

Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial

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1 **Summary**

2

3 **Background** There are no data from prospective studies focused exclusively on patients
4 with advanced lung and thymic carcinoids.

5

6 **Methods** LUNA was a prospective, multicentre, randomised, open-label, 3-arm, phase 2
7 trial. Patients with advanced, progressive, carcinoid tumours of the lung/thymus were
8 enrolled from 36 centres in nine countries. Eligible patients were randomised in a 1:1:1 ratio
9 to receive treatment with long-acting pasireotide (60 mg intramuscularly every 28 days),
10 everolimus alone (10 mg orally once daily), or in combination, for the core 12-month
11 treatment period. Patients were stratified by carcinoid type (typical vs atypical) and line of
12 study treatment (first line vs others). Radiological assessments were performed every 3
13 months. The primary endpoint was the proportion of patients progression-free at month 9,
14 which was defined as the proportion of patients with overall lesion assessment at month 9
15 being complete response (CR), partial response (PR), or stable disease (SD) according to
16 local Response Evaluation Criteria in Solid Tumours, version 1.1, assessed in the intention-
17 to-treat population. Progression-free survival (PFS) and safety were secondary endpoints.
18 Safety was assessed in all patients who received at least one dose of study drug and had at
19 least one post-baseline safety assessment. The trial is registered with ClinicalTrials.gov,
20 NCT01563354; the extension phase of the study is ongoing.

21

22 **Findings** Between Aug 16, 2013, and Sept 30, 2014, a total of 124 patients were enrolled;
23 41 were allocated to long-acting pasireotide (P arm), 42 to everolimus (E arm), and 41 to
24 combination treatment (EP arm). At month 9, the proportion of patients with an overall lesion
25 assessment of CR, PR, or SD in the P arm, E arm, or EP arm, were 16/41 (39.0%; 95% CI
26 24.2–55.5), 14/42 (33.3%; 95% CI 19.6–49.5), and 24/41 (58.5%; 95% CI 42.1–73.7),
27 respectively. The most common grade 1/2 adverse events with a suspected relationship to
28 treatment with long-acting pasireotide monotherapy or long-acting pasireotide + everolimus

29 were diarrhoea (36.6% [15/41] and 46.3% [19/41], respectively) and hyperglycaemia (41.5%
30 [17/41] and 65.9% [27/41]); for everolimus, they were stomatitis (61.9% [26/42]) and
31 diarrhoea (38.1% [16/42]). Eleven patients died during the core 12-month treatment phase
32 or up to 56 days after the last study treatment exposure date: 2/41 (4.9%) in the P arm, 6/42
33 (14.3%) in the E arm, and 3/41 (7.3%) in the EP arm. No deaths were suspected to be
34 related to long-acting pasireotide treatment. One death in the E arm, due to acute kidney
35 injury associated with diarrhoea, and 2 deaths in the EP arm, due to diarrhoea/urinary sepsis
36 in one patient and acute renal failure/respiratory failure in the other patient, were suspected
37 to be related to everolimus treatment. In the latter patient, acute renal failure was not
38 suspected to be related, while respiratory failure was suspected to be related to everolimus
39 treatment.

40

41 **Interpretation** The study met the primary endpoint in all three treatment arms. Safety
42 profiles were consistent with the known safety profiles of these agents. Further studies are
43 needed to confirm the antitumour efficacy of the combination of a somatostatin analogue
44 with everolimus in lung and thymic carcinoids.

45

46 **Funding** Novartis Pharma AG.

47

48 **Introduction**

49 Neuroendocrine tumours (NET) are relatively rare and heterogeneous tumours that arise
50 from neuroendocrine cells, often arising in the gastrointestinal (GI) tract, lung, and
51 pancreas.¹ The World Health Organization (WHO) classifies lung and thymic NET into four
52 major subtypes: typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine
53 carcinoma, and small cell carcinoma.²

54 Given the lack of prospective clinical trial data from large numbers of patients with advanced
55 lung and thymic carcinoids, the majority of treatment recommendations are based on results
56 of studies in GI NET and mixed primary NET populations that include lung and thymic
57 carcinoids^{3,4}; until recently, there has been an absence of approved drugs for this indication.⁴

