O07-02

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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Presented at the 46th Annual Meeting of the *Japanese Society for Investigational Dermatology* (JSID) (Virtual Meeting), December 3–5, 2021

Disclosures and Acknowledgements

Matthias Goebeler: consulting for argenx, Biotest, Janssen, Leo Pharma, Lilly, Novartis, and UCB
Zsuzsanna Bata-Csörgő: advisory boards for Novartis, Sanofi-Genzyme, Ewopharma, Abbvie, and argenx
Clara De Simone: no disclosures to report
Biagio Didona: no disclosures to report
Eva Remenyik: advisory boards of Janssen Cilag Hungary, Lilly Hungary, and Takeda Pharmaceuticals
Nataliya Reznichenko: no disclosures to report
Enno Schmidt: research grants from Novartis, UCB, Incyte, Biotest, argenx, Dompe, Admirx, Synthon/Byondis, Fresenius Medical Care, Euroimmun; honoraria from argenx, Novartis, UCB, Biotest, Fresenius, Roche, Imevax, Topsa, and ThermoFisher
Johanna Stoevesandt: disclosed no conflicts
Wim Parys: employee of argenx
Hans de Haard: employee of argenx
Peter Verheesen: employee of argenx
Pascal Joly: consulting for Roche, Amgen, Principia Biopharma, Argenx, AstraZeneca and ThermoFisher, Sanofi, Akari, Janssen, Novartis, Servier, Chugai, Kezar Life Science, Regeneron, UCB

We thank **E. Sally Ward** and **Patrick Dupuy** for their valuable contributions to this study.
Medical writing and editorial support was provided by Eloquent Scientific Solutions, Fairfield, CT and funded by argenx.

We gratefully acknowledge the clinicians, participants, patient organisations, and scientists who have collaborated on this trial

Introduction and Methods

Efgartigimod

- 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]

Phase 2 Trial Design

- Patients with mild-to-moderate PV or PF were enrolled in an open-label, non-controlled, adaptive phase 2 trial[3]
- Patients on oral prednisone (or equivalent) and/or immunosuppressants at screening were eligible for inclusion, but the immunosuppressant had to be discontinued before baseline assessment

Phase 2 (ARGX-113-1701) Trial Design

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/day)	CS 20 mg/day (patients off therapy) or stable dose (patients on therapy)

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 (haematology, 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. **CS**, corticosteroids; **EoC**, end of consolidation; **FcRn**, neonatal Fc receptor; **IgG**, immunoglobulin G; **PV**, pemphigus vulgaris; **PF**, pemphigus foliaceus; **PDAI**, Pemphigus Disease Area Index; **SoC**, standard of care.

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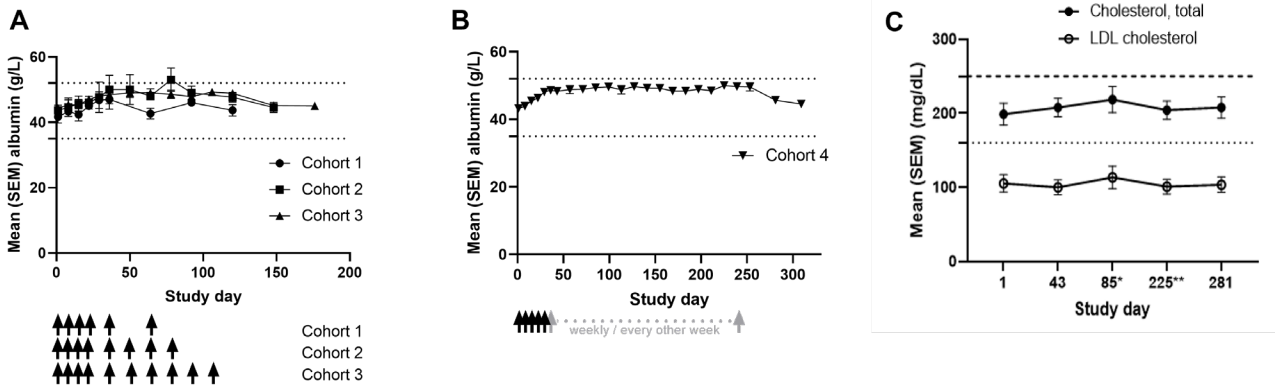
Results

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

- 84% (16/19) of patients treated with efgartigimod at 10 mg/kg and 87% (13/15) at 25 mg/kg experienced at least one TEAE
- 34 patients comprising the safety population received a median of 10 (range 2–24) IV administrations
- Most TEAEs were assessed **as mild or moderate** with no treatment-related SAEs

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



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

*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.

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)

Note: Two SAEs (pneumonia and tibia fracture) reported which 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/m^2) recovered; although assessed to be unrelated, a potential effect of efgartigimod cannot be ruled out.

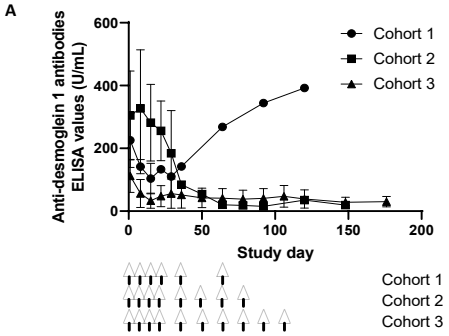
‡Elevated CPK levels observed in one patient were transient and resolved under continued treatment; increases in alanine aminotransferase (ALT) observed in two patients were mild (<2x upper limit of normal) and were resolved by the next study visit.

