swissmedic

Date: 30 October 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vyvgart

International non-proprietary name: efgartigimod alfa
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 400 mg/20 mL
Route(s) of administration: intravenous use
Marketing authorisation holder: argenx Switzerland SA
Marketing authorisation no.: 69286
Decision and decision date: approved on 3 October 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for efgartigimod alfa in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} paragraph no. 2 of the TPA. Orphan drug status was granted on 17 April 2023.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Vyvgart 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.

2.2.2 Approved indication

Vyvgart 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.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Subsequent treatment cycles are to be administered according to clinical evaluation. The frequency of Vyvgart treatment cycles may vary by patient.
In patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	03 May 2023
Formal control completed	31 May 2023
Preliminary decision	27 October 2023
Response to preliminary decision	15 January 2024
Labelling corrections	11 April 2024
Response to labelling corrections	8 May 2024
2nd Labelling corrections	8 August 2024
Response to 2nd labelling corrections	6 September 2024
3rd Labelling corrections	23 September 2024
Response to 3rd labelling corrections	26 September 2024
Final decision	3 October 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority European Medicines Agency (EMA). This SwissPAR relates to the publicly available EMA assessment report for Vyvgart published 23 June 2022, Procedure No. EMEA/H/C/005849/0000.

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA).The SwissPAR relating to quality aspects refers to the publicly available EMA assessment report for Vyvgart published 23 June 2022, Procedure No. EMEA/H/C/005849/0000.

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA). The nonclinical aspects in this SwissPAR refer to the publicly available EMA assessment report for Vyvgart published 23 June 2022, Procedure No. EMEA/H/C/005849/0000.

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority European Medicines Agency (EMA). The clinical aspects in this SwissPAR refer to the publicly available EMA assessment report for Vyvgart published 23 June 2022, Procedure No. EMEA/H/C/005849/0000.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Vyvgart was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See «Undesirable effects» for advice on the reporting of adverse reactions.

Vyvgart®

Composition

Active substances

Efgartigimod alfa.
Efgartigimod alfa is a human recombinant immunoglobulin G1 (IgG1)-derived Fc fragment produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

Excipients

Sodium dihydrogen phosphate, monohydrate, disodium hydrogen phosphate, anhydrous, sodium chloride, arginine hydrochloride, polysorbate 80 (E 433), water for injections.
Each vial contains 67.2 mg sodium.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile concentrate).
Each vial of 20 ml contains 400 mg of efgartigimod alfa (20 mg/ml).
Colourless to slightly yellow, clear to slightly opalescent, pH 6.7.

Indications/Uses

Vyvgart 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.

Dosage/Administration

Efgartigimod alfa must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with neuromuscular disorders.

Usual dosage

The recommended dose is 10 mg/kg as a 1-hour intravenous infusion to be administered in cycles of once weekly infusions for 4 weeks. Administer subsequent treatment cycles according to clinical evaluation. The frequency of treatment cycles may vary by patient (see «Properties/Effects»).

In the clinical development program, the earliest time to initiate a subsequent treatment cycle was 7 weeks from the initial infusion of the previous cycle. The safety of initiating subsequent cycles sooner than 7 weeks from the start of the previous treatment cycle has not been established. In clinical trials, 7 of 19 (37%) patients who did not meet the clinical endpoint after the first treatment

cycle showed a response after the second treatment cycle. No placebo-controlled data are available on the efficacy of further treatment cycles in patients who have not responded after two cycles.

In patients weighing 120 kg or more, the recommended dose is 1’200 mg (3 vials) per infusion (see section «Instructions for handling»).

No experience is available regarding efficacy in patients with generalized myasthenia gravis who have not previously responded to plasma exchange (PLEX) treatment.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and the batch number should be documented for each treatment.

Special dosage instructions

Patients with hepatic disorders

No data in patients with hepatic impairment are available. No dose adjustment is required in patients with hepatic impairment (see «Pharmacokinetics»).