58 Based on the results of the phase 3 RADIANT-4 study, the mammalian target of rapamycin
59 (mTOR) inhibitor everolimus recently received US Food and Drug Administration (FDA) and
60 European Medicines Agency (EMA) approval for the treatment of patients with advanced
61 (unresectable, locally advanced, or metastatic), progressive, well-differentiated, non-
62 functional NET of lung and GI origin, in addition to the previous approval in pancreatic
63 NET.^{5,6} In RADIANT-4, median progression-free survival (PFS) of patients with advanced,
64 well-differentiated NET of GI or lung origin was significantly improved: 11·0 months for
65 patients receiving everolimus, compared with 3·9 months among patients receiving placebo
66 (hazard ratio [HR] 0·48; 95% confidence interval [CI] 0·35–0·67; $p < 0·0001$).⁷ In a subgroup
67 analysis of patients with advanced lung carcinoids, everolimus improved median PFS by 5·6
68 months vs placebo (9·2 vs 3·6 months), as assessed by central review.⁸

69 Current European Neuroendocrine Tumor Society (ENETS) consensus guidelines
70 recommend everolimus as a first-line therapy for progressive, advanced lung carcinoids,
71 unless a somatostatin analogue (SSA; long-acting octreotide or lanreotide) may be
72 considered as first-line therapy for tumours with low proliferative activity (i.e., TC) and
73 somatostatin receptor (SSTR) expression on imaging.⁴ The recommendation for SSA
74 treatment is based on the expectation that TC will respond in a similar manner to grade 1

75 NET of other sites, such as the GI tract,⁴ as well as data from a few retrospective analyses
76 of lung NET.⁹

77 Pasireotide is a novel multireceptor ligand SSA with higher affinity for somatostatin receptors
78 1 (SSTR1), 3 (SSTR3), and 5 (SSTR5) compared with octreotide, but a slightly lower affinity
79 for SSTR2.¹⁰ The antitumour activity of pasireotide (long-acting or short-acting
80 subcutaneous) has been investigated in phase 2 and 3 trials of patients with advanced NET
81 who have symptoms refractory to standard long-acting octreotide dosing,^{11,12} along with a
82 phase 2 trial of treatment-naive patients with metastatic grade 1 or 2 NET.¹³ It is
83 hypothesised that the combined action of long-acting pasireotide on SSTR and inhibition of
84 insulin-like growth factor 1 receptor (IGF-1R), along with the mTOR inhibitor everolimus, may
85 control tumour growth more effectively than either treatment alone.¹⁴

86 The phase 2 LUNA trial aimed to assess the efficacy and safety of long-acting pasireotide
87 and everolimus, administered alone or in combination, in patients with advanced carcinoids
88 of the lung or thymus. LUNA is the first prospective, randomised clinical trial to focus
89 exclusively on this specific patient population.

90

91 **Methods**

92 **Study design and participants**

93 LUNA was a prospective, single-stage, multicentre, randomised, open-label, phase 2 trial
94 conducted at 36 centres across nine countries (appendix, p 1). The study comprised a 12-
95 month core study period, followed by an extension phase that continued until all patients had
96 progressed. Adult patients (aged >18 years) with pathologically confirmed advanced
97 (unresectable or metastatic), well-differentiated, TC or AC of the lung or thymus were
98 eligible. Histopathologic classification was determined using the WHO 2004 classification of
99 tumours of the lung, pleura, thymus, and heart;¹⁵ cytology by endobronchial ultrasound-
100 guided fine needle aspiration alone was not sufficient for classification. Patients of any
101 treatment line (naive or pre-treated) and progressive within 12 months according to

