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3 **High-Dose Biotin in Progressive Multiple Sclerosis: a prospective study of 178 patients**
4
5 **in routine clinical practice**
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52 **Keywords:** Biotin, multiple sclerosis, primary progressive multiple sclerosis, secondary
53 progressive multiple sclerosis, progression, effectiveness
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3 **Abstract**
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5 **Background:** A recent controlled trial suggested that high-dose biotin supplementation
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7 reverses disability progression in patients with progressive multiple sclerosis.
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10 **Objective:** To analyze the impact of high-dose biotin in routine clinical practice on disability
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12 progression at 12 months.
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14 **Methods:** Progressive multiple sclerosis patients who started high-dose biotin at Nantes or
15
16 Rennes Hospital between 3 June 2015 and 15 September 2017 were included in this
17
18 prospective study. Disability outcome measures, patient-reported outcome measures, relapses,
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20 MRI data, and adverse events were collected at baseline, 6 months and 12 months.
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24 **Results:** 178 patients were included. At baseline, patients were 52.0 ± 9.4 years old, mean
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26 Expanded Disability Status Scale (EDSS) score was 6.1 ± 1.3 , mean disease duration was
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28 16.9 ± 9.5 years. At 12 months, 3.8% of patients had an improved EDSS score. Regarding the
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30 other disability scales, scores either remained stable or increased significantly. 47.4% of
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32 patients described stability, 27.6% felt an improvement, and 25% described a worsening. Four
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34 patients (2.2%) had a relapse. Of the 74 patients (41.6%) who underwent an MRI, 20 (27.0%)
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36 had new T2 lesions, eight (10.8%) had gadolinium-enhancing lesions. Twenty-five (14%)
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38 reported adverse event.
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42 **Conclusion:** In this study, high-dose biotin did not seem to be associated with a clear
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44 improvement in disability.
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27 **Introduction**

28 Multiple sclerosis (MS) is the leading cause of nontraumatic disability in young adults. It has
29 a prevalence of 1/1000 and affects more than 2 million people worldwide. Progressive forms
30 of MS can be either active, if there is clinical or radiological inflammatory activity, or
31 nonactive, as recently defined by Lublin et al.¹ The mechanisms underlying MS progression
32 are poorly understood. It has been suggested that axonal degeneration is linked to virtual
33 hypoxia resulting from an increased energy demand from demyelinated axons and a reduction
34 in axonal ATP production owing to mitochondrial injury.²

35 Although some disease-modifying therapies (DMTs) such as mitoxantrone, siponimod, and
36 anti-CD20 antibodies have shown some efficacy in patients with active progressive disease,
37 ^{3,4,5,6} there is still a dearth of therapies for nonactive progressing patients. Biotin is a water-
38 soluble molecule that is usually classified as a B-complex vitamin, and reduced levels are
39 found in the cerebrospinal fluid of patients with MS.⁷ It is a cofactor for four carboxylases:
40 acetyl-CoA carboxylase, pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, and
41 propionyl-CoA carboxylase. These four carboxylases are involved in key steps of energy
42 metabolism and fatty acid synthesis. Through the metabolic activation of these enzymes,
43 biotin may have a neuroprotective effect in two ways. First, it may increase the supply of
44 precursors for fatty acid synthesis, and thus promote myelin repair. Second, it may increase
45 production of ATP, and so reverse virtual hypoxia through enhanced energy production in
46 neurons.^{8,9} Its adequate intake is 30 µg per day for a healthy adult.¹⁰

47 MD1003 is an oral formulation of high-dose pharmaceutical-grade biotin. A double-blind 12-
48 month study found that 12.6% of patients with progressive MS receiving high-dose biotin
49 (100 mg three times daily) achieved a notable improvement in their disability, as scored by
50 the Expanded Disability Status Scale (EDSS) or Timed 25-Foot Walk (T25-FW), compared

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3 51 with none of the placebo-treated patients ($p = 0.005$).¹¹ These findings were consistent with
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5 52 those of a previous pilot study.¹²
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8 53 Our study aimed to determine whether similar benefits could be observed in routine clinical
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10 54 practice, and whether these benefits extended to functional disability, mobility, and quality of
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12 55 life.
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17 57 **Methods**

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21 59 *Patient selection and data collection*

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24 60 Two French MS centers (Nantes and Rennes University Hospitals) participated in this study.

