15 May 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

of an orphan medicinal product submitted for type II variation application

Vyvgart (egartigimod alfa)
Treatment of chronic inflammatory demyelinating polyneuropathy
EU/3/21/2555

Sponsor: Argenx

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Efgartigimod alfa
Other name(s)	Vyvgart, Efgartigimod alfa
International Non-Proprietary Name	Efgartigimod alfa
Tradename	Vyvgart
Orphan condition	Treatment of chronic inflammatory demyelinating polyneuropathy
Sponsor's details:	Argenx Industriepark-Zwijnaarde 7 9052 Gent Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Argenx
COMP opinion	09 December 2021
EC decision	14 January 2022
EC registration number	EU/3/21/2555
Type II variation procedural history	
Rapporteur / Co-rapporteur	Thalia Marie Estrup Blicher / Alexandre Moreau
Applicant	Argenx
Application submission	05 June 2024
Procedure start	22 June 2024
Procedure number	EMA/H/C/005849/II/0020
Invented name	Vyvgart
Proposed therapeutic indication	Vyvgart is indicated as monotherapy for the treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins. Further information on Vyvgart can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/vyvgart
CHMP opinion	25 April 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Darius Matusevicius / Michel Hoffmann
Sponsor's report submission	10 July 2024
COMP discussion and adoption of list of questions	14-16 April 2025
Oral explanation	14 May 2025
COMP opinion	15 May 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 was based on the following grounds:

- the intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on preliminary clinical data showing a reduction in inflammation and an improvement in muscle strength;
- the condition is chronically debilitating and life threatening due to an impairment of motor and sensory functions, resulting in inability to walk without help in a majority of patients;
- the condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in inflammation and an improvement in muscle strength in patients with unstable chronic inflammatory demyelinating polyneuropathy with functional limitations despite previous treatment with currently authorised medications. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing efgartigimod alfa as an orphan medicinal product for the orphan condition: treatment of chronic inflammatory demyelinating polyneuropathy.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots, typically characterized by a relapsing-remitting or progressive course of symmetric weakness of proximal and distal muscles. CIDP is identified by electrodiagnostic and/or pathologic features of demyelination and responsiveness to immunomodulatory treatments.

Typical CIDP (symmetric sensorimotor) accounts for approximately half the cases and is a symmetric sensorimotor polyneuropathy characterized by proximal and distal muscle weakness that exceeds the extent of sensory loss. The presentation is usually one of gradually progressive symptoms over the course of several months or longer (Shefner et al, 2023 uptodate). Several variants of CIDP are distinguished by their clinical presentation and/or pathogenic mechanism, including multifocal, focal, motor, sensory, and distal CIDP as per EAN/PNS guidelines (J periph nerv soc 2021;26(3):242. Epub 2021 Jul 30).

The COMP considers CIDP a distinct medical entity and valid orphan condition; all disease variants are to be encompassed therein.

The approved therapeutic indication *"Vyvgart is indicated as monotherapy for the treatment of adult patients with progressive or relapsing active chronic inflammatory demyelinating polyneuropathy (CIDP) after prior treatment with corticosteroids or immunoglobulins"* falls within the scope of the designated orphan condition "Treatment of chronic inflammatory demyelinating polyneuropathy".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by a positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Many patients with CIDP experience chronic disability due to neurological symptoms and deficits (Lewis 2024). The degree of disability experienced varies from ambulatory to wheelchair-bound or bedridden, and thus the disease can be severely disabling despite existing standards of care (Mahdi Rogers 2014; Hafsteinsdottir 2016). At some point during their illness, 54% of patients with CIDP experience moderate-to-severe disability (Park 2022).

Proximal muscle weakness causes difficulty climbing or descending stairs, rising from a seated position, lifting objects, and debilitating fatigue (Bunschoten 2019b; Merkies 2016; Lunn 1999). Patients have difficulty walking and experience frequent falls, and a substantial proportion are unable to mobilise without aid. In a clinical study, 75.6% of patients reported disability in their upper limbs; at their worst, 58.5% could not walk independently, with 26.8% needing unilateral support and 14.6% needing bilateral support (Mahdi Rogers 2014). CIDP most commonly has an insidious onset with either a chronic progressive or a relapsing course. Occasionally (26% of 38 Japanese patients [Kuwabara 2006]) complete remission occurs. CIDP may occur at any age, but it is more common in the population >50 years of age (Mahdi Rogers 2014; Hagen 2021). A relapsing course and motor dominant CIDP are more common in younger patients (Hagen 2021).

Over recent decades improvements in SoC have led to reductions in the probability of being wheelchair bound (7%) and disease-related mortality to 1.3% over a lifetime (mean age at onset is ~60 years) (Dimachkie 2013; Allen 2021; Mahdi Rogers 2014).

The seriousness of the proposed condition has been previously acknowledged by the COMP. The condition is considered chronically debilitating and life threatening due to an impairment of motor and sensory functions, resulting in inability to walk without help in a majority of patients.

Number of people affected or at risk

At orphan designation stage in January 2022, the COMP accepted a prevalence estimate of approximately 1 in 10,000 persons in the European Union. This value was based on a literature review

from the sponsor covering population-based observational epidemiological studies of CIDP up to January 2021.

For the purpose of orphan maintenance, the sponsor conducted a gap analysis of epidemiological studies of CIDP from 2021 up to the beginning of 2024 (see Table 1). Three relevant articles were identified which provided data from case reviews of public health databases (Glāzere 2023; Broers 2022; Park 2022). Notably, two of these reports include data from EU member states (Glāzere 2023; Broers 2022). Based on the two, relatively small, national epidemiological studies in Latvia and The Netherlands, the prevalence of CIDP ranges from 1.2 to 7.0 per 100,000. Therefore, in the most conservative case, the European prevalence can be estimated to be 7.0 per 100,000.

A systematic literature review (SLR) by Querol 2021 was also identified which presents data from a wider global pool of epidemiology studies and prior SLRs some of which were reported in the original orphan designation application. This broad pool of data possibly contributes to the wide range in the prevalence estimate quoted. In general, the diagnostic criteria applied are those of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS).

The Australian prevalence of 5.0 per 100,000 (Park 2022) is supportive since this lies within the same range of public-health database sourced epidemiology.