102 Response Evaluation Criteria In Solid Tumours, version 1.1 (RECIST v1.1) were eligible.
103 Additional key inclusion criteria included: measurable disease according to computed
104 tomography (CT) scan or magnetic resonance imaging (MRI) as defined by RECIST v1.1;
105 WHO performance status ≤ 2 ; and adequate bone marrow, liver, and kidney function. Due to
106 the potential for other SSA or mTOR inhibitors to interfere with the antitumour efficacy
107 observed in this study, patients were ineligible if they had any of the following: severe
108 functional disease (ie, carcinoid syndrome) requiring symptomatic treatment with SSA
109 (judgement made by study clinicians); previous treatment with any long-acting SSA within 1
110 month of randomisation; or treatment with mTOR inhibitors (sirolimus, temsirolimus, or
111 everolimus). Patients were also ineligible if they had any of the following: radiotherapy within
112 4 weeks of randomisation; Cushing's syndrome requiring treatment within 3 months;
113 radioligand therapy (peptide receptor radionuclide therapy) within 6 months of
114 randomisation; hepatic artery embolisation, cryoablation, or radiofrequency ablation of
115 hepatic metastasis within 3 months of randomisation; participation in a clinical trial testing an
116 investigational drug within 4 weeks or 5 half-lives (whichever is longer) of randomisation;
117 uncontrolled diabetes mellitus (haemoglobin A1C of at least 8%) despite adequate therapy;
118 presence of active or suspected acute or chronic uncontrolled infection; or signs of
119 recurrence of previous or concomitant malignancies within the last 3 years or requiring active
120 treatment. The estimated life expectancy of eligible patients was 24-40 months.^{1,16}

121 The study was conducted in accordance with Good Clinical Practice, the ethical principles of
122 the Declaration of Helsinki, and local regulations. Institutional review boards, independent
123 ethics committee, and the research ethics board reviewed and approved the study and all
124 amendments to the protocol. All patients provided written informed consent. Further details
125 of the protocol are available on clinicaltrials.gov.

126

127 **Randomisation and masking**

128 Patients were randomised (1:1:1) to receive long-acting pasireotide monotherapy (P arm),
129 everolimus monotherapy (E arm), or everolimus and long-acting pasireotide in combination

130 (EP arm). The planned number of patients enrolled was 120, with 40 patients randomised to
131 each treatment arm. At the screening visit, the investigator or their designee assigned a
132 unique number to each patient being considered for the study. Once the eligibility of each
133 patient was confirmed, the investigator or their designee registered the patient using an
134 interactive voice recognition system into one of the three treatment arms. The randomisation
135 allocation sequence was generated by an external company (Perceptive Informatics,
136 Nottingham, UK). Patients were stratified by TC vs AC according to the WHO classification
137 and line of study treatment (first line of systemic medical treatment vs other). Patients and
138 investigators were not masked to treatment allocation.

139

140 **Procedures**

141 Patients randomised to the P arm received long-acting pasireotide at a dose of 60 mg
142 intramuscularly (IM) every 28 days; patients randomised to the E arm received everolimus at
143 a dose of 10 mg taken orally (PO) once daily (QD); and patients randomised to the EP arm
144 received everolimus and long-acting pasireotide at a dose of 10 mg everolimus PO QD and
145 60 mg long-acting pasireotide IM every 28 days. Dose reductions and treatment interruptions
146 for less than 56 days for long-acting pasireotide and less than 28 days for everolimus were
147 allowed for patients who did not tolerate therapy, or to manage treatment-related adverse
148 events (AEs). Two dose reductions were allowed for everolimus: from 10 mg per day to 5 mg
149 per day, with a subsequent reduction to 5 mg every other day. A dose reduction from 60 mg
150 to 40 mg long-acting pasireotide every 28 days was allowed with a subsequent, but
151 transient, reduction to 20 mg. Re-escalation to 40 mg was required within 56 days;
152 otherwise, the patient was discontinued from study.

153 All patients who underwent randomisation were locally assessed for efficacy by triphasic CT
154 or MRI every 3 months for the duration of the treatment phase (12 months) and, if the patient
155 continued into the extension phase, every 3 months thereafter. Safety was monitored by
156 assessing haematology (baseline and weeks 2, 4, and every 4 weeks (q4w) from weeks 8-
157 52), coagulation (weeks 0, 4, 8, and every 8 weeks (q8w) from weeks 12-52; additionally at 3

