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Teriflunomide and Time to Clinical Multiple Sclerosis in Patients With Radiologically Isolated Syndrome

Christine LEBRUN-FRENAY, MD (1), Aksel SIVA, MD (2), Maria Pia SORMANI, PhD (3),
Cassandra LANDES-CHATEAU, MSc (1), Lydiane MONDOT, MD (1), Francesca BOVIS, PhD
(3), Patrick VERMERSCH, MD (4), Caroline PAPEIX, MD (5), Eric THOUVENOT, MD (6),
Pierre LABAUGE, MD (7), Françoise DURAND-DUBIEF, MD (8), Husnu EFENDI, MD (9),
Emmanuelle LE PAGE, MD (10), Murat TERZI, MD (11), Nathalie DERACHE, MD (12),
Bertrand BOURRE, MD (13), Robert HOEPNER, MD (14), Rana KARABUDAK, MD (15),
Jérôme DE SEZE, MD (16), Jonathan CIRON, MD (17), Pierre CLAVELOU, MD (18), Sandrine
WIERTLEWSKI, MD (19), Omer Faruk TURAN, MD (20), Nur YUCEAR, MD (21), Mikael
COHEN, MD (1), Christina AZEVEDO, MD (22), Orhun H. KANTARCI, MD (23), Darin T.
OKUDA, MD (24), and Daniel PELLETIER, MD (22), on behalf TERIS Study group*.

- (1) Nice Côte d'Azur University, Nice University Hospital, MS Clinic, UR2CA-URRIS, Nice, France.
- (2) Istanbul University, Cerrahpasa School of Medicine, Istanbul, Turkiye.
- (3) University of Genoa, Genoa, Italy.
- (4) Univ. Lille, Inserm U1172 LiNCog, CHU Lille, FHU Precise, Lille, France.
- (5) Assistance Publique des Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France.
- (6) Nîmes University Hospital, MS Clinic, Nîmes, France.
- (7) Montpellier University Hospital, MS Clinic, Montpellier, France.
- (8) Hospices Civils de Lyon, MS Clinic, Lyon, France.
- (9) Kocaeli University Faculty of Medicine, Neurology, Kocaeli, Turkiye.
- (10) Rennes University Hospital, MS Clinic, CIC1414 INSERM, Rennes, France ;
- (11) Ondokuz Mayıs University, School of Medicine, Neurology, Samsun, Turkiye.
- (12) Caen University Hospital, MS Clinic, Caen, France.
- (13) Rouen University Hospital, MS Clinic, Rouen, France.
- (14) Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland.
- (15) Hacettepe University Medical Faculty, School of Medicine, Ankara, Turkiye.
- (16) Strasbourg University Hospital, CIC (clinical investigation center) INBSRM 1434, Strasbourg, France.
- (17) Toulouse University Hospital, CRC-SEP, Department of Neurology, F-31059 Toulouse Cedex 9. Université Toulouse III, Infinity, INSERM UMR1291 - CNRS UMR5051, F-31024 Toulouse Cedex 3, France
- (18) Clermont-Ferrand University Hospital, MS Clinic, Clermont-Ferrand, France.
- (19) CRC SEP and CIC Inserm 004, Nantes University Hospital, France and Transplantation and Immunology Transplantation Center (CRTI), UMR 1064, INSERM, Nantes, France.
- (20) Uludag University, School of Medicine, Bursa, Turkiye.
- (21) Ege University Medical Faculty, Bornova, Izmir, Turkiye.
- (22) University of South California, Los Angeles, California, USA.
- (23) Mayo Clinic, Rochester, Minnesota, USA.
- (24) The University of Texas Southwestern Medical Center, Dallas, Texas, USA.

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54

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65 Corresponding author:

66 Christine Lebrun-Frenay, M.D., Ph.D., FAAN.

67 MS Clinic Neurology, Nice University Hospital. UR2CA-URRIS, Nice Cote d'Azur University.

68 Pasteur² Hospital. 30 voie Romaine. 06002. Nice. France.

69 lebrun-frenay.c@chu-nice.fr

70 Phone: (33) 4 92 03 85 27

71 Fax: (33) 4 92 03 80 15

72

73 **KEY POINTS**

74 **Question:** Is it possible to prevent multiple sclerosis with a disease-modifying treatment in
75 preclinical demyelinating disease?

76 **Findings:** In this 96-week randomized clinical trial, a significant reduction in the risk of clinical
77 multiple sclerosis was demonstrated in those treated with disease-modifying treatment, compared to
78 placebo. The observed safety profile was consistent with known outcomes reported in prior pivotal
79 MS studies.

80 **Meaning:** The findings from this randomized clinical trial provide the first evidence of early
81 treatment intervention with teriflunomide in preventing multiple sclerosis in radiologically isolated
82 syndrome subjects.

83

84 **ABSTRACT**

85 **Importance:** Radiologically isolated syndrome (RIS) represents the earliest detectable pre-clinical
86 phase of multiple sclerosis (MS) and defines individuals with incidental magnetic resonance
87 imaging (MRI) white matter anomalies within the central nervous system.

88 **Objective:** The primary endpoint was the time to onset of symptoms consistent with MS.

89 **Design:** This multicenter, double-blind, phase 3 clinical trial investigates teriflunomide's efficacy in
90 delaying symptomatic conversion to MS in individuals with RIS.

91 **Settings:** This referral centers study involved patients from France, Switzerland, and Turkey.

