (Pyzik et al., 2019). It is widely expressed in adult human parenchymal and hematopoietic cells where it binds IgG and albumin in a noncompetitive fashion under acidic conditions, thereby regulating their distribution and persistence in the circulation (Pyzik et al., 2019). FcRn also controls the levels of IgG circulating ICs (CICs), enabling their persistence in the circulation and subsequent ability to deposit in tissues or induce the production of inflammatory cytokines, T-cell activation, and promotion of antibody-producing B cells (Blumberg et al., 2019; Végh et al., 2011). As such, FcRn determines IgG levels, localization, and function without directly affecting B-cell production of IgG (Schneider et al., 2015).

ALXN1830 (SYNT001), is a humanized, affinity-matured IgG4-kappa mAb with a high affinity for the FcRn, which blocks the binding of IgG and IgG ICs to the FcRn and thereby accelerates their breakdown and decreases the associated inflammatory responses. Specific and high-affinity blockade of FcRn with ALXN1830 has been shown to reduce circulating IgG and IgG ICs as well as inhibit IgG

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Abbreviations: CIC, circulating immune complex; DSG, desmoglein; FcRn, neonatal Fc receptor; IC, immune complex; IRB, Institutional Review Board; i.v., intravenous; PDAL, pemphigus disease area index

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**Table 1. Demographic and Clinical Characteristics of the Patients**

Characteristics	10 mg/kg ALXN1830 (N = 8)
Age (y)	
Median (range)	38.0 (18–72)
Sex, n (%)	
Female	5 (62.5)
Male	3 (37.5)
Race, n (%)	
African American	3 (37.5)
White	5 (62.5)
Ethnicity, n (%)	
Not Hispanic or Latino	8 (100)
Pemphigus type, n (%)	
Vulgaris	7 (87.5)
Foliaceus	1 (12.5)
Age at diagnosis (y)	
Median (range)	38.0 (18–72)
Disease duration (y)	
Median (range)	7.35 (0.3–31.7)
Baseline PDAI total activity score	
Median (range)	24.0 (9–55)
Body mass index at study entry (kg/m <sup>2</sup> )	
Median (range)	31.40 (24.9–39.7)

Abbreviation: PDAI, pemphigus disease area index.

IC-mediated immune responses in healthy volunteers (Blumberg et al., 2019). We therefore investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of ALXN1830 in patients with pemphigus as well as its effect on disease activity.

## RESULTS

### Patient population and characteristics

Eight patients (one with pemphigus foliaceus and seven with pemphigus vulgaris) were enrolled (Table 1). All patients completed five weekly i.v. doses of 10 mg/kg ALXN1830 in the treatment period during the first 28 days of the study. Four patients completed the 112-day period of follow-up, and four discontinued after completing treatment (three discontinued owing to the physician's decision to withdraw them after clinical worsening [on study days 34, 78, and 85], and one discontinued owing to the need for increased dose of azathioprine [on study day 34], which was not permitted per the protocol).

### Safety

All the eight patients experienced at least one treatment-emergent adverse event (Table 2). Headache was the most common and was noted in six of the eight patients, with 46% occurring after the first infusion and were either mild (62%) or moderate (38%) in severity and were responsive to acetaminophen. An infusion-related reaction manifesting as an urticarial rash, relieved by oral diphenhydramine, was noted in one patient on the fourth and fifth doses of the drug. Two serious adverse events occurred in one patient (patient 1) who abruptly withdrew oral steroids before initiation of the treatment protocol and developed cutaneous herpes simplex infection and methicillin-resistant *Staphylococcus aureus* infection on day 7. The infection disappeared with

**Table 2. Summary of Adverse Events**

System Organ Class Preferred	10 mg/kg ALXN1830 (N = 8)	
	No. (%)	Events
Patients with any treatment-emergent adverse event	7 (87.5)	37
Related to study drug	7 (87.5)	20
Patients with any serious adverse event	1 (12.5)	2
Related to study drug	0	0
Nervous system disorders	6 (75.0)	15
Headache	6 (75.0)	14
Sinus headache	1 (12.5)	1
General disorders and administration site conditions	4 (50.0)	5
Fatigue	2 (25.0)	2
Disease progression	1 (12.5)	1
Malaise	1 (12.5)	1
Pyrexia	1 (12.5)	1
Gastrointestinal disorders	3 (37.5)	4
Nausea	2 (25.0)	2
Diarrhea	1 (12.5)	1
Vomiting	1 (12.5)	1
Infections and infestations	2 (25.0)	3
Herpes simplex	1 (12.5)	1
Staphylococcal infection	1 (12.5)	1
Tinea barbae	1 (12.5)	1

Abbreviation: No., number.

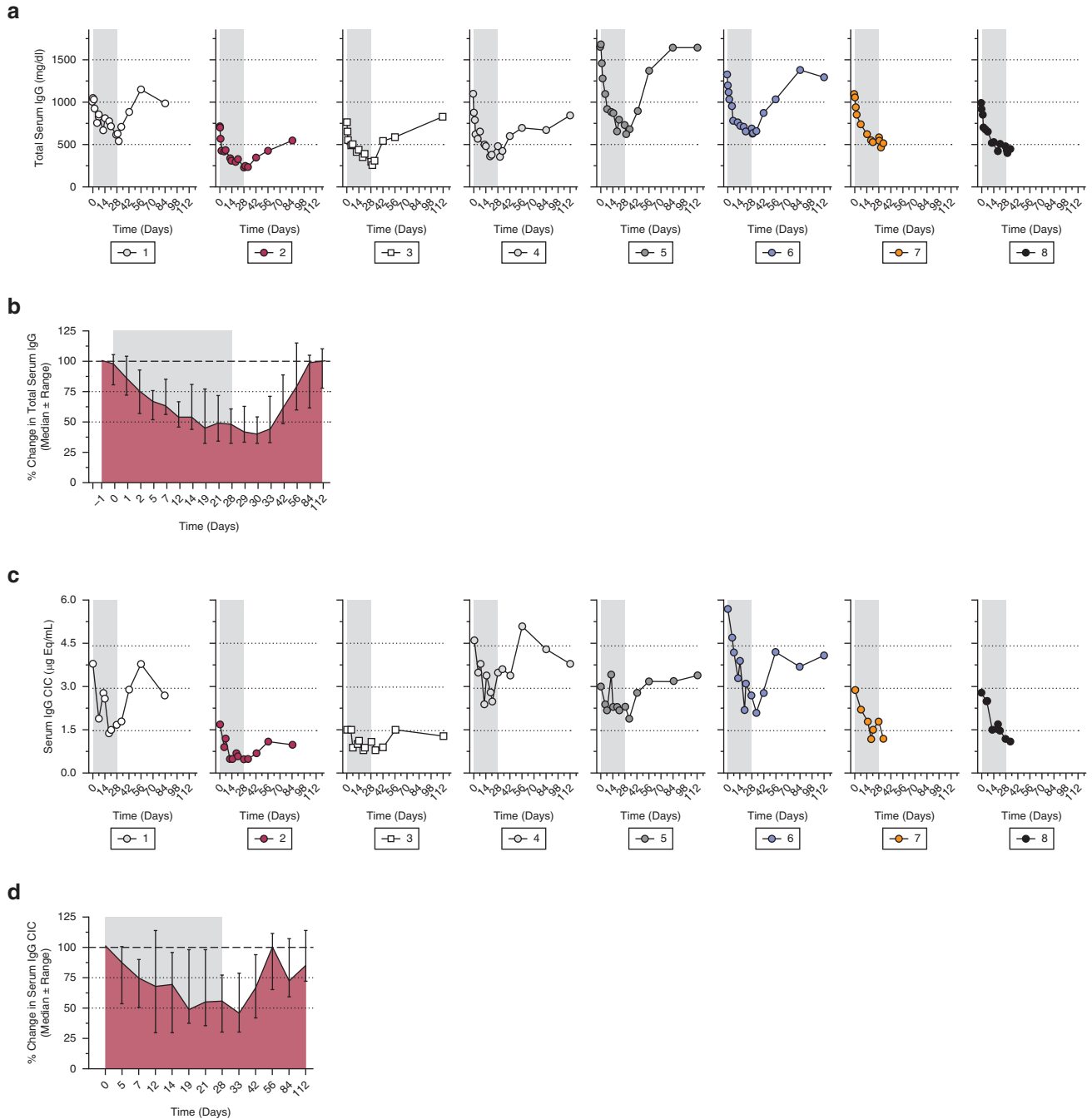
acyclovir, vancomycin, and piperacillin/tazobactam; however, the patient subsequently developed acute kidney injury secondary to the systemic antibiotics. Both the infection and kidney injury were evaluated by the investigator and were deemed to be serious adverse events unrelated to the study drug.

