Journal of the Neurological Sciences 474 (2025) 123533

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Safety assessment of switching from fingolimod to siponimod: An Italian multicenter prospective study

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ARTICLE INFO

Keywords:
Secondary progressive multiple sclerosis
S1P receptor modulator
Fingolimod
Siponimod
Treatment switch
Safety

ABSTRACT

Introduction: Safety concerns have been raised regarding fingolimod to siponimod transition in people with Secondary Progressive Multiple Sclerosis (SPMS).
Objective: To explore factors associated with the choice of switching from fingolimod to siponimod and the safety of this sequencing.
Methods: We conducted a prospective observational study that included patients who had a confirmed diagnosis of SPMS at the time of study entry and had been treated with fingolimod for at least two years. Upon enrollment,

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https://doi.org/10.1016/j.jns.2025.123533
Received 2 February 2025; Received in revised form 28 April 2025; Accepted 5 May 2025
Available online 10 May 2025
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patients either continued fingolimod (comparator group) or transitioned to siponimod (switch group) and were followed up for six months to assess disease activity and changes in laboratory parameters.
Results: Out of 95 SPMS subjects, 42 (44.2 %) switched to siponimod at study entry. The switch group was younger and had more prior treatments than the comparator group ($p = 0.042$ and $p = 0.015$, respectively). Five subjects experienced disease activity (three in the switch group, two in the comparator). Patients switching to siponimod experienced a greater increase in GPT ($p = 0.015$) and GOT levels ($p = 0.041$) at 6 months. Four adverse events were reported: melanoma and grade IV lymphopenia in the comparator group, and grade IV lymphopenia and dizziness in the switch group.
Conclusion: During the 6-month observation period, switching from fingolimod to siponimod was safe in terms of disease reactivation and tolerability.

1. Introduction

Approximately 80 % of untreated relapsing-remitting Multiple Sclerosis (RRMS) subjects convert to a phase of irreversible disability accrual defined secondary progressive MS (SPMS) within 20 years from disease onset [1]. While high efficacy therapies have significantly reduced the conversion rate, most patients still progress to the SPMS stage. Until 2022, no disease-modifying therapies (DMTs) were approved for SPMS in Europe due to insufficient clinical trial evidence, leading to hesitancy in changing the diagnosis from RRMS to SPMS and discontinuing DMTs for RRMS [2,3]. Consequently, treatments effective in RRMS were often continued into the early stages of SPMS, despite their lack of proven benefit in this phase [2–4].

Although in Europe other agents, such as ocrelizumab and cladribine, are currently indicated for the treatment of SPMS [5,6], the approval of siponimod, a selective sphingosine-1-phosphate receptor (S1PR) modulator, might change this scenario [4]. European Medicines Agency (EMA) guidelines recommend treatment with siponimod in SPMS. Further, recent analyses have shown that switching to siponimod in active SPMS patients could be both clinically effective and economically advantageous [4–6].

Among the various treatment transitions, the switch from fingolimod to siponimod has been particularly debated due to their similar mechanisms of action and initial case studies indicating potential complications that require careful monitoring. Recent reports have highlighted instances of clinical or radiological disease reactivation in SPMS patients following the switch [7,8], as well as severe lymphopenia occurring one month after transitioning from fingolimod to siponimod [9]. However, comprehensive data on the clinical, radiological, and laboratory outcomes for MS patients undergoing this switch remain scarce.

To fill this gap of knowledge, we conducted a prospective observational study evaluating Italian MS neurologist treatment strategies and assessing safety parameters associated with switching from fingolimod to siponimod. First, we evaluated the proportion of enrolled subjects who switched from fingolimod to siponimod and examined the demographic and clinical factors associated with the decision to switch. Second, we assessed the clinical, radiological, and laboratory outcomes of SPMS patients following the switch, including the incidence of adverse events, providing comprehensive information on the safety and tolerability of this sequencing strategy.

