Health Technology Briefing
December 2023

Efgartigimod alfa for treating pemphigus vulgaris or pemphigus foliaceus

Company/Developer	Argenx BVBA

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 17226	NICE ID: Not available	UKPS ID: 671777

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Efgartigimod alfa is in clinical development for the treatment of pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Pemphigus is a rare long-term (chronic) condition caused by a problem with the immune system. For reasons not fully understood, antibodies (proteins developed by the body to fight infection) develop in the blood and mistakenly react with surface layers of the body causing painful blisters in the mouth (and other mucous membranes) and on the skin. PF is a rare relatively benign form of pemphigus that produces blisters confined to the skin, and unlike PV does not involve mucous membranes. Pemphigus can be life-threatening without treatment. Treatment is normally with corticosteroids but when taken for long periods corticosteroids can cause a range of side effects.

Efgartigimod alfa is a modified human antibody (a protein produced by the immune system) fragment that is administered under the skin to reduce the disease-causing immunoglobulin G (IgG) antibodies. If licenced, efgartigimod will provide an alternative treatment option for patients with PV and PF.

Proposed Indication

Treatment of adults with pemphigus vulgaris or pemphigus foliaceus.[1,2]

Technology

Description

Efgartigimod alfa (Vyvgart) is a human IgG1 antibody fragment engineered for increased affinity to the neonatal Fc Receptor (FcRn). Efgartigimod alfa binds to FcRn, resulting in a reduction in the levels of circulating IgG including pathogenic IgG autoantibodies. Efgartigimod alfa does not affect the levels of other immunoglobulins (IgA, IgD, IgE or IgM), or those of albumin.[3]

Efgartigimod alfa is currently in clinical development for the treatment of adults with pemphigus (vulgaris or foliaceus). In the two phase 3 clinical trials ADDRESS (NCT04598451) and ADDRESS+ (NCT04598477) efgartigimod alfa was administered subcutaneously over a 30- and 60-week period respectively.[1,2]

Key Innovation

Pemphigus is potentially life-threatening, primarily due to secondary infections. Systemic corticosteroids (CS) have dramatically improved the prognosis, reducing mortality to < 10%. 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. Such high doses and prolonged use are associated with significant side-effects, including metabolic complications, broad immunosuppression and increased risk of infections.[4]

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). FcRn maintains constant levels of IgG and albumin in the serum by recycling these ligands following uptake into cells. Efgartigimod binds to the IgG binding site of FcRn, thereby reducing the levels of circulating IgG without affecting levels of albumin or other immunoglobulins. In healthy volunteers, efgartigimod was well tolerated and induced an early decline of all IgG subclasses.[4] If licensed, efgartigimod alfa SC will offer a novel treatment option for adult patients with pemphigus (vulgaris or foliaceus).

Regulatory & Development Status

Efgartigimod is indicated as an add-on to standard therapy for the treatment of adult patients with generalised Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.[3]

Subcutaneous efgartigimod alfa is in phase II/III clinical development for:[5]

- Bullous Pemphigoid.[6]
- Primary Immune Thrombocytopenia.[7]
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).[8]
- Generalized Myasthenia Gravis.[9]
- Active Idiopathic Inflammatory Myopathy.[10]
- Myositis.[11]

Efgartigimod alfa has the following regulatory designations/awards:

- PIM designation by the MHRA in November 2021.[12]

Patient Group

Disease Area and Clinical Need

PV and PF are debilitating autoimmune disorders triggered by IgG autoantibodies attacking mucosal and epidermal proteins called desmogleins.[13] PV may cause severe blistering of the skin and mucous membranes lining the mouth, nose, throat, eyes and genital area. Blisters develop in the upper layer of the skin and have a thin and fragile outer surface that breaks away easily leaving raw areas (erosions) that can be extensive and painful.[13] In comparison to PV, PF is thought to be less severe and affects only the skin, typically skin erosions appear on the scalp, face, torso, armpits and genital areas.[14] Symptoms for both PV and PF include skin erosions (sores) that are painful and can affect quality of life including disturbing sleep. Mouth and throat lesions can occur in people with PV and interfere with eating and drinking and causing weight loss. PV can also affect other mucous membranes such as the genital area, leading to painful sexual intercourse, urination and bowel movements, the nose causing stuffiness and blood-stained crusts; and the conjunctiva of the eyes causing sore, red eyes. The cause of pemphigus and production of autoantibodies is not yet fully understood but is likely due to a combination of genetic and environmental factors.[13]