Patients with renal disorders

Limited safety and efficacy data in patients with mild renal impairment is available, no dose adjustment is required for patients with mild renal impairment. There is very limited safety and efficacy data in patients with moderate renal impairment and none in patients with severe renal impairment (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is required in patients aged 65 years and older (see «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of efgartigimod alfa in children and adolescents have not yet been established. No data are available.

Delayed administration

If a scheduled infusion is not possible, treatment may be administered up to 3 days before or after the scheduled time point. Thereafter, the original dosing schedule should be resumed until the treatment cycle is completed. If a dose needs to be delayed for more than 3 days, the dose should not be administered to ensure two consecutive doses are given with an interval of at least 3 days.

Mode of administration

This medicinal product should only be administered via intravenous infusion as described in section «Instructions for handling». Do not administer as an intravenous push or bolus injection. It should be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection prior to administration. This medicinal product should be administered over 1 hour. Appropriate treatment for infusion and hypersensitivity-related reactions should be readily available before administration of efgartigimod alfa. In case of infusion reactions, the infusion should be administered at a slower rate, interrupted or can be discontinued (see «Warnings and precautions»).

For instructions on dilution of the medicinal product before administration, see section «Instructions for handling».

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in «Composition».

Warnings and precautions

Myasthenia Gravis Foundation of America (MGFA) Class V patients
Treatment with efgartigimod alfa in patients with MGFA Class V (i.e. myasthenic crisis), defined as intubation with or without mechanical ventilation except in the setting of routine postoperative care, has not been studied. The sequence of therapy initiation between established therapies for MG crisis and efgartigimod alfa, and their potential interactions, should be considered (see «Interactions»).

Infections

As efgartigimod alfa causes transient reduction in IgG levels the risk of infections may increase (see «Undesirable effects» and «Properties/Effects»). The most common infections observed in clinical trials were upper respiratory tract infections and urinary tract infections (see «Undesirable effects»).
Patients should be monitored for clinical signs and symptoms of infections during treatment with Vyvgart. In patients with an active infection, the benefit-risk of maintaining or withholding treatment with efgartigimod alfa should be considered until the infection has resolved. If serious infections occur, delaying treatment with efgartigimod alfa should be considered until the infection has resolved.

Infusion reactions and hypersensitivity reactions

Infusion reactions such as rash or pruritus may occur. In the clinical trial, infusion reactions were mild to moderate and did not lead to treatment discontinuation. Patients should be monitored during administration and for 1 hour thereafter for clinical signs and symptoms of infusion reactions. Should a reaction occur and based on severity of the reaction the infusion should be administered at a slower rate, interrupted or discontinued and appropriate supportive measures should be instituted. Once resolved, administration may be cautiously resumed, based on clinical evaluation.

Cases of anaphylactic reaction have been reported in the post-marketing setting. If an anaphylactic reaction is suspected, administration of Vyvgart should be immediately discontinued and appropriate medical treatment initiated. Patients shall be informed of the possible occurrence and the signs and symptoms of hypersensitivity and anaphylactic reactions and advised to contact their healthcare provider immediately should they occur.

Immunisations

All vaccines should be administered according to immunisation guidelines.
The safety of immunisation with live or live-attenuated vaccines and the response to immunisation with these vaccines during treatment with efgartigimod alfa are unknown. For patients that are being treated with efgartigimod alfa, vaccination with live or live-attenuated vaccines is generally not recommended. If vaccination with live or live-attenuated vaccines is required, these vaccines should be administered at least 4 weeks before treatment and at least 2 weeks after the last dose of efgartigimod alfa.
Other vaccines may be administered as needed at any time during treatment with efgartigimod alfa.

Immunogenicity

In the double-blind placebo-controlled study, pre-existing antibodies that bind to efgartigimod alfa were detected in 25/165 (15%) patients with gMG. Treatment-induced antibodies to efgartigimod alfa were detected in 17/83 (21%) patients. In 3 of these 17 patients, treatment-induced anti-drug antibodies (ADAs) persisted until the end of the study. Neutralising antibodies were detected in 6/83 (7%) of patients treated with Vyvgart, including the 3 patients with persisting treatment-induced ADAs. Retreatment did not cause an increase in incidence or titres of efgartigimod alfa antibodies. There was no apparent impact of antibodies to efgartigimod alfa on clinical efficacy or safety, nor on pharmacokinetics and pharmacodynamic parameters.