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26 61 These centers systematically collect prospective data on all their patients with MS, using

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28 62 European Database for Multiple Sclerosis (EDMUS) software.¹³ Data confidentiality and

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30 63 safety are ensured in accordance with the recommendations of the French Data Protection

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32 64 Authority (CNIL), which approved the use of the EDMUS database in these centers.

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34 65 Patients with primary progressive MS (PPMS) or secondary progressive MS (SPMS) who

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36 66 were started on high-dose biotin (300 mg per day) between 3 June 2015 and 15 September

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38 67 2017 at one of the two university hospitals were systematically included in the study. The

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40 68 biotin was made available under the French Temporary Authorization for Use (TAU) scheme.

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42 69 As this specific TAU required nominative registration, patients were automatically enrolled.

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44 70 The censoring date was 28 September 2018. The study was registered on ClinicalTrials.gov

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46 71 (no. NCT03302806). All participants provided their written informed consent.

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48 72 Data were collected at baseline and at the 6-month and 12-month follow-up visits by treating

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50 73 neurologists. Sociodemographic variables included age and sex. Clinical variables recorded

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52 74 were date of MS onset, duration of MS, type of progressive MS (PPMS or SPMS), previous

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54 75 and currently prescribed DMTs, EDSS score 12 months before the start of high-dose biotin, at
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3 76 baseline and at 12 months, history of relapses, and Clinical Global Impression (CGI) scale at
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5 77 12 months. There was a time window of \pm 3 months for collecting the follow-up data at 12
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8 78 months.

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10 79 When patients underwent MRIs as part of their follow up, their scan data were collected.
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12 80 Adverse events (AEs) were also systematically collected by treating neurologists at each visit,
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14 81 using a specific form.

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17 82 For patients followed at Nantes Hospital, we also systematically collected the following data
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19 83 at baseline and 12 months: T25-FW time, Symbol Digit Modalities Test (SDMT), Nine-Hole
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21 84 Peg Test (NHPT), quality of life measures (three-level version of the EuroQoL five-
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23 85 dimensional questionnaire (EQ-5D-3L) and Two Lives Scale (TLS Coping 10)), and Twelve
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25 86 Item MS Walking Scale (MSWS-12).

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30 88 *Primary outcome*

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33 89 The efficacy of high-dose biotin was assessed as an improvement in disability at 12 months
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35 90 (defined as decrease of \geq 0.5 EDSS point if baseline score was 6 or more, or \geq 1 EDSS point
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37 91 if baseline score was 5.5 or less).

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42 93 *Secondary outcomes*

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44 94 We compared (i) disability and dexterity (EDSS score, T25-FW time and NHPT), (ii)
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46 95 processing speed and sustained attention (SDMT), (iii) quality of life (EQ-5D-3L and TLS
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48 96 Coping 10), and (iv) mobility (MSWS-12) between baseline and 12 months. Other outcomes
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50 97 were the CGI score at 12 months, and clinical and radiological activity (relapse occurrence
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52 98 and MRI data).

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55 99 Finally, safety and tolerance were assessed by collecting any AEs.

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3 101 *Statistical analysis*
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5 102 Statistical analysis was performed using paired z tests to compare EDSS, T25-FW, SDMT,
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7 103 NHPT, TLS Coping 10 and MSWS-12 scores between baseline and 12 months, and
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9 104 McNemar's chi-Square test to compare EQ-5D-3L scores between baseline and 12 months.
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11 105 All results are presented as mean \pm SD. Statistical analysis was performed using Stata 14.2.
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13 106 The significance threshold was set at $p = 0.05$. Intention to treat analysis was performed in
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15 107 this study. Thus, the entire cohort of 178 patients was included in the efficacy and safety
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17 108 analyses.
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25 **Results**
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28 112 *Patients' characteristics*
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30 113 A total of 178 patients with progressive MS (102 from Nantes Hospital and 76 from Rennes
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32 114 Hospital), aged 24-74 years ($M = 52.0 \pm 9.4$ years) were included in the study (Fig. 1). Their
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34 115 clinical and demographic characteristics are summarized in Table 1. Among these patients, 84
35
36 116 had PPMS and 94 had SPMS. At the time of high-dose biotin initiation, mean disease
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38 117 duration was 16.9 ± 9.5 years and the mean EDSS score was 6.1 ± 1.3 . A total of 44 (24.7%)
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40 118 patients were treated with a concomitant DMT. The concomitant DMT was started at the
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42 119 same time as the biotin (± 3 months) in four patients. The mean interval between the
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44 120 introduction of the DMT and the start of high-dose biotin was 36.6 ± 33.4 months. The
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46 121 annualized relapse rate for the 12 months before biotin was 0.05 ± 0.2 . In the previous year, 9
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48 122 patients (among 174 patients, i.e 5,2%) had a relapse. Eighty-eight patients had an MRI
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50 123 within the previous year, and among us 5 (i.e 5,7%) presented radiological evidence of
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52 124 activity (defined by an MRI with at least one gadolinium-enhancing lesion).
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126 *Efficacy of high-dose biotin*