158 and 7 weeks for those treated with pasireotide), biochemistry (weeks 0, 2, 4, and q4w from
159 weeks 8-52), fasting glucose (weeks 0, 2-4, and q4w from weeks 7-52), liver function tests
160 (weeks 0, 2, 4, and q4w from weeks 8-52; additionally at 3 and 7 weeks for those treated
161 with pasireotide), serum lipid profile (weeks 2, 4, and q4w from weeks 8-52), thyroid function
162 test (weeks 12, 24, and 52), urinalysis (weeks 0, 2, 4, and q4w from weeks 8-52),
163 chromogranin-A and 5-hydroxyindoleacetic acid measurement (weeks 12, 24, 36, 48, and
164 52), electrocardiogram (weeks 0, 3, 8, 16, 28, 40, and 52), gallbladder assessment (only
165 those treated with pasireotide; weeks 12, 24, 36, 48, 52), and WHO performance status and
166 vital signs (weeks 0, 2, 4, and q4w from weeks 8-52). Adverse events were assessed
167 continuously throughout the study and were evaluated for severity grade and duration,
168 suspected relationship to treatment, whether a dose adjustment, interruption, or
169 discontinuation was required, outcome, and whether concomitant medication was required.
170 Study treatment continued for 12 months or until disease progression, intolerable toxicity,
171 start of new cancer therapy, withdrawal of consent, or discontinuation for any other reason.
172 Patients who demonstrated clinical benefit, and who were not experiencing unacceptable
173 toxicity, were allowed to continue treatment in an extension phase until disease progression,
174 intolerable toxicity, start of new cancer therapy, withdrawal of consent, or discontinuation for
175 any other reason. The end of the study was defined as the final study visit 2 years after the
176 start of the last randomised patient, or when all patients had progressed (whichever came
177 first). All patients were requested to participate in a safety follow-up 56 days after their last
178 dose of study treatment to assess AEs.

179

180 **Outcomes**

181 The primary efficacy endpoint was the progression-free rate at month 9, defined as the
182 proportion of patients with overall response at month 9, including complete response (CR),
183 partial response (PR), or stable disease (SD) according to local RECIST v1.1. Patients with a
184 missing or unknown tumour assessment at month 9, and with CR, PR, or SD at month 11 or
185 12, were considered as progression free at month 9. Patients with no tumour assessment

186 performed in the 211-294 study day period (9 month window) were classified as not
187 assessed at month 9. Patients with progressive disease, not assessed, or unknown response
188 at month 9 were classified as non-progression free.

189 Overall PFS, defined as the time from first study drug administration to tumour progression or
190 death from any cause according to RECIST v1.1, was a secondary endpoint. Patients who
191 did not experience a PFS event were censored at the date of the patient's last adequate
192 tumour assessment. The probability of patients remaining event free (i.e., no objective
193 tumour progression or death from any cause) up to the specified timepoint were obtained
194 from the Kaplan-Meier survival estimates for all treatment groups; the Greenwood formula
195 was used for confidence intervals of Kaplan-Meier estimates. Tumour shrinkage was
196 evaluated according to best response per RECIST v1.1.

197 The safety and tolerability of long-acting pasireotide and everolimus alone or in combination
198 was assessed by measuring the rate and severity of AEs, which were assessed according to
199 the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (CTCAE grade 5
200 [death] was not used in this study). The relationship of AEs to treatment was assessed per
201 investigator decision.

202

203 **Statistical analysis**

204 All randomised patients who received at least one dose of study drug constituted the full
205 analysis set (FAS). Following the intention-to-treat principle, patients were analysed
206 according to the treatment and stratum they were assigned to at randomisation. Primary
207 efficacy analyses were assessed on the FAS. The safety set included all patients who
208 received at least one dose of study drug and had at least one post-baseline safety
209 assessment.

210 For the primary endpoint, a Fleming single-stage design was employed for each treatment
211 arm, where p_0 (the null hypothesis) represents the highest proportion of patients progression
212 free at 9 months that indicated the treatment is clearly ineffective, and p_1 (the alternative
213 hypothesis) represented the minimum required proportion of patients who were progression