### Pharmacokinetics

The median maximum serum concentration of ALXN1830 decreased from 315.5 µg/ml (range = 230–408 µg/ml) after infusion on day 0 to 260.0 µg/ml (range = 204–488 µg/ml) after infusion on day 28. The time to maximum serum concentration was 1.17 hours (range = 1.05–6.97 hours) on day 0 and 1.080 hours (range = 1.03–7.00 hours) on day 28. The median area under the curve from the end of the infusion to the last measurable serum concentration of ALXN1830 was 3,514.6 h × µg/ml (range = 2,093–6,203 h × µg/ml) on day 0 and 2,537.2 h × µg/ml (range = 1,884–6,190 h × µg/ml) on day 28. There was no apparent serum accumulation of ALXN1830 after five weekly doses at 10 mg/kg or accumulation of drug between doses. The median serum half-life of ALXN1830 was 5.19 hours (range = 4.16–9.43 hours) after the first dose and 7.85 hours (range = 4.87–10.84 hours) after the last dose.

### Pharmacodynamics

ALXN1830 induced a rapid reduction in serum IgG levels with a median reduction of 32.5% (range = 18.9–45.1%; *P* = 0.0078) (Figure 1a and b) on day 5 after the first dose. The total IgG nadir was reached on day 30, when the median total IgG levels were reduced by 57.6% (range = 46.9–65.4%; *P* = 0.0078) from baseline (Figure 1b). By day 30, IgG1 was reduced by a median of 64.3% (range = 52.0–



**Figure 1. IgG and IgG CIC levels in patients with pemphigus after treatment with five weekly doses of ALXN1830.** (a) Change in total serum IgG concentrations in an individual patient with pemphigus, (b) median (range) percent change in total serum IgG levels relative to median concentration immediately before the first dose (baseline), (c) change in serum IgG CIC concentrations in an individual patient with pemphigus, and (d) median (range) percent change in serum IgG CIC levels relative to baseline. The gray-shaded area indicates the dosing period. Each color-coded point corresponds to an individual patient, with circles representing patients with pemphigus vulgaris and a square representing the patient with pemphigus foliaceus. CIC, circulating immune complex.

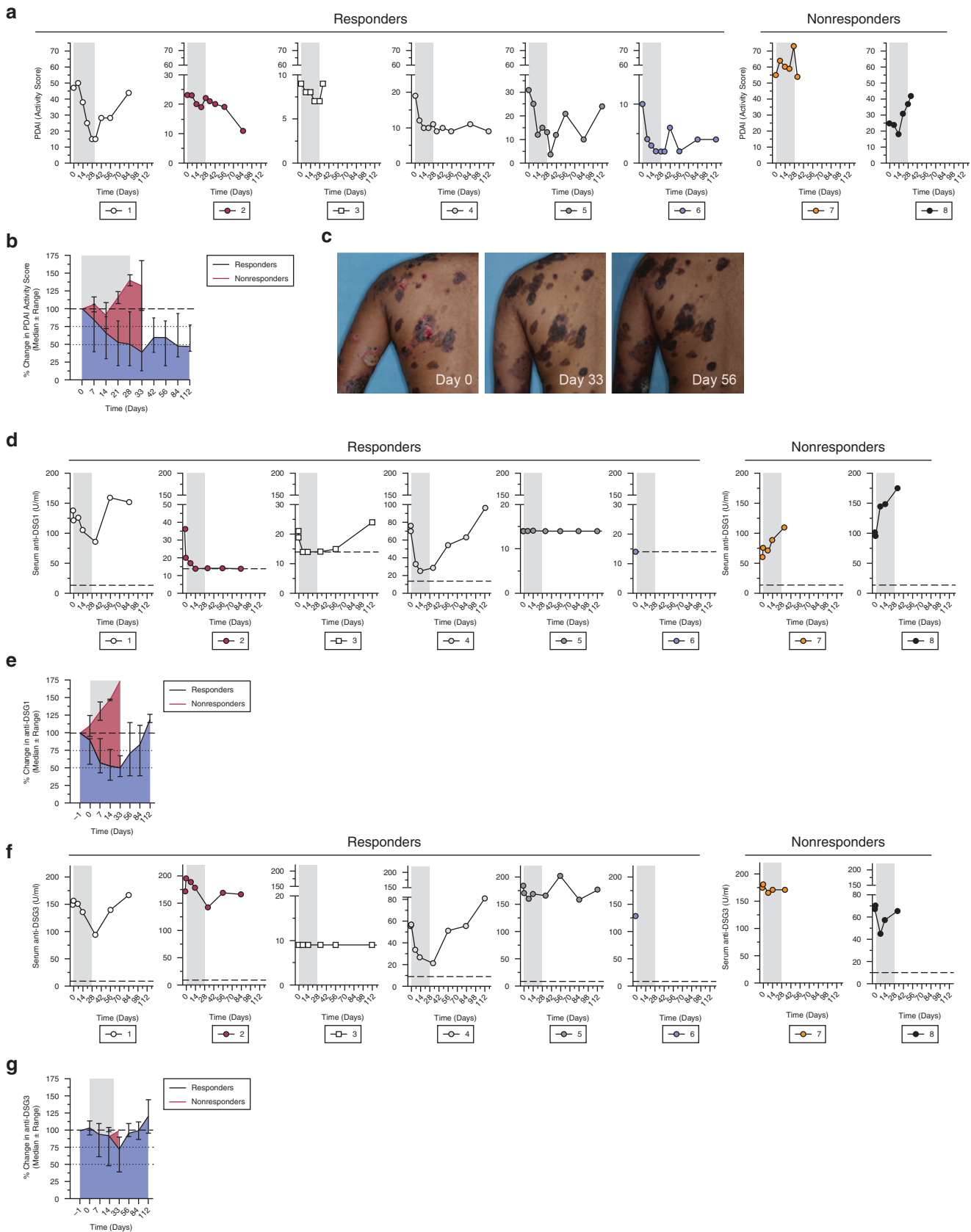
73.6%;  $P = 0.0078$ ), IgG2 by 51.8% (range = 39.3–61.9%;  $P = 0.0078$ ), IgG3 by 71.7% (range = 55.2–75.8%;  $P = 0.0078$ ), and IgG4 by 52.8% (range = 20.0–70.5%;  $P = 0.0156$ ) (Supplementary Figure S1a and b).