Table 1. Literature Review of Population-Based Worldwide Prevalence Rates of CIDP (amended from sponsor Table 12)

Study author, year	Prevalence year or period	Study region	Case ascertainment	Total prevalence per 100 000 population (95% CI)[a]
Glāzere 2023	2015-2021	Latvia	EFNS/PNS (2021)	1.21
Querol 2021[c]	May 2009-May 2019	Italy, Iceland, England, Netherlands, Middle East, Africa, North America, South America, East Asia	EFNS (2006), AAN	0.8 -10.3
Broers 2022	2008-2017	The Netherlands	NR	7.00 (95% CI 5.41-8.93)
Park 2022	09 August 2016	Australia regions (North Queensland, Tasmania)	EFNS/PNS (2010)	5.00

In conclusion, based on the updated European epidemiologic data, the prevalence of CIDP in the EU, in the most conservative case, can be estimated as 0.7 per 10,000 persons. This is a slightly lower prevalence than calculated at the time of the orphan designation in 2021 where the total number of persons affected in the EU was estimated at 1.03 per 10 000 persons. The sponsor did not indicate that there was a general trend in CIDP becoming less prevalent. The COMP considered the entirety of the epidemiologic data for CIDP in the EU as reported in the initial orphan designation and the orphan maintenance review and concluded that the previously accepted prevalence estimate of approximately 1 in 10,000 persons in the European Union should be maintained.
Thus, based on all available prevalence data, CIDP continues to fulfil the prevalence criterion for an orphan disease designation, as the condition affects less than 5 persons per 10,000 in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Intravenous Immunoglobulin products (IVIg) and Subcutaneous Immunoglobulin products (SCIg) are the only approved therapies for treatment of CIDP in Europe.

The sponsor provided the below overview table including currently recommended CIDP treatments including information on their on- or off-label use in CIDP in the EU (Table 2).

Table 2. Overview of CIDP treatments and MA status in the EU (as of June 2024)

EFNS/PNS-recommended CIDP treatments	**Compound, product**	**CIDP indication**	**Registration Procedure**	**Marketing Authorisation Holder (MAH)**
First line				
IVIg human normal immunoglobulin	Flebogamma DIF Privigen Kiovig Gamunex Octagam Panzyga Ig Vena Intratect IqYmune Nanogam Multiple other IVIgs	Y	CP 2007 CP 2008 CP 2006 MRP 2006 MRP 2008 MRP 2016 MRP 2006 MRP 2005 MRP 2015 MRP 2004 National	Instituto Grifols S.A CSL Behring GmbH Baxter AG Grifols GmbH Octapharma GmbH Octapharma GmbH Kedrion SPa Biotest Pharma GmbH LFB Prothya Biosolutions BV Multiple MAHs
SCIg human normal immunoglobulin	Hizentra HyQvia	Y	CP 2011 CP 2024	CSL Behring GmbH Baxalta Innovations GmbH
Corticosteroids	Prednisone Prednisolone Dexamethasone	N	National	Multiple MAHs
Medical procedure	PLEX	-	-	Guideline recommended (Van den Bergh 2021)

Second and later lines				
Immunosuppressive agents	Methothrexate	N	National	Multiple MAHs
	INF-β-1a (e.g., Avonex)	N	CP	Multiple MAHs
	Fingolimod	N	CP	Multiple MAHs
	Azathioprine	N	National	Multiple MAHs
	Cyclophosphamide	N	National	Multiple MAHs
	Cyclosporin A	N	National	Multiple MAHs
	Mycophenolate mofetil	N	National	Multiple MAHs
	Rituximab	N	CP	Multiple MAHs

CIDP=chronic inflammatory demyelinating polyneuropathy; CP=centralised procedure; EFNS=European Federation of Neurological Societies; EU=European Union; IVIg=intravenous immunoglobulin; MA=marketing authorisation; MAH=marketing authorisation holder; MRP=mutual recognition procedure; PLEX=plasma exchange; PNS=Peripheral Nerve Society; SCIg=subcutaneous immunoglobulin.

The current European guidelines for the treatment of CIDP remain those referenced in the initial orphan drug designation application namely the updated treatment recommendations of the European Academy of Neurology (EAN)/Peripheral Nerve Society (PNS), published in 2021 (Van den Bergh 2021). The induction and maintenance treatment algorithm recommended by this expert group is provided in Figure 1.

First-line therapies include IVIg (with option to give subcutaneous Ig [SCIg] as maintenance therapy), corticosteroids (CS), and plasmapheresis/PLEX as effective first-line treatments in approximately two-thirds of patients (Dalakas, 2011). When first-line treatments are inadequate, immunosuppressants or other immunomodulatory agents are generally prescribed, including azathioprine, methotrexate, mycophenolate, cyclosporine, and cyclophosphamide. Their use is based on the proposed pathogenesis of CIDP as an immune-mediated condition, though for most of these there is no clear evidence of a beneficial treatment effect.

For the purposes of demonstrating significant benefit of Vyvgart, only IVIg products approved for treatment of CIDP in the EU, are considered satisfactory methods (see Table 2). This is based on the fact that the two authorized SCIg products for CIDP, Hizentra and HyQvia, are only indicated for maintenance therapy in CIDP and thus require previous treatment with IVIg products. This is not the case for Vyvgart.

IVIg products approved for treatment of CIDP in the EU have a very broad therapeutic indication wordings, as exemplified by the two IVIg product examples below, Privigen and Gamunex:

4.1 Privigen

Immunomodulation in adults, and children and adolescents (0-18 years) in:

Chronic inflammatory demyelinating polyneuropathy (CIDP). Only limited experience is available of use of intravenous immunoglobulins in children with CIDP.

