Matching-Adjusted Indirect Comparison of Subcutaneous Immunoglobulin IgPro20 and Efgartigimod in Patients with Chronic Inflammatory Demyelinating Polyneuropathy

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Background

- IgPro20 (a subcutaneous immunoglobulin) and subcutaneous efgartigimod (a neonatal Fc receptor antagonist) are approved treatment options for adults with chronic inflammatory demyelinating polyneuropathy (CIDP)[1,2,9,10]
- The efficacy and safety of IgPro20 and efgartigimod were evaluated in the PATH[3] and ADHERE[4] pivotal trials, respectively
- No randomized head-to-head comparison of IgPro20 and efgartigimod has been conducted
- An anchored matching-adjusted indirect comparison (MAIC) was conducted to estimate relative effects of IgPro20 versus efgartigimod while adjusting for selected cross-trial population differences

Objective

To compare the relative efficacy **of subcutaneous IgPro20 (0.4 g/kg) versus efgartigimod (1,000 mg)** for maintenance treatment in adults with CIDP using **matching-adjusted indirect comparison** (MAIC) methods

Methods

Anchored MAICs for IgPro20 versus efgartigimod were conducted using methods outlined in the NICE DSU TSD 18.[5] Outcomes were assessed during the randomized phase of both trials

Data sources:

- Individual patient data (IPD) were obtained from the PATH trial (IgPro20 0.4 g/kg and placebo)[3,6]
- Summary-level data were obtained from the ADHERE trial (efgartigimod 1,000 mg and placebo), from primary trial publications, regulatory documents, and congress presentations[4;7-8]

Feasibility assessment:

- A qualitative feasibility assessment was conducted to identify sources of cross-trial heterogeneity and ensure validity in the MAICs
- The study designs, eligibility criteria, baseline characteristics, and outcome measures were broadly comparable
- Key sources of heterogeneity between studies were identified (**Table 1**)

Outcomes feasible for comparison:

- Occurrence of CIDP relapse during the randomized treatment period. CIDP relapse was defined as a ≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score from baseline

Table 1. Sources of heterogeneity

Source	PATH	ADHERE
CIDP treatment prior to study entry	• IVIg within 8 weeks before enrollment	• Treatment within 6 months before screening
Treatment history	• Enrolled only IVIg-treated	• Enrolled a mix of Ig-treated, corticosteroid-treated, and off-treatment patients
Follow-up duration	• 24 weeks	• 48 weeks
Run-in period	• IVIg withdrawn to confirm Ig dependency, then IVIg-restabilization	• Ig or corticosteroids withdrawn to confirm active disease for treatment-experienced patients
Randomized populations	• Ig-dependent patients restabilized on IVIg	• Randomized responders to open-label efgartigimod
aINCAT at screening	• No requirement	• ≥2

aINCAT = adjusted inflammatory neuropathy cause and treatment; CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; IVIg = intravenous immunoglobulin

Eligibility criteria alignment:

- Differences in aINCAT eligibility criteria between the trials were assessed (**Table 1**), but no additional aINCAT-based restriction was applied to PATH patients to avoid substantial sample size reduction and potential selection bias
- Instead, baseline aINCAT was included as an adjustment factor in the MAIC, because it was considered an important treatment effect modifier

Factor adjustment:

- To improve comparability between the two trial populations, IPD from PATH were reweighted to match important treatment effect modifiers reported in ADHERE (**Table 2**)
- The following factors were selected for adjustment by clinical experts based on clinical relevance and expected association with CIDP relapse status:

CIDP Duration · **aINCAT Score** · **Age** · **Grip Strength**

- Grip strength was measured in the dominant hand
- All adjustments were based on covariate measurements taken at randomization, except for CIDP duration which was taken at screening
- An unadjusted analysis was also conducted

Statistical analyses:

- Results of comparative efficacy were estimated as hazard ratios (HRs) with 95% confidence intervals (CIs) using a binomial model with a complementary log-log link function and a follow-up time offset to account for differences in follow-up between studies (24-weeks in PATH and 48-weeks in ADHERE)

Results

Unadjusted result:

- In the unadjusted analysis without MAIC reweighting of PATH IPD to match ADHERE baseline characteristics, the point estimate numerically favored IgPro20 over efgartigimod in reducing the occurrence of CIDP relapse (**Table 3**); this result was not statistically significant

Adjusted result:

- After adjusting for CIDP duration, aINCAT score, age, and grip strength (dominant hand), baseline characteristics of PATH aligned with those in ADHERE (**Table 2**)
- Point estimate for CIDP relapse numerically favoured IgPro20 versus efgartigimod (**Table 3**); however, this result was not statistically significant

Table 2. Baseline characteristics before and after weighting

	ADHERE target population (N=221)	PATH before weighting (N=115)	PATH after weighting (ESS=69)
CIDP duration	3.8 (4.53)	4.90 (5.36)	3.8 (4.56)
aINCAT	3.2 (1.54)	2.38 (1.72)	3.2 (1.55)
Age (>= 55)	50%	55.7%	50%
Grip strength	56.4 (26.56)	70.17 (31.44)	56.4 (26.72)

aINCAT = adjusted inflammatory neuropathy cause and treatment; CIDP = chronic inflammatory demyelinating polyneuropathy; ESS = effective sample size; N = number of patients

Table 3. Summary of MAIC results

Analysis	N/ESS	HR[c] (95% CI[d]) IgPro20 vs. efgartigimod
Unadjusted		
PATH vs. ADHERE	N=115	0.56 (0.25-1.24)
Adjusted[a]		
PATH vs. ADHERE	ESS=69[b]	0.79 (0.29-2.18)

CI = confidence interval; CIDP = chronic inflammatory demyelinating polyneuropathy; ESS = effective sample size; HR = hazard ratio; N = number of patients
[a]Adjusted for CIDP duration, aINCAT, age, and grip strength (dominant hand)
[b]The ESS decreased from 115 to 69 following weighting, reflecting variability in patient weights, including some extreme weights (**Table 4**)
[c]An HR < 1 favours IgPro20
[d]Standard errors for the trial-specific log HRs were estimated using a robust (sandwich) estimator. The standard error for the ITC was the square root of the sum of the trial-specific log-HR variances. 95% Wald CIs were calculated on the log-HR scale and exponentiated to the HR scale

Table 4. Adjusted MAIC weight[a] diagnostics

Median (IQR)	Range	N (%) Weights ≥ 4
0.78 (0.39, 1.35)	0.04-4.51	1 (0.9%)

IQR = interquartile range; N = number of patients
[a] Results represent the scaled weights

Strengths and limitations

- Cross-trial differences in study design, eligibility criteria, baseline characteristics, and outcome definitions were systematically assessed and addressed where feasible to improve comparability and inform selection of the most appropriate indirect treatment comparison (ITC) approach
- The analysis leveraged IPD from PATH, enabling population-adjusted ITCs based on key treatment effect modifiers identified through the feasibility assessment and validated by clinical experts
- Differences in follow-up time between studies were accounted for in the statistical analysis, allowing for a more unbiased comparison
- Residual cross-trial design differences that could not be addressed by population-adjusted ITCs remained, which may have affected comparability despite adjustment efforts
- The proportional hazards assumption underlying the binomial complementary log-log model may not hold throughout the follow-up periods, potentially introducing uncertainty into the indirect comparison estimates

Conclusions

- After adjustment, the point estimate numerically favoured IgPro20, indicating a lower estimated hazard of CIDP relapse with IgPro20 versus efgartigimod in the ADHERE trial population
- None of the comparisons were statistically significant, though this does not establish equivalence or similar effectiveness between treatments
- Findings should be interpreted in the context of residual cross-trial differences

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