Lanreotide Autogel Every 6 Weeks Compared With Lanreotide Microparticles Every 3 Weeks in Patients With Well Differentiated Neuroendocrine Tumors

A Phase III Study

Emilio Bajetta, MD[1]
Giuseppe Procopio, MD[1]
Laura Catena, MD[1]
Antonia Martinetti, DSc[1]
Sara De Dosso, MD[1]
Sergio Ricci, MD[2]
Alberto S. Lecchi, MD[3]
Paolo F. Boscani, MD[3]
Stefano Iacobelli, MD[4]
Giacomo Carteni, MD[5]
Filippo De Braud, MD[6]
Paola Loli, MD[7]
Andreas Tartaglia, MD[8]
Roberto Bajetta, PhD[1]
Leonardo Ferrari, DSc[1]†

[1] Oncology Unit 2, Fondazione IRCCS "Istituto Nazionale dei Tumori", Milan, Italy.

[2] Oncology Unit, Santa Chiara Hospital, Pisa, Italy.

[3] Ipsen SpA, Milan, Italy.

[4] Oncology Unit, Santissima Annunziata Hospital, Chieti, Italy.

[5] Oncology Unit, Cardarelli Hospital, Naples, Italy.

[6] Oncology Unit, Istituto Europeo di Oncologia, Milan, Italy.

[7] Endocrinology Unit, Niguarda Cà Granda Hospital, Milan, Italy.

[8] Medical Unit, Bellaria Hospital, Bologna, Italy.

BACKGROUND. The noninferiority of a 6-week dosing schedule of lanreotide Autogel (Lan ATG) at a dose of 120 mg compared with a 3-week dosing schedule of lanreotide microparticles (Lan MP) at a dose of 60 mg was investigated in patients with neuroendocrine tumors (NET).

METHODS. Patients who had sporadic, well differentiated NET with a low grade of malignancy were recruited for this open-label, Phase III, multicenter trial. Patients were randomized to receive either 3 deep subcutaneous injections of Lan ATG (120 mg, every 6 weeks) or 6 intramuscular injections of Lan MP (60 mg, every 3 weeks). Tumor markers, tumor size, and symptoms were assessed between baseline and Week 18. Success was classified as a response that ranged from disappearance to an increase <25% in tumor marker, tumor size, or symptom frequency.

RESULTS. Sixty patients were randomized, and 46 patients completed the study. Both for tumor markers and for tumor size, Lan ATG was not inferior to Lan MP (55% and 59% of patients responded on tumor markers, respectively; 68% and 66% of patients responded on tumor size, respectively). There were too few symptomatic patients to compare carcinoid symptoms. Both treatments were tolerated well, and no safety concerns were identified.

CONCLUSIONS. Lan ATG at a dose of 120 mg every 6 weeks was as effective for controlling NET as Lan MP at a dose of 60 mg every 3 weeks. ***Cancer* 2006;107: 2474–81.** © *2006 American Cancer Society.*

KEYWORDS: neuroendocrine tumors, lanreotide Autogel, microparticles, somatostatin analogues.

Neuroendocrine tumors (NET) are rare malignant neoplasms that may secrete various amines and hormones according to their site of origin and histology. Symptoms of NET are caused mainly by their secretory activity; for example, the most common form of NET, carcinoid tumors, can cause the diarrhea and flushing of carcinoid

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†Deceased.

Address for reprints: Emilio Bajetta, MD, Medical Oncology Unit 2, Istituto Nazionale per lo Studio e la Cura dei Tumori di Milano, Via G. Venezian 1, 20133 Milan, Italy; Fax: (011) 39 0223902149; E-mail: emilio.bajetta@istitutotumori.mi.it

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syndrome.[1] Medical therapy for patients with NET has 2 main objectives: symptom control, which may be obtained with a decrease in circulating hormones and biogenic amines, and control of tumor growth. Between 80% and 90% of NETs express somatostatin receptors on their cell surfaces, allowing the somatostatin analogues lanreotide and octreotide to bind with high affinity to receptor subtypes 2 and 5.[2,3] These analogues inhibit the signal-transmission pathways mediated by the somatostatin receptors, causing a reduction in hormone and amine secretion that may ameliorate tumor-related syndromes and stabilize tumor growth.