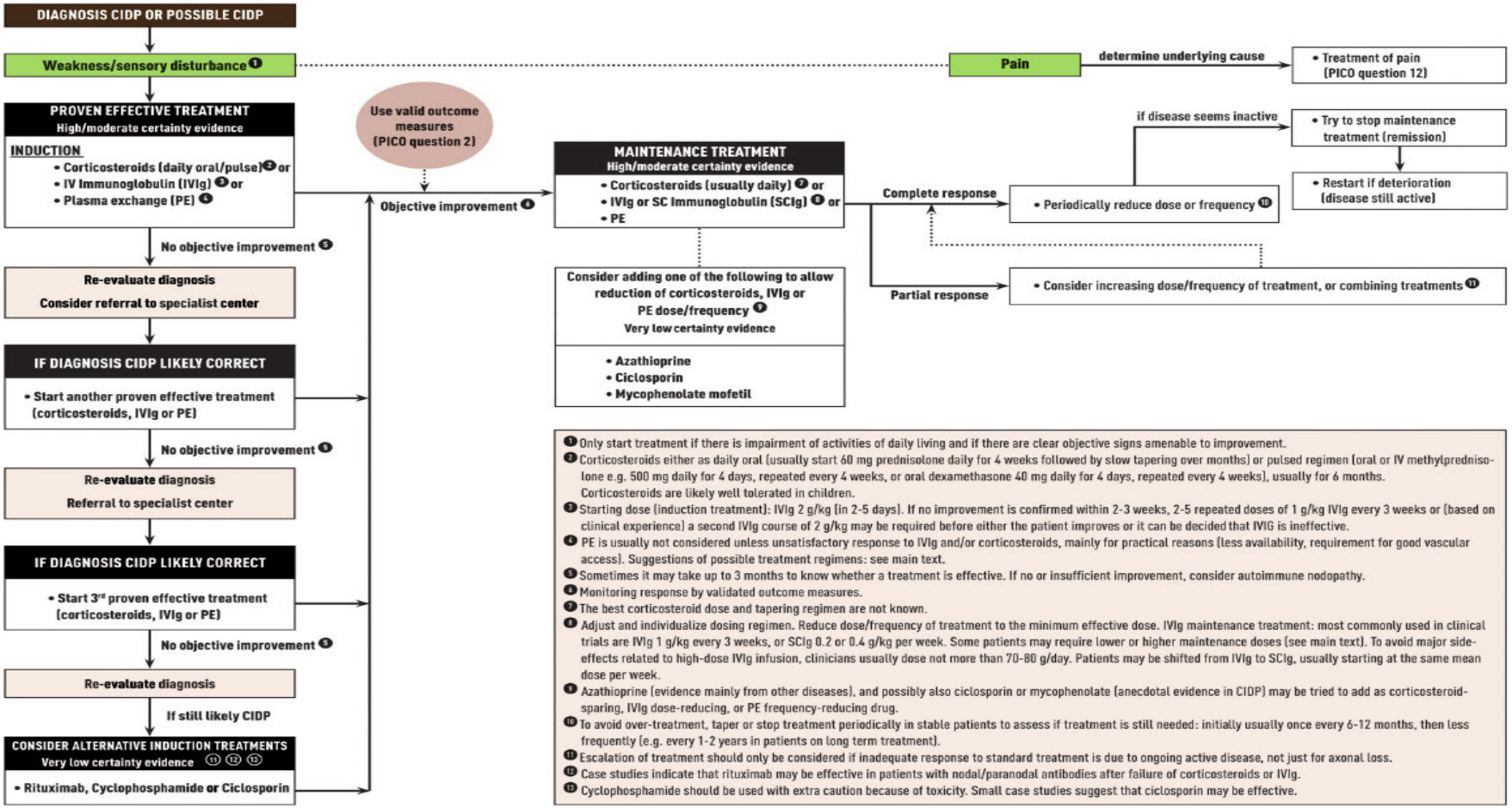
4.1 Gamunex

Immunomodulation in adults, and children and adolescents (0-18 years) in:

Chronic inflammatory demyelinating polyneuropathy (CIDP).

Of note, both products are contraindicated in patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA containing product can result in anaphylaxis.

Figure 1. EFNS/PNS induction and maintenance treatment algorithm for CIDP



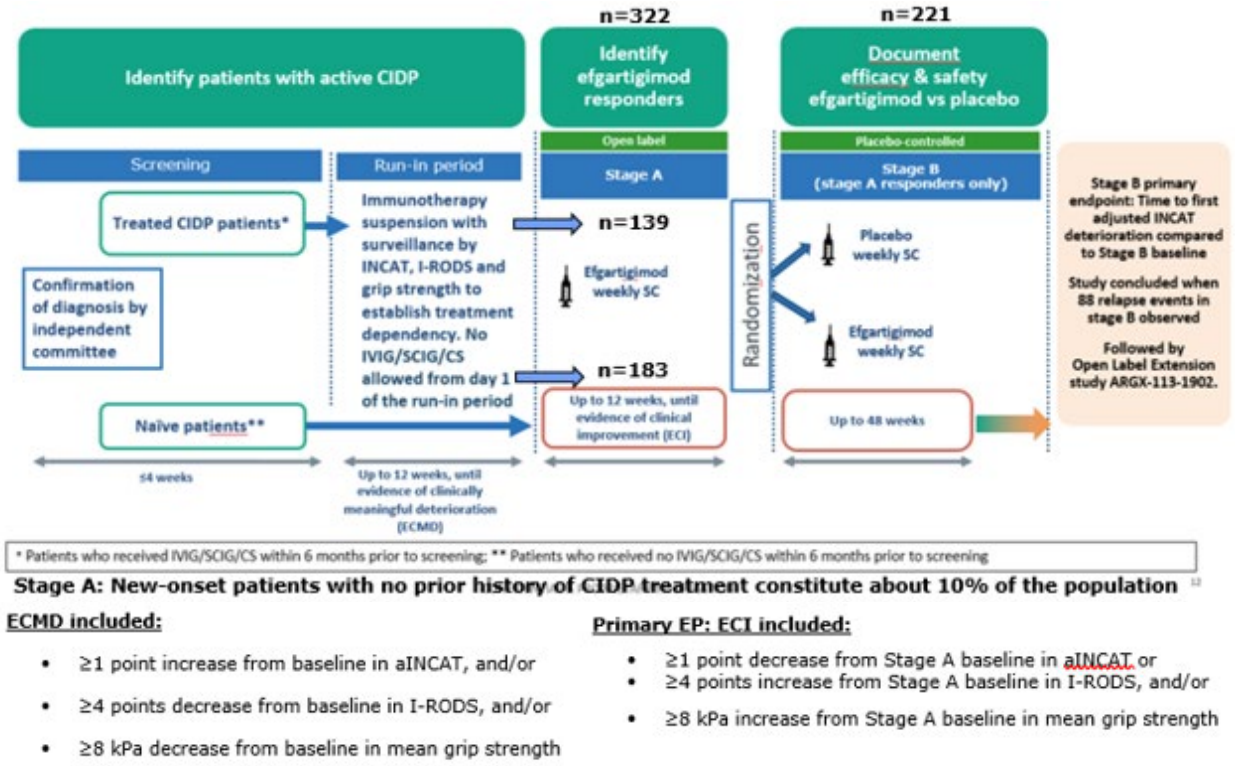
Source: Van den Bergh 2021
CI=confidence interval; EFNS=European Federation of Neurological Societies; CIDP=chronic inflammatory demyelinating polyneuropathy; IV=intravenous; PICO=population, intervention, comparison, and outcome; PNS=Peripheral Nerve Society; SC=subcutaneous(ly).

Significant benefit

Several claims are presented by the sponsor to support the significant benefit of Vyvgart over IVIg and SCIg products. As only IVIg products are considered to be satisfactory methods by the COMP, only relevant aspects of the sponsors' application are reflected and discussed in this report. Claims pertaining to the significant benefit of Vyvgart over IVIg products are a major contribution to patient care based on reduced patient burden and patient harm due to lack of availability of human plasma derived immunoglobulin products, which include IVIg products.