IgG CICs were detected in all patients at baseline, and three of the eight patients had levels above the reference normal range (0–3.9 µgEq/ml). Patients experienced reductions from baseline IgG CIC levels by a median of 55.6% (range = 21.7–70.6%;  $P = 0.0078$ ) by day 33 (Figure 1c and

d). The median total IgG and IgG isotypes and the mean IgG CIC levels returned to within 25% of the baseline levels by the end of the study on day 112.

#### Clinical responses to ALXN1830

Six of eight patients exhibited clinical improvement in response to ALXN1830 as evidenced by reduced pemphigus disease area index (PDAI) scores on day 28 in five patients and on day 84 in a sixth patient (Figure 2a). The patient with



**Figure 2. Clinical responses in patients with pemphigus after treatment with five weekly doses of ALXN1830.** (a) Change in PDAI total activity score in individual patients with pemphigus. (b) Median (range) percent change in PDAI total activity score relative to the baseline (median value immediately before the first dose on day 0). (c) Improvement of lesions in the dorsolumbar region of the representative patient after treatment with ALXN1830 (day 0 through days 33 and 56). (d) Change in serum anti-DSG1 concentrations in individual patients with pemphigus. (e) Median (range) percent change in serum anti-DSG1 levels relative to the baseline. (f) Change in serum anti-DSG3 concentrations in individual patients with pemphigus. (g) Median (range) percent change in serum



pemphigus vulgaris (patient 2) displayed a delayed response, achieving approximately a 50% decrease in PDAI total activity score during the follow-up period after the last dose on day 28, whereas the patient with pemphigus foliaceus (patient 3) returned to baseline activity after the last dose (Figure 2a and b). Clinical responses were first observed on day 14 after the administration of the second dose of ALXN1830 because the PDAI total activity score was reduced by a median of 23.6% (range = -9.1 to 70.0%;  $P = 0.0156$ ) (Figure 2b and c). In responders, the median PDAI activity score on day 33 was reduced to a median of 39.64% of the baseline levels (range = 0–87.09%;  $P = 0.1250$ ) (Figure 2b and Supplementary Table S1). Four of the six patients who improved maintained the clinical response beyond the treatment period for up to 84 days of follow-up until the end of the study (Figure 2a and b). Of the remaining two patients, one displayed no evidence of clinical improvement (patient 7), whereas the other initially showed improvement but rebounded at week 3 of the treatment period (patient 8). These patients discontinued the study before day 42 to receive azathioprine and rituximab, respectively (Figure 2a).

#### Autoantibodies to DSG1 and 3 and correlation with the clinical response

Anti-DSG1 antibodies were present in all patients at baseline (median = 45.0 U/ml, range = 14–122 U/ml). Anti-DSG3 antibodies were present in all patients at baseline (median level in patients with pemphigus vulgaris = 149 U/ml, range = 56–184 U/ml) except in the patient with pemphigus foliaceus (patient 3). The anti-DSG1 and 3 titers were reduced in four of six patients who responded clinically (Figure 2d and f). In contrast, the two patients who showed clinical worsening had an increase in the levels of anti-DSG1, whereas there was no major change in anti-DSG3 levels (Figure 2d and f and Supplementary Table S1). On day 14 in the total cohort, anti-DSG1 and 3 titers were reduced by a median of 13.9% (range = -55.2% to 64.3%;  $P = 0.6875$ ) and 8.7% (range = 0–52.6%;  $P = 0.0313$ ), respectively (data not shown). On day 33, anti-DSG1 and 3 levels were reduced by a median of 26.3% (range = -82.3% to 58.6%;  $P = 0.6250$ ) and 5.7% (range = 0–61.4%;  $P = 0.0625$ ), respectively. On day 84, 56 days after the last infusion, anti-DSG1 and anti-DSG3 antibody levels were not different from baseline levels in all the four patients in the responder group from whom sera were available for measurement (Figure 2d and f and Supplementary Table S1). Of note, two patients with pemphigus vulgaris (patients 5 and 6) were at the lower limit of detection for anti-DSG1 (<14 U/ml) at the testing laboratory. Four patients exhibited anti-DSG3 titers above 100 U/ml; however, further testing with dilution for anti-DSG3 levels >100 U/ml was not performed, and as a result, the absolute level of anti-DSG antibodies may have been even greater than the reported level. On day 33, the ALXN1830-induced reduction of anti-DSG1 but not of anti-DSG3 levels

correlated with an improvement of the PDAI total activity score (Pearson correlation coefficient = 0.7871;  $P = 0.0375$ ) (Supplementary Figure S2).

#### Effect on albumin, monocytes, and other blood markers

No noteworthy changes were detected in circulating albumin (Figure 3a and Supplementary Figure S3a), IgA (Figure 3b), IgM (Figure 3c), C-reactive protein (Figure 3d), alanine aminotransferase (Supplementary Figure S3b), or monocytes (Supplementary Figure S3c and d).