Long-acting formulations of somatostatin analogues substantially lower the number of injections required to control NET. Lanreotide Autogel™ (Lan ATG) (Ipsen, Paris, France) is injected every 4 weeks at a dose of 60 mg, 90 mg, or 120 mg[4]; whereas lanreotide microparticles (Lan MP) (Ipsen) at a dose of 30 mg are injected every 7 to 14 days or every 14 to 28 days for the 60-mg dose (available only in some markets).[5–8] Therapeutic equivalence has been demonstrated between Lan ATG and Lan MP in the control of hormone hypersecretion in patients with acromegaly.[9,10] Recent studies also have suggested that Lan ATG at a dose of 120 mg is as effective for controlling acromegaly when injected every 4 to 8 weeks as Lan MP every 7 to 14 days.[11] However, both equivalence between the lanreotide formulations and the use of a dosing interval for Lan ATG extended beyond 4 weeks have yet to be investigated in NET. Therefore, the objective of the current study was to assess the equivalence between Lan ATG at a dose of 120 mg every 6 weeks and Lan MP at a dose of 60 mg every 3 weeks in patients with NET.

MATERIALS AND METHODS

Patients

Eligible patients age 18 years or older who had a histopathologic diagnosis of sporadic, well differentiated NET with low-grade of malignancy according to the 2000 World Health Organization international histologic classification. Eligibility criteria also included the absence of central nervous system metastasis and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2.[12] Newly diagnosed patients and previously treated patients could be enrolled; however, treatment with interferon, chemotherapy, or any other experimental drug was not allowed within 30 days prior to inclusion. Patients who had previously received lanreotide were ineligible. A wash-out period of 3 weeks or 6 weeks was sufficient after use of immediate-release or slow-release octreotide, respectively.

Previously treated patients were required to have evidence of progressive disease, which was defined as an increase $\geq$25% over the previous month's assessment of symptoms, and/or tumor markers and/or lesion size. Patients with uncontrolled diabetes mellitus or severe renal or liver impairment and women who were pregnant, breastfeeding, or had the potential to become pregnant during their participation in the study were ineligible. All patients gave written, informed consent, and the study was approved by the institutional ethics committee of each participating center. The study was conducted in full conformance with the principles of the Declaration of Helsinki[13] and according to good clinical practice guidelines.[14]

Study Design

The study was an open-label, Phase III trial that took place in 17 centers across Italy. After a screening visit and an appropriate wash-out period, patients were randomized by an interactive voice-response system to receive 1 of 2 treatments: Lan MP at a dose of 60 mg (intramuscular injections every 3 weeks) or Lan ATG at a dose of 120 mg (deep subcutaneous injections every 6 weeks). Injections occurred at Weeks 0, 3, 6, 9, 12, and 15 with Lan MP and at Weeks 0, 6, and 12 with Lan ATG. The duration of the study was 18 weeks, and final assessments occurred at Week 18. Patients were withdrawn from the study if they required other anticancer treatments (e.g. chemotherapy, interferon, or radiotherapy) during the study, if they received somatostatin analogues other than the study drug, or if progression of the underlying disease or a serious adverse event occurred.

Efficacy and Safety Assessments

Efficacy was measured according to the criteria proposed by the Italian Trials in Medical Oncology (ITMO) Group[15] for evaluating syndrome control (symptomatic response), marker control (biochemical response), and tumor control (objective response; bidimensional assessments). These criteria are reported in Table 1.

Patients with tumor-related carcinoid syndrome used a diary to record their symptoms. They ranked the presence and severity of diarrhea, flushing, perspiration, or any other symptoms on a 4-point scale during the 7 days before the Week 0, 6, 12, and 18 visits.