92 **Participants:** Adult participants meeting the 2009 RIS criteria were randomized (1:1) to oral
93 teriflunomide 14mg daily or placebo up to week 96 or optionally to week 144. Eighty-nine
94 participants were enrolled (placebo n=45; teriflunomide n=44).

95 **Interventions:** Clinical, MRI, and PROs were collected at baseline, yearly until week 96, with an
96 optional third year in the allocated arm if no symptoms have occurred.

97 **Main outcomes:** The primary analysis was done in the intention-to-treat population, and safety was
98 assessed accordingly. Secondary endpoints included MRI new T2 lesions and patients-related
99 outcomes (fatigue, cognition, quality of life).

100 **Results:** The time to the first clinical event was significantly extended in the teriflunomide arm
101 compared to the placebo, in both unadjusted (HR=0.37,95% confidence interval (CI)=0.16-0.84,
102 p=0.018) and adjusted (HR=0.28,95% CI=0.11-0.71, p=0.007) analysis. For the secondary imaging
103 endpoint outcomes, the cumulative number of new/newly enlarging T2 lesions (RR=0.57, 95%
104 CI=0.27-1.20, p=0.139), new Gd+ lesions (RR=0.33, 95%CI:0.09-1.17, p=0.086), and the
105 proportion of participants with new lesions (OR=0.72, 95%CI:0.25-2.06, p=0.537) were reduced in
106 the teriflunomide arm.

107 **Conclusion and relevance:** Treatment with teriflunomide resulted in a risk reduction of 63%
108 relative to placebo in preventing a first clinical event in participants with RIS. These data add to the

109 benefit of early, even presymptomatic immunomodulation in the MS disease spectrum.

110 **Trial registration:** NCT03122652.

111

112 **Funding:** Sanofi

113 **Study Sponsor:** The University Hospital (CHU) Nice. Nice Cote d'Azur University, Radiologically

114 Isolated Syndrome Consortium (RISC)

115

116 **Running Title:** Radiologically Isolated Syndrome Treatment

117

118 **Abbreviations:** CIS: Clinically Isolated Syndrome; CNS: Central Nervous System; CSF:

119 Cerebrospinal fluid; DMT: Disease-modifying treatment; MRI: Magnetic resonance imaging MS:

120 Multiple sclerosis; OCB: Oligoclonal bands; PP: Primary Progressive; RIS: Radiologically isolated

121 syndrome; RR: Relapsing-remitting, HR: hazard ratio; DIS: Dissemination in space; DIT:

122 Dissemination in time; PASAT: Paced Auditory Serial Addition Test, CSCT: Computerized Speed

123 Cognitive Test, MFIS: Modified Fatigue Impact Scale.

124 **Introduction**

125 Multiple sclerosis (MS) is a common cause of severe neurological disability in young adults
126 resulting from an inflammatory immune-mediated insult of myelin, axons, and their supporting
127 cells within the central nervous system (CNS). The diagnosis can only be made following clinical
128 symptoms consistent with acute or progressive CNS injury disseminated in time and space by
129 further clinical or MRI criteria.¹ When these MRIs reveal unexpected anomalies highly
130 suggestive of demyelinating plaques given their size, location, and shape in the absence of
131 symptomatology explained by these lesions, they can fulfill formally validated criteria for the
132 radiologically isolated syndrome (RIS).^{2,3} This preclinical stage, defined objectively by MRI,
133 expands the spectrum of at-risk individuals for future clinical demyelinating events.

134

135 The dissemination in space (DIS) requirement for RIS incorporates the 2005 McDonald criteria⁴,
136 requiring 3 or 4 of four imaging criteria to be met. The RIS criteria³, when applied to individuals
137 with incidental demyelinating-appearing MRI lesions without defining clinical features of MS,
138 predict conversion to a first clinical event at a rate of 34% at five years and 51% at ten years.^{5,6}
139 Conversion to primary progressive MS (PPMS)⁷ or pediatric MS⁸ has also been described, further
140 validating a pre-clinical MS phase.

141

142 The early use of disease-modifying treatments (DMTs) is typically recommended in established
143 MS.⁹ Despite advancements in the characterization of RIS subjects^{2,3,7,8} and our understanding of
144 risk factors for initial symptom development^{5,6,10}, the support for DMTs in RIS was only recently
145 demonstrated in the ARISE study¹¹ with oral dimethyl fumarate, in extending the time to the first
146 clinical event in RIS.

147

148 Teriflunomide (HMR1726; Aubagio[®]) is an oral immunomodulator, taken once daily and
149 approved in more than 80 countries for treating relapsing-remitting MS.^{12,13} This study

150 investigated the efficacy of teriflunomide in extending the time to a first clinical event related to
151 MS. The rationale for this proposed early treatment intervention trial was to test another DMT
152 with a different mode of action and confirm the impact of an immune intervention at the
153 preclinical stage of MS.

154

155 **Methods**

156 *Study oversight and ethics statement*

157 The RIS Consortium (RISC) designed the trial and named adjudication referees for clinical and
158 MRI application of RIS criteria in screened subjects. Referees were also asked to adjudicate
159 neurological events when reported by participants. An independent safety monitoring committee
160 reviewed all safety data (*See online only the trial oversight section, eFigure 1 and eFigure 2*). All
161 RISC core group members independently authored and developed the study protocol and
162 participated in writing the manuscript. All authors approved the draft sent to Sanofi, which was
163 only involved in funding support. The trial was conducted according to the provisions of the
164 International Conference on Harmonization Guidelines for Good Clinical Practice.¹⁴ The
165 Declaration of Helsinki was followed during the TERIS trial.¹⁵ The study protocol, patient
166 information, and consent form were accepted by the relevant Ethics Committee (IEC) and
167 registered as EUDRA-CT 2016-002428-97. The Study Sponsor was the University Hospital of
168 Nice and registered at ClinicalTrials.gov as NCT03122652 (TERIS). Data were secured by
169 clinical research organizations and remained confidential throughout the study. Data analysis was
170 performed solely by the investigators independent of the funding source.