2. Methods

2.1. Study design and participants

In this multicenter, prospective observational study, we consecutively enrolled subject diagnosed with SPMS from 14 Italian MS centers. The study enrollment began in April 2021 with the availability of siponimod on the market for SPMS subjects in Italy. According to the inclusion criteria, all participants had been undergoing fingolimod treatment for a minimum of two years. SPMS was diagnosed according to the EMA guidance criteria [10], which define SPMS as "patients exhibiting sustained disability progression—with or without superimposed relapses." In our protocol, sustained disability progression was defined as confirmed disability progression (CDP), i.e. an initial worsening of the Expanded Disability Status Scale (EDSS) score that was still present at a follow-up assessment 3 months later, independent of any acute relapse.

Exclusion criteria:

1. RRMS subjects.
2. SPMS subjects treated with DMTs other than fingolimod at the time of enrollment.
3. SPMS subjects who had been on fingolimod for less than two years at the time of enrollment.
4. SPMS subjects who switched to other DMTs than siponimod.

Once enrolled, participants either continued with fingolimod or switched to siponimod, based on the decision of the treating neurologist. Thus, two groups were identified: the "switch group" (comprising those who switched from fingolimod to siponimod) and the "comparator group" (consisting of those who remained on fingolimod).

At the time of enrollment (baseline), each center collected demographic data (age and sex) and MS history [age at onset, disease duration, number of previous DMTs, number of relapses in the 12 months prior to enrollment and EDSS score at baseline and 12 months prior to enrollment, and the latest magnetic resonance imaging (MRI) report available]. Furthermore, a laboratory draw report from the 3 months prior to enrollment was collected, including data on white blood cells (WBC), neutrophils, lymphocytes, monocytes, glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), gamma-glutamyl transferase (GGT), Immunoglobulins IgM, IgG, and IgA.

Then, enrolled subjects were prospectively followed up for six months to evaluate the occurrence of disease activity (relapse, new T2 lesion or gadolinium-enhancing lesion), adverse events or infections. At six months of follow-up, subjects underwent laboratory tests (blood cell and liver enzymes) and clinical evaluation with EDSS assessment.

Laboratory changes were expressed both as the difference between each six-month follow-up value and its corresponding baseline value, and as the number and percentage of subjects with abnormal levels classified according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [11], at six-month follow-up.

Clinical relapses were defined as new or worsening neurologic symptoms for at least 24 h in the absence of fever or infection.

Reports for brain and spinal cord (cervical and thoracic) MRI were collected when available from 12 months pre-study entry to 6 months after the enrollment. Neuroradiological activity was defined as the presence of new T2-weighted hyperintense lesions and/or T1-weighted Gadolinium enhancing (Gd+) lesions.

The reasons for switching to siponimod were listed in disease activity, disease progression, safety reason or intolerance and others. Disease activity was defined as either the presence of clinical relapse or radiological activity in the previous 12 months. Disease progression was defined as an increase in the EDSS score of at least 1.5 points for those with a baseline EDSS of 0, at least 1.0 point for those with a baseline EDSS between 1.0 and 5.5, or at least 0.5 points for those with a baseline EDSS between $\geq$6, in the previous 12 months [12].

The ethical Committee of the University of Campania "Luigi

Vanvitelli" approved the study protocol (n. 20,415/2022).

2.2. Statistical methods

Descriptive data are presented as mean with standard deviation or median with interquartile range (25th and 75th percentiles) for continuous variables, as appropriate, and as absolute and relative frequencies for categorical variables. Group differences in continuous variables were assessed using the Mann-Whitney *U* test. The distribution of frequencies and associations between categorical variables was evaluated using the chi-square test or Fisher's exact test, depending on the data type.

The factors associated with the presence of a predetermined outcome were evaluated using either a binary regression model or a linear regression model. The results are expressed as odds ratios with 95 % confidence intervals (CI) or as beta coefficients with standard errors and *p*-values. Analyses were conducted in R studio.

3. Results

3.1. Practice and rationale for switching

We included 95 SPMS subjects treated with fingolimod. Forty-two out of 95 (44.2 %) were switched to siponimod (61.9 % female) at the study entry. The remaining continued on fingolimod (60.4 % female). The switch group was significantly younger at enrollment (50.0 ± 6.97 years) compared to the comparator group (53.1 ± 8.14 years, $p = 0.042$). No significant difference in disease duration was observed. The number of previous treatments was higher in the switch group (2.2 ± 1.10) compared to the comparator group (1.7 ± 1.20, $p = 0.015$). No difference in disease activity was noticed between groups in the 12 months preceding the study entry. Demographic and clinical characteristics of patients are reported in Table 1.