Chromogranin A (CgA) was the main tumor marker assessed, and its levels were determined from blood samples drawn at Weeks 0, 6, 12, and 18. The

TABLE 1
Criteria for Evaluating Tumor Response According to the Italian Trials in Medical Oncology Group*

Syndrome control (symptomatic response)
CR: Disappearance of all symptoms of syndrome
PR: Decrease by 50% in the number of symptoms or their severity
SD: Slight changes (worsening or improvement) of symptoms
PD: Increase by >25% of symptoms
Marker control (biochemical response)
CR: Marker levels within normal range
PR: Decrease by ≥50% of markers levels
SD: Slight changes (decrease by <50% or increase by <25%) of marker levels
PD: Increase by >25% of marker levels
Tumor control (objective response)
CR: Disappearance of all previous lesions
PR: Decrease by ≥50% of all previous lesions
SD: Decrease by <50% of all previous lesions or increase <25% of all previous lesions
PD: Increase by >25% of all previous lesions or onset of new lesions

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease.
* See Bajetta et al., 1993.[15]

analysis of CgA was performed at a central laboratory. The method used was an enzyme-linked immunosorbent assay from DAKO Automation (Glostrup, Denmark) for the quantitative determination of CgA in human plasma. The normal range was from 2 U/L to 18 U/L.

Concentrations of 5-hydroxyindoleacetic acid (5-HIAA) in the urine over 24 hours were assessed only in symptomatic patients. If they were tested for 5-HIAA, then patients were asked to amend their diet for the 3 days before the test, so that it would not interfere with the test. Thus, patients were asked not to consume coffee, tea, alcohol, chocolate, vanilla, bananas, tomatoes, peanuts, walnuts, almonds, liver, or smoked fish. When appropriate, other markers were determined: These included calcitonin, gastrin, and glucagon.

Tumor size was measured by using either computerized axial tomography (CT), magnetic resonance imaging (MRI), X-ray, echotomography or, in some patients, by using esophagogastroduodenoscopy or bone scan. This assessment was performed at screening if such data had not been collected within 30 days prior to screening, and evaluations were repeated at Weeks 9 and 18. The same assessment method was used at each time point: If different assessment methods were used, then the patient was not considered evaluable. Progression-free survival (PFS) and overall survival were determined both for tumor markers and for tumor size.

Quality of life (QoL) was evaluated at Week 0, 6, 12, and 18 visits by means of the European Organization for Research and Treatment in Cancer (EORTC) QoL questionnaire (QLQ-C30). Patients were questioned using the functional scales (physical, role, cognitive, emotional, and social function), the symptom scale, the financial difficulties scale, and the global health-related QoL scale. Tolerability was assessed through the recording of adverse events throughout the study. Blood samples drawn at Weeks 0, 6, and 18 were used for standard biochemical and hematologic assessments. Gall bladder echotomography studies were obtained at the same time as the blood samples.

Analytic and Statistical Plans

The primary endpoint of the study was to demonstrate the noninferiority of Lan ATG at a dose of 120 mg compared with Lan MP at a dose of 60 mg, as assessed using the symptomatic, biochemical, or objective responses, according to the ITMO criteria. Data were processed by using the Dunnett and Gent test, grouping responses as successes (complete symptomatic response [CR], partial response [PR], stable disease [SD]) or failures (progressive disease or interruption of treatment for progressive disease or death). Treatment with Lan ATG at a dose of 120 mg was considered noninferior to Lan MP at a dose of 60 mg if the lower confidence limit (CL) of the difference between Lan ATG at a dose of 120 mg and Lan MP at a dose of 60 mg, for the proportion of patients whose treatment was successful, was included within the noninferiority margin of 0.20.

For the sample size calculation, it was estimated that the proportion of positive responses was ≥85% in the Lan MP treatment arm, with an expected difference of 3% compared with the with Lan ATG treatment arm. The α level was set to 5% (1-sided), and the power was set to 80%. The primary analysis population was the intention-to-treat (ITT) population: This comprised all randomized patients who received at least 1 dose of study drug and for whom the baseline assessment and at least 1 postbaseline assessment were available or patients who discontinued the study because of death or inefficacy. The safety population comprised all randomized patients who received at least 1 dose of study drug. Patients who discontinued treatment or who were lost to follow-up were considered to have had a treatment failure. A "last observation carried forward" approach was adopted for all other missing data. The Dunnett and Gent test was used to determine proportional noninferiority using 2×2 contingency tables. Differences between treatments were determined by comparing the 95% lower CL with the noninferiority margin; comparisons between survival curves were made using the log-rank test. Quantitative analyses