171

172 *Participants*

173 Written informed consent from participants was required. Inclusion criteria were i) age >18 years,
174 ii) fulfillment of 2009 RIS criteria⁴ (*eFigure 1*) with structural neuroimaging abnormalities not

175 explained by another disease process, and no historical accounts of remitting clinical symptoms
176 consistent with neurological dysfunction.
177 Exclusion criteria comprised severe hepatic, renal, and immune system impairments, lactating or
178 pregnant women, or previous exposure to immunosuppressive or disease-modifying therapy.
179 Subjects of reproductive potential were eligible only if the teriflunomide use guidelines were met
180 (*online only*).¹⁶

181

182 *Study design*

183 TERIS was planned as a 96-week, multi-center, randomized (1:1), double-blinded study of
184 teriflunomide 14mg daily or placebo in RIS subjects fulfilling 2009 criteria³ (*eFigure 1*), with the
185 option to continue in the randomization arm up to week 144. Medication, placebo capsules, and
186 packaging were identical to those used in the pivotal teriflunomide studies.⁶⁻⁸ An independent
187 clinical adjudication committee (AS, MC, DTO) verified study entry criteria before
188 randomization. MRI scans were analyzed through adjudicated consensus by the Advanced
189 Imaging in Multiple Sclerosis (AIMS) Laboratory (LM, CJA, DP) in Los Angeles, California.
190 Each clinical center was responsible for recruitment, treatment, evaluation of participants, and
191 collection of study data according to the protocol. Randomization was stratified according to
192 geographic region and was performed centrally by an independent interactive web-response
193 system. Expanded Disability Status Scale (EDSS) scores, functional scores, Paced Auditory
194 Serial Addition Test (PASAT-3), Computerized Speed Cognitive Test (CSCT) assessments,
195 Modified Fatigue Impact Scale (MFIS), and quality of life (EQ-5D-5L and MUSICOL) were
196 performed at baseline, every six months, and any unscheduled visit following a neurological
197 event.

198

199 RIS subjects who completed the 96-week study without symptoms suggestive of MS or side effects
200 to the allocated drug were offered to enter the third year in the same arm. RIS subjects who

201 converted to MS or did not wish to continue in the assigned treatment were included in the safety
202 follow-up. Patients diagnosed with MS were offered to start or continue oral teriflunomide.

203

204 The wash-out procedure was applicable for women in the event of pregnancy while on study
205 medication, for women who planned to become pregnant, for premature discontinuation before or at
206 the end of the study, or in specific situations according to the investigator's decision (*online only*
207 *material*).

208

209 *Brain and Spinal Cord MRI protocols:*

210 Imaging studies were conducted on 1.5 Tesla (T) or 3T MRI units from different manufacturers
211 using a standardized protocol (*online only material*). Baseline MRI anomalies were verified as
212 consistent with CNS demyelinating disease and meeting spatial dissemination criteria by a central
213 reading unit. MRI scans were performed at baseline, week 48, week 96, week 144, and any time
214 during the study if warranted by the investigator.

215

216 **Outcomes**

217 The primary outcome was the time to a first acute or progressive neurological event resulting from
218 CNS demyelination, expressed as a rate of conversion to clinical MS. An acute neurological event
219 was defined by a clinical symptom localized to the optic nerve, brainstem, cerebellum, spinal cord,
220 or long sensory or motor tracts, lasting >24 hours and followed by symptom improvement. A
221 progressive event was defined by the onset of a clinical symptom with the temporal profile
222 revealing at least a 12-month progression.

223

224 Secondary outcomes included the following brain MRI metrics; the cumulative number of new
225 and/or enlarging T2-weighted hyperintense lesions, the cumulative number of new gadolinium-
226 enhancing (Gd+) lesions, changes in T2-weighted hyperintense lesion volumes, and the proportion

227 of participants with new or newly enlarging T2-weighted hyperintense lesions and new Gd+
228 lesions. The additional clinical metrics (PASAT-3, CSCT, MFIS, EQ-5D-5L, and MUSICOL) were
229 assessed at baseline and yearly.

230

231 **Statistical Analysis**

232 Sample size calculations using Cox proportional hazards regression indicated that 80 patients per
233 arm would have been needed to have 80% power to detect a 50% reduction in the risk of the first
234 clinical event if 25% of participants experienced a first clinical event at two years having a trial
235 duration of 5 years. The prior distribution for the effect of teriflunomide versus placebo was derived
236 from the TOPIC¹⁷ (NCT 000622700), TEMSO¹⁸ (NCT 00134563), and TOWER¹⁹ (NCT 00751881)
237 trials in RRMS.

238

239 Survival curves were computed using the Kaplan-Meier method to display the treatment effect.
240 Both adjusted and unadjusted Cox proportional-hazards regression models were used to assess the
241 impact of treatment from randomization to the first acute or initial progressive neurological event.
242 The adjusted model used key baseline variables to adjust for potential confounding effects, such as
243 sex, age at the time of RIS diagnosis, MS family history, brain T2-weighted hyperintense lesion
244 volume (log-transformed), and presence of Gd+/- lesions. The statistical analyses for the secondary
245 and the exploratory endpoints are detailed in the online-only *material*. All statistical analyses (MPS,
246 FB) were performed using SAS software, version 9.4 (SAS Institute), or R, version 4.1.3.

