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Treating Pemphigus Vulgaris (PV) and Foliaceus (PF) by Inhibiting the Neonatal Fc Receptor: A Phase 2 Open-label Trial With Efgartigimod

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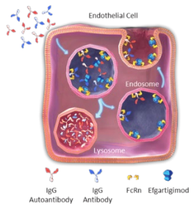
BACKGROUND

PEMPHIGUS: an IgG-Mediated Autoimmune Disease[1–3]

- Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) belong to a heterogeneous group of autoimmune blistering diseases and are clinically characterised by mucosal erosions (PV) and cutaneous blisters (PV and PF)
- PV is characterised by the presence of pathogenic immunoglobulin (IgG) autoantibodies targeting desmoglein (Dsg) 3 and, in 50% of the cases, also against Dsg-1
- PF is attributed to the presence of IgG autoantibodies solely directed against Dsg-1
- Pemphigus is potentially life-threatening, primarily due to secondary infections

EFGARTIGIMOD: IgG1 Fc Fragment With ABDEG™ Mutations[4–6]



- Efgartigimod is a human IgG1 Fc fragment engineered for increased affinity for the neonatal Fc receptor (FcRn)
- Efgartigimod blocks FcRn, outcompeting endogenous IgG binding, preventing recycling of IgG and thereby decreasing serum IgG concentration, including that of pathogenic autoantibodies that mediate autoimmune diseases
- Efgartigimod is an investigational drug proposed for the treatment of PV and PF
- The safety, pharmacodynamics (PD), pharmacokinetics (PK), efficacy, and conditions of use (dosage and frequency of administration at maintenance) of efgartigimod were evaluated in a phase 2 trial in patients with newly diagnosed or relapsing mild-to-moderate PV or PF

METHODS

Phase 2 (ARGX-113-1701) Trial Design

Efgartigimod Open-label, Non-controlled, Adaptive Trial in Patients with Mild-to-Moderate PV or PF

	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)

CS, corticosteroids; **EoC**, end of consolidation; **SoC**, standard of care.

PRIMARY ENDPOINT: SAFETY

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Serious adverse events (SAEs)
- Vital signs, electrocardiogram parameters, physical examination abnormalities, and routine clinical laboratory assessments (hematology, biochemistry, urinalysis)

KEY SECONDARY ENDPOINTS

- Pharmacodynamic (PD) analyses
- PDAI assessment
- Time to disease control (DC)*
- Time to relapse†
- Time to complete clinical remission (CR)‡

*DC = no new lesions, established lesions starting to heal. †Appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week, or extension of established lesions, evaluated after DC. ‡CR = absence of new lesions and established lesions completely healed except for post-inflammatory hyperpigmentation or erythema from resolving lesions. **PDAI**, Pemphigus Disease Area Index.

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RESULTS

Table 1. Baseline Demographics

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 (76)	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)
Disease history, n (%)		
Newly diagnosed	14 (41)	12 (39)
Relapsing	20 (59)	19 (61)
Baseline PDAI 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)		
Overall population	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 + CS	23 (68)	23 (74)

*3 patients excluded from efficacy analysis by IDMC (insufficient drug exposure, impetigo as pre-existing non-drug–related confounding factor, and violation of exclusion criteria). **CS**, corticosteroids; **IMDC**, Independent Data Monitoring Committee; **min**, minimum; **max**, maximum; **PDAI**, Pemphigus Disease Area Index; **SE**, standard error.

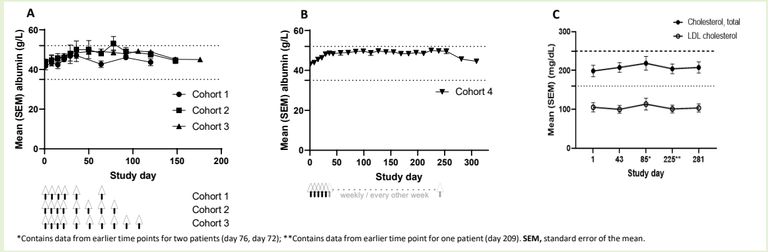
Table 2. Efgartigimod Was Well Tolerated, as Determined by the Independent Data Monitoring Committee

- Sixteen of 19 **(84%)** patients treated with efgartigimod at 10 mg/kg and 13 of 15 **(87%)** at 25 mg/kg experienced at least one TEAE
- Most TEAEs were assessed **as mild or moderate** with no related SAEs
- Severity and causality of TEAEs were assessed by the investigator
- Thirty-four patients comprising the safety population received a median of 10 (range 2–24) IV administrations
- **Serum albumin, cholesterol, and LDL levels** remain within **normal limits** across all cohorts and time points

TEAEs Occurring in ≥2 Patients Per Dose Group, Patients, n (%) by System Organ Class and Preferred Term, All Were Grade 1–2 (Mild or Moderate)	Efgartigimod 10 mg/kg N=19	Efgartigimod 25 mg/kg N=15
Infections and infestations		
Bronchitis	2 (11)	0
Nasopharyngitis	0	4 (27)
Rhinitis	0	2 (13)
Urinary tract infection	1 (5)	2 (13)
Gastrointestinal disorders		
Abdominal pain	1 (5)	2 (13)
Diarrhoea	2 (11)	2 (13)
Vomiting	2 (11)	1 (7)
General disorders and administration site conditions		
Influenza-like illness	1 (5)	2 (13)
Nervous system disorders		
Headache	1 (5)	3 (20)
Dizziness	2 (11)	1 (7)
Blood and lymphatic system disorders		
Anaemia	1 (5)	2 (13)
Investigations		
Alanine aminotransferase increased	0	2 (13)