Before discussing the individual significant benefit claims, a brief presentation of the pivotal study with Vyvgart (ADHERE/ ARGX-113-1802) is made (see also below Figure 2) and the main results summarised: The pivotal phase 2 study ARGX-113-1802 was a randomized withdrawal study in 2 treatment stages: an open-label Stage A in which responders to Vyvgart were identified, and a randomized-withdrawal, double-blinded, placebo-controlled Stage B. The long-term efficacy of Vyvgart was evaluated in the ongoing, open-label study ARGX-113-1902, which is an extension of ARGX-113-1802. In both Stage A and Stage B the efficacy was evaluated in the overall population and in a pre-defined subgroup, the pretreated population. The pretreated population was defined as participants who received CIDP therapy within 6 months prior to screening and had a CDAS score of at least 4, indicating active disease, at screening. Patients who received active CIDP therapy at time of screening, were discontinued from their respective treatment during the run-in period and only enrolled into Stage A of the study, if they showed evidence of clinically meaningful deterioration (ECMD, see defined in Figure 2 below) within a period of up to 12 weeks. The primary endpoint in Stage A was the percentage of participants with confirmed evidence of clinical improvement (ECI), e.g. efgartigimod responders. The proportion of responders (ECI in Stage A) was 66.5% (95% CI: 61-71.6) in the overall population and 67.6% (95% CI: 59.2-75.3) in the pre-treated population. The median (min, max) time to confirmed ECI was 31 (23-43) days in the pre-treated population and 43 (31.0-51.0) days in the overall population. The primary endpoint in Stage B was time to first deterioration on the aINCAT score. Participants in Stage B, treated with efgartigimod, had a reduced risk of relapse compared to placebo. In the overall population, relapse occurred in 31 patients (27.9%) in the efgartigimod group versus n=59 (53.6%) in the placebo group with a HR of 0.394 (95% CI: 0.253-0.614). In the pretreated population relapse was also more frequent in the placebo group compared to the efgartigimod group (68.1% versus 27.1%, respectively). This corresponds to a HR of 0.269 (95% CI 0.138-0.523).

Figure 2. Schema of pivotal study with Vyvgart (ADHERE/ ARGX-113-1802)



The COMP took particular note of the patient subset who received prior therapy with standard of care treatment options prior to enrolling into the ADHERE study. Out of the 322 patients enrolled into Stage A, 165 (51.2%) received prior therapy with IVIg or SCIg therapy (see Table 3). Below Table 3 does however not specify previous IVIg therapy separately from SCIg and does also not specify response to prior treatment. The COMP is of the opinion that a significant benefit of Vyvgart vs IVIg therapy could in principle be established, if it could be shown that patients who have failed/did not respond to prior IVIg therapy derived a clinical benefit from treatment with Vyvgart. In case the CDAS classification is used by the sponsor, a limitation to patients with a CDAS score of 5C appears most appropriate. However, the sponsor needs to discuss if this classification into 5C at screening is sufficiently reliable to conclude that these patients are non-responders to previous (active) IVIg therapy. The sponsor should also discuss if these patients improved sufficiently under Vyvgart treatment as compared to their prior IVIg therapy. Furthermore, lacking a placebo group in stage A, the sponsor should discuss if patients in stage 5C could in principle also improve without treatment. Evidence of efficacy with Vyvgart in patients who failed prior IVIg therapy would be regarded as a clinically relevant advantage by the COMP. The sponsor may consider such an analysis, including a discussion on the above points.

Table 3. Baseline Disease Characteristics of patients in Stage A (SAF-A)

1	**Efgartigimod alfa SC (N=322)**
Entry status Stage A, n (%)	
Entered Stage A from screening	36 (11.2)
Non–treatment-naïve	0
Treatment-naïve	36 (11.2)
Evidence of worsening	35 (10.9)
No evidence of worsening	1 (0.3)
Entered Stage A from run-in with	286 (88.8)
No ECMD	4 (1.2)
ECMD	282 (87.6)
Time since CIDP diagnosis (years)	
N	322
Mean (SD)	4.9 (6.09)
Median (min, max)	2.8 (0, 46)
CIDP disease evolution, n (%)	
Relapsing	147 (45.7)
Progressive	174 (54.0)
Unknown	1 (0.3)
CIDP disease activity status (CDAS) n (%)	
2 to 4	125 (38.8)
5	197 (61.2)
Prior CIDP therapy (screening), n (%)	
Corticosteroids	63 (19.6)
IVIg or SCIg	165 (51.2)
Treatment-naïve	94 (29.2)
Total INCAT score at Stage A baseline	
N	317
Mean (SD)	4.6 (1.67)
Median (min, max)	4.0 (2, 9)

a The CIDP diagnosis was determined by the investigator and verified by the CCC.
INCAT=inflammatory neuropathy cause and treatment; CCC=CIDP confirmation committee; CIDP=chronic inflammatory demyelinating polyneuropathy; ECMD=evidence of clinically meaningful deterioration; ICF=informed consent form; IVIg=intravenous immunoglobulin; I-RODS=Inflammatory Rasch-built Overall Disability Scale; max=maximum; min=minimum; N=number of participants in SAF-A; n (for categorical data)=number of participants for whom the observation was reported; n (for continuous data)=number of participants with data; SAF-A=Stage A safety analysis set; SC=subcutaneous(ly); SCIg=subcutaneous immunoglobulin; SD=standard deviation. Notes: Time since CIDP diagnosis (years) was calculated as follows: (date of ICF − date of diagnosis)/365.25. Treatment-naïve participants were defined as participants with no history of prior CIDP therapy or having discontinued their CIDP therapy (corticosteroids, IVIg, or SCIg therapy) for ≥6 months before screening. The denominator for the percentage calculations was the total number of participants in SAF-A, excluding missing values.