TABLE 2
Patient Characteristics at Baseline (Safety Population)

Characteristic	No. of patients (%)		
	Lan MP, 60 mg (N = 30)	Lan ATG, 120 mg (N = 30)	Total (N = 60)
Gender			
Male	16 (53.3)	24 (80.0)	40 (66.7)
Female	14 (46.7)	6 (20.0)	20 (33.3)
Race			
White	30 (100.0)	29 (96.7)	59 (98.3)
Black	0 (0.0)	1 (3.3)	1 (1.7)
Age (mean ± SD), y	58.4 ± 14.9	57.5 ± 13.1	57.9 ± 13.9
Tumor markers			
Over the clinical cutoff value	28 (93.3)	25 (83.3)	53 (88.3)
Chromogranin A	28 (93.3)	25 (83.3)	53 (88.3)
Urinary 5-HIAA	1 (3.3)	7 (23.3)	8 (13.3)
Others	3 (10.0)	5 (16.7)	8 (13.3)
Site of primary tumor			
Unknown	6 (20.0)	5 (16.7)	11 (18.3)
Known	24 (80.0)	25 (83.3)	49 (81.7)
Bowel	10 (33.3)	12 (40.0)	22 (36.7)
Pancreas	9 (30.0)	7 (23.3)	16 (26.7)
Lung	4 (13.3)	4 (13.3)	8 (13.3)
Other	1 (3.3)	2 (6.7)	3 (5.0)
Metastases present	27 (90.0)	30 (100.0)	57 (95.0)
Carcinoid syndrome			
Present	7 (23.3)	12 (40.0)	19 (31.7)
Diarrhea	3 (10.0)	10 (33.3)	13 (21.7)
Flushing	5 (16.7)	8 (26.7)	13 (21.7)
Other	3 (10.0)	1 (3.3)	4 (6.7)
Previous treatment			
None	7 (23.3)	6 (20.0)	13 (21.7)
Surgery	24 (80.0)	33 (110.0)*	57 (95.0)
Chemotherapy	6 (20.0)	7 (23.3)	13 (21.7)
Radiotherapy	1 (3.3)	3 (10.0)	4 (6.7)
Octreotide	14 (46.7)	18 (60.0)	32 (53.3)
Interferon	1 (3.3)	2 (6.7)	3 (5.0)

Lan indicates lanreotide; MP, microparticles; ATG, Autogel; SD, standard deviation; HIAA, hydroxyindoleacetic acid.

* Some patients underwent more than 1 surgery.

of tumor marker levels and EORTC scores were conducted by using repeated-measures analyses of variance. Only clinical symptoms were described, because a limited number of patients presented with symptoms.

RESULTS

Patient Demographics and Disposition

Sixty patients were recruited into the current study and were randomized equally between the Lan MP and ATG treatment groups. Patient characteristics at screening are listed in Table 2. All 60 patients received 1 dose of study drug and comprised the safety population. One patient in each group did not undergo a postbaseline efficacy assessment: Therefore, the ITT population comprised the remaining 58 patients. The study was completed by 46 patients. In the Lan ATG group, 7 patients withdrew because of disease progression, and 1 each withdrew because of noncompliance and withdrawn consent. In the Lan MP group, 2 patients withdrew because of disease progression, 1 patient died, 1 patient was lost to follow-up, and 1 patient discontinued because of progression in tumor marker levels (but not in tumor size).