247

248 **Results**

249 **Participants**

250 From September 25, 2017, to October 31, 2022, 124 RIS patients were screened. Thirty-Three
251 subjects were excluded due to RIS diagnostic criteria not being fulfilled (18), study consent
252 withdrawals (16), and loss of follow-up (1). Of the 89 randomized RIS subjects from 20 centers

253 in France, Switzerland, and Turkey, 63 (70.8%) were female. The mean (\pm SD) age at study
254 enrolment was 39.8 (\pm 12.1) years, and the mean (\pm SD) age at index MRI was 37.9 (\pm 12) years.
255 The baseline demographic and clinical data were well-balanced between groups (*Table 1*). The
256 most common reasons for obtaining the index MRIs were headache (46.1%), follow-up for other
257 neurological diseases (28.1%), dizziness/vertigo (16.9%), and visual symptoms (6.7%) (*Table 1*).
258 Adverse reactions and reasons for study discontinuation are provided in the appendix (*eTable 1*,
259 *and eTable2*). The retention rate for the study was 82%. Follow-up MRI studies performed at
260 week 96 were acquired in 62 (69.7%) of subjects, 32 within the placebo group and 30 in the
261 teriflunomide group (*eFigure2*).

262

263 **Efficacy**

264 *Primary outcome*

265 After randomization, 28 primary clinical endpoints were detected; four (14.3%) were consistent
266 with a progressive clinical syndrome qualifying as primary progressive MS, and 24 (85.7%) were
267 consistent with acute relapses. Syndromic localization of the acute events was optic nerve (4
268 (14.3%)), spinal cord (8 (28.5%)), brainstem/cerebellum (3 (10.7%)), and subcortical white matter
269 (9 (32.1%)). Progressive events involved cognitive impairment (2 (7.2%)) and progressive
270 paraparesis (2 (7.2%)).

271 The mean (\pm SD) time to the first clinical event was 119.0 (\pm 5.2) weeks.

272

273 The risk of a first clinical event was significantly reduced in the teriflunomide arm (mean time to
274 event=128.2 (\pm 7.25) weeks, eight clinical events; six acute, two progressive) versus the placebo arm
275 (mean time to event=109.6 (\pm 7.44) weeks, 20 clinical events; 18 acute, two progressive), with an
276 unadjusted HR=0.37, 95% confidence interval (CI)=0.16-0.84, $p=0.018$ (*Figure 1* and *Table 2*).

277 This result corresponded to a 63% reduction in the risk of a first MS-related clinical event favoring
278 teriflunomide.

279

280 Results from the adjusted Cox proportional-hazards regression model were consistent with those of
281 the unadjusted analysis, with a significant effect favoring teriflunomide on reducing the risk of the
282 first event after adjusting for sex, age at the time of diagnosis, MS family history, EDSS, T2-
283 weighted hyperintense volume (log-transformed) and the presence of gadolinium-enhancing lesions
284 (HR=0.28, 95% CI=0.11-0.71, p=0.007; *Table 2*).

285

286 *Secondary outcomes*

287 Compared to placebo, the cumulative number of new and/or newly-enlarging T2 lesions (RR=0.57,
288 95% CI=0.27-1.20, p=0.139) and the cumulative number of Gd+ lesions (RR=0.33, 95%CI:0.09-
289 1.17, p=0.086) were reduced in the teriflunomide arm in the adjusted analysis, although statistical
290 significance was not achieved. The proportions of subjects with new and/or newly-enlarging T2
291 lesions (OR=0.72 95% CI=0.25-2.06), p=0.537) and with Gd+ activity (OR=0.28 95% CI=0.07-
292 1.13), p=0.075) were also reduced in the teriflunomide arm, but not statistically significant.

293 Like imaging metrics, the results in other secondary clinical outcomes favored the teriflunomide
294 arm but without statistical significance (*Table 3*). The largest difference between teriflunomide
295 and placebo was observed for the EQ-5D-5L (mean difference in the annualized change +3.69
296 (95%CI=-0.56; 7.95), p=0.089).

297

298 *Safety*

299 Adverse events were closely monitored during the follow-up. The treatment arm reported one
300 severe COVID infection declared as possibly related to the drug. Only one patient stopped the

301 study due to side effects (*eTable 2*). The most common adverse events observed more often in
302 patients treated with teriflunomide were gastrointestinal disorders (11.4%), dysmenorrhea (9.1%),
303 benign respiratory infections (6.8%), general disorders conditions (6.8%), and transient increase
304 of transaminases (4.5%) (*eTable 1*). Reasons for study discontinuation after randomization were
305 loss of follow-up (27.8%), consent withdrawal (22.2%), patient's decision (22.2%), adverse event
306 (16.7%), pregnancy (5.5%), and sponsor decision (5.5%).

307

308 **Discussion**

309

310 Following the recent ARISE study¹¹, TERIS is the second randomized multi-center study to
311 demonstrate the benefit of a DMT previously approved for use in established MS in delaying or
312 preventing the development of clinical MS in subjects with RIS with a risk reduction of over 60%
313 relative to placebo. An overwhelming number of natural history studies and clinical trials in
314 clinically isolated syndrome (CIS) and early MS support the paradigm that earlier treatment is
315 beneficial in delaying long-term disability accumulation.^{9,20} The TERIS study and ARISE 11
316 demonstrate that different DMTs with different immune mechanisms of action, studied in
317 different populations derived from diverse healthcare systems, yield comparable results,
318 supporting that early intervention in RIS may improve clinical outcomes.