Immunosuppressant and anticholinesterase therapies

When non-steroidal immunosuppressants, corticosteroids and anticholinesterase therapies are decreased or discontinued, patients should be monitored closely for signs of disease exacerbation.

Sodium content

This medicinal product contains 67.2 mg sodium per vial, equivalent to 3.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

No interaction studies have been performed.

Efgartigimod alfa may decrease concentrations of compounds that bind to the human neonatal Fc Receptor (FcRn), i.e., immunoglobulin products, monoclonal antibodies, or antibody derivatives

containing the human Fc domain of the IgG subclass. If possible, it is recommended to postpone initiation of treatment with these products to 2 weeks after the last dose of any given treatment cycle of Vyvgart. As a precaution, patients receiving Vyvgart while on treatment with these products should be closely monitored for the intended efficacy response of those products.

Plasma exchange, immunoadsorption, and plasmapheresis may reduce circulating levels of efgartigimod alfa.

All vaccines should be administered according to immunisation guidelines.
The potential interaction with vaccines was studied in a nonclinical model using Keyhole limpet hemocyanin (KLH) as the antigen. The weekly administration of 100 mg/kg to monkeys did not impact the immune response to KLH immunisation.
For patients that are being treated with efgartigimod alfa, vaccination with live or live-attenuated vaccines is generally not recommended. If vaccination with live or live-attenuated vaccines is required, these vaccines should be administered at least 4 weeks before treatment and at least 2 weeks after the last dose of a treatment cycle efgartigimod alfa(see «Warnings and Precautions»).

Pregnancy, lactation

Pregnancy

There is no available data on the use of efgartigimod alfa during pregnancy. Antibodies including therapeutic monoclonal antibodies are known to be actively transported across the placenta (after 30 weeks of gestation) by binding to the FcRn.

Efgartigimod alfa may be transmitted from the mother to the developing foetus. As efgartigimod alfa is expected to reduce maternal antibody levels, and is also expected to inhibit the transfer of maternal antibodies to the foetus, reduction in passive protection to the newborn is anticipated. Therefore, risks and benefits of administering live / live-attenuated vaccines to infants exposed to efgartigimod alfa *in utero* should be considered (see «Warnings and Precautions»).

Treatment of pregnant women with Vyvgart should only be considered if the clinical benefit outweighs the risks.

Lactation

There is no information regarding the presence of efgartigimod alfa in human milk, the effects on the breastfed child or the effects on milk production. Animal studies on the transfer of efgartigimod alfa into milk have not been conducted, and therefore, excretion into maternal milk cannot be excluded. Maternal IgG is known to be present in human milk. No studies are available on possible changes in maternal IgG in human milk and passive protection of the newborn during treatment with Vyvgart.

Treatment of lactating women with efgartigimod alfa should only be considered if the clinical benefit outweighs the risks.

Fertility

There is no available data on the effect of efgartigimod alfa on fertility in humans. Animal studies showed no impact of efgartigimod alfa on male and female fertility parameters (see «Preclinical data»).

Effects on ability to drive and use machines

Vyvgart has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most frequently observed adverse reactions were upper respiratory tract infections and urinary tract infections (10.7% and 9.5%, respectively).

List of adverse reactions

The safety of Vyvgart was evaluated in 167 patients (84 patients treated with efgartigimod and 83 patients treated with placebo) with gMG in the 26-week Phase 3 double-blind placebo-controlled clinical study.

