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Prognostic value of the neutrophil/lymphocyte ratio in enteropancreatic neuroendocrine tumors

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Accessible prognostic tools are needed to individualize treatment of neuroendocrine tumors (NETs). Data suggest neutrophil/lymphocyte ratios (NLRs) have prognostic value in some solid tumors, including NETs. In the randomized double-blind CLARINET study (NCT00353496; EudraCT 2005-004904-35), the somatostatin analog lanreotide autogel/depot increased progression-free survival (PFS) compared with placebo in patients with inoperable or metastatic intestinal and pancreatic NETs (grades 1–2, Ki-67<10%). The exploratory post-hoc analyses presented here evaluated the prognostic value of NLR in the CLARINET study cohort, in the context of and independently from treatment. Kaplan–Meier PFS plots were generated for patients with available NLR data, in subgroups based on NLR values, and 24-month survival rates were calculated. *P* values and hazard ratios for prognostic effects were generated using Cox models. 31216222Baseline characteristics were balanced between lanreotide autogel/depot 120 mg (*n*=100) and placebo (*n*=101) arms. Irrespective of treatment, raw 24-month PFS rates were comparable across subgroups based on NLR tertiles [37.3% (low), 38.8% (middle), 38.8% (high); *n*=67 per group] and NLR cutoff of 4 [38.1% (NLR≤4; *n*=176), 40.0% (NLR>4; *n*=25)]. Furthermore, NLRs were not prognostic in Cox models, irrespective of subgroups used. The therapeutic effect of lanreotide autogel/depot 120 mg was independent of NLRs (*P*>0.1). These exploratory post-hoc analyses in patients with advanced intestinal and pancreatic NETs contrast with previous data suggesting NLR has prognostic potential in NETs. This may reflect the inclusion of patients with lower-grade tumors or use of higher NLR cutoff values in the current analysis.

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Introduction

Gastroenteropancreatic neuroendocrine tumors (NETs) are considered rare, although recent estimates from an analysis of the population-based Surveillance, Epidemiology, and End Results (SEER) database indicate an age-adjusted annual incidence rate of 6.98/100 000 in 2012 [1]. Data from SEER, as well as other sources, also indicate that the incidence of NETs is increasing [2]. For example, in England, the age-standardized incidence rate for NETs in 2015 was estimated to be 8.84 per 100 000, compared with 3.9 per 100 000 in 2001 [3]. Overall survival (OS) has also been increasing for NETs, probably due to earlier diagnosis and availability of a wider range of treatments, for distant gastroenteropancreatic NETs in particular. OS varies according to the stage of the NET, the grade and its location, with NETs of the small intestine generally associated with longer OS than those of the pancreas [1].

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Notwithstanding such differences in OS based on the tumor site, 5-year survival-plot data suggest there is primary-site heterogeneity, such that organ typing alone is an inadequate prognostic tool [4]. A clearer understanding of prognostic factors for OS and progression-free survival (PFS) in patients with NETs may therefore facilitate the implementation of treatment guidelines recommending the individualization of therapy [5].

Chronic inflammation appears to play a complex role in the natural history of NETs and other neoplasms. It can promote carcinogenesis and tumor growth, or suppress tumor initiation and progression, depending on the predominant immune cell types [6,7]. Enteroendocrine cells can be hyperstimulated by chronic inflammation, a setting that can result in hyperplasia, neoplastic transformation, and the increased occurrence of gastroenteropancreatic NETs [6,8,9]. These tumors are highly vascularized and express growth factors, proinflammatory cytokines, and tyrosine kinase receptors that might be involved in tumor pathogenesis [10,11]. Elevated levels of inflammatory markers, such as C-reactive protein, vascular endothelial growth factor, and interleukins, have been associated with poor outcomes in various solid tumors, including NETs [11–13]. Relative levels of immune cells, as measured by platelet/lymphocyte ratio and neutrophil/lymphocyte ratio (NLR), for example, can similarly be incorporated in inflammation-based prognostic scores [12–14]. Indeed, studies suggest NLR, an easily accessible marker of inflammation, has a prognostic value in a variety of solid tumors [14–17], including NETs [18–23].

The Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumours (CLARINET) was a large, randomized, double-blind trial involving over 200 patients with enteropancreatic NETs [24]. In this study, PFS was longer in patients treated with the somatostatin analog lanreotide autogel (depot in the USA) 120 mg every 28 days compared with placebo. The CLARINET study provided robust evidence of the antitumor effects of lanreotide autogel/depot 120 mg, underpinning its position as a first-line medical therapy [5], but the study also provided an invaluable dataset for assessing which patients are most likely to benefit from the treatment. The aim of the post-hoc analyses presented here was thus to evaluate the prognostic value of NLR in intestinal and pancreatic NETs, both in the context of and independently from treatment, using data from the CLARINET study.

Methods

Overview of the CLARINET study

As reported in detail previously, the CLARINET study was an international, 96-week randomized, double-blind, placebo-controlled phase-3 trial (ClinicalTrials.gov: NCT00353496; EudraCT 2005-004904-35) [24]. Patients had metastatic or locally advanced well- or moderately differentiated nonfunctioning somatostatin receptor-positive NETs (originating in the pancreas, midgut, or hindgut, or of unknown origin) with a Ki-67 value of up to 10% (grade 1 or 2). Disease-progression status was documented prior to treatment onset, at baseline and every 3 months on therapy (or placebo) using response evaluation criteria in solid tumors (RECIST) version 1.0. Patients received lanreotide autogel/depot 120 mg (fixed dose) or placebo by deep subcutaneous injection once every 28 days for 96 weeks or until progressive disease (PD; as assessed using RECIST 1.0) or death. PFS was defined as time from first treatment administration to death/centrally assessed PD.

As stated previously [24], the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Trial documentation was approved by the institutional review board at each study site.

Neutrophil/lymphocyte ratio assessment and relationship to progression-free survival

Hematology tests were conducted at baseline and throughout the study and were assessed centrally [24]; assessments included white blood cell (WBC) count with differential cell count.

Post-hoc exploratory analyses of NLR were conducted using data from all patients in the intention-to treat (ITT) population (all patients randomly allocated to treatment) with data available for absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) at baseline. NLR was calculated as ANC/ALC, a formula previously shown to have predictive power in patients with cancer [25]. The effect of NLR was investigated in patient subgroups based on the tertiles of the CLARINET study cohort, as well as in subgroups with elevated or nonelevated NLR. The cutoff value of 4 in the latter subgroups was the median cutoff from a meta-analysis of 100 studies of NLR and clinical outcome in solid tumors [25]. PFS plots were generated for subgroups based on NLR values using the Kaplan–Meier method, and raw survival rates at 24 months were calculated. *P* values and hazard ratios for prognostic effects were obtained using Cox proportional hazards models with terms for treatment along with each NLR parameter. Cox proportional hazards models including an interaction term were used to assess the potential influence of NLR on the treatment effect.

Results

Patients and baseline neutrophil/lymphocyte ratio

Baseline characteristics of the overall CLARINET study population have been reported previously and were similar in the two treatment groups [24]. NLR was calculable for 201/204 patients in the ITT population (lanreotide autogel/depot 120 mg, $n = 100$; placebo, $n = 101$); most patients [$n = 176$ (88%)] did not have an elevated NLR at baseline (Table 1). Baseline characteristics were broadly similar in patients with NLR ≤4 or >4, although a higher proportion of patients in the >4 group were men,

Table 1 Baseline characteristics of the study participants, according to baseline neutrophil/lymphocyte ratio[a]

