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Abstract number

Treating pemphigus vulgaris (PV) and foliaceus (PF) by inhibiting the neonatal Fc receptor: phase 2 multicentre open-label trial with efgartigimod

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INTRODUCTION

PEMPHIGUS
- Rare autoimmune skin disorders comprised of both pemphigus vulgaris (PV) and pemphigus foliaceus (PF)
- PV is characterized by the presence of IgG autoantibodies targeting desmoglein 3 (Dsg-3) and, in 50% of the cases also against desmoglein 1 (Dsg-1)
- PF is attributed to the presence of autoantibodies solely to Dsg-1
- Clinical manifestations of PV and PF differ significantly, and include mucosal erosions in PV patients positive for Dsg-3 autoantibodies, mucosal and skin lesions in PV patients positive for Dsg-3 and Dsg-1 autoantibodies, and only skin lesions in PF patients

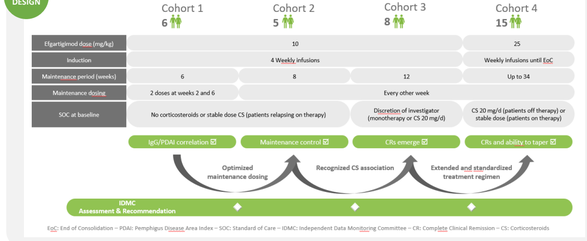
EFGARTIMOD
- Human IgG1 antibody Fc fragment, natural ligand of FcRn, engineered for increased binding affinity to FcRn[1,2]
- Outcompetes binding of endogenous IgG to FcRn[1,2]
- Prevents recycling of IgG and promotes IgG lysosomal degradation[1,2]

METHODS

- This is an open-label, non-controlled, adaptive-design Phase 2 study to evaluate the safety, PD, PK, efficacy, and conditions of use (dosage, frequency of administration at maintenance) of efgartigimod in patients with mild to moderate PV or PF (PDAI <45 at baseline), either newly diagnosed or relapsing
- Patients on oral prednisone (or equivalent) and/or immunosuppressant at screening were eligible for inclusion, but the immunosuppressant had to be discontinued before baseline

TRIAL DESIGN

ARGX-113-1701



EoC: End of Consolidation – PDAI: Pemphigus Disease Area Index – SOC: Standard of Care – IDMC: Independent Data Monitoring Committee – CR: Complete Clinical Remission – CS: Corticosteroids

STUDY OBJECTIVE AND ENDPOINTS

PRIMARY OBJECTIVE AND ENDPOINT
Safety, including 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)

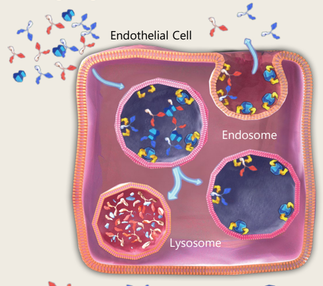
KEY SECONDARY ENDPOINTS
Pharmacodynamic analyses, PDAI assessment, Time to DC (no new lesions, established lesions starting to heal), Time to relapse (appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week, or extension of established lesions, evaluated after DC), Time to CR (absence of new lesions and established lesions completely healed except for post-inflammatory hyperpigmentation or erythema from resolving lesions)

KEY ELIGIBILITY CRITERIA

INCLUSION
- Male or female patients aged ≥ 18 years
- Clinical diagnosis of PV or PF, that has been confirmed by positive direct immunofluorescence, and positive indirect immunofluorescence and/or enzyme-linked immunosorbent assay (ELISA)
- Mild to moderate disease severity (Pemphigus Disease Area index [PDAI] < 45)
- Newly diagnosed patients or relapsing patients off therapy; or patients who relapse despite oral prednisone at tapered dose +/- a conventional immunosuppressant (e.g. azathioprine, mycophenolate mofetil)
- Identified serum levels of autoantibodies directed against Dsg-3 and/or Dsg-1 antigen at Screening, using indirect immunofluorescence or ELISA
- Ability to understand the requirements of the study, provide written informed consent, and comply with the study protocol procedures

EXCLUSION
- Confirmed diagnosis of paraneoplastic pemphigus, drug-induced pemphigus or any other non-PV/non-PF autoimmune blistering disease
- History of refractory disease to active third line therapy (e.g. intravenous polyvalent human immunoglobulins [IVIg], rituximab, plasma exchange/immunoadsorption)
- Use of therapies other than oral prednisone and conventional immunosuppressants, that can interfere in the clinical course of the disease within 2 months of the Baseline visit
- Use of rituximab and other CD20 target biologics within 6 months prior to Baseline visit

Efgartigimod Mechanism of Action



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 (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)
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 (exclusion criterion violation; pre-existing wound infection; insufficient exposure)

DISCLOSURES

This phase 2 study was funded by argenx. WP, HH, PD, and PV are employees of argenx. Efgartigimod is an investigational agent that is not currently approved for use by any regulatory agency. Editorial and graphics support was provided by Symbiotix, LLC and funded by argenx.