Efficacy Assessments

At screening, 19 patients had carcinoid syndrome (Table 2), and symptomatic response data were available for 11 patients from the ITT population at the last assessment. At baseline, diarrhea was reported by 3 patients in the Lan MP group and by 9 patients

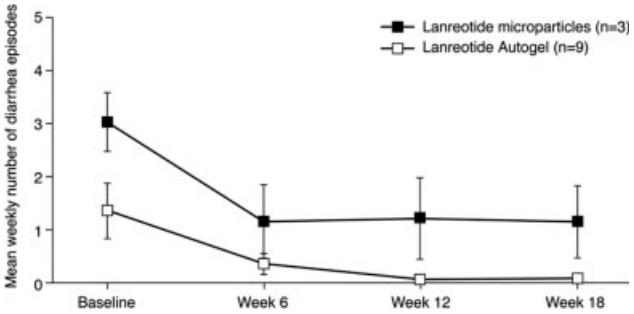

FIGURE 1. This chart illustrates that there was a reduction in the mean weekly number of diarrhea episodes from baseline to Week 18 of treatment (intention-to-treat population). For the Lanreotide Autogel group, there were 6 patients at 12 weeks and 7 patients at 18 weeks.

in the Lan ATG group. The mean number of weekly episodes decreased progressively from baseline (Fig. 1). At baseline, flushing was experienced by 3 patients in the Lan MP group and by 9 patients in the Lan ATG group, with a mean number of weekly episodes of 0.80 and 0.90, respectively. After 18 weeks of treatment, the mean number of weekly episodes was 1.39 in the Lan MP group and 0.36 in the Lan ATG group. Three patients who received Lan ATG achieved a CR over the course of the study, 3 patients achieved a PR, and 3 patients had SD. One patient who received Lan MP achieved a PR, and 1 patient had SD. Because of the low number of symptomatic patients, no statistical analysis was undertaken. Of the 11 patients who were assessed, none had progression of symptoms over the study period (Table 3).

At the screening visit, 53 patients had elevated CgA levels, and 8 patients had increased levels of urinary 5-HIAA (Table 2). From baseline to the end of the study, median CgA levels decreased 20.2% with Lan MP and 27.6% with Lan ATG. (The decrease in CgA was evident from the first injection of Lan ATG and was maintained up to Week 18.) Median levels of urinary 5-HIAA decreased from 17.8 mg/24 hours at baseline to 16.0 mg/24 hours at Week 18 of the study in the 3 assessable patients in the Lan ATG group (10.1%). A decrease from 111.0 mg/24 hours to 79.0 mg/24 hours (29%) was observed in the 1 patient on Lan MP who had 5-HIAA assessed at study end. A slightly greater proportion of patients had successful biochemical response in the Lan ATG group (59%) compared with the Lan MP group (55%), and the noninferiority was significant at $P \leq .032$. The lower CL of the difference in proportional success between Lan ATG and Lan MP (0.1765) was within the margin of noninferiority.

At screening, 90% of lesions in the ITT population were measured with CT, 2% of lesions were measured with MRI, and 8% of lesions were measured with techniques. The majority of patients in both treatment groups had stable tumor dimensions during the course of the study, and treatment was categorized as a success in 68% of patients in the Lan ATG group and in 66% of patients in the Lan MP group ($P = .032$ vs. ATG) (Table 3). The lower limit of the CL between treatments was 0.1819.

There was no significant difference in PFS between the 2 treatment groups measured either by tumor marker or by tumor size (log-rank test; $P > .05$) (Fig. 2) up to the final visit at Week 18. Furthermore, there was no difference in the EORTC QLQ-C30 sum of items score or in the individual subscale scores between treatment groups at baseline or at study end (Table 4).

Safety

Both Lan ATG and Lan MP were well tolerated. With both formulations, the most frequent adverse events were those that affected the gastrointestinal system (Table 5). There were no serious or significant events related to treatment. The patient who died during participation in the study had an NET of pancreatic origin with hepatic involvement, secondary localizations in the abdominal cavity, abdominal lymph node involvement, and carcinoid syndrome. This patient suffered from anxiety and depression and had an episode of psychomotor agitation. He had received a single, 60-mg injection of Lan MP and died while he was hospitalized for a planned locoregional treatment of the liver. The investigator considered it unlikely that the event was related to the somatostatin analogue treatment. The precise circumstances and immediate cause of death are unknown.