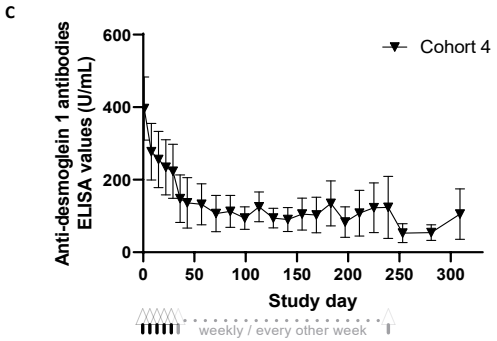
Results

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

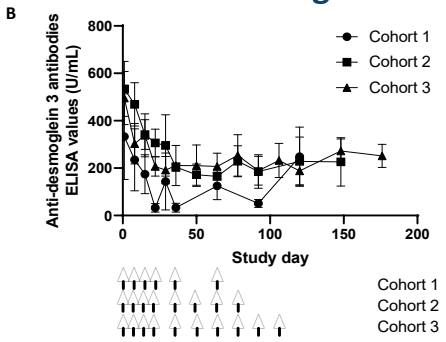
Serum autoantibody levels

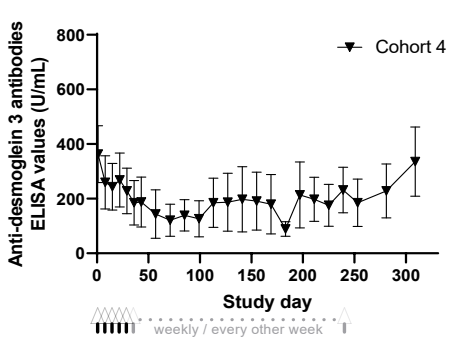
Anti-Dsg-1





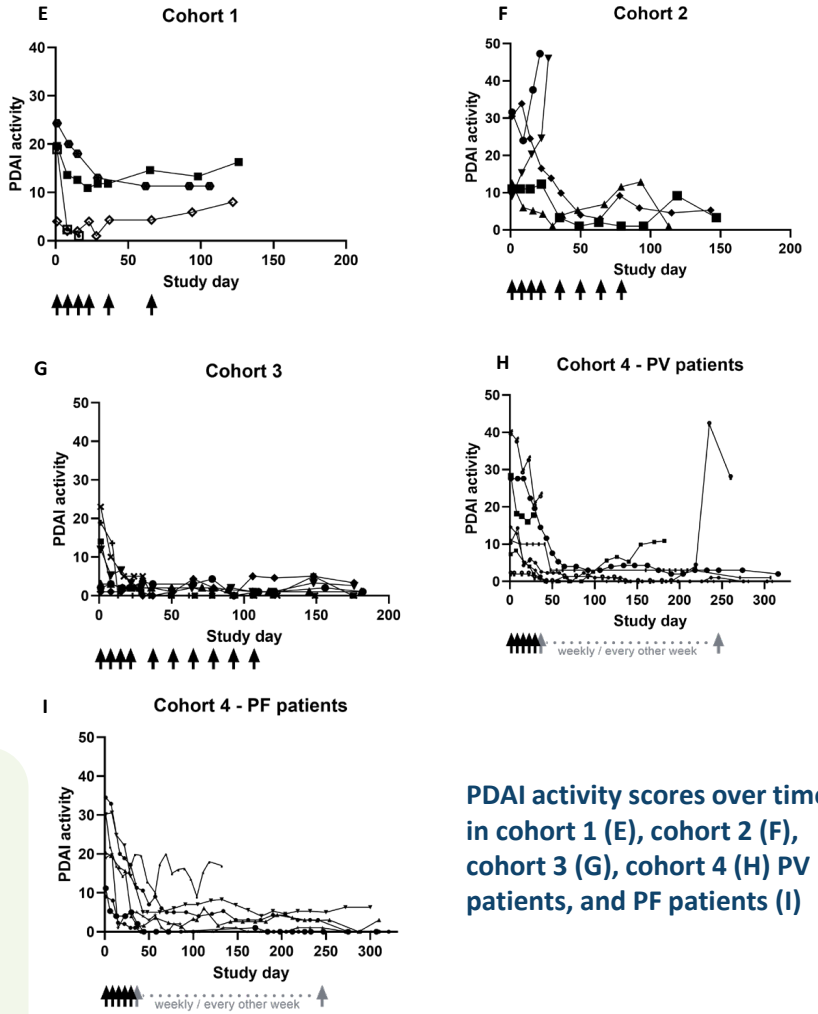
Anti-Dsg-3





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 cohort 1 (E), cohort 2 (F), cohort 3 (G), cohort 4 (H) PV patients, and PF patients (I)

- Patients with pemphigus treated with efgartigimod exhibited an approximately **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, while 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 (**Figure 2**)
- 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

Dsg, desmoglein; ELISA, enzyme-linked immunosorbent assay.

Results

Efgartigimod, as Monotherapy and Combined With Prednisone, Demonstrated an Early Onset of Disease Control and Complete Clinical Remission

	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 (%)			
Relapsing	18/19 (95)	7/13 (54)	7/18 (39)
Newly diagnosed	10/12 (83)	7/9 (78)	4/10 (40)

- 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 was achieved at a median daily concomitant prednisone dose of **0.26 mg/kg** (range 0.06–0.48)

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