INTRODUCTION

Intravenous immunoglobulins (IVIg) are the gold-standard first-line treatment in multifocal motor neuropathy (MMN) as recommended by both European Federation of Neurological Societies/Peripheral Nerve Society Guidelines for MMN management (1) and EFNS guidelines for the use of IVIg to treat neurological diseases (2). IQYMUNE® is a highly purified 10% liquid preparation of normal human immunoglobulin for intravenous administration that has been approved in this indication since 2013 in Europe. This study aimed to determine whether IQYMUNE® is non-inferior to KIOVIG® (3) (both references), primarily based on efficacy criteria. Investigation of the safety of IQYMUNE® was a secondary objective.

MATERIALS AND METHODS

PHASE III, MULTICENTRE, RANDOMISED, DOUBBLE-BLIND, ACTIVATION-COMPANY-CONTROLLED, CROSS-OVER STAGE 3 STUDY VERSUS KIOVIG® - THE LIME STUDY

Patients and treatment

• 33 patients randomised to sequence A (KIOVIG® then IQYMUNE®, N=12) or B (IQYMUNE® then KIOVIG®, N=21)

• Analysis were performed on the ITT population (N = 22) and on the PPS (N = 21)

Baseline characteristics of patients were similar in the two groups:

- Most of the participants were male (86.4% of CSR)
- Median age was 48.8 years
- All participants were already on stable dose of IVIg therapy for MMN for at least 3 months before inclusion in the study
- Median time from initial diagnosis to study entry was 4.3 years

Efficacy

Primary efficacy criterion: mean MMRC sum score

Primary efficacy criterion was for the Medical Research Council (MRC) sum score on 10 predefined muscle groups, as described by Cats, during the evaluation period. The comparison test was based on a linear mixed model estimating the effect of product, period, and sequence. No sequence or period effect was detected. No inter-individual effect was observed between IQYMUNE® and KIOVIG® was -0.01; 95.0% CI [-0.51, 0.48] in the mITT population (Figure 1) and -0.02 [-0.53, 0.49] in the PPS population (Table 1). The between-treatment difference was not significant in all secondary efficacy criteria.

Secondary efficacy criteria

No statistically significant difference between IQYMUNE® and KIOVIG® was detected in all secondary efficacy criteria:

- MRC sum score
- Rasch-Built MMRC sum score
- MRC new sum score
- Total INCAT disability scale score or normalized grip strength measures maintained during the evaluation period.
- Improvement in clinical global impression (CGI) measured at the end of each period was also similar for the two products, with no specific change observed in more than half of the patients.

At the time study protocol was designed, there was no validated functional disability scale for MMN. The Rasch-built overall disability scale for MMN (MMN-RODS®) does overcome the shortcomings of ordinal scales was proposed in 2010 by Cats et al. (3) and has been validated in several studies (4,5).

Table 1: Primary efficacy outcomes – estimated means of MMRC 10-sum scores, 13 to 26 weeks after the start of administration for each product, linear mixed model – mITT and PPS

<table>
<thead>
<tr>
<th>Population</th>
<th>Covariate</th>
<th>Least square mean (MRC-10)</th>
<th>Differences: (MRC-10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT N=22</td>
<td>Product</td>
<td>IQYMUNE® 93.1 [92.6, 93.7]</td>
<td>0.0 [-0.6, 0.4]</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>KIOVIG®</td>
<td>93.1 [92.6, 93.7]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period*</td>
<td>1</td>
<td>93.1 [92.6, 93.7]</td>
<td>0.24 [-0.73, 0.23]</td>
<td>0.29</td>
</tr>
<tr>
<td>2</td>
<td>94.7 [93.7, 95.7]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence*</td>
<td>A</td>
<td>94.3 [93.4, 95.3]</td>
<td>0.39 [-0.86, 1.55]</td>
<td>0.30</td>
</tr>
<tr>
<td>B</td>
<td>94.1 [93.5, 94.7]</td>
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</tbody>
</table>

Range of mean MMRC 10-sum score 0 (complete recovery) to 100 (total disability).

DISCUSSION

• The use of MMRC 10-sum score for assessing muscle strength in MMN was approved by the European Medicines Agency. MMRC new 10-sum score focuses more strongly on upper limbs than the original MMRC 10-sum score. Based on the results obtained in Cats cross-sectional study (3), this scale includes clinically relevant dexterity upper limbs muscle commonly affected in MMN and excludes irrelevant lower limb muscles not usually affected.

• MMRC new 10-sum score yielded lower values by 5.4 points than original MMRC score (difference not tested statistically) so that as anticipated it captured more weakness in a pattern considered to be typical of MMN.

• Patients had a mean INCAT disability scale score of 2.5 points on therapy, demonstrating persistent disability despite treatment. Mean grip strength two weeks after last course of each product was higher than that just before the course concerned, demonstrating ongoing benefit from IVIg treatment.

• This study was limited by the absence of high quality outcome measures covering all domains of disability, impairment, and quality of life in MMN which need to be simple, valid, reliable, and responsive, and correlate with disease severity (6).

At the time this study protocol was designed, there was no validated functional disability scale for MMN. The Rasch-built overall disability scale for MMN (MMN-RODS®) does overcome the shortcomings of ordinal scales was proposed in 2010 by Cats et al. (3) and still needs to be validated in new series.

CONCLUSION

• In summary, this Phase III randomised, comparative, active-control, double-blind study with a crossover design demonstrated the non-inferiority both in efficacy and safety of IQYMUNE® compared with KIOVIG® in the maintenance treatment of MMN.