127 Primary outcome

128 Twenty-six (14.6%) patients stopped treatment before 12 months, while 152 (85.4%)
129 continued treatment for at least 12 months. Mean treatment duration was 10.9 ± 2.9 months.

130 Data concerning EDSS at baseline or at 12 months were missing for 21 of the 178 patients.

131 Among the 157 patients with available data, six (3.8%) exhibited an improvement in disability
132 at 12 months. All of them had SPMS. Three of them were receiving a concomitant DMT.

133 None of these patients had started the concomitant DMT at the same time as the high-dose
134 biotin. Two of them had been concomitantly taking mycophenolate mofetil for 36 months and
135 93 months respectively, while the third had been taking glatiramer acetate for 24 months.

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137 Secondary outcomes

138 We found that the EDSS score rose from 5.8 ± 1.3 at 12 months before high-dose biotin
139 initiation to 6.0 ± 1.3 at baseline ($p < 0.0001$). The fact that the EDSS score at biotin initiation
140 was higher than it had been the previous year explains why the high-dose biotin treatment was
141 started. However, 12 months into the high-dose biotin treatment, we observed a further
142 significant increase in the EDSS score (6.3 ± 1.3 at 12 months vs. 6.1 ± 1.3 at baseline, $p <$
143 0.0001) (Fig. 2A).

144 When we looked at the proportions of patients whose condition improved, stabilized or
145 worsened between M-12 and baseline and between baseline and M12, we failed to find any
146 significant difference ($p = 0.29$, chi-square test): 4.2% of patients improved (between M-12
147 and baseline), compared with 3.8% (between baseline and M12); 65.7% of patients remained
148 stable (between M-12 and baseline), compared with 73.9% (between baseline and M12); and
149 30.1% of patients worsened (between M-12 and baseline), compared with 22.3% (between

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3 150 baseline and M12). Among the 41 patients whose symptoms had worsened before starting
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5 151 biotin, 12 continued to worsen, 25 were stable, and four improved. Among the 84 who had
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7 152 been stable in the preceding year, 67 remained stable, 2 improved, but 15 worsened after
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9 153 starting biotin (see supplementary table).

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12 154 Concerning the T25-FW, we observed a significant increase at 12 months compared with
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14 155 baseline (46.6 ± 59.0 s at 12 months vs. 39.4 ± 53.3 s at baseline, $p = 0.0005$) (Fig. 2B).
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17 156 However, among the 87 patients with available data for T25-FW at baseline and at 12 months,
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19 157 nine (10.3%) improved their T25-FW time (defined as a $\geq 20\%$ decrease), and 12 (14.1%)
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21 158 patients improved either their EDSS score or their T25-FW time, but no patient improved
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23 159 both (among the 85 patients with EDSS and T25-FW data available at baseline and at 12
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25 160 months).

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28 161 NHPT scores remained stable (29.5 ± 25.2 s at 12 months vs. 30.7 ± 36.1 s at baseline, *ns*)
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30 162 (Fig. 2C), and there were no significant difference in mobility, as evaluated by scores on the
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32 163 self-report MSWS-12 scale (74.7 ± 25.4 at 12 months vs. 76.4 ± 18.6 at baseline, *ns*).

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35 164 In terms of processing speed and sustained attention, we observed no significant difference in
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37 165 SDMT scores at baseline and 12 months (37.6 ± 12.2 good answers at 12 months vs. $37 \pm$
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39 166 11.0 at baseline, *ns*) (Fig. 2D).

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42 167 Regarding quality of life, there was a significant improvement in the pain and discomfort
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44 168 dimension of the EQ-5D-3L ($p = 0.0015$). The other EQ-5D-3L dimensions (mobility, self-
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46 169 care, usual activities, anxiety/depression) remained stable (Table 2), as did scores on the TLS
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48 170 Coping 10 (6.0 ± 1.7 at 12 months vs. 5.9 ± 1.7 at baseline, *ns*).