319 Even with demonstrated efficacy and reassuring teriflunomide long-term safety data^{12,13,16,21}, the
320 indication of starting a DMT needs to be thoroughly discussed in a presymptomatic situation, as
321 not all RIS subjects might benefit from it. The cornerstone of the risk-benefit balance is the
322 absence of an induced severe adverse event for a drug prescribed at the preclinical stage of the
323 disease. Several retrospective and prospective data-driven RISC cohorts have identified risk
324 factors for developing a first clinical event and have demonstrated a risk stratification with an
325 increased risk for developing MS at a younger age, the presence of spinal cord or infratentorial
326 lesions, the identification of new MRI lesions over time, and the presence of gadolinium-

327 enhancing lesions or OCBs in the CSF.^{5,6,10,22} Whether these observed risk factors should be used
328 to guide the decision to initiate treatment in RIS patients remains to be seen. The risk-benefit
329 calculation should favor patient safety at the preclinical stage of the disease.

330 This is the first limitation of our study as we could not stratify at-risk subgroups according to the
331 aforementioned risk factors for developing MS, mainly because our proof-of-concept study was
332 powered to detect the overall impact of active treatment versus placebo arms. Any such
333 stratification would require a much larger clinical trial with a different research question and pre-
334 selection of high and low-risk groups rather than post-hoc analyses, which are inappropriate for
335 the current study. Now that two studies (ARISE and TERIS) have proven the efficacy of DMTs
336 in RIS, future study designs can focus on identifying the ideal subjects who would benefit most
337 from treatment. As expected, TERIS shares additional limitations similar to the preceding ARISE
338 study.¹¹ TERIS was also prematurely discontinued by the study sponsor, mainly due to the
339 reduced pace of study enrollment. When the study started, the sample size was calculated from
340 published pivotal teriflunomide CIS and RRMS studies.¹⁷⁻¹⁹ A sample size calculation based on
341 data-driven cohorts was proposed for RIS studies more recently.¹⁰

342

343 The onset of PPMS in the current study is in keeping with the overall expected incidence of
344 PPMS in MS and RIS populations.^{4,23} In the ARISE study, primary progressive clinical courses
345 were not observed during the two-year study period.¹¹ In TERIS, PPMS onset was observed in 4
346 (14%) individuals diagnosed during the third year of the study. Taken together, these results
347 suggest that we may, for the first time, have an opportunity to better identify those at risk for a
348 primary progressive clinical course at this preclinical stage and prevent or delay clinical
349 progression from the onset, a clear unmet need in MS clinical practice.

350

351 MRI is now the most helpful tool to predict conversion to MS in patients with CIS²⁴. Particularly
352 gadolinium-enhancing and spinal cord lesions at baseline and enhancing lesions at one year and

353 three years best predict future physical and cognitive disability, including conversion to
354 secondary progressive MS at 15 years.²⁵ RISC cohorts demonstrated a similar risk profile for the
355 presymptomatic phase.^{4,5,6,10} In TERIS, although all the secondary MRI measures favored
356 teriflunomide over placebo, none achieved statistical significance. MRI activity in RIS is less
357 known than those in established MS. Consequently, the individual variance may have led to
358 reduced statistical power. Similarly, statistical trends toward benefit in the present study were
359 also observed on fatigue, quality of life, and cognitive metrics. Since all secondary outcome
360 measures consistently trended in the same direction, such results support the primary clinical
361 endpoint and provide an opportunity to properly power future clinical trials in RIS to detect DMT
362 impact on secondary endpoints.

363

364 The MS community now has two randomized, multi-center, placebo-controlled, double-blind
365 studies showing that an active treatment extends the time to symptomatic MS in RIS individuals
366 meeting a previously unmet need. Earlier treatment during the presymptomatic phase of MS can
367 delay disability even further after symptomatic MS onset. However, before considering any
368 immune intervention, it is essential to highlight the risk of misdiagnosing individuals with non-
369 specific MRI anomalies as having RIS, which underlines the role of MS tertiary centers in
370 managing the diagnosis and intervention in RIS.^{26,27}

371

372

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380 Research Clinic Direction of Nice University Hospital for her constant support.

381

382 **Data availability**

383 Anonymized data collected for the study, including individual participant data and a data dictionary
384 defining each field in the set, will be made available to others for publication six months later. Data
385 not published within this article will be made available by request from any qualified investigator.
386 The full study protocol, statistical analysis plan, and informed consent form will also be
387 supplementary data.

388

389 **Contributions**

390 CLF, AS, MPS, OHK, DTP, and DP designed the study. CLF, AS, PV, CP, ET, PL, FDD, HE,
391 ELP, MT, ND, BB, RH, RK, JDS, JC, PC, SW, OFT, NY, MC, CJA, OHK, DTO and DP were
392 study investigators. CLC collected data. CLF and CLC verified the data. MPS, LM, and FB
393 analyzed and verified the data. All authors interpreted the data, reviewed, and revised the
394 manuscript,
395 and had full access to all data in the study and provided final approval of all content in this Article.
396 The corresponding author had final responsibility for the decision to submit the manuscript for
397 publication. All named authors met the International Committee of Medical Journal Editors criteria
398 for authorship for this manuscript and take responsibility for the integrity of the work as a whole.