Characteristic	NLR≤4 (n=176)	NLR>4 (n=25)
Age in years	62.8±10.2	62.8±11.9
Sex		
Men	86 (48.9)	20 (80.0)
Women	90 (51.1)	5 (20.0)
Treatment		
Lanreotide autogel/depot 120 mg	88 (50.0)	12 (48.0)
Placebo	88 (50.0)	13 (52.0)
BMI in kg/m^2	27.1±5.5	25.9±4.0
WHO performance score		
0	149 (84.7)	17 (68.0)
1	25 (14.2)	8 (32.0)
2	2 (1.1)	0 (0)
Primary tumor location		
Pancreas	80 (45.5)	8 (32.0)
Midgut	62 (35.2)	11 (44.0)
Hindgut	13 (7.4)	1 (4.0)
Other/unknown	21 (11.9)	5 (20.0)
Tumor grade[b]		
G1	121 (68.8)	17 (68.0)
G2	53 (30.1)	8 (32.0)
Missing	2 (1.1)	0 (0)
Hepatic tumor load		
≤25%	121 (68.8)	13 (52.0)
>25%	55 (31.3)	12 (48.0)
Time since diagnosis in months	34.2±43.3	29.9±49.1
Progressive disease at baseline		
Yes	7 (4.0)	1 (4.0)
No	169 (96.0)	24 (96.0)
Previous therapy at entry		
Yes	26 (14.8)	6 (24.0)
No	150 (85.2)	19 (76.0)

Data are mean±SD or n (%) patients.
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; HPF, high-power fields; NLR, neutrophil/lymphocyte ratio; WBC, white blood cell count.
[a]Based on the intention-to-treat population, excluding patients with missing NLR values (NLR could not be calculated for two patients in the placebo group and one in the lanreotide group owing to missing ALC, ANC or WBC data).
[b]G1=mitotic count <2 mitoses per 10 HPF or Ki-67 ≤2%, G2=mitotic count 2–20 mitoses per 10 HPF or Ki-67 >2–20% (patients in this study had Ki-67 only up to 10%).

Table 2 Effect of treatment and neutrophil/lymphocyte ratio on progression-free survival

Parameter	Hazard ratio [95% CI]	P value
Cox proportional hazards model without interaction		
Lanreotide autogel/depot 120 mg (compared with placebo)	0.444 [0.288; 0.685]	0.0002
NLR (tertiles)		0.6692
Middle tertile (compared with low)	1.197 [0.718; 1.997]	
High tertile (compared with low)	1.257 [0.746; 2.118]	
NLR >4 (compared with ≤4)	1.167 [0.634; 2.149]	0.6195
Cox proportional hazards model with interaction		
Interaction: treatment group–NLR tertile	N/A	0.1042
Interaction: treatment group–NLR ≤ or >4	N/A	0.4335

Patients with NLR data available at baseline were included (n=201). Cox proportional hazards models were adjusted for the following baseline factors: progressive disease (yes/no); prior therapy for nonfunctioning NET (yes/no); age; sex; BMI; time since diagnosis; duration of exposure to treatment.
CI, confidence interval; N/A, not applicable; NLR, neutrophil/lymphocyte ratio.

and those with high NLRs tended to be patients with a higher hepatic tumor load and a WHO performance score ≥1 (between-group differences were not tested for statistical significance). Assigning patients to subgroups based on baseline NLR tertiles (n=67 per group) resulted in the following designations: low NLR, <1.94; middle NLR, 1.94–2.96; high NLR, >2.96.

Progression-free survival according to treatment and neutrophil/lymphocyte ratio

Results of the Cox proportional hazards modeling (Table 2) showed that, in accordance with the hazard ratio of 0.47 [95% confidence interval (CI): 0.30, 0.73] reported in the overall CLARINET study population [24], lanreotide autogel/depot 120 mg significantly prolonged PFS compared with placebo after adjusting for baseline NLR [hazard ratio=0.44 (95% CI: 0.29, 0.69), P=0.0002]. Comparison of each of the middle and high tertiles of baseline NLR with the low tertile showed that baseline NLR had no prognostic influence on PFS (P=0.67). The same result was found when comparing NLR according to the cutoff value of 4 (P=0.62), although it should be noted that only 25 patients had NLR >4. There was no interaction between treatment group and NLR tertile or NLR ≤4/>4 (Table 2).

The findings from the Cox proportional hazards modeling, in which baseline NLR was not prognostic for PFS, were corroborated by the overall proportions (raw rates) of patients surviving without PD at 96 weeks according to baseline NLR. Across subgroups based on NLR tertiles (irrespective of treatment, n=67 per tertile), 37.3, 38.8, and 38.8% of patients in low, middle, and high tertiles, respectively, survived without PD at 96 weeks. Similarly, raw survival rates for patients with NLR ≤4 and >4 were 38.1% (n=176) and 40.0% (n=25), respectively (irrespective of treatment).