In the switch group, the primary reason for switching was disease progression (88.1 %), followed by ineffectiveness due to activity (7.1 %), safety reasons or intolerance (2.4 %), and other reasons (2.4 %) (Fig. 1). The mean duration of washout before starting siponimod was 13.4 ± 22.74 days.

Table 1
Baseline characteristics of the study population. The table compares demographic and clinical characteristics between the switch group (patients transitioning to siponimod) and the comparator group (patients staying in fingolimod). Bold values indicate statistical significance.

Baseline characteristics				
		Switch group (No = 42)	Comparator group (No = 53)	p
Sex	Female	26 (61.9 %)	32 (60.4 %)	0.88
	Male	16 (38.1 %)	21 (39.6 %)	
Age at enrollment, y		50.0 ± 6.97	53.1 ± 8.14	**0.042**
Disease duration, y		20.6 ± 8.38	22.0 ± 11.12	0.75
Age at start date of fingolimod, y		43.9 ± 7.51	47.4 ± 8.17	0.05
EDSS in the previous 12 months		5.5 (5.0–6.0)	6.0 (4.5–6.5)	0.12
EDSS at diagnosis		2.5 (2.3–4.0)	2.5 (1.5–4.0)	0.36
EDSS at study entry		5.5 (5–0 - 6.0)	6.0 (4.5–6.5)	–
EDSS 6 months after study entry		6 (5.0–6.5)	6 (5.5–6.5)	–
No. of relapses in the previous 12 months		0.1 ± 0.40	0.3 ± 0.52	0.10
No. of previous treatments (except fingolimod)		2.2 ± 1.10	1.7 ± 1.20	**0.015**
Comorbidities	No	9 (29.0 %)	11 (37.9 %)	0.47
	Yes	22 (71.0 %)	18 (62.1 %)	

No, Number; *p*, p-value; *y,* years; *EDSS*, Expanded Disability Status Scale.

3.2. Disease activity and laboratory changes

Over the follow-up period, only five subjects experienced a relapse: three in the switching group and two in the comparator group. Importantly, two of these subjects discontinued therapy. Of these five subjects, only one (from the switch group) experienced a relapse in the year prior to enrollment. Furthermore, none of them presented with new T2 or Gd + lesions in the last MRI before enrollment.

Forty-eight subjects underwent an MRI exam after 6-month follow-up, with 25 of them in the switch group. None of these subjects showed new T2 or Gd + lesions, indicating stable neuroradiological outcomes across groups.

Laboratory data changes from baseline to the end of the follow-up are reported in Table 2. Patients switching to siponimod experienced a greater increase in both GPT (4.0 [−12.0–89.0] vs. -1.5 [−31.0–23.0], $p = 0.015$) and GOT levels (3.0 [−17.0–37.0] vs. -2.0 [−75.0–7.0], $p = 0.041$) compared to those continuing fingolimod. Changes in WBC, neutrophils, monocytes, lymphocytes, IgA, IgG, IgM, and GGT levels did not show significant differences between the groups.

The analysis of factors associated with liver enzyme serum level and lymphocyte counts at six months is reported in Table 3.

The presence of lymphopenia (grade I or higher) and the levels of GOT and GPT at 6 months after study entry were all significantly associated with their respective baseline values. Additionally, both GOT and GPT were inversely associated with the number of previous disease-modifying treatments, with $\beta = -3.24$ (std. error = 1.29, $p = 0.012$) for GOT and $\beta = -10.97$ (std. error = 2.34, $p < 0.001$) for GPT. Moreover, lower GOT and GPT values were observed in the comparator group compared to the switch group, with $\beta = -9.70$ (std. error = 2.94, $p = 0.001$) for GOT and $\beta = -22.45$ (std. error = 5.36, $p < 0.001$) for GPT.