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51 171 For the CGI score, at 12 months, 47.4% of patients described stability (CGI score = 4), 27.6%
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53 172 felt an improvement (CGI score < 4), and 25% described a worsening (CGI score > 4) (Fig.
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55 173 3). Among the six patients whose EDSS score improved, four reported an improvement in the

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3 174 CGI score at 12 months and one described stability. Information was unavailable for the
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5 175 remaining patient.

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8 176 At 12 months, four patients had had a relapse (2.2%) and the mean annualized relapse rate
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10 177 was 0.02 ± 0.1 (vs. 0.05 ± 0.2 for the previous 12 months, ns).

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12 178 A total of 74 patients (41.6%) underwent an MRI during the follow up, 7.3 ± 5.1 months after
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14 179 the start of high-dose biotin. Time since the previous MRI was 24.3 ± 22.8 months. We found
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16 180 radiological disease activity for 22 (29.7%) of them : 20 patients (27.0%) had new T2 lesions,
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18 181 eight (10.8%) had at least one gadolinium-enhancing lesion, and 6 (8.1%) had both (two of
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20 182 these patients had a clinical relapse). Finally, 16/35 (45.7%) of the patients whose condition
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22 183 worsened underwent an MRI scan during the follow up, compared with 48/122 (39.3%) of the
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24 184 stable/improved patients ($p = 0.499$, chi-square test). In patients with an available follow-up
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26 185 MRI, we found clinical or radiological activity (relapse, new T2 lesions, or at least one
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28 186 gadolinium-enhancing lesion) in 8/16 (50%) patients with worsening MS, compared with
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30 187 14/48 (25%) of stable/improved patients.

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36 37 189 *Tolerance and safety during high-dose biotin treatment*

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39 190 A total of 25 (14%) patients reported at least one AE during treatment, leading to definitive
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41 191 treatment discontinuation in five cases (2.8%) (Table 3). Most of the AEs were considered to
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43 192 be mild. The most common AE was the disruption of thyroid assays (four patients; 2.2%).
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45 193 Three cases of asthenia and three cases of edema were reported (each 1.7%). There were two
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47 194 cases of weight gain, two of sleep disorders, and two of rash. No patient died during
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49 195 treatment. One atrioventricular blockage, one suicide attempt, and one acute limb ischemia
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51 196 occurred under high-dose biotin, but were not considered to be related to the treatment.
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53 197 High-dose biotin was stopped before 12 months in 26 patients (14.6%) because of an
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55 198 unsatisfactory therapeutic effect ($n = 8$, 4.5%), patients' wish to discontinue treatment ($n = 5$,

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3 199 2.8%), progression of the disease ($n = 5$, 2.8%), suspected AE ($n = 5$, 2.8%), deterioration in
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5 200 general status ($n = 1$, 0.6%), difficulty coming to the hospital for treatment ($n = 1$, 0.6%), or
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7 201 for unknown reasons ($n = 1$, 0.6%).
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11 203 **Discussion**