#### DISCUSSION

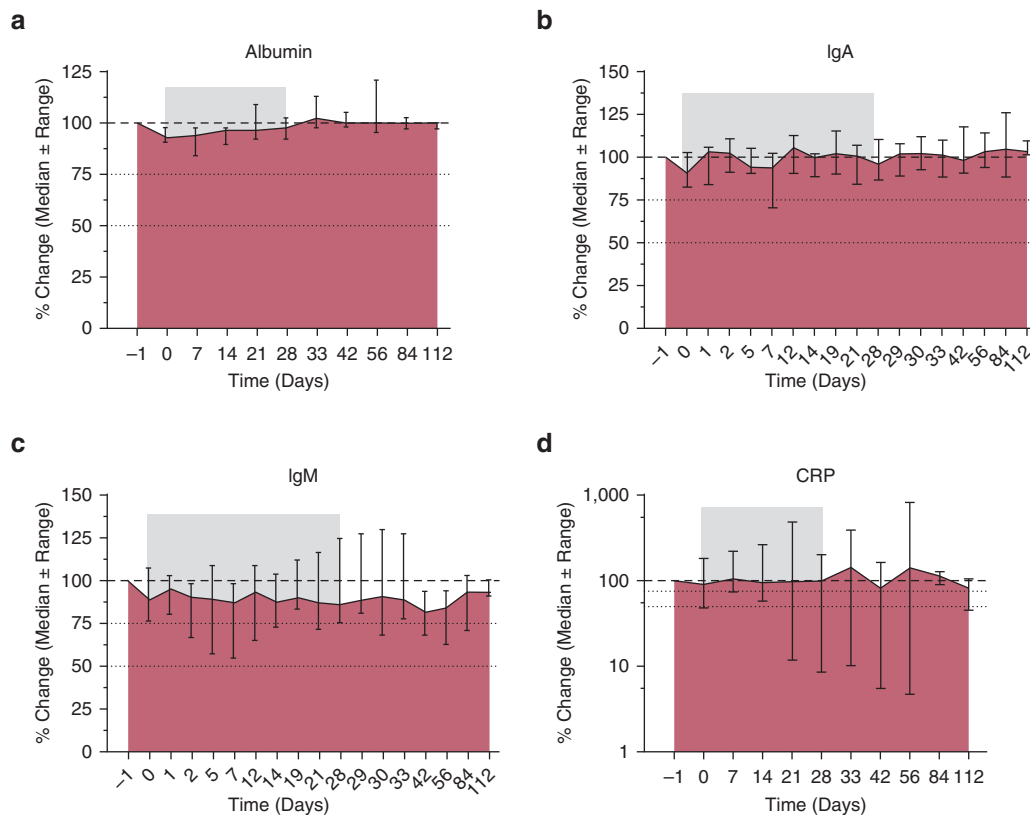
This proof-of-concept study of ALXN1830 in the treatment of pemphigus showed clinically meaningful efficacy and an overall acceptable safety and tolerability profile in a cohort of eight patients who had chronic active disease that did not satisfactorily respond to available pemphigus treatments, including high-dose prednisone, immunosuppressive therapy, or anti-CD20 treatment. A demonstrable clinical improvement in both cutaneous and mucosal disease was shown by a rapid reduction in the total PDAI activity score within 14 days of initiating treatment in five of the eight patients and improvement in another during the follow-up period on day 84. These clinical responses were maintained after cessation of therapy and persisted for up to 84 days after the last dose.

ALXN1830-associated clinical improvement was accompanied by a similarly rapid and significant decrease in the levels of total IgG, all individual IgG subclasses, and IgG CICs, indicative of a pharmacodynamic response that did not differ between responders and nonresponders. This study also supports evidence that IgG CICs may be involved in the pathogenesis of pemphigus (Jordon and McDuffie, 1976; Miyagawa and Sakamoto, 1977; Tappeiner et al., 1977). Tappeiner et al. (1977) utilized a C1q binding assay to show that about 40% of sera from patients with pemphigus contained IgG CICs, as observed in this study, and elevated levels correlated with more severe disease activity (Jordon and McDuffie, 1976). Moreover, deposition of IgG and components of the complement pathway in pemphigus lesions have been found in the intracellular space, suggesting the involvement of complement activation in pemphigus (Edwards et al., 2019; Ellebrecht and Payne, 2017).

Consistent with the pathogenic presence of anti-DSG antibodies in pemphigus, the clinical responses observed correlated with reductions in anti-DSG1 autoantibody levels. In contrast, no major decrease in anti-DSG3 levels between baseline and day 33 was seen in the responding patients, which may reflect that serum samples were not diluted before performing the assay, and thus reductions in these high titers might have been undetected. In patients who did not respond, anti-DSG1 levels increased on day 33, and no noteworthy changes in anti-DSG3 levels were observed despite decreases in serum IgG levels.

The changes in serum IgG, IgG CICs, and anti-DSG1 and DSG3 antibody levels returned to baseline levels during the

anti-DSG3 levels relative to the baseline. The patients are divided into responders and nonresponders. The gray-shaded area indicates the dosing period. Each color-coded point corresponds to an individual patient, with circles representing patients with pemphigus vulgaris and a square representing the patient with pemphigus foliaceus. The patient consented to the publication of the images in panel c. DSG, desmoglein; PDAI, pemphigus disease area index.



**Figure 3. Immune and nonimmune responses in patients with pemphigus after treatment with five weekly doses of ALXN1830.** Median (range) percent change in total serum relative to baseline (median value immediately before the first dose on day 0) is shown in (a) albumin, (b) IgA, (c) IgM, and (d) CRP levels relative to the baseline levels. The gray-shaded area indicates the dosing period. CRP, C-reactive protein.

follow-up period, consistent with the reversible nature of ALXN1830-induced blockade of IgG protection by FcRn without specifically targeting B cells. Nonetheless, the clinical effects persisted in three of six responders, despite the return of endogenous IgG to baseline levels and the short circulating half-life of the drug. The same prolonged but reversible effect on IgG levels was observed in a previously reported phase 1a study of ALXN1830 (Blumberg et al., 2019). This observation warrants further evaluation in future studies. Because FcRn primarily functions within intracellular acidic endosomes, this prolonged response suggests that ALXN1830 exerts durable effects on intracellular FcRn function. Importantly, ALXN1830 administration did not disrupt FcRn-mediated albumin protection, consistent with the mode of ALXN1830 engagement of FcRn, which blocks the amino acid residues involved in IgG but not in albumin binding.

On the basis of the results of this pilot study, five weekly doses of 10 mg/kg ALXN1830 appear to be well-tolerated with a good safety profile. The drug resulted in rapid improvement in the PDAI total activity score, indicative of a clinical response that correlates with declining IgG, IgG CICs, and disease biomarkers associated with circulating autoantibodies but without affecting albumin levels. The clinical responses were also durable despite normalization of the serum IgG levels after cessation of therapy. These studies support the importance of FcRn and the potential application of ALXN1830 therapy in treating pemphigus and related blistering disorders.

## MATERIALS AND METHODS

### Study design and enrollment

This was a multicenter, open-label safety and tolerability phase 1b/2 trial conducted in the United States from July 2017 to January 2019 (NCT03075904). The trial was registered on 9 March 2017, and patients were enrolled from the following sites: Duke University Medical Center, Duke University (Durham, NC) (site 201); Clinical & Translational Research Center, North Carolina Translational and Clinical Sciences Institute, University of North Carolina (Durham, NC) (site 205); and the Ruth & Raymond Perelman Center for Advanced Medicine, University of Pennsylvania (Philadelphia, PA) (site 206). Institutional approval of the study was given by each of the Institutional Review Boards (IRBs) enrolling patients: Duke University Health System IRB (site 201), University of North Carolina IRB (site 205), and University of Pennsylvania Office of Regulatory Affairs (site 206). IRB approval was also obtained from Emory University IRB (site 202) and University of Buffalo IRB (Buffalo, NY) (site 204), but neither of these sites enrolled patients.