399 **Conflicts of interest**

400 CLF is the principal investigator of the TERIS Study, with no personal fees.

401

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406 Novartis, Alexion. Received honoraria for lectures from Sanofi-Genzyme, Novartis, Roche Ltd,
407 Teva. Registration coverage for attending scientific congresses or symposia from Sanofi-Genzyme,
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412

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414

415 LM none

416

417 FB reports personal fees outside the submitted work from Biogen, Novartis, Chiesi, and Eisai.

418

419 PV received Honoraria from Biogen, Sanofi-Genzyme, Novartis, Teva, Merck, Roche, Imcys, AB
420 Science, et BMS-Celgene, and grants from Novartis, Sanofi-Genzyme et Roche

421

422 CP received honoraria for scientific conferences, boards or consulting for the following
423 laboratories for the last 3 years from Alexion, Biogen, Roche

424

425 ET has received honoraria, travel grants, or research grants from the following pharmaceutical
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427

428 PL received honoraria and grants from Biogen, Sanofi Genzyme, Merck, Novartis, Alexion and
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430

431 FDD none

432

433 HE has received speaking honoraria, personal compensation for participating on advisory boards
434 and travel grants from: Alexion, Biogen Idec/Gen Pharma of Turkey, Merck-Serono; Novartis;
435 Teva, Sanofi, -Aventis, Alexion, Abdi Ibrahim İlaç Turkey, Genveon İlaç Turkey, Sanovel İlaç
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437

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439

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445

446 ND none

447

448 BB serves on scientific advisory board, has received funding for travel and honoraria from Alexion,
449 Biogen, BMS, Merck, Novartis, Sanofi and Roche

450

451 RH received speaker/advisor honorary from Merck, Novartis, Roche, Biogen, Alexion, Sanofi,
452 Janssen, Bristol-Myers Squibb, Teva/Mepha and Almirall. He received research support within the
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456 Nervous System disease. All conflicts are not related to this work.

457

458 RK Rana Karabudak has received honoraria for giving educational lectures, consultancy fees for
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460 from Roche, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey ,
461 Sanovel , Abdi İbrahim Pharma & Alexion.

462

463 JDS none

464

465 JC has received personal compensation for consulting, serving on a scientific advisory board,
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468

469 PC none

470

471 SW received consultancy fees, speaker fees, honoraria and clinical research grants from Alexion,
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473

474 OFT Received honoraria or consultancy fees for participating to advisory boards giving lectures
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476 Genzym, Merck Serono, Novartis, Teva, Biogen Idec/Gen Pharma of Turkey, Alexion , Abdi Ibrahim
477 Ilac Turkey, Genveon , Ali Raif, Deva Turkey

478

479 NY Received research grants from The Scientific and Technological Research Council Of Turkey
480 and Ege University Research Support Funds

481 Received honoraria or consultancy fees for participating to advisory boards, giving educational
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485

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506

507

508 **Advisory Committee**

509 Christine Lebrun-Frenay, M.D., Ph.D., Nice Cote d'Azur University, Nice, France; Aksel

510 Siva, M.D., Cerrahpasa School of Medicine, Istanbul, Turkiye; Darin T. Okuda, M.D., The

511 University of Texas Southwestern Medical Center, Dallas, Texas, U.S.A.; Orhun Kantarci,

512 M.D., Mayo Clinic, Rochester, Rochester, Minnesota, U.S.A; Daniel Pelletier, M.D.,

513 University of Southern California, Los Angeles, California, U.S.A.

514

515 **Independent Core Clinical Committee**

516 Christine Lebrun-Frenay, M.D., PhD, Nice Cote d'Azur University, Nice, France; Aksel Siva,

517 M.D., Cerrahpasa School of Medicine, Istanbul, Turkiye; Mikael Cohen, M.D., Nice Cote d'Azur

518 University, Nice, France, Orhun Kantarci, M.D., Mayo Clinic, Rochester, Rochester, Minnesota,

519 U.S.A., Darin T. Okuda, M.D., The University of Texas Southwestern Medical Center, Dallas,

520 Texas, U.S.A.

521

522 **Independent Magnetic Resonance Imaging Committee and Central Analysis Center**