Looking at the percentage of subjects experiencing grade III lymphopenia or higher (CTCAE v5.0), no significant difference was found between the groups (fingolimod: 24.5 % vs siponimod: 33.3 %; adjusted $p = 0.46$; Table 4). Grade 4 lymphopenia was rarely reported, with 2.4 % of patients (1 subject) in the switch group and 1.9 % (1 subject) in the comparator group (Table 4). No subjects experienced an increase in liver enzyme serum levels >200 U/L (grade III or higher, CTCAE v5.0, Table 4).

3.3. Therapy discontinuation and adverse events

During the first six months of the observation period, the overall rate of therapy discontinuation was low, with 95.8 % of the total cohort continuing treatment (91 out of 95 subjects). Specifically, 97.6 % (41 out of 42) of patients in the switch group and 94.3 % (50 out of 53) in the comparator group maintained their respective therapies. Reasons for discontinuation included melanoma (1 subject), new relapse (1 subject) and disease progression (1 subject) in the comparator group, while grade IV lymphopenia (1 subject) was the sole reason for discontinuation in the switch group.

Adverse events were noted in both groups, with the comparator group reporting a case of melanoma and one case of severe lymphocytopenia (grade IV). In the switch group, there was a case of severe lymphocytopenia (grade IV), and a case of dizziness.

Infections during the observation period included a urinary tract infection lasting 14 days in the comparator group. In the switch group, there were three reported infections: a urinary tract infection lasting 19 days and two gastrointestinal infections, both lasting 19 days.

4. Discussion

This cohort study provides insights into the safety and rationale behind the decision to switch from fingolimod to siponimod in patients

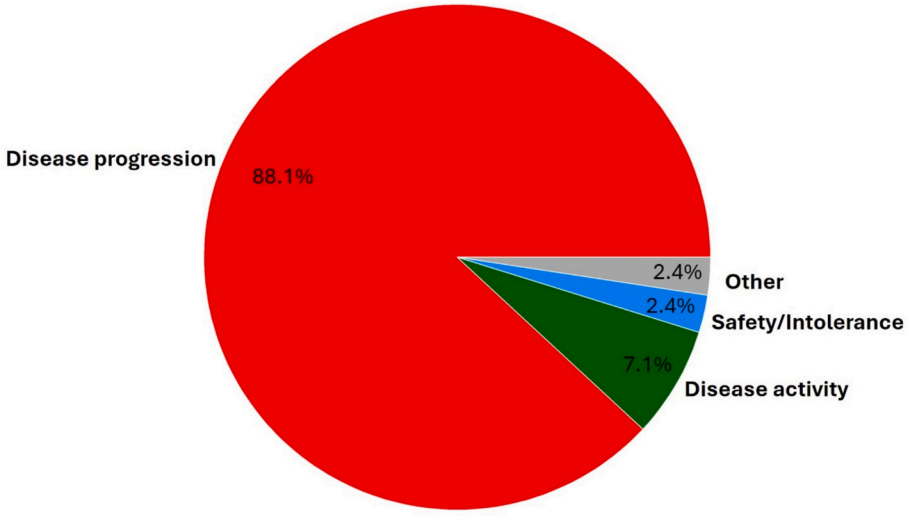

Fig. 1. Reasons for switching from fingolimod to siponimod in patients with SPMS.

Table 2
Changes in laboratory data. The table presents variations in laboratory parameters for the switch group (patients transitioning to siponimod) and the comparator group (patients staying in fingolimod). Bold values indicate statistical significance.

Changes in laboratory data			
	Switch group (No = 42)	Comparator group (No = 53)	p
WBC	149.0 (−4520.0–3690.0)	300.0 (−1780.0–3440.0)	0.73
Neutrophils	220.0 (−1685.0–3630.0)	−50.0 (−1420.0–1779.0)	0.27
Monocytes	30.0 (−187.0–280.0)	5.0 (−250.0–220.0)	0.20
Lymphocytes	−60.0 (−569.0–380.0)	0.0 (−828.0–500.0)	0.11
IgA	−33.0 (−37.0–0.0)	−6.0 (−6.0 - -6.0)	0.80
IgG	−96.0 (−184.0–47.0)	−52.0 (−100.0–29.0)	0.40
IgM	18.0 (−12.0–85.0)	−2.5 (−4.0 - -1.0)	0.80
GOT	3.0 (−17.0–37.0)	−2.0 (−75.0–7.0)	**0.041**
GPT	4.0 (−12.0–89.0)	−1.5 (−31.0–23.0)	**0.015**
GGT	3.0 (−27.0–23.0)	1.5 (−55.0–63.0)	0.72