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14 204 We evaluated the impact of high-dose biotin in patients with progressive MS, in routine
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16 205 clinical practice, on disability, mobility, processing speed and sustained attention, and quality
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18 206 of life. To our knowledge, our observational prospective study was the largest real world
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20 207 study to analyze the effectiveness and safety of high-dose biotin in patients with progressive
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22 208 MS.
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26 209 In our observational study, we found a lower impact of high-dose biotin than in the pivotal
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28 210 controlled trial.¹¹ Only six patients (3.8%) in the cohort presented an improvement in
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30 211 disability, as measured with the EDSS score (in contrast to 9.7% in the pivotal trial). It seems
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32 212 surprising that in the pivotal trial, none of the patients in the control group had an
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34 213 improvement in disability, given that progressive MS may fluctuate and improvements in
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36 214 disability may occur naturally. Indeed, in one PPMS cohort, Tremlett et al. reported an EDSS
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38 215 improvement at 12 months in 23.8% of patients, and a 6-month sustained EDSS improvement
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40 216 in 8.4% of patients¹⁴. This was in accordance with our study, as 4.2% of patients had a
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42 217 spontaneous improvement in their EDSS score in the 12 months before starting high-dose
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44 218 biotin.
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49 219 In our study, EDSS scores increased significantly under high-dose biotin at 12 months, and
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51 220 the progression was close to the EDSS progression observed in the placebo group of the
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53 221 pivotal trial (mean EDSS increased from baseline by 0.2 in our study, and by 0.13 in the
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55 222 placebo group of the pivotal study)¹¹, and was also consistent with previous placebo data in
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57 223 progressive MS trials.^{11,15,16} Our results are in accordance with another prospective
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3 224 observational study featuring a smaller cohort, which did not report any improvement in
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5 225 EDSS with high-dose biotin.¹⁷
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8 226 Surprisingly, in our study, we found that a higher proportion of patients improved on the T25-
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10 227 FW, as 10.3% presented an increase of at least 20% in their T25-FW time, compared with
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12 228 only 4.9% in the pivotal trial. When we consider improvements in EDSS or T25-FW, 14.1%
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14 229 of the patients with MS in our study presented a disability reversal (as in the pivotal trial).
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17 230 Our results concerning processing speed and sustained attention failed to reach significance,
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19 231 contrary to the data reported by Donze et al.¹⁸, who observed an improvement in the SDMT
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21 232 score after 12 months of treatment for the group of patients with a baseline EDSS score of
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23 233 6-6.5. However, in their cohort, patients were assessed for SDMT at baseline, 3, 6 and 12
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25 234 months, suggesting a potential learning effect.
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28 235 There was no significant improvement in quality of life, except for the pain and discomfort
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30 236 dimension of the EQ-5D-3L, which interestingly improved significantly. Another important
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32 237 outcome was the CGI score, with more than a quarter of patients feeling that their condition
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34 238 had improved under high-dose biotin. These last two results point to a symptomatic or
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36 239 placebo effect of high-dose biotin.
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39 240 The annualized relapse rate under high-dose biotin was low in our study, but we found
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41 241 evidence of radiological disease activity in 29.7% of the patients who underwent an MRI
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43 242 during the follow up. MRI scans were not systematically carried out in our study, and the
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45 243 results must be interpreted with considerable caution, even if scans were performed in the
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47 244 same proportion of worsening patients as of stable/improved patients. In addition, the time
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49 245 since the previous MRI was sometimes long ($M = 24.3 \pm 22.8$ months), making the
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51 246 comparison with the previous imaging less relevant. However, our results were consistent
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53 247 with the new MS-specific lesions observed in 23.4% of MD1003-treated patients (vs. 13.0%
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55 248 of placebo-treated patients, $p = 0.36$) in the pivotal trial.¹¹
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3 249 Other studies have recently reported an unexpectedly high rate of clinical or radiological
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5 250 disease activity under high-dose biotin.^{19,20,21,22} Distinct changes in immune cell frequencies
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8 251 in patients treated with high-dose biotin have also been observed and associated with clinical
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10 252 or MRI deterioration.²³

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13 253 There are several possible explanations for the differences between our results and those
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15 254 reported in the pivotal trial, especially concerning the rate of EDSS improvement. First, there
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17 255 was a higher proportion of patients with PPMS in our cohort (47.2%) than in the cohort of
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19 256 MD1003-treated patients in the pivotal trial (40.8%), as well as a longer MS duration ($16.9 \pm$
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21
22 257 9.5 years vs. 14.8 ± 8.9 years) and a significant longer T25-FW time (39.4 ± 53.3 s vs. $21.8 \pm$
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24 258 27 s), suggesting that our cohort probably had a more advanced disease. The notion that there
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26 259 is less of a response to high-dose biotin in more disabled patients is supported by the results of
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28
29 260 the subgroup analysis of the pivotal trial.¹¹ Second, there was a smaller proportion of patients
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31 261 with a concomitant DMT in our study (24.7% vs. 40.8% in the cohort of MD1003-treated
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33 262 patients), which may partly explain the higher proportion of patients whose disability
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36 263 improved in the pivotal trial. Third, contrary to the pivotal trial, we did not exclude patients
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38 264 with clinical or radiological evidence of inflammatory activity within the previous 12 months,
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40 265 and this too may partly explain the significant disability worsening in our study.

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43 266 We noticed relatively good tolerance of high-dose biotin: AEs were mostly mild or moderate,
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45 267 and included mainly asthenia, edemas, skin problems and disruption of thyroid assays (as
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47 268 previously reported).^{24,25} Only 2.8% of patients had to stop treatment because of these AEs.