Table 1 contains adverse reactions from the completed 26-week double-blind placebo-controlled phase 3 clinical trial with efgartigimod alfa and spontaneous reports. Adverse reactions are listed by system organ class and preferred term. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1’000 to < 1/100), rare (≥ 1/10’000 to < 1/1’000) or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 1. Adverse reactions

System organ class	Adverse reaction	Frequency category
Infections and infestations*	Upper respiratory tract infections (10.7%)	Very common
	Urinary tract infections	Common
	Bronchitis	Common
Immune system disorders	Anaphylactic reaction[a]	Not known

Musculoskeletal and connective tissue disorders	Myalgia	Common
Injury, poisoning and procedural complications*	Procedural headache	Common

* See paragraph «Description of specific adverse reactions and additional information»

[a] From spontaneous post-marketing reporting

Description of specific adverse reactions and additional information

Infections

The most frequently reported adverse reactions in the controlled phase 3 study were infections, and the most reported infections were upper respiratory tract infections (10.7% [n = 9] of patients treated with efgartigimod alfa and 4.8% [n = 4] of patients treated with placebo) and urinary tract infections (9.5% [n = 8] of patients treated with efgartigimod alfa and 4.8% [n = 4] of patients treated with placebo).
Infections were mostly mild to moderate in severity in patients who received efgartigimod alfa (≤ Grade 2 according to the Common Terminology Criteria for Adverse Events).
Overall, in the 26-week controlled phase 3 study treatment emergent infections were reported in 46.4% (n = 39) of patients treated with efgartigimod alfa and 37.3% (n = 31) of patients treated with placebo. The median time from treatment initiation to emergence of infections was 6 weeks.

Procedural headache

Procedural headache was reported in 4.8% of the patients treated with efgartigimod alfa and 1.2% of patients treated with placebo. Procedural headache was reported when a headache was judged to be temporally related to the intravenous infusion of efgartigimod alfa. All were mild or moderate except one event which was reported as severe (Grade 3).

All other adverse reactions were mild or moderate with the exception of one case of myalgia (Grade 3).
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no known specific signs and symptoms of overdose with efgartigimod alfa. In the event of an overdose the adverse events are not expected to be different from those observed at the recommended dose. Patients should be monitored for adverse reactions, and appropriate

symptomatic and supportive treatment initiated. There is no specific antidote for overdose with efgartigimod alfa.

Properties/Effects

ATC code

L04AA58

Mechanism of action

Efgartigimod alfa 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.

IgG autoantibodies are the underlying cause of the pathogenesis of MG. They impair neuromuscular transmission by binding to acetylcholine receptors (AChR), muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4).

Pharmacodynamics

In a double-blind placebo-controlled study in gMG patients, efgartigimod alfa decreased serum IgG levels and AChR autoantibody levels at the recommended dose and schedule (see «Dosage/Administration»). Maximum mean percentage decrease in total IgG levels compared to baseline reached 61% one week after the last infusion of the initial treatment cycle and returned to baseline levels 9 weeks after the last infusion. Similar effects were also observed for all subtypes of IgG. Decrease in AChR autoantibody levels followed a similar time course with maximum mean percentage decrease of 58% one week after the last infusion and return to baseline levels 7 weeks after the last infusion. Similar changes were observed during the second cycle of the study.

Clinical efficacy

Efficacy of efgartigimod alfa for the treatment of adults with generalised Myasthenia Gravis (gMG) was studied in a 26-week, multicentre randomised double-blind placebo-controlled trial.

In this study, patients had to meet the following main criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II, III or IV;
- Patients with either positive or negative serologic tests for antibodies to AChR;
- MG-Activities of Daily Living (MG-ADL) total score of ≥ 5;
- On stable doses of MG therapy prior to screening, that included acetylcholinesterase (AChE) inhibitors, steroids or non-steroidal immunosuppressive therapy (NSIST), either in combination or alone [NSISTs included but were not limited to azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide];

- IgG levels of at least 6 g/l.

Patients with MGFA Class V gMG, patients with documented lack of clinical response to plasma exchange (PLEX); patients treated with PLEX, intravenous Immunoglobulin (IVIg) one month and monoclonal antibodies six months prior to starting treatment; patients who had undergone thymectomy in the three months prior to study entry and patients with active (acute or chronic) hepatitis B infection, hepatitis C seropositivity, and diagnosis of AIDS, a severe infection in the last 8 weeks or an underlying malignant disease that has not been successfully treated in the last three years including malignant thymoma, were excluded from the trials.