An increase in the number of patients with hyperglycemia was noted over the treatment period. At screening, 6 patients (10%) had blood fasting glucose levels above the normal range, including 2 patients who were positive for noninsulin-dependent diabetes mellitus. At the final visit of the study, 15 patients (25%) had glucose values above the normal ranges, including 8 patients in the Lan ATG group and 7 patients in the Lan MP group; but no patients developed diabetes or clinically significant changes in blood glucose levels. Low blood calcium levels were noted at the final visit in 1 patient in the Lan MP group and in 2 patients in the Lan ATG group. No effect of Lan MP or Lan ATG was apparent on biliary echography: In both treatment arms, 9 of 53 patients (17%) had abnormal scans at baseline, and 5 of 31 patients (16%) had abnormal scans at the end of the study. Lithiasis was present in 3 of 53 patients

TABLE 3
Treatment Success Over the Course of the Study Assessed by Using the Italian Trials in Medical Oncology Group Criteria (Intention-to-Treat Population)*

	No. of patients (%)					
	Tumor markers (N = 56)		Tumor size (N = 56)		Symptoms (N = 11)	
Response	Lan MP, 60 mg	Lan ATG, 120 mg	Lan MP, 60 mg	Lan ATG, 120 mg	Lan MP, 60 mg	Lan ATG, 120 mg
Complete	1 (3.6)	3 (11.1)	0 (0)	0 (0)	0 (0)	3 (33.3)
Partial	4 (14.3)	8 (29.6)	1 (3.6)	0 (0)	1 (50)	3 (33.3)
Stable	11 (39.3)	5 (18.5)	18 (64.3)	19 (67.9)	1 (50)	3 (33.3)
Progressive	12 (42.9)	11 (40.7)	9 (32.1)	9 (32.1)	0 (0)	0 (0)
Success	16 (55.2)	16 (59.3)†	19 (65.5)	19 (67.9)†	—	—
Failure‡	13 (44.8)	11 (40.7)	10 (34.4)	9 (32.1)	—	—
Lower CL		−0.1765		−0.1819	—	—

Lan indicates lanreotide; MP, microparticles; ATG, Autogel; CL, confidence limit (calculated from differences between treatment success with Lan ATG and Lan MP).

* See Bajetta et al., 1993.[15]

† $P < .032$ Lan ATG versus Lan MP for "noninferiority."

‡ Failures included 1 death that occurred 3 weeks after baseline.

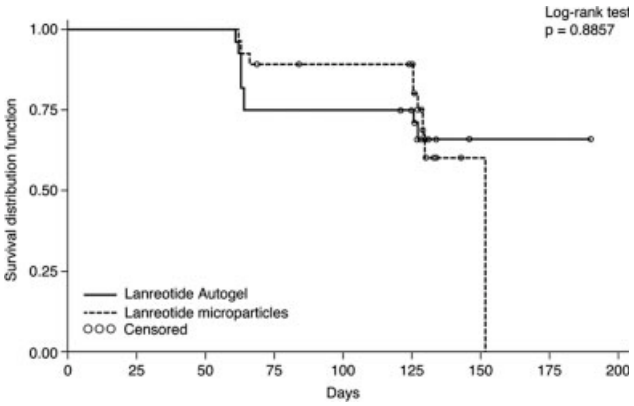

FIGURE 2. This chart illustrates progression-free survival assessed by tumor size (intention-to-treat population).

(6%) at baseline and in 4 of 31 patients (13%) at the end of the study.

DISCUSSION

The current results demonstrated that Lan ATG at a dose of 120 mg every 6 weeks was as effective as Lan MP at a dose of 60 mg injected every 3 weeks in patients with sporadic, well differentiated NET with a low grade of malignancy. These results were statistically significant both for the lowering of tumor marker levels and for the reduction in tumor size.

Responses were categorized as successful if patients had a CR, PR, or SD, according to the ITMO Group criteria. Applying this system to CgA levels, 55% of patients had a successful response with Lan MP at a dose of 60 mg compared with a 59% successful response rate with Lan ATG at a dose of 120 mg. Likewise, with regard to tumor size, the rate of success was 65% with Lan MP at a dose of 60 mg and 68% with Lan ATG at a dose of120 mg. Symptoms were present in too few patients for a reliable comparison between the 2 treatment groups. However, of the 11 patients who had symptoms at the end of the study, none had developed disease progression.