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50 269 On account of its real world status, our study had several methodological limitations. It was
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52 270 an observational study, with no randomization or placebo arm. MRI scans were not
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55 271 systematically carried out in our study, making it difficult to know the true proportion of
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57 272 patients with radiological activity under high-dose biotin. Finally, our cohort had a more
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273 advanced and disabling disease than the cohort of MD1003-treated patients in the pivotal trial,
274 which may partly explain the different results.

275 In conclusion, this observational study is, to date, the largest prospective real world analysis
276 of high-dose biotin in patients with progressive MS, collecting data on disability, quality of
277 life, mobility, dexterity, processing speed and sustained attention. High-dose biotin does not
278 seem to be associated with a clear improvement in disability, even if it may have an impact on
279 quality of life in terms of pain and discomfort. Our study could provide useful insights on the
280 limitations of high-dose biotin treatment of progressive MS in the real world. The
281 demonstration of the usefulness of this drug in these patients needs additional scientific data
282 from well-designed randomized controlled trials: an ongoing randomized clinical trial (SPI2
283 study) may help researchers to reach a conclusion on the real impact of high-dose biotin.

284

285 **Acknowledgments:** We would like to thank Sita SHAH and Elizabeth PORTIER for
286 reviewing the English style.

287

288 **Declaration of Conflicting Interests:**

289 L Couloume: The author declares that there is no conflict of interest.

290 L Barbin: The author declares that there is no conflict of interest.

291 E Leray reports consulting, lecture fees or travel grants from Biogen, Genzyme, MedDay
292 Pharmaceuticals, Merck, Novartis, and Roche.

293 S Wiertlewski received consultancy fees, speaker fees, honoraria and clinical research grants
294 (non-personal) from Biogen-Idex, Genzyme, Novartis, Merck, Roche, Sanofi-Aventis and
295 Teva.

296 E Le Page received consultancy fees, speaker fees, and honoraria from Biogen, Genzyme,
297 Merck Serono, Novartis, Roche, and Teva.

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3 298 A Kerbrat: The author declares that there is no conflict of interest.
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5 299 S Ory: The author declares that there is no conflict of interest.
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8 300 D Le Port: The author declares that there is no conflict of interest.
9

10 301 G Edan was principal investigator for clinical trials in multiple sclerosis funded by MedDay
11
12 302 Pharmaceuticals.
13

14 303 DA Laplaud received honoraria from Biogen, Sanofi Genzyme, Teva, Roche, Merck and
15
16 304 MSD.
17

18
19 305 L Michel received honoraria from Biogen, Teva, Novartis, Roche, Merck and Sanofi
20
21 306 Genzyme.
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25
26 308 **Funding:** This work was supported by MedDay Pharma and by the ANTARES association.
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Table 1. Clinical and demographic characteristics of our cohort.

Women (%)	111 (62.4)
Age in years	
Mean \pm SD	52.0 \pm 9.4
Median (range)	51 (24-74)
Disease phenotype	
PPMS (%)	84 (47.2)
SPMS (%)	94 (52.8)
Duration of MS in years	
Mean \pm SD	16.9 \pm 9.5
Median (range)	16 (0-50)
EDSS	
Mean \pm SD	6.1 \pm 1.3
Median (range)	6 (3-9.5)
Concomitant DMT (%)	44 (24.7)
Mycophenolate mofetil, n(%)	20 (11.2)
Rituximab (%)	7 (3.9)
Glatiramer acetate (%)	4 (2.2)
Natalizumab (%)	3 (1.7)
Fingolimod (%)	3 (1.7)
Interferon beta (%)	3 (1.7)
Cyclophosphamide (%)	2 (1.1)
Dimethylfumarate (%)	1 (0.6)
Methotrexate (%)	1 (0.6)

Table 2. Changes in quality of life measured with the three-level version of the EuroQoL five-dimensional questionnaire (EQ-5D-3L).

Mobility		M12		$p = 1$
		No problems	Problems	
M0	No problems	1	2	
	Problems	2	75	

Self-care		M12		$p = 0.3$
		No problems	Problems	
M0	No problems	44	10	
	Problems	5	21	

Usual activities		M12		$p = 1$
		No problems	Problems	
M0	No problems	3	6	
	Problems	5	66	

Pain/Discomfort		M12		$p = 0.0015$
		No problems	Problems	
M0	No problems	4	0	
	Problems	12	64	

Anxiety/Depression		M12		$p = 1$
		No problems	Problems	
M0	No problems	23	8	
	Problems	8	41	

Table 3. Description of the adverse events reported in our study.