### Patient population

Male and female patients aged  $\geq 18$  years with a confirmed clinical diagnosis of pemphigus (vulgaris or foliaceus) and with active disease defined by the presence of anti-DSG1 or anti-DSG3 autoantibodies above the upper limit of normal and a history of at least one positive tissue-based test (skin biopsy or direct immunofluorescence) were required for inclusion. Further requirements for active disease were the presence of lesions lasting  $>2$  weeks with three active lesions in the skin or mucosa or two active lesions with at least one

being a skin lesion >1 cm in diameter (with a PDAI total activity score  $\geq 4$ ) despite being on a stable dose of corticosteroids ( $\leq 1$  mg/kg/day) for 2 weeks with or without immunosuppressants for 6 weeks before screening. Background medications are listed in [Supplementary Table S2](#). Patients with serum IgG level <600 mg/dl and patients who had received i.v. Ig, who had undergone plasmapheresis, or who had undergone immunoadsorption within 30 days of screening were excluded, as were patients who had received treatment with an anti-CD20 depleting mAb within 9 months of screening (complete inclusion and exclusion criteria are provided in the [Supplementary Materials and Methods](#) and in [Supplementary Table S2](#)). This study was approved by the local ethics committee of the participating centers and was conducted in accordance with ethical standards as set by the Helsinki Declaration. All patients signed informed consent.

### Treatment protocol

The study consisted of three periods: a screening period for up to 2 weeks, a dosing period of 4 weeks in which patients received five weekly i.v. doses of ALXN1830 at 10 mg/kg (actual weight), and a follow-up period through day 112 (study termination). Premedication with diphenhydramine or acetaminophen was allowed if medically indicated by the investigator.

### Pharmacokinetics and pharmacodynamic markers

Serum samples to assess the pharmacokinetic behavior of ALXN1830 in serum over time, maximum serum concentration, time to maximum serum concentration, serum half-life, and area under the curve ([Blumberg et al., 2019](#)) were collected from patients on days 0 (first dose) and 28 (fifth and final dose) before the start of each i.v. infusion with 10 mg/kg ALXN1830; 5 minutes after the end of each infusion; and 2, 4, 6, 24, and 48 hours after the end of each infusion. Serum and blood samples were collected for serial analysis of total IgG, IgG subtypes, IgG CICs, IgG anti-DSG1 and IgG anti-DSG3 autoantibodies, albumin, C-reactive protein, blood chemistries, and blood counts before infusion and on treatment days (days 0, 7, 14, 21, and 28) and every 14 days during the follow-up period (days 28 to 112). Assays used have been described previously ([Blumberg et al., 2019](#)). Anti-DSG1 and/or anti-DSG3 antibody levels were analyzed by Quest Diagnostics (Secaucus, NJ) by ELISA. Anti-DSG levels >100 U/ml were reported without further dilution.

### Safety assessments

Safety assessments included monitoring for adverse events, monitoring for serious adverse events, clinical safety laboratory evaluations, assessing reasons for treatment discontinuations owing to toxicity, and monitoring treatment-emergent adverse events. A treatment-emergent adverse event was defined as any medical occurrence or adverse event, whether or not considered drug related, that started on or after the first dose of study drug, during the treatment period, and during the follow-up period.

### Efficacy assessment

Efficacy was assessed on the basis of change in the median PDAI total activity score from baseline, during the treatment, and during the follow-up period as previously described ([Hébert et al., 2019](#); [Rahbar et al., 2014](#)).

The results of the physical examination, PDAI, adverse events, and concomitant medications at the start of and during the trial were documented on predesigned forms for each patient. Photographs of active lesions were taken on days 0, 33, and 56, including the day

when a steroid taper was initiated, if applicable. Photographs shown in [Figure 2c](#) are published with the consent of the patient. The study was terminated after the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy were characterized in the eight patients. The patient consented to the publication of the images in [Figure 2c](#).

### Statistical analysis

Descriptive values obtained in the study are presented as median and range (unless otherwise mentioned) for quantitative variables and as frequency for qualitative ones. Treatment-emergent adverse events, serious adverse events, and adverse events leading to withdrawal or treatment discontinuation are summarized as incidences and percentages per patient for those who received at least one dose of the drug. *P*-values were calculated using the Wilcoxon signed-rank test. All descriptive and inferential statistical analyses were performed using Statistical Analysis System software, version 9.4.

### Data availability statement

Alexion will consider requests for disclosure of clinical study participant-level data provided that participant privacy is assured through methods such as data deidentification, pseudonymization, or anonymization (as required by applicable law) and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at <https://alexion.com/our-research/research-and-development>. The link to the Data Request Form is <https://alexion.com/contact-alexion/medical-information>.

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### CONFLICT OF INTEREST

VPW and RPHIII consulted and had research funding from Syntimmune. DAC was a principal investigator clinical trial for Principia Biopharma and Syntimmune, was in Data and Safety Monitoring Board for Cabaletta, and was a consultant for Principia Biopharm. JSG was an employee at Syntimmune during the conduct of this study and is currently an employee at Alexion Pharmaceuticals, Inc. LJB is an equity holder and patent inventor in Syntimmune. RSB had equity interests in Syntimmune, a company developing therapeutic agents to target neonatal Fc receptor. Syntimmune is now a wholly owned subsidiary of Alexion Pharmaceuticals, Inc after its acquisition by Alexion Pharmaceuticals, Inc. The remaining authors state no conflict of interest.

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#### AUTHOR CONTRIBUTIONS

Conceptualization: VPW, RSB, RPHIII, LJB; Data Curation: VPW, JSG, RSB, RPHIII, MP; Formal Analysis: JSG, RSB, MP; Investigation: VPW, RPHIII, DAC, JSSC, JO; Methodology: VPW, RPHIII, LJB; Project Administration: VPW, RPHIII, LJB; Resources: VPW; Supervision: VPW, RPHIII, LJB; Visualization: RSB, MP, JSG; Writing - Original Draft Preparation: VPW, JSG, RSB, RPHIII, MP, JSSC; Writing - Review and Editing: VPW, DAC, JSSC, JSG, LJB, JO, MP, RSB, RPHIII

#### SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at [www.jidonline.org](http://www.jidonline.org), and at <https://doi.org/10.1016/j.jid.2021.04.031>.