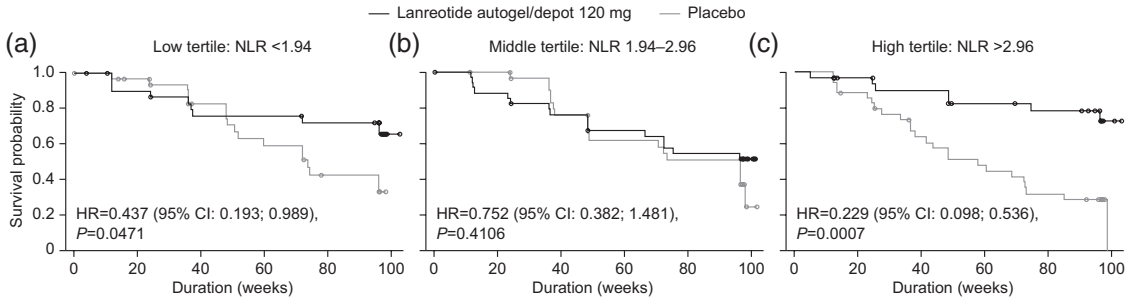
PFS plots for lanreotide autogel/depot 120 mg compared with placebo according to NLR tertile (Fig. 1) or NLR cutoff value of 4 (Fig. 2) showed a clear benefit for lanreotide autogel/depot 120 mg in each NLR subgroup (hazard ratios from 0.23 to 0.75, P≤0.05) except for the middle NLR tertile, in which the benefit did not reach statistical significance [hazard ratio=0.75 (95% CI: 0.38, 1.48), P=0.41]. In placebo-treated patients, median PFS was >73 weeks in the low and middle NLR tertiles, and 57 weeks in the high NLR tertile (Fig. 1).

Discussion

The post-hoc analyses presented here indicated that NLR had no prognostic value for PFS in patients with well differentiated, low-grade advanced intestinal and pancreatic NETs in the CLARINET study. PFS was not significantly different among patient subgroups according to NLR tertiles at baseline or according to an NLR cutoff value of 4. These findings were irrespective of treatment with lanreotide autogel/depot 120 mg, which extended PFS compared with placebo in patients with high or low NLR at baseline, and there was no interaction between treatment and NLR in the survival analysis.

The lack of prognostic value for NLR reported in the present analyses stands in contrast to findings from published data for other solid tumors [14–17], including NETs [18–23]. In a multivariate analysis of data from 52 Turkish

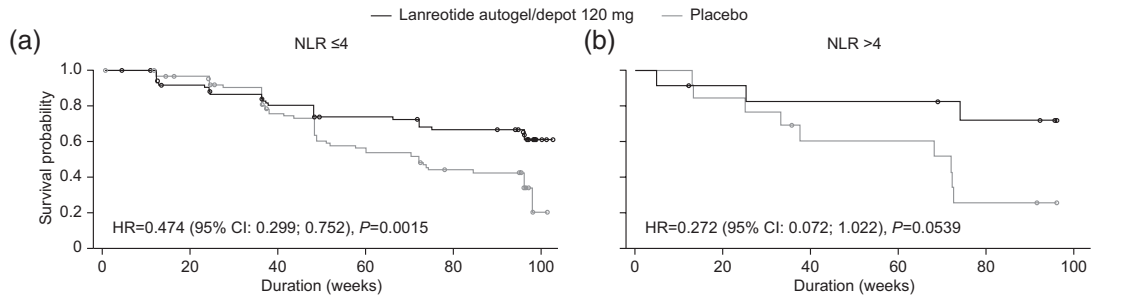
Fig. 1



	Patients, n			Events, n (%)			Median (95% CI) PFS, weeks		
NLR tertile:	Low	Middle	High	Low	Middle	High	Low	Middle	High
Lanreotide autogel/ depot 120 mg	33	35	32	9 (27)	16 (46)	7 (22)	NR (96.29; NR)	NR (66.29; NR)	NR (NR; NR)
Placebo	34	32	35	17 (50)	18 (56)	24 (69)	73.86 (50.71; NR)	96.14 (48.29; 97.71)	57.57 (37.71; 72.71)

PFS for lanreotide autogel/depot 120 mg compared with placebo in patients with (a) low NLR tertile, (b) middle NLR tertile and (c) high NLR tertile. Data are from the intention-to-treat population. CI, confidence interval; HR, hazard ratio; NLR, neutrophil/lymphocyte ratio; NR, not reached; PFS, progression-free survival.