523 Daniel Pelletier, M.D., Christina J. Azevedo, M.D., Saeed Moazami, Jean-Felix Pelletier,

524 Genevieve Rodriguez, Advanced Imaging in Multiple Sclerosis (AIMS) Laboratory,

525 University of Southern California, Los Angeles, California, U.S.A, Lydiane Mondot, M.D.

526 Cote d'Azur University, Nice, France.

527

528 **Data and Safety Monitoring Committee**

529 Cassandre Landes-Chateau, CCS, and Samir Yamani, Nice University Hospital, Nice France.

530

531

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611

612 **Table 1:** Baseline characteristics of the study population

	Total (n=89)	Teriflunomide (n=44)	Placebo (n=45)
Age at RIS diagnosis (years), mean (SD)	37.88 (12.0)	37.24 (13.10)	38.51 (10.93)
Sex, n (%)			
Female	63 (70.79)	31 (70.45)	32 (71.11)
Male	26 (29.21)	13 (29.55)	13 (28.89)
MS family history, n (%)	3 (3.37)	2 (4.54)	1 (2.22)
MRI Motives, n (%)			
Headaches	41 (46.07)	23 (52.27)	18 (40.00)
Trauma	1 (1.12)	1 (2.27)	0 (0.00)
Amenorrhea	2 (2.25)	0 (0.00)	2 (4.44)
Anxiety/Depression	2 (2.25)	1 (2.27)	1 (2.22)
Dizziness/Vertigo	15 (16.85)	3 (6.82)	12 (26.67)
Optic complaints	6 (6.74)	2 (4.54)	4 (8.89)
Follow-up of other diseases	25 (28.09)	13 (29.54)	12 (26.67)
Presence of Gd+ lesions, n (%)	25 (28.09)	13 (29.55)	12 (26.67)
T2-lesion volume (log-transformed), mean (SD)	3.39 (0.45)	3.34 (0.43)	3.43 (0.46)
EDSS, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)
PASAT, median (IQR)	37.50 (24-49)	33 (20-45)	40 (30-50)
CSCT, mean (SD)	42.01 (13.21)	39.87 (14.04)	44.00 (12.22)
MFIS, median (IQR)	35 (16-61.5)	46 (15-77)	30 (20-53)
EQ-5D-5L, median (IQR)	80 (60-90)	75 (60-90)	80 (65-90)
MUSIQOL, mean (SD)	44.90 (11.92)	47.37 (9.80)	42.54 (13.33)

613 Abbreviations: RIS=Radiologically abbreviated syndromes, SD=Standard Deviation,
614 IQR=Interquartile Range, Gd+=gadolinium-enhancing, EDSS=Expanded Disability Status Scale,
615 PASAT= Paced Auditory Serial Addition Test, CSCT= Computerized Speed Cognitive Test,
616 MFIS=Modified Fatigue Impact Scale, EQ-5D-5L = Health-related quality of life, MUSICOL=
617 Multiple Sclerosis International Quality of Life Questionnaire.

618 **Table 2:** Primary and Secondary End Points (Intention-to-treat Population)

	Teriflunomide n=44	Placebo n=45	Unadjusted analysis		Adjusted analysis^a	
Primary End Point						
	n (%)		Hazard Ratio (95%CI)	p value	Hazard Ratio (95%CI)	p value
Number of patients with a first clinical event during follow up ^b	8 (18.2)	20 (44.4)	0.37 (0.16-0.84)	0.018	0.28 (0.11-0.71)	0.007
Secondary MRI end points						
	Mean value (95%CI)		Rate Ratio (95%CI)		Rate Ratio (95%CI)	
Cumulative number of New/Newly Enlarging T2-Lesions ^c	1.49 (0.82-2.69)	3.04 (1.81-5.09)	0.50 (0.22-1.12)	0.094	0.57 (0.27-1.20)	0.139
Cumulative number of New Gd+ Lesions ^c	0.22 (0.09-0.55)	0.50 (0.25-1.00)	0.44 (0.13-1.58)	0.211	0.33 (0.09-1.37)	0.086
	n (%)		Odds Ratio (95%CI)		Odds Ratio (95%CI)	
Participants with New/Newly Enlarging T2-Lesions	20 (58.8) N=34	24 (64.9) N=37	0.78 (0.29-2.06)	0.613	0.72 (0.25-2.06)	0.537
Participants with New Gd+ lesions ^d	5 (15.1) N=33	12 (33.3) N=36	0.35 (0.11-1.16)	0.086	0.28 (0.07-1.13)	0.075

	Median annualized percentage change (range)		Median difference (range)			
T2 lesion volume ^e	1.14 (15.0- 67.3) N=35	0.95 (17.121- 406.6) N=37	0.19 (-14.99 – 406.66)	0.942		0.896

619 Abbreviations: CI=Confidence Interval, Gd+=Gadolinium-enhancing lesions,

620

621 ^aAll the adjusted analyses were corrected for sex, age at RIS diagnosis, MS family history, EDSS, T2-lesion volume (log-transformed), and
622 gadolinium-enhancing lesions at baseline.

623 ^bCox proportional hazard model

624 ^cNegative binomial regression model with an offset term accounting for follow-up duration.

625 ^dLogistic regression model with an offset term to account for follow-up duration.

626 ^eGeneralized linear model with an offset term for follow-up duration.

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632 **Table 3:** Exploratory End Points (Intention-to-treat Population)

	Teriflunomide	Placebo				
	Mean annualized change* (95%CI)		Unadjusted mean difference (95% CI)	p value	Adjusted mean difference (95% CI)	p value
MFIS	-1.33 (-.36;2.70) N=36	1.19 (-2.67;5.06) N=39	-2.52 (-8.16; 3.13)	0.377	-1.67 (-7.24; 3.90)	0.551
EQ-5D-5L	2.07 (-0.89;5.04) N=35	-0.99 (-3.80;1.81) N=39	3.06 (-1.03;7.16)	0.140	3.69 (-0.56; 7.95)	0.089
MUSICQOL	-0.26 (-2.60;2.07) N=35	1.12 (-1.12 ;3.36) N=38	-1.38 (-4.65;1.88)	0.400	-1.36 (-4.62;1.89)	0.406
PASAT	1.03 (-1.34;3.40) N=36	-0.09 (-2.27 to 2.08) N=39	1.12 (-2.14;4.38)	0.495	1.02 (-2.22;4.27)	0.531
CSCT	1.99 (0.15; 3.83) N=33	1.43 (-0.33; 3.19) N=36	0.56 (-2.00;3.14)	0.661	0.57 (-4.40; 5.54)	0.820

633 *Mean annualized changes were calculated as the difference between baseline and the last follow-up available