As regards the significant benefit claims by the sponsor on a major contribution to patient care (MCPC), the COMP emphasized that it should first be demonstrated that the efficacy of Vyvgart is at least equivalent to the one of currently authorized IVIg products (reference is made to *EC Notice 2016/C 424/03*). In principle this should also be demonstrated for the safety of Vyvgart, however the COMP acknowledged that the safety data at time of marketing authorization is often very limited, as is also the case for Vyvgart in CIDP. Furthermore, the safety data available for Vyvgart in Myasthenia gravis cannot be considered due to the different dosing frequency recommended for CIDP. While the

aspect of equivalent efficacy has not been explicitly discussed by the sponsor in the context of their MCPC claim, the COMP acknowledged the sponsors efforts of comparing the efficacy of Vyvgart to IVIg products. In this regard, the sponsor conducted a matched-adjusted indirect comparison. Only two clinical trials (PRIMA, Léger 2013 and PATH, van Schaik 2018) that included an IVIg product (Privigen) authorised through the Centralised Procedure were identified that had designs and endpoints somewhat compatible with the ones of single-arm, open label phase of the single pivotal efficacy study with Vyvgart (i.e. Stage A of the ADHERE study), i.e., "broadly similar" Ig restabilisation period designs and endpoint criteria (i.e., change from baseline in aINCAT, I RODS or MGS, and time to initial aINCAT response). The weighting to match the ADHERE population to the PRIMA and PATH comparator study populations was unsuccessful. The effective sample size (ESS) was very small, ranging from 2.1 to 4.7 (3.6% to 8.4% of the available population) across the Stage A endpoint comparisons. Thus, it was not possible to draw conclusions from comparisons between ADHERE Stage A endpoints and corresponding PATH Ig restabilisation period and PRIMA endpoints. Therefore, a descriptive comparison of the clinical data presented in the SmPCs and discussed in the literature has been conducted. The SmPCs for Flebogamma DIF, Kiovig, Panzyga, Intratect, Iqyumme, and Nanogam do not include any clinical data relating to the CIDP indication, as CIDP was added only after multiple revisions to the list of indications in the core SmPC that can be claimed for IVIg products. Therefore, the descriptive review of the SmPC data is limited to the following IVIg products, where their respective SmPCs include clinical data in CIDP: Privigen, Gamunex, Octagam, and Ig Vena (Table 4).

The sponsor concludes that whilst not all these SmPCs report the same efficacy parameters based on the same endpoints and/or necessarily from fully comparable study designs, the data presented in Table 3 support that the high response rate, fast onset of action, and effects of efgartigimod alfa SC on other established endpoints (i.e., MGS and MRC sum scores) in CIDP are broadly comparable with the treatment effects of IVIg medicinal products.

Table 4. SmPC Clinical Data in CIDP: Efgartigimod and Currently Centrally Approved IVIgs

CIDP efficacy parameter/endpoint [Source]	**Efgartigimod**	**Privigen [Centralised SmPC (Oct 2022)] [Léger 2013]**	**Gamunex [IE SmPC (Sep 2022)] [Hughes 2008]**	**Octagam [DE SmPC (May 2023)]**	**Ig Vena [DE SmPC (Jul 2021)]**
Response rate	66.5% [Stage A at 12 weeks]	60.7% [at Week 25]	54% vs 21% PBO [over 24 weeks]	41.7% of treatment I patients based on ONLS	Not defined in SmPC
Onset	Median time to ECI was 43.0 days; 40% ECI at Week 4	~7 weeks	Most within 6 weeks	Not reported	Not reported

Risk of clinical deterioration	Risk reduced by 61% compared to PBO (based on INCAT score)	Not reported	Not reported	Not reported	Not reported
Relapse rate (aINCAT)	Risk reduction of 25.7 compared with placebo	Not assessed	13% relapse rate on active, 45% on pbo	Not reported	45.8 %
MGS – Dom (or RH) (kPa)	+2.1 active vs. -8.2 PBO OR From BL: +12.3	From BL: +14	13.2 IVIg vs 1.5 PBO	Not reported	Change from BL: +19.4
MGS non-Dom (or LH) (kPa)	+2.0 EFG vs. -6.9 PBO OR From BL:+11.2	Not reported	13.3 IVIg vs. 4.3 PBO	Not reported	Change from BL: +16.9
MRC (score)	Stage A- Change from BL: + 3.8; Stage B- Change from BL: -0.3 EFG vs -3.0 PBO	Change from BL: +6.5	Change from BL: 3.3 IVIg vs 0.2 PBO	Not reported	Change from BL: +4.7
Maintenance of response (RWD period)	Hazard ratio of 53.7% compared to placebo	Not assessed	22 weeks to relapse for IVIg vs. 16 weeks for PBO	Not reported	Not reported

aINCAT=adjusted Inflammatory Neuropathy Cause and Treatment; BL= baseline; CIDP=chronic inflammatory demyelinating polyneuropathy; ECI=evidence of clinical improvement; EFG =efgartigimod; Ig=immunoglobulin; INCAT=Inflammatory Neuropathy Cause and Treatment; IVIg=intravenous immunoglobulin; LH=left hand; MRC=medical research council; ONLS=Overall Neuropathy Limitations Scale; PBO=placebo; RH=right hand; RWD=randomised withdrawal; SmPC=Summary of Product Characteristics.

Furthermore, the sponsor concludes that the response rates for efgartigimod alfa SC are comparable with those observed in the results of a range of recently reported clinical trials of IVIg products (van Schaik 2018; Cornblath 2022), see Table 5. A majority of participants in all of the prior CIDP therapy subgroups responded to efgartigimod alfa SC, with 49 (77.8%), 97 (58.8%), and 68 (72.3%) having confirmed evidence of clinical improvement (ECI) in the corticosteroid (CS), IVIg or SCIg, and treatment-naïve groups, respectively (Table 4). The sponsor notes that for centrally authorised products, based on studies with broadly comparable definitions of response (improvement in aINCAT ≥ 1 point), response rates were comparable, but time to response favours efgartigimod alfa SC (Table 4), given that responses to Privigen [Léger 2013] and Gamunex [Hughes 2008] were assessed over longer time periods (24/25 weeks vs 12 weeks for efgartigimod alfa SC). However, the COMP noted that this was not the case for Panzyga (PROCID study), where response was measured at Week 6 versus baseline and maintained at Week 24.

Table 5. Responder Rates in Studies of IVIg

Product	Study	Population	Responder rate
Efgartigimod alfa SC	ADHERE (N=322)	SAF-A	66.5%a
		Prior CS	77.8%
		Prior Ig	58.8%
		Naïve	72.3%
Gamunex	ICE (Hughes 2008)	ITT	54%b
Privigen	PATH (van Schaik 2018; Merkies 2019)	Overall	72.9%c
Privigen	PRIMA (Léger 2013; Merkies 2019)	Overall	60.7%
		Pretreated	76.9%
		Naïve	46.7%
Panzyga	PROCID (Cornblath 2022)	1 g/kg group	79.7%d

Responder definitions:
a Responder aINCAT score decrease of ≥1 point vs Stage A baseline; or improvement on I-RODS (increase ≥4 points vs Stage A baseline) and/or MGS (increase ≥8 kPa vs Stage A baseline) after up to 12-weeks efgartigimod alfa SC treatment.
b Improvement in INCAT disability score of ≥1 point over 24 weeks treatment.
c Improvement in INCAT disability score of ≥ 1 point at any visit during the 13-week observation period (response definition and rate as reported in Merkies 2019).
d Improvement ≥1 point in aINCAT score at Week 6 versus baseline and maintained at Week 24. Response rate in 1 g/kg group.
CS=corticosteroids; Ig=immunoglobulin; TT=intent-to-treat; IVIg=intravenous immunoglobulin; SAF-A=Stage A safety (analysis set); SC=subcutaneous(ly).