A total of 167 patients were enrolled in the study and were randomised to either efgartigimod alfa (n = 84) or placebo (n = 83). Baseline characteristics were similar between treatment groups, including median age at diagnosis [45 (19-81) years], gender [most were female; 75% (efgartigimod alfa) versus 66% (placebo)], race [most patients were white; 84.4%] and median time since diagnosis [8.2 years (efgartigimod alfa) and 6.9 years (placebo)].

The majority of patients (77% in each group) tested positive for antibodies to AChR (AChR-Ab) and 23% of patients tested negative for AChR-Ab.

During the study, over 80% of patients in each group received AChE inhibitors, over 70% in each treatment group received steroids, and approximately 60% in each treatment group received NSISTs, at stable doses. At study entry, approximately 30% of patients in each treatment group had no previous exposure to NSISTs.

Median MG-ADL total score was 9.0 in both treatment groups, and median Quantitative Myasthenia Gravis (QMG) total score was 17 and 16 in the efgartigimod alfa and placebo groups, respectively.

Patients were treated with efgartigimod alfa at the recommended dose regimen and received a maximum of 3 treatment cycles (see «Dosage/Administration»).

The efficacy of efgartigimod alfa was measured using the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions. A total score ranges from 0 to 24 with the higher scores indicating more impairment. In this study, an MG-ADL responder was a patient with ≥ 2-point reduction in the total MG-ADL score compared to the treatment cycle baseline, for at least 4 consecutive weeks with the first reduction occurring no later than 1 week after the last infusion of the cycle.

The efficacy of efgartigimod alfa was also measured using the QMG total score which is a grading system that assesses muscle weakness with a total possible score of 0 to 39 where higher scores

indicate more severe impairment. In this study, a QMG responder was a patient who had a ≥ 3-point reduction in the total QMG score compared to the treatment cycle baseline, for at least 4 consecutive weeks with the first reduction occurring no later than 1 week after last infusion of the cycle.

The primary efficacy endpoint was the comparison of the percentage of MG-ADL responders during the first treatment cycle (C1) between treatment groups in the AChR-Ab seropositive population.

A key secondary endpoint was the comparison of the percentage of QMG responders during C1 between both treatment groups in the AChR-Ab seropositive patients.

Table 2. MG-ADL and QMG responders during cycle 1 in AChR-Ab seropositive population (mITT analysis set)

	Population	Efgartigimod alfa n/N (%)	Placebo n/N (%)	P-value	Difference Efgartigimod alfa-Placebo (95% CI)
MG-ADL	AChR-Ab seropositive	44/65 (67.7)	19/64 (29.7)	< 0.0001	38.0 (22.1; 54.0)
QMG	AChR-Ab seropositive	41/65 (63.1)	9/64 (14.1)	< 0.0001	49.0 (34.5; 63.5)

AChR-Ab = acetylcholine receptor-antibody; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; mITT = modified intent-to-treat; n = number of patients for whom the observation was reported; N = number of patients in the analysis set; CI = confidence interval;
Logistic regression stratified for AChR-Ab status (if applicable), Japanese/Non-Japanese and standard of care, with baseline MG-ADL as covariate / QMG as covariates
Two-sided exact p-value

Analyses show that during the second treatment cycle MG ADL responder rates were similar to those during the first treatment cycle (see Table 3).

Table 3. MG-ADL and QMG responders during cycle 2 in AChR-Ab seropositive population (mITT analysis set)

	Population	Efgartigimod alfa n/N (%)	Placebo n/N (%)
MG-ADL	AChR-Ab seropositive	36/51 (70.6)	11/43 (25.6)
QMG	AChR Ab seropositive	24/51 (47.1)	5/43 (11.6)

AChR-Ab = acetylcholine receptor-antibody; MG-ADL = Myasthenia Gravis Activities of Daily Living; QMG = Quantitative Myasthenia Gravis; mITT = modified intent-to-treat; n = number of patients for whom the observation was reported; N = number of patients in the analysis set.