#### REFERENCES

- Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol* 1999;40:167–70.
- Blumberg LJ, Humphries JE, Jones SD, Pearce LB, Holgate R, Hearn A, et al. Blocking FcRn in humans reduces circulating IgG levels and inhibits IgG immune complex-mediated immune responses. *Sci Adv* 2019;5:eaa9586.
- Edwards G, Diercks GFH, Seelen MAJ, Horvath B, van Doorn MBA, Damman J. Complement activation in autoimmune bullous dermatoses: a comprehensive review. *Front Immunol* 2019;10:1477.
- Ellebrecht CT, Payne AS. Setting the target for pemphigus vulgaris therapy. *JCI Insight* 2017;2:e92021.
- Hébert V, Boulard C, Houivet E, Duvert Lehembre S, Borradori L, Della Torre R, et al. Large international validation of ABSIS and PDAI pemphigus severity scores. *J Invest Dermatol* 2019;139:31–7.
- Huijbers MG, Plomp JJ, van der Maarel SM, Verschuuren JJ. IgG4-mediated autoimmune diseases: a niche of antibody-mediated disorders. *Ann N Y Acad Sci* 2018;1413:92–103.
- Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hébert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *Lancet* 2017;389:2031–40.
- Jordon RE, McDuffie FC. Serum and blister fluid anticomplementary activity in pemphigus and bullous pemphigoid. Sucrose density gradient studies. *Proc Soc Exp Biol Med* 1976;151:594–8.
- Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, et al. Pemphigus. *Nat Rev Dis Primers* 2017;3:17026.
- Ludwig RJ, Vanhoorelbeke K, Leyboldt F, Kaya Z, Bieber K, McLachlan SM, et al. Mechanisms of autoantibody-induced pathology. *Front Immunol* 2017;8:603.
- Miyagawa S, Sakamoto K. Characterization of cryoprecipitates in pemphigus: demonstration of pemphigus antibody activity in cryoprecipitates using the immunofluorescent technique. *J Invest Dermatol* 1977;69:373–5.
- Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulins. *Blood Coagul Fibrinolysis* 2005;16:313–8.
- Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm Venereol* 2007;87:206–18.
- Pyzik M, Sand KMK, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The neonatal Fc receptor (FcRn): a misnomer? *Front Immunol* 2019;10:1540.
- Rahbar Z, Daneshpazhooh M, Mirshams-Shahshahani M, Esmaili N, Heidari K, Aghazadeh N, et al. Pemphigus disease activity measurements: pemphigus disease area index, autoimmune bullous skin disorder intensity score, and pemphigus vulgaris activity score. *JAMA Dermatol* 2014;150:266–72.
- Schneider Z, Jani PK, Szikora B, Végh A, Kövesdi D, Iliás A, et al. Overexpression of bovine FcRn in mice enhances T-dependent immune responses by amplifying T helper cell frequency and germinal center enlargement in the spleen. *Front Immunol* 2015;6:357.
- Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994;121:259–62.
- Suurmond J, Diamond B. Autoantibodies in systemic autoimmune diseases: specificity and pathogenicity. *J Clin Invest* 2015;125:2194–202.
- Tappeiner G, Heine KG, Kahl JC, Jordon RE. C1q binding substances in pemphigus and bullous pemphigoid. Detection with a [<sup>131</sup>I] C1q binding assay. *Clin Exp Immunol* 1977;28:40–8.
- Végh A, Cervenak J, Jankovics I, Kacsokovics I. FcRn overexpression in mice results in potent humoral response against weakly immunogenic antigen. *MAbs* 2011;3:173–80.
- Yeoh SC, Byth-Wilson K, Murrell DF, Schifter M, Lin MW, Fulcher DA. Pemphigus vulgaris disease activity: the role of antibodies to desmogleins and their isotype. *J Oral Pathol Med* 2019;48:619–25.



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**SUPPLEMENTARY MATERIALS AND METHODS****Complete list of inclusion and exclusion criteria**

**Inclusion criteria.** Subjects were eligible for enrollment in the study only if they met all the following criteria:

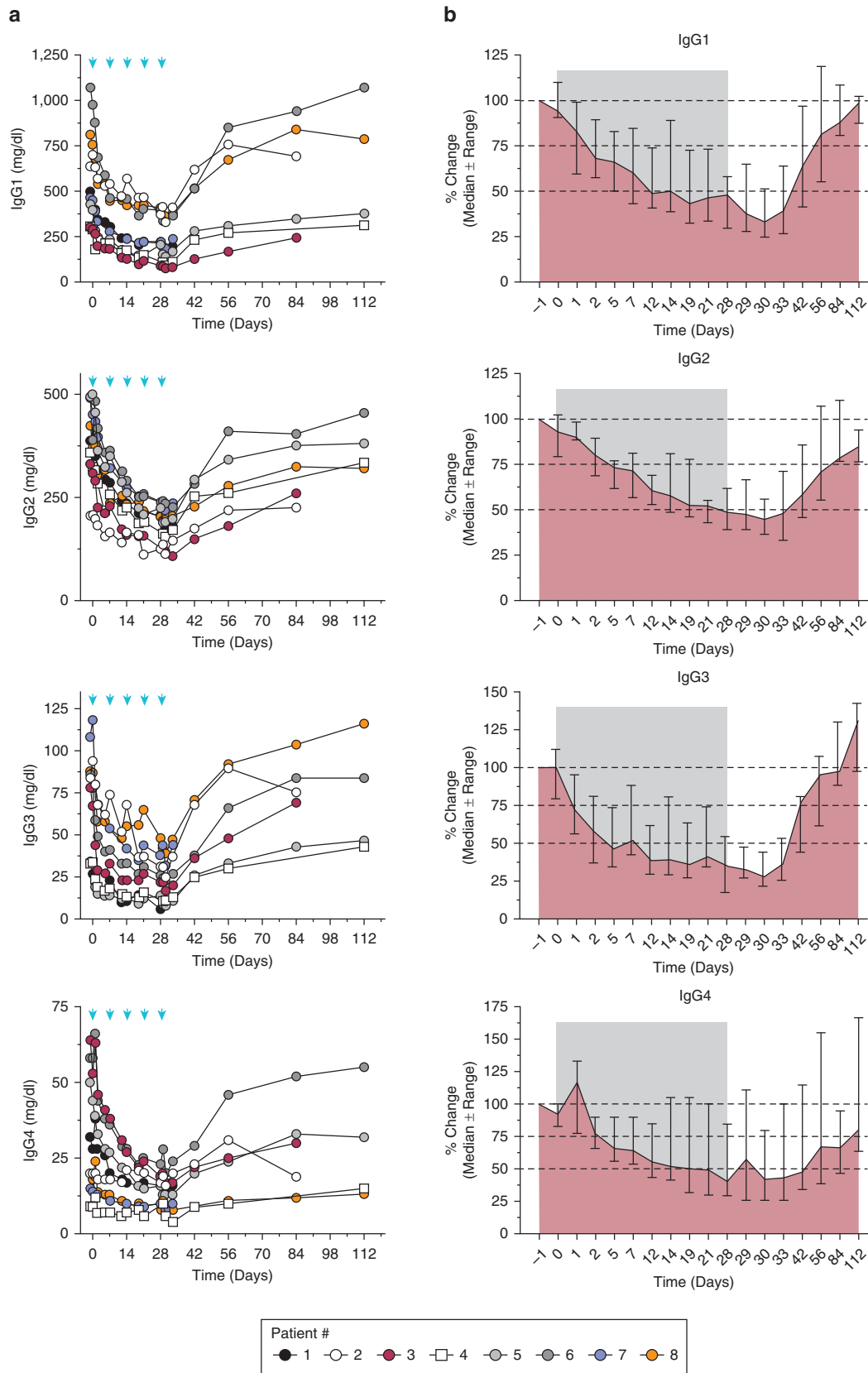
1. willing and able to read, understand, and sign an informed consent form;
2. male or female aged  $\geq 18$  years at the time of screening;
3. documented diagnosis of pemphigus vulgaris or foliaceus on the basis of all the three of the following criteria: documented clinical history consistent with pemphigus vulgaris or foliaceus (clinical presentation defined as mucosal and/or skin lesions), presence of anti-desmoglein 1 or anti-desmoglein 3 antibodies above the upper limit of normal, and history of at least one positive tissue-based test (e.g., biopsy, direct immunofluorescence);
4. active disease defined as lesions lasting  $>2$  weeks and three active lesions in the skin or mucosa or two active lesions with at least one being a skin lesion ( $>1$  cm in diameter), including (i) if treated with rituximab or other anti-CD20 mAbs, the last dose was  $>9$  months before screening; (ii) if being treated with other immunosuppressants (i.e., azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, tacrolimus, sirolimus, or low-dose cyclophosphamide [ $\leq 100$  mg/day]), the dose must be stable, defined as  $<25\%$  change in dose, for 4 weeks before screening; (iii) receiving a stable dose of corticosteroids, defined as  $\leq 1$  mg/kg of prednisone or equivalent and that may not be increased by  $>50\%$  in the 2 weeks before screening; (iv) allowing topical therapies for pemphigus lesions on entering the study, including petroleum jelly or Aquaphor for the skin or chlorhexidine for the mouth; (v) allowing stable use of topical low-strength hydrocortisone ( $\leq 1\%$ ), tacrolimus, sirolimus, or pimecrolimus for lesions contributing  $<10\%$  of the pemphigus disease area index total activity score for the 4 weeks before screening. Stable use of dexamethasone elixir solution (swish and spit only) for oral lesions for the 4 weeks before screening was allowed; (vi) if not on regular corticosteroids, no pulse corticosteroids are allowed in the 2 weeks before screening; (vii) body mass index  $>18.5$  kg/m<sup>2</sup>; and (viii) having a negative pregnancy test documented before the first dose of the study drug (for women of childbearing potential);
5. females of childbearing potential must have agreed to be abstinent or else agree to use any two of the following medically acceptable forms of contraception ( $< 1\%$  per year failure rate) from the screening period through the final study visit—oral contraceptive, condom with or without spermicidal jelly, diaphragm or cervical cap with