The COMP agreed with the sponsor in that there is a general problem with comparability of the studies, endpoints and patient populations between the ADHERE study (Stage A and B) with the one of currently authorized IVIg products for CIDP. For example, for the IVIg product Privigen, the attempted matching led to an extremely small ESS <5, and therefore it was correctly concluded by the sponsor that the comparison was not suitable for comparing Vyvgart with Privigen. The presented "descriptive comparison with authorised IVIg product based on SmPCs and literature" (Table 3 and Table 4), are basically a naïve side-by-side comparison that are methodologically not suitable in this situation where the small ESS indicates basically no overlap between the study populations.

The sponsor may consider preparing at least a qualitative assessment of the differences in relevant studies with IVIg products and the ADHERE study and discuss whether the study populations are as such that Vyvgart would not have been favored in the ADHERE study, due to the distribution of known prognostic variables and effect modifiers. A comparison of IVIg treatments and Vyvgart may also be conducted with the Bucher method, incorporating the uncertainty of the effect estimates. The sponsor should then also discuss an acceptable equivalence margin (the amount of difference in the confirmed ECI responders that would be considered negligible) that the resulting confidence interval should be compared with. Whether the results of such a qualitative analysis would be accepted, would be subject to the forthcoming COMP discussion and the degree of remaining uncertainty.

As mentioned above, one of the sponsors MCPC claim is a reduction of treatment burden due to different routes of administration. Privigen is administered as intravenous infusion. The recommended starting dose for Privigen is 2 g/kg body weight divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks. This is the same for Gamunex. In comparison, Vyvgart is administered subcutaneously at a dose of 1g as once-weekly injection (possibly adjusted to every other week based on clinical evaluation). Vyvgart may be administered at home by a patient or caregiver after adequate training in the subcutaneous injection technique (after the first 4 injections which must be administered either by or under the supervision of

a healthcare professional). The sponsor supports their MCPC claim of a reduction of treatment burden with data from a patient reported outcome tool, i.e. the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) which was an exploratory endpoint in the pivotal study with Vyvgart (ADHERE/ ARGX-113-1802). The TSQM-9 assess treatment satisfaction on three domains: convenience, effectiveness, and overall satisfaction. The methodology is not described by the sponsor, but patients were asked at the beginning of the run-in period (RI V1) to fill in the TSQM-9 to judge their prior CIDP treatment, i.e. (IVIg/SCIg or corticosteroids, CS) as they remembered it– *at this timepoint patients were already off IVIg/SCIg or CS* – and this was then compared to TSQM-9 values from assessments conducted throughout the pivotal study with Vyvgart (single-arm phase Stage A; RCT phase Stage B; Follow-up Extension study). The sponsor grouped the analysis of the TSQM-9 score for patients who received previous therapy with IVIg or SCIg therapy. However, the COMP noted that a re-analysis of the TSQM-9 score for patients who received previous therapy only with IVIg therapy should be conducted, as SCIg therapies are not considered to be satisfactory methods. Furthermore, the analysis for patients who received previous therapy with corticosteroid therapy has no relevance for this procedure, as these products are also not considered to be satisfactory methods. The sponsor conducted separate analyses for Vyvgart responders and non-responders, the scores in the complete group of previously treated patients is not reported. However, as regards the baseline TSQM-9 scores, it does not seem as if the sponsor considered response vs non-response to previous therapy (i.e. IVIg etc), in their analysis. The COMP questioned the validity of such a methodology in terms of allowing a clear interpretation of the data. In the IVIg/SCIg prior therapy subgroup, the convenience score improved from run-in baseline to Stage A last assessment in study ARGX-113-1802 for both Stage A Vyvgart responders and non-responders while the Vyvgart effectiveness score only improved in the Vyvgart responder group but declined in the Vyvgart non-responder group. The complete scores (irrespective of Vyvgart response) were not provided by the sponsor for the two TSQM-9 domains of convenience and effectiveness. The scores for the third TSQM-9 domain of overall satisfaction have not been reported by the sponsor at all, neither in the Vyvgart responders nor non-responders. These methodological limitations do not allow an interpretation of the TSQM-9 data and an improvement of Vyvgart vis a vis IVIg therapy cannot be concluded.

As regards the sponsors second MCPC claim of patient harm due to lack of availability of human plasma derived immunoglobulin (Ig) products, which include IVIg products, the following information was discussed:

IVIg products belong to guideline recommended and authorized first-line treatments for CIDP in the EU (Van den Bergh 2021). The sponsor presented a comprehensive analysis of the shortage situation of human plasma derived Ig products throughout Europe. This shortage is well recognized in the EU and also reflected in a recent notification in the EMA-maintained Shortages Catalogue; there are currently shortages of normal human Igs (solutions for injection or infusion) in Austria, Belgium, Croatia, France, Hungary, Italy, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden (EMA/120056/2024). In support of documented patient harm due to the shortage, the sponsor presents as main evidence an analysis conducted at one French referral center (N'kaoua et al., 2022). This was a retrospective, single-centre study, conducted from October 2017 to October 2018. The authors assessed patient data one year before the shortage, in 2016, and one year after the shortage, in 2019. The analysis included 142 patients in total who were treated with IVIg therapy for several dysimmune neuromuscular diseases, including chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis and Sumner syndrome (LSS), multifocal motor neuropathy (MMN), or myasthenia gravis. Out of the 142 patients, 47 had CIDP (33%). While this publication provides the distribution of IVIg treatment changes by condition, this was unfortunately not the case for the data which captured deteriorating clinical scores, i.e. these were grouped together for all conditions (Table 6). There was no

significant difference in median dose before (i.e. 2016) versus after (i.e. 2019) the shortage for CIDP however, the median delay between IVIg courses increased from 7 (range 4.5–13) to 7.5 (range 5–13) weeks (P = 0.018).

Table 6. Distribution of patients with deteriorating clinical score (Table 5 N'kaoua et al., 2022)

Table 5 – Distribution of patients with deteriorating clinical score.