In patients with a history of thymectomy, 27 (60%) patients were MG-ADL responders in the efgartigimod group compared to 8 (27%) patients in the placebo group.

Exploratory data shows that onset of response was observed within 2 weeks of initial infusion in 37/44 (84%) patients treated with efgartigimod alfa in the AChR-Ab seropositive MG-ADL responders.

In the double-blind placebo-controlled study (ARGX-113-1704) according to the clinical study protocol, a subsequent treatment cycle could only be initiated if all of the following criteria were met:
(1) the minimum time between cycles was 8 weeks from the first infusion of the previous cycle;
(2) the patient had a total MG-ADL score of ≥5 points with > 50% of the total score due to non-ocular symptoms; and
(3) only for patients who achieved responder status (see definition above) in the previous treatment cycle and now show a loss of response (defined as a reduction in the MG-ADL total score < 2 points compared to the corresponding initial cycle value).
In the overall population the mean time to the second treatment cycle in the efgartigimod alfa group was 13 weeks (SD 5.5 weeks) and the median time was 10 weeks (8-26 weeks) from the initial infusion of the first treatment cycle.

In patients that responded to treatment (≥ a 2-point reduction in MG-ADL total score within the respective cycle versus baseline), the duration of clinical improvement was 5 weeks in 5/44 (11%) patients, 6-7 weeks in 14/44 (32%) of patients, 8-11 weeks in 10/44 (23%) patients and 12 weeks or more in 15/44 (34%) patients.

Pharmacokinetics

Distribution

Based upon patient population PK data analysis the volume of distribution is 13 l.

Metabolism

Efgartigimod alfa is expected to be degraded by proteolytic enzymes into small peptides and amino acids.

Elimination

The terminal half-life is 80 to 120 hours (3 to 5 days). Based upon patient population PK data analysis, the clearance is 0.108 l/h. The molecular weight of efgartigimod alfa is approximately 54 kDa, which is at the boundary of molecules that are renally filtered.

Linearity/non-linearity

The pharmacokinetics profile of efgartigimod alfa is linear, independent of dose or time, with negligible accumulation. The geometric mean accumulation ratio based on observed peak concentrations was 1.12.

Kinetics in specific patient groups

Hepatic impairment

No dedicated pharmacokinetic study has been performed in patients with hepatic impairment.

The effect of hepatic function markers as covariates in a population pharmacokinetic analysis did not show any impact on the pharmacokinetics of efgartigimod alfa.

Renal impairment

No dedicated pharmacokinetic studies have been performed in patients with renal impairment.

The effect of renal function marker estimated glomerular filtration rate [eGFR] as a covariate in a population pharmacokinetic analysis showed a reduced clearance resulting in a limited increase in exposure in patients with mild renal impairment (eGFR 60-89 ml/min/1.73 m^2). No specific dose adjustment is recommended in patients with mild renal impairment.

There is insufficient data on the impact of moderate renal impairment (eGFR 30-59 ml/min/1.73 m^2) on efgartigimod alfa pharmacokinetic parameters. There is no data on the impact of severe renal impairment (eGFR < 30 ml/min/1.73 m^2) on pharmacokinetic parameters of efgartigimod alfa.

Age, gender, race and bodyweight

The pharmacokinetics of efgartigimod alfa were not affected by age (19-78 years), gender and race.

A population pharmacokinetic analysis showed that the effect of bodyweight on efgartigimod alfa exposure was limited at a dose of 10 mg/kg in patients up to 120 kg as well as in patients of 120 kg and above who received a capped dose of 1’200 mg/infusion. There was no effect of bodyweight on

the extent of IgG reduction. In the double-blind placebo-controlled study, 5 (3%) patients were over 120 kg. The median bodyweight of patients on efgartigimod alfa in the study was 76.5 kg (min 49; max 229).

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

In reproduction studies in rats and rabbits, intravenous administration of efgartigimod alfa did not result in adverse effects on fertility and pregnancy nor were teratogenic effects observed up to dose levels corresponding to 11-fold (rats) and 56-fold (rabbits) to the exposure (AUC) at the maximum recommended therapeutic dose.