spermicidal jelly, or intrauterine device—or a female whose male partner has had a vasectomy must have agreed to use one additional form of medically acceptable contraception;

6. females of nonchildbearing potential, defined as surgically sterile (status posthysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or postmenopausal for at least 12 months, did not require contraception during the study;
7. males with female partners of childbearing potential, including males who were surgically sterile (post-vasectomy), must have agreed to be abstinent or else agreed to use a medically acceptable form of contraception from the screening period through the final study visit; and
8. a pemphigus disease area index total activity score  $>4$  at screening (criterion added with amendment 4).

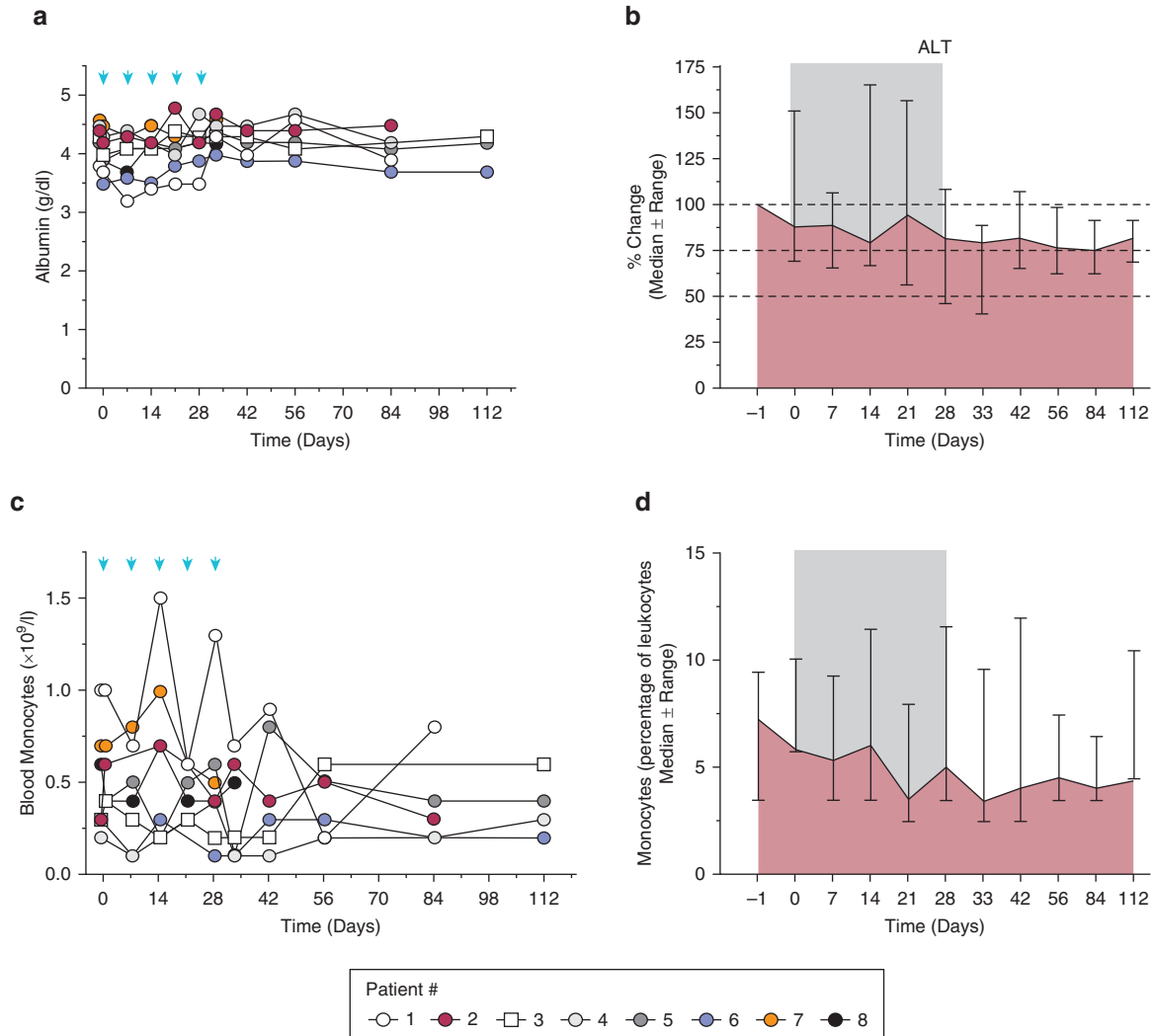
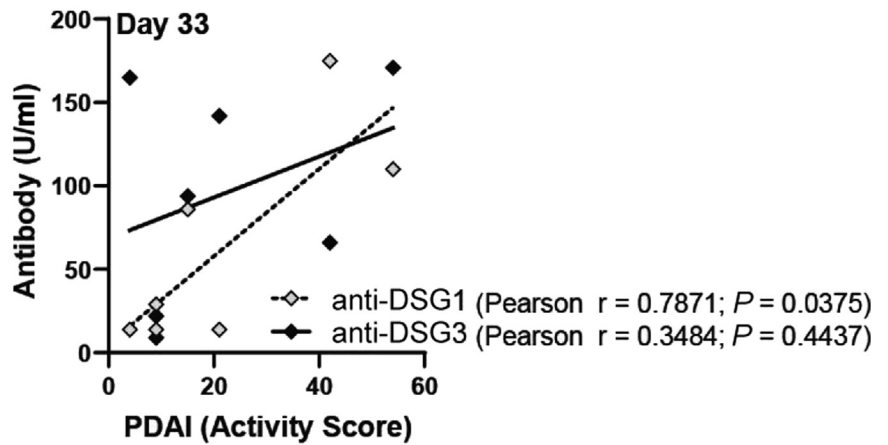
**Exclusion criteria.** Subjects were excluded from study enrollment if they met any of the following criteria:

1. subject unable or unwilling to comply with the protocol;
2. active nonhematologic malignancy or history of non-hematologic malignancy in the 3 years before screening (exclusive of nonmelanoma skin cancer and cervical cancer in situ);
3. positive for HIV or hepatitis C antibody;
4. positive for hepatitis B surface antigen;
5. active infection or history of recurrent infections;
6. Intravenous Ig treatment within 30 days of screening;
7. received any cytotoxic (other than azathioprine) or any non-anti-CD20 mAb therapy in the 3 months before screening;
8. any exposure to an investigational drug or device within the 30 days before screening;
9. plasmapheresis or immunoadsorption within 30 days of screening;
10. cellular therapy, including chimeric antigen receptor and T cell, at any time before screening;
11. use of any systemic or topical immunosuppressive drugs within 3 months of screening, not including dose allowed by the inclusion criteria;
12. serum total IgG  $<600$  mg/dl at screening;
13. subject has any current medical condition that in the opinion of the investigator could compromise their safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of the results (e.g., a significant pre-existing illness or other major comorbidities that the investigator considers may confound the interpretation of the study results); and
14. any vaccination within 2 weeks of screening.



**Supplementary Figure S1. IgG subclass levels in patients with pemphigus after treatment with five weekly doses of ALXN1830. (a)** Change in serum IgG1, IgG2, IgG3, or IgG4 concentrations in individual patients with pemphigus. **(b)** Median (range) percent change in serum IgG1, IgG2, IgG3, or IgG4 levels relative to the baseline (median value immediately before the first dose on day 0). The green downward arrows and the gray-shaded areas indicate dosing days and dosing period, respectively. Each color-coded point corresponds to an individual patient, with circles representing patients with pemphigus vulgaris and a square representing the patient with pemphigus foliaceus.

Supplementary Figure S2. Correlation between PDAI total activity score and anti-DSG1 or anti-DSG3 levels on day 33 in patients with pemphigus after treatment with five weekly doses of ALXN1830. DSG, desmoglein; PDAI, pemphigus disease area index.



Supplementary Figure S3. Immune and nonimmune responses in patients with pemphigus after treatment with five weekly doses of ALXN1830. (a) Variation in patient absolute serum albumin levels. (b) Median percent change in total serum ALT levels relative to the baseline (median value immediately before the first dose on day 0). (c) Variation in patient blood monocyte numbers. (d) Median (range) percent change in blood monocyte levels relative to the baseline. The green downward arrows and the gray-shaded areas indicate the dosing days and dosing period, respectively. Each color-coded point corresponds to an individual patient, with circles representing patients with pemphigus vulgaris and a square representing the patient with pemphigus foliaceus. ALT, alanine aminotransferase.

**Supplementary Table S1. Summary of Individual Clinical Responses by Patients**

Patient	PDAI Total Activity			Anti-DSG1 (U/ml)			Anti-DSG3 (U/ml)		
	Baseline	Day 33	Day 84	Baseline	Day 33	Day 84	Baseline	Day 33	Day 84
1	47	15	44	122	86	152	156	94	167
2	23	21	11	20	14	14	195	142	166
3	9	9	ND	19	14	ND	9	9	ND
4	19	9	11	70	29	63	57	22	56
5	31	4	10	14	14	14	171	165	159
6	10	2	4	14 <sup>1</sup>	ND	ND	128 <sup>1</sup>	ND	ND
7	55	54	ND	76	110	ND	181	171	ND
8	25	42	ND	96	175	ND	70	66	ND

Abbreviations: DSG, desmoglein, ND, not determined; PDAI, pemphigus disease area index.

PDAI total activity score, anti-DSG1 level, and anti-DSG3 level at baseline, on day 33, and on day 84 are provided, if available. Note that anti-DSG1 values <14 U/ml were imputed to 14 U/ml and that anti-DSG3 values <9 U/ml were imputed to 9 U/ml.

<sup>1</sup>Baseline value is unavailable; screening value was used instead.

**Supplementary Table S2. Concomitant Medications**

Patient	Disease Duration (y)	Prednisone Usage, mg/day (Study Days)	Additional Immunosuppressants	Topical Corticosteroids/Immunosuppressants
1	0.6	60 (days -67 to 2) 60 (day 9 onward)	Azathioprine 100 mg daily (days -181 to -42)	NA
2	3.7	60 (day -42 onward)	NA	NA
3	0.3	6 (days -24 to 34) 4 (days 35-65) 2 (days 66-107) 1 (day 108 onward)	Mycophenolate mofetil 1,000 mg twice daily (day -102 onward)	NA
4	2.5	20 (days -22 to 57) 15 (day 58 onward)	Rituximab 686 mg weekly (days -663 to -649)	NA
5	11	10 (days -72 to 37) 9 (day 38 onward)	NA	NA
6	31.8	NA	NA	Dexamethasone mouthwash 10 ml three times daily (day -1,490 onward)
7	15.7	NA	Rituximab 701 mg weekly (day 34 onward)	Hydrocortisone cream 1% daily (day 24 onward) Triamcinolone ointment 0.1% every other day (day 34 onward)
8	14.3	10 (day -289 onward)	Azathioprine 150 mg daily (days -289 to 29) Azathioprine 100 mg twice daily (day 30 onward)	Tacrolimus 0.1% every 2 days (days -258 to -44) Hydrocortisone cream 1% (day 19 onward) Clobetasol ointment 0.05% twice daily (days 26-34)

Abbreviation: NA, not available.

Note that the duration of the disease and relevant concomitant therapy usage during or before the study is reported. Study days are indicated; negative study days occurred before the initiation of the study, and the absence of a final day implies that the patient was still using the indicated therapy at the last visit. NA implies that the use of a relevant therapy was not indicated.