No, Number*; p*, *p*-value; *WBC*, White Blood Cells; *GOT*, Glutamic Oxaloacetic Transaminase; *GPT*, Glutamic Pyruvic Transaminase; *GGT*, Gamma-glutamyl Transferase; *IgA*, Immunoglobulin A; *IgG*, Immunoglobulin G; *IgM*, Immunoglobulin M.

Table 3
Factors associated with laboratory data changes at 6 months follow-up. The table reports the associations between selected variables and changes in lymphopenia, GOT, and GPT levels. Bold values indicate statistical significance.

Factors associated with laboratory data changes at 6 months			
	Lymphopenia	GOT	GPT
	OR (95 %CI); p	*β (std. error); p*	*β (std. error); p*
Sex (Males vs Females)	1.08 (0.39–2.99); 0.89	0.27 (2.75); 0.92	−0.31 (5.23); 0.95
Age at enrollment, y	0.94 (0.76–1.16); 0.57	0.20 (0.53); 0.71	0.26 (0.94); 0.79
No. of previous treatments (except fingolimod)	1.05 (0.65–1.68); 0.85	−3.24 (1.29); **0.012**	−10.97 (2.34); **<0.001**
Age at Fingolimod start, y	1.07 (0.87–1.32); 0.52	−0.20 (0.55); 0.71	−0.04 (0.98); 0.97
Group (Comparator vs Switch)	1.47 (0.53–4.06); 0.46	−9.70 (2.94); **0.001**	−22.45 (5.36); **<0.001**
Lymphocytes (absolute number) at baseline	1.00 (1.00–1.01); **0.004**	–	–
GOT (value) at baseline	–	0.27 (0.08); **0.001**	–
GPT (value) at baseline	–	–	0.90 (0.14); **<0.001**

OR, Odds Ratio; *CI,* Confidence Interval; *β*, Beta coefficient; *p*, p-value; *std. error*, Standard Error; *y,* years; *No,* Number; *GOT*, Glutamic Oxaloacetic Transaminase; *GPT*, Glutamic Pyruvic Transaminase.

with SPMS. Several concerns have been recently raised regarding this sequencing, primarily based on case reports [7–9]. Nevertheless, our findings suggest that this sequencing is safe, with no evidence of disease reactivation or severe adverse events over a 6-month follow-up period.

Across 14 Italian MS centers, less than 50 % of these patients were switched to siponimod. Our findings reveal that this switch is predominantly driven by disease progression rather than disease activity or intolerance, with the switch group being significantly younger and having undergone more prior treatments compared to people continuing fingolimod. The therapeutic strategy observed across the Italian MS centers may be influenced by the reimbursement policy of the Italian National Health Service (SSN), which covers siponimod only for patients under 60 years old. This policy likely contributes to the preference for younger patients when switching from fingolimod to siponimod. Nevertheless, post-hoc analyses from the EXPAND trial have shown that siponimod efficacy and safety are consistent across various age groups and disease durations [13]. Thus, while the clinical decision-making in Italy may be shaped by individual patient characteristics and the specific regulatory context, it may not be fully aligned with the trial evidence, which supports siponimod use across a broader age range.

Efficacy and safety data from the pivotal clinical trials are generally similar for the four S1P agents [14]. However, because no head-to-head clinical studies were conducted, direct efficacy comparisons cannot be made. Our analysis suggests that switching from fingolimod to siponimod does not result in significant clinical reactivation of the disease, as evidenced by the low relapse rate and the absence of new T2 or Gd + lesions on MRI over the six-month follow-up period. This stability is a reassuring indicator for clinicians considering this switch in the treatment of SPMS. Patients who switched to siponimod experienced a significant increase in GOT and GPT levels compared to those who remained on fingolimod, although absolute lymphocyte count was similar between the groups. The lack of significant differences in the frequency of moderate or severe (grade III or higher lymphopenia and grade III or higher liver enzyme elevation) laboratory changes between the groups further supports the notion that while the risk is present, it is not markedly higher in those switching from fingolimod to siponimod.