In the UK, PV incidence was stable for the period 2010 to 2020, with a range of 3.1 to 4.2 cases per million. The prevalence increased steadily over the period from 38 in 2010 to 249 in 2020 (4.5 to 22.9 per million).[15] In England (2022-23) there were 542 finished consultant episodes (FCEs) and 423 admissions for PV (ICD10 code L10.0), which resulted in 336-day cases and 1,478 FCE bed days. There were 118 (FCEs and 93 admissions for PF (ICD10 code L10.2), which resulted in 80-day cases and 203 FCE bed days.[16]

Recommended Treatment Options

There are no NICE recommended treatment options. Current treatments include medicines to manage the body's immune response, such as steroids and immuno-suppressants, such as rituximab, mycophenolate mofetil and azathioprine or methotrexate.[17] [18,19]

Clinical Trial Information

Trial	**ADDRESS+**, NCT04598477, 2020-002917-16; An Open-Label, Multicentre, Follow-up Trial of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus. **Phase: III –** Recruiting **Location(s):** 9 EU countries, UK, USA, Australia, and other countries **Primary completion date:** September 2024
Trial Design	Single group assignment, open label
Population	N=213 (estimated), adult participants with pemphigus (vulgaris or foliaceus); aged 18 years and over
Intervention(s)	Biological: efgartigimod PH20 SC Drug: prednisone.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure:

	• Incidence of Treatment-Emergent Adverse Events (TEAE), Adverse Events of Special Interest (AESI), and Serious Adverse Events (SAE) [Time frame: up to 60 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ADDRESS,** NCT04598451, 2020-002915-23; A Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Pemphigus (Vulgaris or Foliaceus) **Phase: III –** Completed **Location(s):** 9 EU countries, UK, USA, Australia, and other countries **Primary completion date:** August 2023
Trial Design	Randomised, parallel assignment, quadruple masked
Population	N=222 (actual) adult participants aged from 18 years with PV or PF
Intervention(s)	Biological: efgartigimod PH20 SC Drug: prednisone
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: • Proportion of pemphigus vulgaris participants who achieve complete clinical remission (CR) on minimal prednisone therapy [Time frame: 30 weeks treatment period]. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT03334058; 2017-002333-40; An Open-label, Non-controlled, Phase II Study to Evaluate the Safety, Pharmacodynamics, Pharmacokinetics, Efficacy and Conditions of Use of ARGX-113 in Patients With Mild to Moderate Pemphigus (Vulgaris and Foliaceus) **Phase: II –**Completed **Location(s):** 3 EU countries, Ukraine, and Israel **Primary completion date:** October 2020
Trial Design	Single group assignment, open label

Population	N=34 (actual), patients with mild to moderate Pemphigus (Vulgaris or Foliaceus), either newly diagnosed or relapsing; aged 18 years and older
Intervention(s)	ARGX-113 (Efgartigimod)
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • Safety and tolerability as measured by the incidence and severity of treatment-emergent (serious) adverse events over the study. [Time frame: up to 6 months] See trial record for full list of other outcomes
Results (efficacy)	Treatment resulted in reduction of total IgG as well as autoreactive IgG antibody levels. Surprisingly, unlike total IgG and vaccine- or natural-infection-elicited IgG, which returned to baseline levels after stopping efgartigimod treatment, autoreactive antibody levels remained low in several study participants. Efgartigimod showed no effect on total leukocytes, neutrophils, monocytes, or lymphocytes in patients treated with extended efgartigimod therapy. Intriguingly, antigen-specific analyses revealed a loss of desmoglein-specific B cells in several participants responding to efgartigimod, in line with prolonged reduction of pathogenic IgG levels.[20]
Results (safety)	Efgartigimod was well tolerated overall, and most adverse events were of mild or moderate. Adverse events profiles were similar between doses. At least one treatment-emergent adverse events was reported by 16 of 19 (84%) patients receiving efgartigimod 10 mg/kg^{-1} and 13 of 15 (87%) receiving 25mg/kg^{-1}.[4]

Estimated Cost

The cost of efgartigimod is not yet known.

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Rituximab for Immunobullous Disease. Version:2.0. 16035/P. July 2021.

Other Guidance

- Diagnosis and management of pemphigus: Recommendations of an international panel of experts. 2020.[21]
- British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017.[22]

- Pemphigus. S2 Guideline for diagnosis and treatment–guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). 2015.[19]

Additional Information

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