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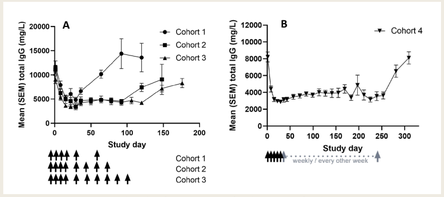
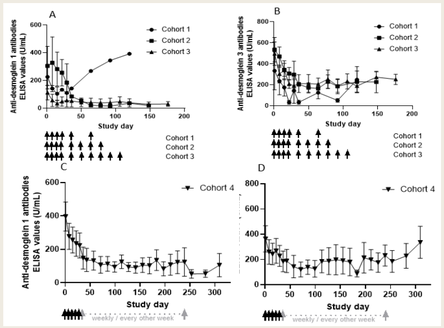
Strong Correlation Between Serum IgG Level Reduction, Autoantibody Level Reduction and PDAI Improvement

- Pemphigus patients treated with efgartigimod exhibited approximately 40% reduction in total serum IgG levels following the first infusion as compared to baseline
- The median pharmacodynamic (PD) effect at 10 mg/kg following 4 weekly infusions at day 29 was a 62% reduction (range 54, 74) of total IgG, while for the 25 mg/kg dose it was 66%



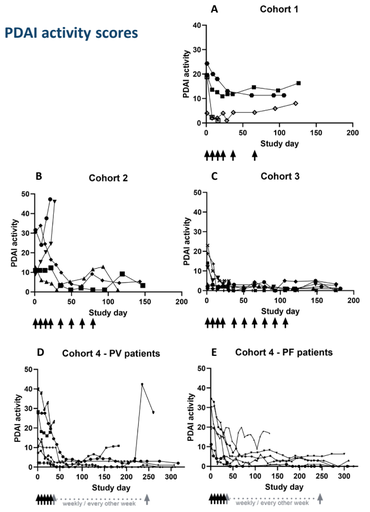
Serum levels of total IgG in A) cohort 1-3, B) cohort 4

- Serum levels of anti-Dsg-1 and Dsg-3 IgG, the pathogenic autoantibodies in pemphigus which are predominantly of the IgG4 subclass, decreased over time following total IgG reductions
- A rapid clearance of anti-Dsg antibodies was observed and reached a median 61% reduction from baseline for anti-Dsg-1 and 49% reduction for anti-Dsg-3 antibodies at the end of the induction phase
- A correlation between anti-Dsg-1/3 autoantibody level reduction and improvement in the PDAI score was observed throughout the trial



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)

PDAI activity scores



PDAI activity scores over time in A) cohort 1, B) cohort 2, C) cohort 3, D) cohort 4 PV patients, and E) PF patients

Efgartigimod, as Monotherapy and Combined with Prednisone, Demonstrated a Rapid Onset of Action with DC in 90% and CR in 64% of Patients

	Disease Control	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 (8-92)	92 (13–287)	211 (10-211)
On efgartigimod monotherapy, n	8	-	-
Yes, n (%)	6 (75)	-	-
No, n (%)	2 (25)	-	-
Median time to (range), days	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)

- At the end of 4 weeks of fixed dosing, the median reduction in PDAI activity scores was 75% (ranging between increase of 411% and reduction of 100% in the 10 mg/kg dose group and 52% (range, 9 to 89%) in the 25 mg/kg group
- Fourteen of 22 (64%) patients on efgartigimod treatment with prednisone 0.1-0.5 mg/kg/d achieved complete remission (10 mg/kg: median 36 days, range 13-93; 25mg/kg: 92 days, range 41-287)

Favorable Tolerability Determined by Independent Data Monitoring Committee

- 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
- Sixteen out of 19 (84%) patients treated with efgartigimod at 10 mg/kg and 13 out of 15 (87%) at 25 mg/kg experienced at least one TEAE

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)

Two SAEs reported which were assessed as unrelated to efgartigimod (pneumonia and tibia fracture). Five grade 3 TEAEs were reported, 3 as not related to the drug (syncope, pneumonia, and tibia fracture), the remaining 2 (tooth infection and blood creatine phosphokinase (CPK) increase) as possibly related to the drug. Elevated CPK levels observed in one patient were transient and resolved under continued treatment; increases in ALT observed in two patients were mild (<2x ULN) and were resolved by the next study visit.

SUMMARY

- In this phase 2 study, efgartigimod was well tolerated in pemphigus patients, consistent with previous studies of this FcRn inhibitor in other indications.
- A strong correlation was observed between serum IgG level reduction, autoantibody level reduction and improvement of pemphigus disease area index (PDAI) scores and clinical outcomes.
- Efgartigimod demonstrated a good safety profile, a fast onset of action in reaching DC and CR and thus presents a promising first line treatment, as add-on therapy to prednisone, in the overall population of pemphigus patients.
- These data provide support for further evaluation of efgartigimod as a therapy for pemphigus. For more information on the currently ongoing ADDRESS Phase 3 clinical trial in adults with pemphigus, please visit: https://clinicaltrials.gov/ct2/show/NCT04598451