The results from this study are in agreement with previous studies of lanreotide or octreotide, the majority of which have shown efficacy in the control of symptoms of carcinoid syndrome and a reduction in the concentrations of tumor markers.[4,5,16] Chromogranins are markers of secretory activity because they are released from NET at the same time as amines and peptide hormones. Therefore, the reduction in circulating levels can parallel a decline in hormone secretion and symptom severity or frequency, although declining tumor markers do not necessarily reflect a loss of tumor mass. Similar to the current study, it was demonstrated previously that somatostatin analogues stabilized tumor masses in patients with progressive NET.[5,6,17] Reductions in tumor size has been reported but only as a minor response in a small proportion of patients.[18,19] Stabilization of tumor mass itself is a relevant outcome for patients with NET.

In the current study, no differences were observed between the 2 treatment groups in the QoL assessment using the EORTC QLQ-C30 questionnaire, and no significant changes were observed between baseline and study end for any of the EORTC QLQ-C30 scales. There are several possible explana-

TABLE 4
Quality of Life Evaluated Using the European Organization for Research and Treatment in Cancer Quality-of-Life Questionnaire QLQ-C30*

	Mean score ± SD			
	Lan MP, 60 mg		Lan ATG, 120 mg	
Scale	Baseline (N = 28)	Last assessment (N = 24)	Baseline (N = 28)	Last assessment (N = 25)
Sum of items	40.00 ± 14.33	38.92 ± 11.11	39.04 ± 7.58	36.24 ± 7.67
Functioning scales	21.36 ± 8.10	20.75 ± 6.07	20.93 ± 4.34	19.36 ± 4.59
Symptom scales	18.64 ± 6.55	18.17 ± 5.25	18.11 ± 4.09	16.88 ± 3.30
Global health-related QoL scale	10.50 ± 2.46	10.33 ± 2.44	10.75 ± 2.35	10.88 ± 2.80

SD indicates standard deviation; Lan, lanreotide; MP, microparticles; ATG, Autogel; QoL, quality of life.
* Note that the maximal range of the scale was from 0 to 100.

TABLE 5
Adverse Events that Occurred in More than 1 Patient (Safety Population)*

	No. of patients	
Adverse event	Lan MP (60 mg)	Lan ATG (120 mg)
Abdominal pain	3	3
Constipation	0	2
Diarrhea	4	2
Pyrexia	2	3
Cholelithiasis	2	0
Dizziness	1	1
Bronchitis	0	2
Hypertension	0	2

Lan indicates lanreotide; MP, microparticles; ATG, Autogel.
* Multiple occurrences of the same adverse event in the same patient were counted only once.

tions for these similar scores. It is likely that, as a generic oncology questionnaire, the QLQ-C30 is not sufficiently specific for this patient population; thus, it would be relatively insensitive to the changes in patient QoL. This is acknowledged by the EORTC, which currently is developing a tool that will be specific to NET. Therefore, it is possible that the expected benefit for the patient related to the simplified mode of administration and fewer injections has not been picked up by the QLQ-C30 questionnaire. A further contributory factor may be that >75% of patients had received previous treatment for NET, and many may have been receiving a monthly somatostatin analogue.

One limitation of the current study was that the relative symptomatic efficacy of the 2 formulations could not be assessed because of low patient numbers. The reason that few symptomatic patients were recruited may be because many patients with carcinoid syndrome are treated with lanreotide, and this was an exclusion criterion for the study. It is noteworthy that the low number of symptomatic patients at baseline suggests that physicians want to prescribe a drug with an antitumor effect for these patients rather than a drug that is active against a cancer-related syndrome.

Treatment with either Lan MP at a dose of 60 mg or Lan ATG at a dose of 120 mg generally was tolerated well, and no safety issues were identified. The most common adverse events were gastrointestinal in nature, as reported previously. The proportion of patients with cholelithiasis was not modified significantly over the course of the study.