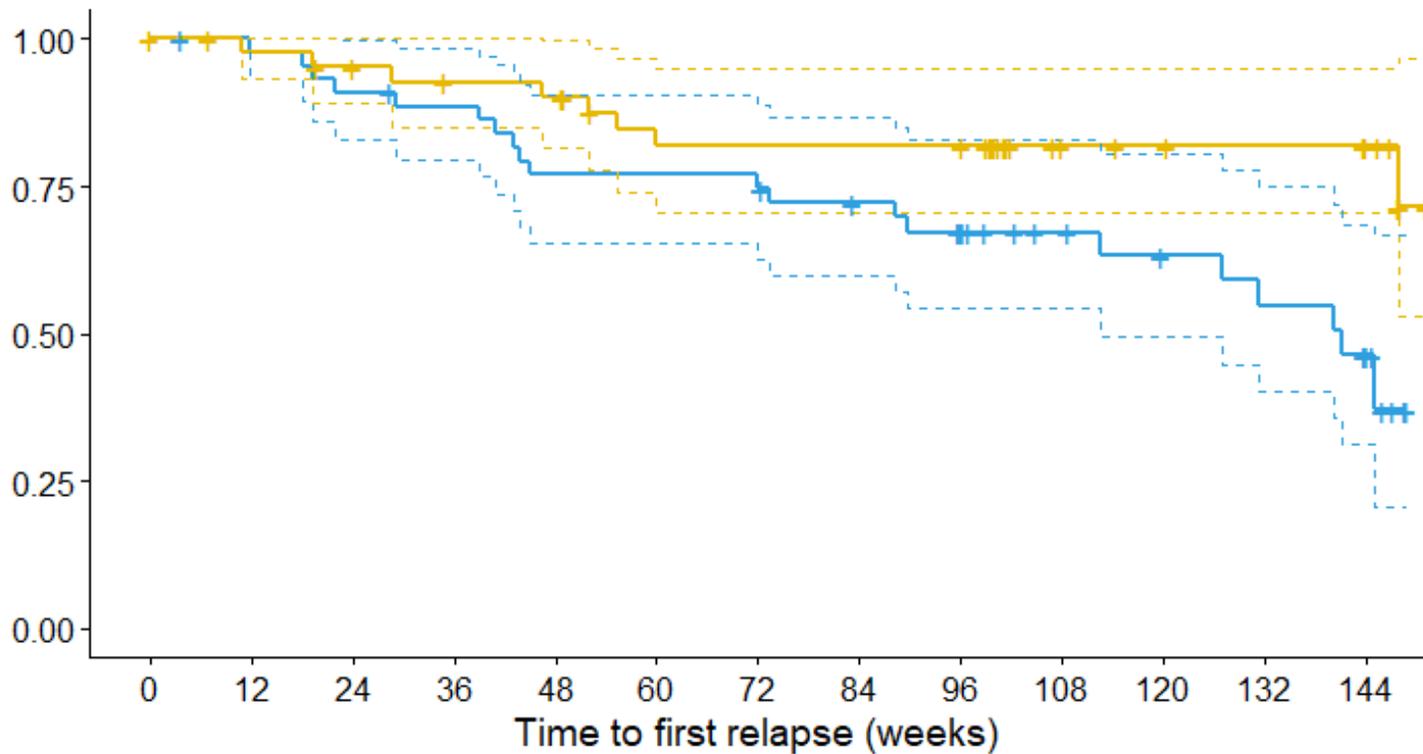
634

635 All the adjusted analyses were corrected for sex, age at RIS diagnosis, MS family history, EDSS, T2-lesion volume (log-transformed), and presence of
636 gadolinium-enhancing lesions at baseline.637 Means, differences, and p-values were calculated using a generalized regression model, with the follow-up value as the dependent variable after
638 controlling for the corresponding baseline value and with an offset term to account for follow-up duration.

639

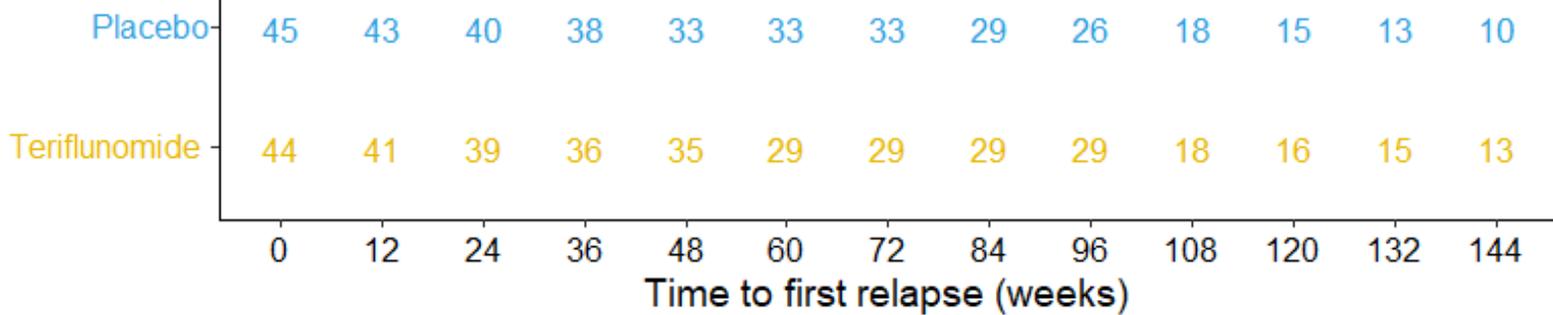
640 **Figure 1:** Kaplan-Meier estimates of time from randomization to the first demyelinating event
641 (unadjusted analysis)
642
643

Survival probability



Number at risk

Strata



Strata + Placebo + Teriflunomide

Figure S2. CONSORT flow diagram