Type of adverse event	Number of patients	Treatment stopped
Disruption of thyroid assays	4	0
Asthenia	3	0
Edema	3	1
Weight gain	2	0
Sleep disorders	2	1
Cutaneous eruption rash	2	1
Arthralgia	1	1
Nausea	1	1
Spasms	1	1
Sweating	1	1
Pruritus	1	0
Eczema	1	0
Increase in bladder-sphincter disorders	1	0
Atrioventricular block	1	0
Increase in cognitive disorders	1	0
Suicide attempt	1	0
Acute limb ischemia	1	0
Weight loss	1	0
Total	28 adverse events (for 25 patients)	7 adverse events (for 5 patients)

Figure legends

Figure 1. Cohort follow up. 178 patients were included in the study: 26 patients stopped treatment before 12 months, and the remaining 152 continued treatment for at least 12 months.

Figure 2. Changes in disability and executive functions between initiation of biotin treatment and 12-month follow up.

(A) Expanded Disability Status Scale (EDSS) scores increased from 5.8 ± 1.3 12 months prior to initiation of biotin treatment to 6.0 ± 1.3 at baseline ($n = 143$, $p < 0.0001$, paired z test). Twelve months after the start of high-dose biotin, EDSS scores had increased significantly, from 6.1 ± 1.3 at baseline to 6.3 ± 1.3 at 12 months ($n = 157$, $p < 0.0001$, paired z test).

(B) Timed 25-foot Walk (T25-FW) time increased from 39.4 ± 53.3 s at baseline to 46.6 ± 59.0 at 12 months ($n = 87$, $p = 0.0005$, paired z test).

(C) Nine-Hole Peg Test (NHPT) scores remained stable between initiation of high-dose biotin (30.7 ± 36.1 s) and 12-month follow up (29.5 ± 25.2 s) ($n = 87$).

(D) Symbol Digit Modalities Test (SDMT) scores remained stable between initiation of high-dose biotin (37.0 ± 11.0 good answers) and 12-month follow up (37.6 ± 12.2 good answers) ($n = 85$).

Figure 3. Clinical Global Impression scale at 12 months.

47.4% ($n = 74$) of patients reported stability (CGI score = 4), 27.6% ($n = 43$) felt an improvement (CGI score < 4), and 25% ($n = 39$) described a worsening (CGI score > 4).