Table 4
Distribution of laboratory change grade. No significant differences were observed between the two groups in terms of lymphocyte, GOT, and GPT abnormality. The distribution of lymphopenia grades was comparable across groups, with grade 2 being the most frequent in both (switch: 50.0 % and comparator: 50.9 %). Mild increase in GOT and GPT values were slightly more common in the switch group (respectively 12.9 % vs 2.7 % and 33.3 % vs 21.1 %), but these differences were not statistically significant.

Laboratory parameters	CTCAE v5.0 grades	Switch group		Comparator group		*p*
		No	*%*	*No*	*%*	
Lymphocytes	> LLN (1000/mm^3)	3	(7.1 %)	5	(9.4 %)	0.85
	Grade I (<LLN – 800/mm^3; <LLN – 0,8 × 10^9/L)	4	(9.5 %)	8	(15.1 %)	
	Grade II (800–500/mm^3; 0,8–0,5 × 10^9/L)	21	(50.0 %)	27	(50.9 %)	
	Grade III (500–200/mm^3; 0,5–0,2 × 10^9/L	13	(31.0 %)	12	(22.6 %)	
	Grade IV (<200/mm^3; <0,2 × 10^9/L)	1	(2.4 %)	1	(1.9 %)	
GOT	<ULN (40 IU/L)	27	(87.1 %)	36	(97.3 %)	0.17
	Grade I (>ULN–3,0 × ULN)	4	(12.9 %)	1	(2.7 %)	
GPT	<ULN (40 IU/L)	22	(66.7 %)	30	(78.9 %)	0.29
	Grade I (>ULN–3,0 × ULN)	11	(33.3 %)	8	(21.1 %)	

CTCAE, Common Terminology Criteria for Adverse Events; *p*, p-value; *No*, Number; *LLN*, Lower Limit of Normal; *ULN*, Upper Limit of Normal; *GOT*, Glutamic Oxaloacetic Transaminase; *GPT*, Glutamic Pyruvic Transaminase.

The occurrence of severe lymphocytopenia in one patient in both groups, highlights the importance of close hematological monitoring, particularly in switching patients with a low baseline lymphocyte count, a predictor of lymphopenia at six months.

Both groups reported few and mild infections, with no significant differences. The low rate of therapy discontinuation in both groups underscores the overall tolerability of siponimod, even in a population that had previously been on a similar S1P modulator, fingolimod.

Overall, the switch did not result in significant differences in disease activity, clinically relevant laboratory changes, or infection rates, highlighting its feasibility and safety. These findings support the sequencing from fingolimod to siponimod as a viable treatment strategy for patients with SPMS.

The strengths of our study include the inclusion of data from 14 MS centers, providing a comprehensive view of clinical practices across Italy, and the use of a comparison group of subjects who remained on fingolimod with a comparable mean treatment duration. This design effectively controls the sequencing effect between fingolimod and siponimod, allowing for a more accurate assessment of the safety and tolerability of the switch. However, our study has some important limitations. First, the relatively short follow-up period did not allow for an in-depth exploration of the long-term effects of the two agents on disease progression. Second, the observational design and lack of randomization may have introduced selection bias, potentially affecting the comparability between groups. Third, due to the multicenter nature of the study, there were gaps in certain baseline characteristics and follow-up MRI data, which may limit the generalizability of our findings.

5. Conclusions

This multicenter study reveals that only a subset of SPMS patients previously treated off-label with fingolimod were transitioned to siponimod following its introduction to the Italian market.

The clinical decision-making in Italy might be influenced by both patient characteristics and regulatory factors. Importantly, the study confirms that switching from fingolimod to siponimod in SPMS patients is safe and well-tolerated, with no significant increase in disease activity.

These findings offer guidance for clinicians managing SPMS, particularly in transitioning between S1P modulators. Further research with extended follow-up and comprehensive immune monitoring is needed to fully assess the long-term safety and efficacy of this approach.

S1PRm study group

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Funding statement

No funding.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

Data availability: Available upon reasonable request to the corresponding author.

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