Fig. 2



	Patients, n		Events, n (%)		Median (95% CI) PFS, weeks	
NLR tertile:	≤4	>4	≤4	>4	≤4	>4
Lanreotide autogel/ depot 120 mg	88	12	29 (33)	3 (25)	NR (96.29; NR)	NR (74.14; NR)
Placebo	88	13	50 (57)	9 (69)	72.14 (48.57; 96.14)	72.00 (33.29; NR)

Progression-free survival for lanreotide autogel/depot 120 mg compared with placebo in patients with (a) non-elevated NLR (≤4) and (b) elevated NLR (>4). Data are from the intention-to-treat population. CI, confidence interval; HR, hazard ratio; NLR, neutrophil/lymphocyte ratio; NR, not reached; PFS, progression-free survival.

patients with NETs, an NLR >5 was a significant negative independent predictor of 3-year OS [22]. Similarly, in a separate study of 132 Turkish patients with GEP-NETs, patients with an NLR value below the median (2.17) had a significantly longer PFS than patients with an NLR score above the median [21]. There was also a strong negative correlation between NLR and PFS outcome ($r = -0.862$; $P < 0.001$). In two further studies involving only patients with pancreatic NETs, an NLR >2.4 was a negative independent predictor for OS ($n = 147$) (20) and ≥2.4 for postoperative recurrence and liver metastases ($n = 58$) [18]. The seemingly discrepant findings may reflect between-study differences in the grades of NETs, the preponderance (96%) of data in the present analyses from patients with relatively stable disease (according to RECIST) in the 3–6 months before randomization, and the small number of patients with an elevated NLR [>4; $n = 25$ (compared with $n = 176$ for NLR ≤4)] at baseline. The prognostic benefit seen in previous studies may relate to inclusion of patients with higher tumor grades. Furthermore, most of the previous studies were retrospective analyses of data from patients treated in clinical practice and included relatively small numbers of patients with less homogeneous NET features compared

with CLARINET (e.g., patients with non-metastatic and metastatic disease) [18–23].

Among the 14 endocrine cell types characterized in the gastrointestinal tract and pancreas, enterochromaffin cells are the most frequent source of intestinal NETs and can also give rise to a minority of pancreatic NETs [26]. Nevertheless, hyperplastic and neoplastic pathways leading from these cells to NETs remain poorly defined. Chronic inflammation may cause hyperplasia in enterochromaffin cells, and these cells are involved in some inflammatory conditions of the gut, such as inflammatory bowel disease and celiac disease. Evidence for an epidemiologically relevant link between these conditions and enterochromaffin-cell tumors is, however, currently lacking [26].

Neutrophilia is thought to inhibit the cytolytic activity of tumor-infiltrating lymphocytes (TILs), providing a potential link between inflammation/high NLR and poor prognosis [25]. Tumor infiltration by cytotoxic $CD8^+$ T cells and $CD4^+$ follicular helper T cells correlates with positive patient prognosis in some solid tumors, and boosting the activity of these cells is the goal of some immunotherapy strategies [27,28]. The potential relevance of TILs in NETs has been investigated. Infiltration of midgut carcinoid tumors by $CD4^+$ and $CD8^+$ T cells has been demonstrated, occurring alongside an increase in regulatory $CD4^+$ $FoxP3^+$ (Treg) cells, which can hinder T cell antitumor activity [29]. Pancreatic NETs also display infiltration by $CD3^+$, $CD4^+$, and $CD8^+$ T cells [30]. Katz *et al*. [31] investigated the potential prognostic relevance of TILs following resection of well-differentiated pancreatic NET and NET liver metastases (NETLMs) (total $n = 126$), and found that 68% of NETs and 97% of NETLMs were infiltrated by T cells. When data from all patients with NETs were analyzed, the degree of T cell infiltration did not correlate with recurrence. However, in patients with intermediate-grade primary NETs, the presence of a dense $CD3^+$ T cell infiltrate was associated with longer median recurrence-free survival in univariate, but not in multivariate analyses. Levels of $CD4^+$ and $CD8^+$ T cells were not significantly associated with outcome. In NETLMs, low levels of Treg cells were predictive of prolonged survival but, again, only in univariate analyses. The authors proposed that protracted recurrence-free intervals in patients with low-grade NETs are likely to render the impact of TILs imperceptible or irrelevant. A similar argument may apply to the CLARINET study population, among whom disease progression was slow [24].