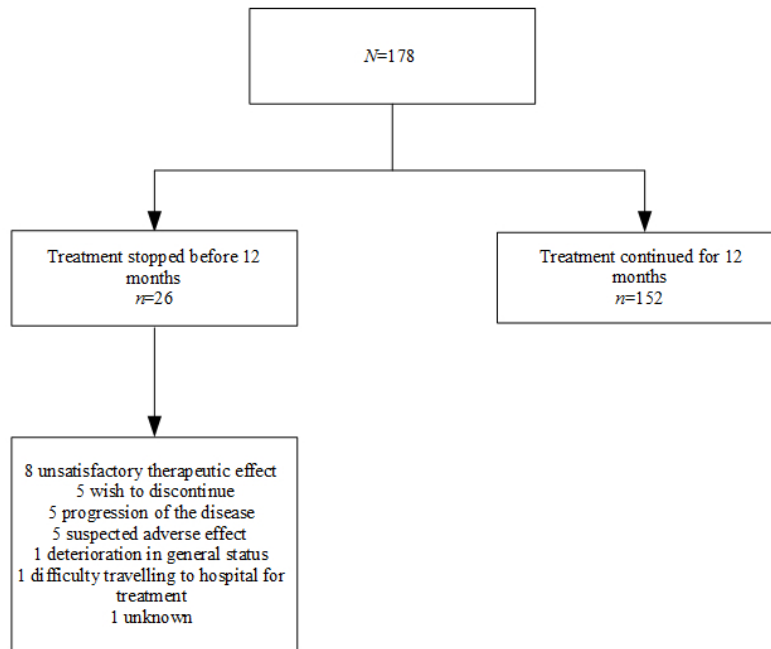
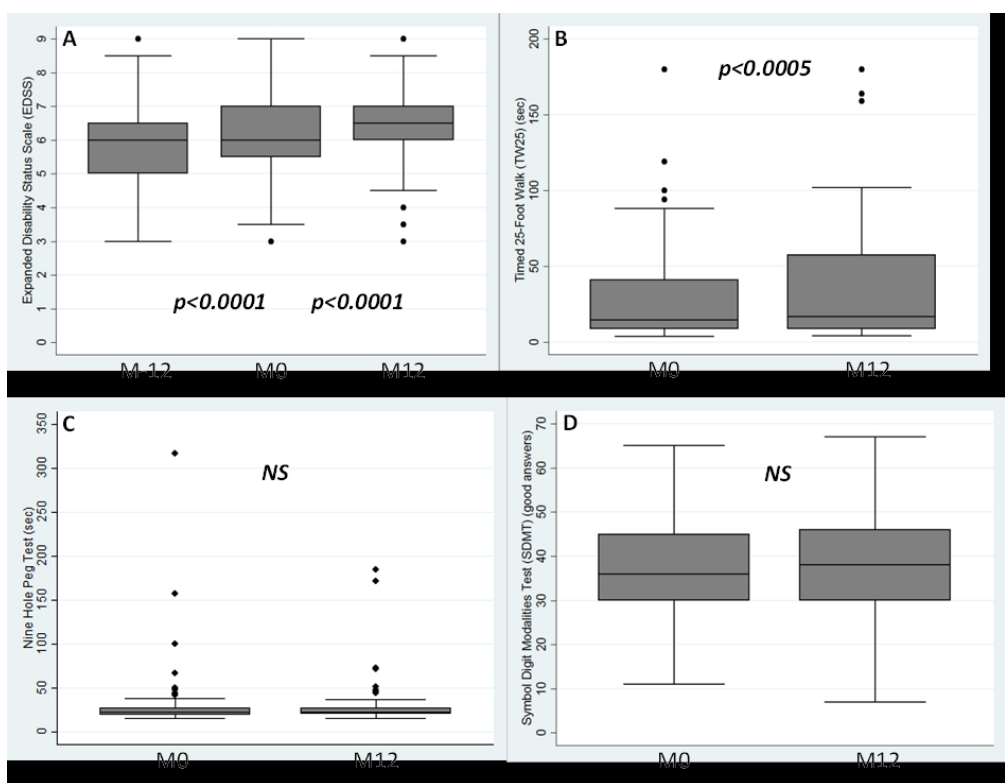


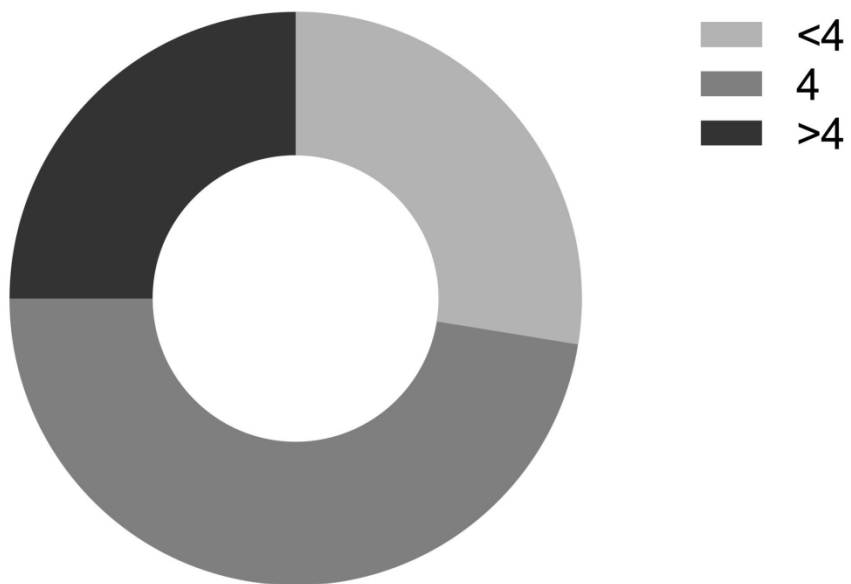
Figure 1

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159x123mm (150 x 150 DPI)

Figure 3



Clinical Global Impression (CGI) scale

185x157mm (300 x 300 DPI)

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Supplementary table. The before and after table : disability progression before and after the start of high-dose biotin.

EDSS		AFTER M0 M12			
		Improved	Stabilized	Worsened	Total
BEFORE M-12 M0	Improved	0	5	1	6
	Stabilized	2	67	15	84
	Worsened	4	25	12	41
	Total	6	97	28	131