	Group 0 Low score deterioration	Group 1 Moderate deterioration	Group 2 Clinically significant deterioration	Total
Patients with two types of IVIg treatment changes at least*	7 (26%)	8 (38%)	3 (30%)	18
Patients with one type of IVIg treatment change*	20 (74%)	13 (62%)	7 (70%)	40
Total	27	21	10	58

Criteria: Group 0: Same ONLS score, RODS score decrease < 4 points, myasthenia muscle score decrease < 5 points; Group 1: ONLS score increase ≥ 1 point; RODS score decrease ≥ 4 and < 6 points; myasthenia muscle score decrease ≥ 5 and < 10 points; Group 2: ONLS score increase ≥ 2 points, RODS score decrease ≥ 6 points and myasthenia muscle score decrease ≥ 10 points.

* We consider here 3 types of IVIg treatment changes: IVIg treatment delay, discontinuation of IVIg treatment and IVIg dose decrease.

In addition, the sponsor briefly mentions information from an online medical journal in Romania 360 medical, describing that a survey from 2022 indicates that between 60-70% of patients including those prescribed for neurological conditions (including CIDP) had a treatment interruption of at least 3 months and that more than 75% of prescribers had implemented a 30% dose reduction as means of preserving finite supplies of Igs. Data specific for CIDP seems not to be available.

The sponsor further emphasizes that several national medicines authorities in the EU have issued recommendations prioritising IVIg for use in particular conditions, to prevent patients clearly benefiting from this treatment from being at serious risk of a lack of product. At the French National Agency for Medicines and Health Products Safety (ANSM) the Ig indication hierarchisation in 2019 effectively restricted the use of Igs in CIDP to emergency use or in the event of failure of therapeutic alternatives (ANSM 2019). This was reinforced in 2020 (ANSM 2020). In 2022, the Italian Medicines Agency (AIFA) and the Italian National Blood Centre (CNS) co-ordinated the publication of a multi-stakeholder guideline on the use of human immunoglobulins in case of shortages (AIFA-CNS 2022). These guidelines urge a 20-50% reduction in usage of Igs when supply/inventory levels are low for a short or prolonged period and greater than 50% reduction during critical and prolonged Ig shortages. In these situations, corticosteroids (CSs) and/or plasma exchange (PLEX) are to be considered whenever possible with initial and maintenance treatment with Igs only in cases of failure, contraindication or intolerance to immunosuppressive therapy. Igs are recommended only when there are no viable alternatives; and/or the condition is life-threatening or there is a risk for irreversible disability. The COMP concluded that the currently presented data makes it difficult to establish the claim of patient harm as no specific data for CIDP is presented. Furthermore, above mentioned IVIg prioritization plans appear to aim at avoiding patient harm based on a clinical evaluation and availability of treatment alternatives.

The COMP also took note of the sponsors claim of improved safety of Vyvgart vis a vis currently authorized treatment options (and IVIg in particular). However, despite the low prevalence of the disease, the safety database for Vyvgart in CIDP is considered small and the safety data available for Vyvgart for Myasthenia gravis cannot be considered due to the higher dose recommended for CIDP. Also, the sponsor points out that IVIg therapy is contra-indicated in patients with IgA deficiency. However, the relevance of IgA deficiency in CIDP has not been discussed by the sponsor and neither has the sponsor submitted data with Vyvgart in this patient subset which would demonstrate that Vyvgart could be a viable treatment option in these patients.

The COMP adopted a list of question on significant benefit.

4. COMP list of issues

Significant benefit

The Sponsor is requested to explain/justify whether Vyvgart, based on the final indication, can be used in a broader patient population, compared to currently authorized IVIg products. This should be substantiated with available data.

In order to be regarded as making a major contribution to patient care (MCPC), it should be demonstrated that Vyvgart has at least equivalent efficacy as compared to IVIg products, authorized for the treatment of CIDP (reference is made to *EC Notice 2016/C 424/03)*.

As regards the data on the "Treatment Satisfaction Questionnaire for Medication (TSQM-9)", the sponsor is asked to:

- Describe the used methodology, in particular how baseline values were generated.
- Provide a re-analysis only with data in patients previously treated with IVIg therapy and failed vs patients treated with IVIg who discontinued treatment due to other reasons).
- To provide the scores for all 3 domains of the TSQM-9 and for the total Stage A population (not divided into effects in responders and non-responders).

The sponsor is asked to further substantiate the evidence of patient harm in the EU due to the lack of availability of human immunoglobulin products, considering availability of alternative treatment options.

Comments on sponsor's response to the COMP list of issues

Efficacy of Vyvgart in a broader patient population, compared to currently authorized IVIg products

The sponsor provided further evidence of efficacy with Vyvgart in a subset of patients from the pivotal trial, ADHERE, i.e. those whose disease was progressive or could not be well controlled with their prior IVIg therapy. In the pivotal trial, ADHERE, patients on previous treatment were included and had to undergo a wash-out period of the effect of the previous treatment. A subset of 46 patients were categorized as CDAS 5C, which is defined as "Unstable active disease: abnormal examination with progressive or relapsing course; On treatment." The sponsor clarified that 44 out of these 46 patients received previous IVIg treatment for at least 3 months. The sponsor shows that the confirmed response rate on evidence of clinical improvement (confirmed ECI) in Stage A of the study in the CDAS 5C IVIg group was 56.5% (41.1-71.1), which is in line with the overall response rate of the prior IVIg/SCIg group (58.8% [50.9-66.4]) and largely similar to the treatment effect in the overall study population in the ADHERE study (single arm Stage A period) of 66.5% (61.0-71.6) (Table 7).

In addition, the placebo arm from Stage B showed that more CDAS 5C patients relapsed in the absence of Vyvgart as compared to those CDAS 5C patients who continued Vyvgart treatment during Stage B of the ADHERE study (stage B time to deterioration analysis – Vyvgart vs placebo). These results are in line with the overall Stage B data of the prior IVIg/SCIg group.

Table 7. The Stage A ECI response rate in the CDAS 5C IVIg group was 56.5% (41.1-71.1), which is in line with the overall response rate of the prior IVIg/SCIg group (58.8% [50.9-66.4])

	Efgartigimod PH20 SC Overall Population (N=322)		Efgartigimod PH20 SC Participants with IVIg or SCIg as prior CIDP medication (N=165)		Efgartigimod PH20 SC Participants with IVIg as prior CIDP medication and a CDAS score of 5C at screening (N=46)	
	n (%)	Exact 2-sided Clopper-Pearson 95% CI	n (%)	Exact 2-sided Clopper-Pearson 95% CI	n (%)	Exact 2-sided Clopper-Pearson 95% CI
Number of participants with confirmed ECI	**214 (66.5)**	**61.0-71.6**	**97 (58.8)**	**50.9-66.4**	**26 (56.5)**	**41.1-71.1**
Number of participants without confirmed ECI	108 (33.5)		68 (41.2)		20 (43.5)	
Completed Stage A treatment without confirmed ECI	21 (6.5)		8 (4.8)		2 (4.3)	
Discontinued treatment in Stage A	87 (27.0)		60 (36.4)		18 (39.1)	
Ongoing in Stage A at 88th event in Stage B	18 (5.6)		7 (4.2)		0	
Discontinued early for other reasons	69 (21.4)		53 (32.1)		18 (39.1)	

The single-arm trial design (Stage A) followed by a randomized withdrawal (Stage B) and contextualised with historical evidence was considered sufficient for demonstrating the efficacy of Vyvgart by the CHMP. The COMP considered that Vyvgart is also efficacious in CDAS 5C patients, where the confirmed ECI rate was similar to the overall study population (ADHERE study). Therefore, Vyvgart is effective in patients whose disease was progressive or could not be well controlled on prior IVIg therapy and thereby addresses a wider population. The COMP considered these data sufficient to establish the significant benefit of Vyvgart vis a vis IVIg products.