Carcinogenicity and genotoxicity

No studies have been conducted to assess the carcinogenic and genotoxic potential of efgartigimod alfa.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section «Instructions for handling».

Shelf life

Do not use this medicine after the expiry date «EXP» stated on the pack.

Shelf life after dilution

The diluted preparation for infusion is not preserved. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
For microbiological reasons, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Special precautions for storage

Store in a refrigerator (2 - 8 °C).
Do not freeze.
Store in the original packaging in order to protect the contents from light. Do not shake.
For storage conditions after dilution of the medicinal product, see section «Shelf life after dilution».
Keep out of the reach of children.

Instructions for handling

The efgartigimod alfa solution diluted in sodium chloride 9 mg/ml (0.9%) solution for injection can be administered using polyethylene (PE), polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and ethylene/polypropylene copolymer bags (polyolefins bags), as well as with PE, PVC and polyurethane/polypropylene infusion lines, together with polyurethane (PUR) or PVC filters with polyethersulfone (PES) or polyvinylidene fluoride (PVDF) filter membrane.

Using the formula in the table below, calculate the following:

- The dose of Vyvgart required based on the patient's bodyweight at the recommended dose of 10 mg/kg. For patients weighing over 120 kg use a bodyweight of 120 kg to calculate the dose. The maximum total dose per infusion is 1'200 mg. Each vial contains 400 mg of efgartigimod alfa at a concentration of 20 mg/ml.
- The number of vials needed.
- The volume of sodium chloride 9 mg/ml (0.9%) solution for injection. The total volume of diluted medicinal product is 125 ml.

Table 4. Formula

Step 1 – Calculate the dose (mg)	10 mg/kg x weight (kg)
Step 2 – Calculate the volume of concentrate (ml)	dose (mg) ÷ 20 mg/ml
Step 3 – Calculate the number vials	volume of concentrate (ml) ÷ 20 ml
Step 4 – Calculate the volume of sodium chloride 9 mg/ml (0.9%) solution for injection (ml)	125 ml – concentrate volume (ml)

Dilution

- Visually inspect that the vial content is clear to slightly opalescent, colourless to slightly yellow, and devoid of particulate matter. If visible particles are observed and/or the liquid in the vial is discoloured, the vial must not be used. Do not shake the vials.
- Using aseptic technique throughout the preparation of the diluted solution:
  - Gently withdraw the required amount of Vyvgart from the appropriate number of vials with a sterile syringe and needle (see Table 4). Discard any unused portion of the vials.
  - Transfer the calculated dose of the product into an infusion bag.
  - Dilute the withdrawn product by adding the calculated amount of sodium chloride 9 mg/ml (0.9%) solution for injection to make a total volume of 125 ml.
  - Gently invert the infusion bag containing the diluted product **without shaking** to ensure thorough mixing of the product and the diluent.

Administration

- Inspect the solution visually for particulate matter prior to administration.

- Infuse the total 125 ml of diluted medicinal product over 1 hour using a 0.2 µm filter. Administer the full amount of solution, flushing the entire line with sodium chloride 9 mg/ml (0.9%) solution for injection at the end.
- Vyvgart should be administered immediately after dilution and the infusion of diluted solution should be completed within 4 hours of dilution.
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Do not freeze. Allow the diluted medicinal product to reach room temperature before administration. Complete the infusion within 4 hours of removal from the refrigerator. The diluted medicinal product should not be heated in any other manner than via ambient air.
- Should infusion reactions occur, the infusion should be administered at a slower rate, interrupted or discontinued (see «Warnings and precautions»).
- Other medicinal products should not be injected into infusion side ports or mixed with Vyvgart.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

69286 (Swissmedic)

Packs

Concentrate in single-dose 20 ml glass vials (Type I) with rubber stopper (butyl, siliconised), aluminium seal and polypropylene flip-off cap.

Pack size of 1 vial. (A)

Marketing authorisation holder

argenx Switzerland SA, 1202 Genève

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