In tumor microenvironments, interaction between programmed death ligand 1 (PD-L1) and its receptor, programmed death 1 (PD-1), suppresses the activity of cytotoxic T cells and provides an immune escape for tumor cells. It has been shown that TILs in some types of NETs express PD-1 [32], with concomitant expression of PD-L1 detected in tumor cells [33,34]; this raises the possibility of using antibodies against PD-1 or PD-L1 to enhance an endogenous antitumor response leading to regression of high-grade NETs. However, it was recently shown that monotherapy with the PD-1 inhibitor, pembrolizumab, had only limited antitumor activity in patients with previously treated advanced NETs [35]. This suggests that immunomodulation may not be the most important mediator of the pathogenesis of NET and this may explain, in part, the lack of prognostic value of NLR in CLARINET.

As well as contributing to the development of immunotherapies for cancer, better characterization of the role of inflammatory responses in the initiation and progression of NET is needed to improve prognostic accuracy and identify the patients most likely to benefit from current treatments. Our study suggests that treatment with lanreotide autogel/depot 120 mg can extend PFS in patients with low or high NLR at baseline, and that NLR therefore cannot be used to predict the treatment effect.

Although based on a large and well described clinical trial cohort, weaknesses of our analysis are that it was conducted *post hoc*, and included relatively few patients with elevated NLRs. The value for elevated NLRs (>4) was based on the median NLR from a meta-analysis of studies in solid tumors [14], rather than a value determined using formal receiver-operating characteristics. The most sensitive and accurate cutoff NLR in NETs therefore remains to be determined. Interestingly, in a meta-analysis of studies evaluating the prognostic value of NLR in NETs, five of the six studies used cutoff values of ≤2.4 [23].

In conclusion, contrary to previous research involving patients with NETs, NLR in the present post-hoc analyses seemed to have no prognostic value for PFS in advanced intestinal and pancreatic NETs of grades 1–2 (Ki-67 < 10%) in the CLARINET study. This finding, although based on relatively few patients with NLR >4 ($n = 25$ compared with $n = 176$ for NLR ≤ 4), might be explained by lack of inflammation affecting the tumor microenvironment in this cohort and the relatively slow rate of disease progression in patients in the CLARINET trial. However, the results should be interpreted with caution in view of the exploratory, post-hoc nature of the analyses and the potential use of NLRs as a clinically useful marker in intermediate- and high-grade NETs will require further validation.

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Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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Conflicts of interest

M.E.P. reports the payment of study fees from Ipsen for the CORE study to her former institution, and has served as an advisory board member for Ipsen, Novartis, Lexicon and Pfizer. P.R. has served as an advisory board member for Novartis, Ipsen, AAA, Keocyt and ITM. J.C. reports the payment of study fees from Ipsen for the SPINET and FORTE studies to himself and to his institution, and has received payment for lectures from Ipsen. M.R. reports the payment of study fees from Ipsen for the CLARINET study. E.S. reports the payment of fees from Ipsen and Novartis. G.C. has served as an advisory board member for Ipsen, Novartis, AAA, Keocyt and Pfizer. E.M.W. has served as an advisory board member for Ipsen. J.B.C. reports the payment of study fees from Ipsen for the CLARINET study, and has served as an advisory board member for Novartis, Ipsen, Pfizer, Bayer, Eisai, Sanofi, Amgen, Merck and Advanced Accelerator Applications. L.W. reports the payment of fees from Ipsen. X.M.T.T. is a salaried employee of Ipsen. M.E.C. has served as an advisory board member for Ipsen, AAA, Novartis and Pfizer. There are no conflicts of interest for the remaining authors.

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