Equivalent efficacy of Vyvgart as compared to IVIg products

The sponsor has mostly repeated the arguments and evidence, such as the ECI response rates in historical CIPD studies vs the ones from the ADHERE study with Vyvgart. The COMP pointed out that the provided evidence, basically side-by-side comparisons of response rates from different single-arm studies that differed regarding the included populations and endpoint definitions, is not sufficient to robustly demonstrate that the efficacy of Vyvgart is at least equivalent to the IVIg products. Methodologically more acceptable approaches that account for differences in population characteristics failed due to severe differences between the trial populations. Ultimately, the differences between the to-be compared studies and the failure of suitable methodology to statistically adjust for these differences, prevented any conclusion on how Vyvgart compares to the other IVIg products.

With a methodologically robust analysis not being feasible, based on the data provided by the sponsor, a conclusion of non-inferiority or equivalence of Vyvgart vis a vis IVIg products could not be established.

Additional analyses/clarifications of the "Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The sponsor has provided data on the TSQM-9 stratified by CDAS score (of the population subset which had previously received IVIg therapy) at run-in baseline and at the end of Stage A (Table 8 and 9).

Table 8. TSQM-9: Descriptive Statistics of Actual Values at Run-In Baseline of ARGX-113-1802 by CDAS Score Category in Participants With IVIg as Prior CIDP Medication (SAF-A)

	CDAS 5C	Other CDAS
	Efgartigimod PH20 SC (N=46)	Efgartigimod PH20 SC (N=97)
TSQM-9 Convenience		
	N=42	N=92
Mean (SD)	49.0 (24.91)	49.0 (19.96)
Median (min, max)	50.0 (0, 100)	50.0 (0, 100)
TSQM-9 Effectiveness		
	N=42	N=92
Mean (SD)	55.5 (20.93)	57.3 (20.96)
Median (min, max)	50.0 (0, 100)	56.0 (0, 100)
TSQM-9 Global Satisfaction		
	N=42	N=92
Mean (SD)	59.5 (21.04)	60.4 (20.36)
Median (min, max)	53.5 (0, 100)	57.0 (0, 100)

Table 9. TSQM-9: Descriptive Statistics of Actual Values at Stage A Last Assessment of ARGX-113-1802 by CDAS Score Category in Participants With IVIg as Prior CIDP Medication (SAF-A)

	CDAS 5C	Other CDAS
	Efgartigimod PH20 SC (N=46)	Efgartigimod PH20 SC (N=97)
TSQM-9 Convenience		
	N=38	N=84
Mean (SD)	62.6 (21.33)	63.8 (19.10)
Median (min, max)	61.0 (0, 100)	67.0 (0, 100)
TSQM-9 Effectiveness		
	N=38	N=84
Mean (SD)	52.0 (32.79)	54.6 (27.59)
Median (min, max)	58.5 (0, 100)	56.0 (0, 100)
TSQM-9 Global Satisfaction		
	N=38	N=84
Mean (SD)	53.8 (33.42)	56.7 (29.09)
Median (min, max)	60.5 (0, 100)	64.0 (0, 100)

The COMP did not consider this data to be sufficient to support the sponsors claim for a decrease in patient burden. Comparing results from table 8, run-in baseline, to results in table 9, TSQM after stage A of ADHERE, the median ratings consistently increase from run-in baseline to Stage A last assessment in CDAS 5C. The mean scores for effectiveness and global satisfaction decrease however under treatment with Vyvgart.

Evidence of patient harm in the EU due to the lack of availability of human immunoglobulin products

The sponsor provided additional information to support the evidence of patient harm due to the lack of availability of IVIg products. Shortages of Ig products may necessitate patients to switch between different Ig products. The sponsor references several reports from the UK, Canada and Belgium which point out that switching between IVIg and SCIg products can be challenging for patients mainly due to differences in tolerability (Bethune and Herriot, 2019; Immunodeficiency UK website, 2025; Institut National de Santé Publique du Québec, 2024; de Meester et al, 2020).

No specific quantitative data specifically in CIDP patients has been provided by the sponsor in their responses. There was little further discussion on this aspect during the oral hearing.

Patient representatives at oral hearing

The oral hearing was attended by two CIDP patient representatives, one invited from sponsor side, and one invited by the EMA. Both patient representatives emphasized the importance of having additional effective medicines for CIDP which are not human plasma derived. This would avoid risks associated with Ig shortages including administration of lower doses or having to switch to a different Ig product which may be less well tolerated. Of note, efgartigimod alfa (the active substance of Vyvgart) is a human recombinant immunoglobulin G1 (IgG1) derived Fc fragment produced by recombinant DNA technology and its production is therefore independent of human plasma. Furthermore, having a medicinal product which could be self-administered at home instead of the hospital and take much less time to be administered was considered an advantage over IVIg therapy.

COMP overall conclusion

The COMP adopted a positive opinion for this procedure. Vyvgart has demonstrated efficacy in a subset of patients whose disease was progressive or not well controlled despite previous treatment with

intravenously administered immunoglobulins. The Committee considered that this constitutes a clinically relevant advantage.

5. COMP position adopted on 15 May 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of chronic inflammatory demyelinating polyneuropathy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life threatening and chronically debilitating due to motor dysfunction in both upper and lower limbs as well as impairment in sensory functions;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Vyvgart is of significant benefit to those affected by the orphan condition is established. Vyvgart has demonstrated efficacy in a subset of patients whose disease was progressive or not well controlled despite previous treatment with intravenously administered immunoglobulins. The Committee considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Vyvgart, Efgartigimod alfa for treatment of chronic inflammatory demyelinating polyneuropathy (EU/3/21/2555) is not removed from the Community Register of Orphan Medicinal Products.