In conclusion, the current results indicated that a 6-week dosing schedule with Lan ATG at a dose of 120 mg was as effective in controlling NET, as measured by tumor markers and tumor size, as a 3-week dosing schedule with Lan MP at a dose of 60 mg. The treatment was tolerated well, and no safety concerns were identified. Therefore, an extended interval of injection is an option for patients who respond well to a somatostatin analogue; although, in clinical practice, the dose would be titrated according to the patient's requirements.

REFERENCES

1. Caplin ME, Buscombe JR, Hilson AJ, et al. Carcinoid tumour. *Lancet.* 1998;352:799–805.
2. Reubi JC, Maurer R, von Werder K, Torhorst J, Klijn JG, Lamberts SW. Somatostatin receptors in human endocrine tumors. *Cancer Res.* 1987;47:551–558.
3. Janson ET, Westlin JE, Eriksson B, Ahlstrom H, Nilsson S, Oberg K. [111In-DTPA-D-Phe1]octreotide scintigraphy in patients with carcinoid tumours: the predictive value for somatostatin analogue treatment. *Eur J Endocrinol.* 1994;131: 577–581.
4. Ruszniewski P, Ish-Shalom S, Wymenga M, et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology.* 2004;80:244–251.

5. Wymenga AN, Eriksson B, Salmela PI, et al. Efficacy and safety of prolonged-release lanreotide in patients with gastrointestinal neuroendocrine tumors and hormone-related symptoms. *J Clin Oncol.* 1999;17:1111–1117.
6. Tomassetti P, Migliori M, Gullo L. Slow-release lanreotide treatment in endocrine gastrointestinal tumors. *Am J Gastroenterol.* 1998;93:1468–1471.
7. Ricci S, Antonuzzo A, Galli L, et al. Long-acting depot lanreotide in the treatment of patients with advanced neuroendocrine tumors. *Am J Clin Oncol.* 2000;23:412–415.
8. Ruszniewski P, Ducreux M, Chayvialle JA, et al. Treatment of the carcinoid syndrome with the long-acting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut.* 1996;39:279–283.
9. Caron P, Beckers A, Cullen DR, et al. Efficacy of the new long-acting formulation of lanreotide (lanreotide Autogel) in the management of acromegaly. *Clin Endocrinol (Oxf).* 2002;87:99–104.
10. Caron P, Bex M, Cullen DR, et al. One-year follow-up of patients with acromegaly treated with fixed or titrated doses of lanreotide Autogel. *Clin Endocrinol (Oxf).* 2004;60:734–740.
11. Lucas T, Astorga R. Efficacy of lanreotide Autogel administered every 4–8 weeks in patients with acromegaly previously responsive to lanreotide microparticles 30 mg: a phase III trial. *Clin Endocrinol (Oxf).* 2006;65:320–326.
12. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649–655.
13. World Medical Association. Declaration of Helsinki. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975; the 35th WMA General Assembly, Venice, Italy, October 1983; the 41st WMA General Assembly, Hong Kong, September 1989; the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Ferney-Voltaire: World Medical Association, 1964.
14. International Conference of Harmonisation Tripartite Guidelines E6. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), 1996.
15. Bajetta E, Zilembo N, Di Bartolomeo M, et al. Treatment of metastatic carcinoids and other neuroendocrine tumors with recombinant interferon-alpha-2a. A study by the Italian Trials in Medical Oncology Group. *Cancer.* 1993;72:3099–3105.
16. Tomassetti P, Migliori M, Corinaldesi R, Gullo L. Treatment of gastroenteropancreatic neuroendocrine tumours with octreotide LAR. *Aliment Pharmacol Ther.* 2000;14:557–560.
17. Aparicio T, Ducreux M, Baudin E, et al. Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. *Eur J Cancer.* 2001;37:1014–1019.
18. Ducreux M, Ruszniewski P, Chayvialle JA, et al. The antitumoral effect of the long-acting somatostatin analog lanreotide in neuroendocrine tumors. *Am J Gastroenterol.* 2000;95:3276–3281.
19. Saltz L, Trochanowski B, Buckley M, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer.* 1993;72:244–248.