IV, intravenous. **Note**: Two reported SAEs (pneumonia and tibia fracture) were assessed by the treating investigators as unrelated to efgartigimod. Five grade 3 TEAEs reported, 3 as not related (syncope, pneumonia†, and tibia fracture), the remaining 2 (tooth infection and blood creatine phosphokinase [CPK]‡ increase) as possibly related.
†Pneumonia: 29 year old female (body weight 35 kg, BMI 15.0 kg/m²) recovered; although assessed unrelated, a potential effect of efgartigimod cannot be ruled out. ‡Elevated CPK levels observed in one patient were transient and resolved under continued treatment; increases in alanine aminotransferase (ALT) observed in two patients were mild (<2x upper limit of normal) and were resolved by the next study visit.

Figure 1. Serum Albumin, Cholesterol, and Low-density Lipoprotein (LDL) Levels Remain Within Normal Limits Across All Cohorts and Time Points



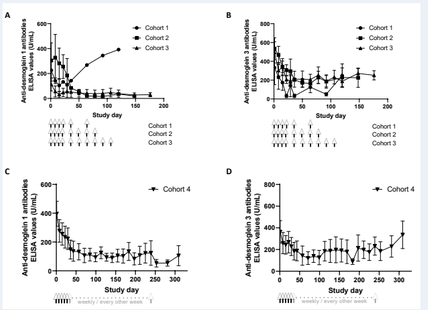
*Contains data from earlier time points for two patients (day 76, day 72); **Contains data from earlier time point for one patient (day 209). **SEM**, standard error of the mean.

Serum levels of albumin in (A) cohort 1–3, (B) cohort 4, and (C) cholesterol and LDL levels in 11 patients in cohort 4

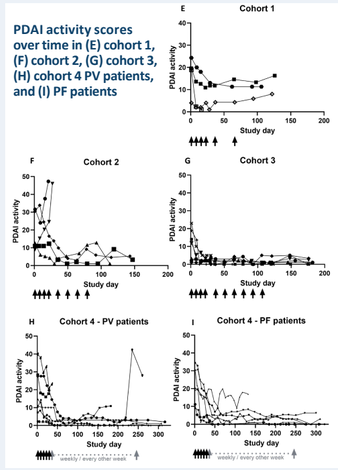
CONCLUSIONS

- In this phase 2 study, **efgartigimod was well tolerated in patients with pemphigus**, consistent with previous studies of this FcRn inhibitor in other indications
- Treatment with efgartigimod led to **serum IgG level reduction, autoantibody level reduction, and improvement of PDAI scores** and clinical outcomes
  - Disease control in **90%** of patients after a median of **17 days**
  - Complete clinical remission in **64%** of patients after a median of **92 days**
- These data provide support for further evaluation of efgartigimod as a therapy for pemphigus
- The phase 3 ADDRESS clinical trial (NCT04598451) in adults with pemphigus is currently ongoing

Figure 2. Autoantibody Level Reduction and PDAI Score Improvement Were Observed After Treatment With Efgartigimod



Serum levels over time of anti-Dsg-1 autoantibodies in cohorts 1–3 (A), in cohort 4 (C), and anti-Dsg-3 autoantibodies in cohorts 1–3 (B) and cohort 4 (D). ELISA, enzyme-linked immunosorbent assay.



- Patients with pemphigus treated with efgartigimod exhibited **~40% reduction in total serum IgG levels** following the first infusion compared with baseline
- The median PD effect at 10 mg/kg following four weekly infusions at day 29 was a **62% reduction** of total IgG; for the 25 mg/kg dose, the reduction was **66%**
- Serum levels pathogenic autoantibodies reached a median **61% reduction** from baseline for **anti-Dsg-1** and **49% for anti-Dsg-3** at the end of the induction phase and remained low during the maintenance phase
- 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 and a **median 52%** PDAI reduction to a mean of 9.4 ± 1.9 (median 5.0; range 1.0–20.8) in the 25 mg/kg dose group

Table 3. Efgartigimod, as Monotherapy and Combined With Prednisone, Demonstrated an Early Onset of Action with DC in 90% and CR in 64% of Patients

	Disease Control (DC)	Complete Clinical Remission	Relapse (From DC)
Overall, n	31	22	28
Yes, n (%)	**28 (90)**	**14 (64)**	11 (39)
No, n (%)	3 (10)	8 (36)	17 (61)
Median time to (range), days	17 (6–92)	92 (13–287)	211 (10–211)
Efgartigimod monotherapy, n	8	–	–
Yes, n (%)	6 (75)	–	–
No, n (%)	2 (25)	–	–
Median time to (range), days	16 (8–30)	–	–
PV, n/N (%)	22/24 (92)	9/15 (60)	9/22 (41)
PF, n/N (%)	6/7 (86)	5/7 (71)	2/6 (33)
Disease history, n/N (%)	18/19 (95)	7/13 (54)	7/18 (39)
Relapsing	10/12 (83)	7/9 (78)	4/10 (40)
Newly diagnosed			

- Efgartigimod treatment achieved **disease control in 28 of 31 patients (90%)** after a **median of 17 days** (range 6–92)
- **Fourteen of 22 (64%)** patients on efgartigimod treatment with prednisone 0.1–0.5 mg/kg/d **achieved complete clinical remission** after a median of **92 days** (range 13–287)
- Complete clinical remission achieved at a median daily concomitant prednisone dose of **0.26 mg/kg** (range 0.06–0.48)

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