214 free to show that the treatment is effective. The trial tested the null hypothesis H_0 that the
215 observed proportion of patients who were progression free, p , was less than or equal to p_0
216 against the alternative hypothesis H_1 that p was greater than or equal to p_1 . It consisted of
217 entering a predetermined number of patients and deciding in favour of p_0 or p_1 based on the
218 success rate observed by using an appropriate cutoff between p_0 and p_1 . If the number of
219 responses was greater than or equal to $R+1$, p_0 was rejected. If the number of responses
220 was less than or equal to R , p_1 was rejected. In this trial, p_0 and p_1 were set equal to 0.20
221 and 0.45, respectively, and target alpha and beta were 5% and 10%, respectively. The
222 number of patients required per treatment arm to determine whether the proportion
223 responding was less than or equal to p_0 or greater than or equal to p_1 was determined to be
224 40. If the number of responses was 13 or more, the hypothesis that $p \leq p_0=20\%$ was rejected
225 with a target alpha error rate of 5% and an actual alpha error rate of 4.3%; if the number of
226 responses was 12 or less, the hypothesis that $p \geq p_1=45\%$ was rejected with an actual beta
227 error rate of 4%. No dropout percentage was considered in this calculation.

228 The 95% confidence interval (CI) for the progression-free rate at 9 months was computed
229 using an exact binomial method. PFS was estimated using the Kaplan-Meier method, with a
230 95% CI. Tumour shrinkage data were presented as waterfall plots by treatment arm. All data
231 were analysed using SAS version 9.4.

232 An independent data monitoring committee reviewed safety-related issues and provided
233 oversight in study conduct. This study was registered with the EU Clinical Trials Register,
234 number EudraCT 2011-002872-17, protocol CSOM230DIC03, and with ClinicalTrials.gov,
235 number NCT01563354.

236

237 **Role of the funding source**

238 The study was designed by academic investigators and representatives of the funder
239 (Novartis Pharma AG). The first draft of the report was prepared by PF, GG, NS, MS, KÖ,
240 EB, and a medical writer employed by the funder. All authors vouch for the accuracy and
241 completeness of the data and attest that the study conformed to the protocol and statistical

242 analysis plan. The corresponding author had full access to all data in the study and had final
243 responsibility, along with KÖ and EB, for the decision to submit for publication.

244

245 **Results**

246 Between Aug 16, 2013, and Sept 30, 2014, a total of 124 patients with advanced,
247 progressive, TC or AC of the lung or thymus were enrolled and randomly assigned to receive
248 treatment with either long-acting pasireotide (P arm; n=41), everolimus (E arm; n=42), or
249 everolimus and long-acting pasireotide (EP arm; n=41) (figure 1). The core 12-month
250 treatment phase was completed on Dec 30, 2015. All randomised patients received at least
251 one dose of study drug and constituted the FAS used for efficacy analyses (n=124). All
252 patients received at least one dose of medication and had at least one post-baseline safety
253 assessment, and therefore were all included in the safety set (n=124). Baseline
254 demographics and disease characteristics at baseline are summarised in table 1. The
255 median age of the patients was 64 years, 62.1% (77/124) were male, the majority (98.4%;
256 122/124) were Caucasian and 63.7% (79/124) had an Eastern Cooperative Oncology Group
257 performance status of 0. The vast majority (116/124; 93.5%) of patients presented with
258 primary tumours in the lung, around two-thirds (85/124; 68.5%) of patients presented with
259 AC, and 77.4% (96/124) had non-functional disease. The most common metastatic sites
260 were the liver (95/124; 76.6%), bone (69/124; 55.6%), lung (48/124; 38.7%),
261 cervical/thoracic lymph nodes (38/124; 30.6%), and pleura (10/124; 8.1%). Characteristics
262 were generally well balanced across treatment arms, with the exception of bone metastases,
263 which were more frequently reported in the long-acting pasireotide treatment arm.
264 Prior therapies are presented in the appendix (p 2). Approximately a third (40/124; 32.3%) of
265 patients were treated for advanced disease in the first line. Prior SSA use was well balanced
266 among the treatment groups; 48.4% (60/124) of patients had received prior SSAs, with the
267 length of SSA exposure ranging from less than 6 months to 5 or more years. Prior
268 antineoplastic therapy was more frequently reported in the EP arm.

269 During the core 12-month treatment phase, 65.3% (81/124) of randomised patients
270 discontinued treatment, mainly due to AEs (n=33) and disease progression (n=33) (figure 1).
271 In the P arm, 68.3% (28/41) of patients discontinued treatment, with 18/28 due to disease
272 progression and 5/28 due to AEs as the primary reason. In the E arm, 64.3% (27/42)
273 discontinued treatment, with 15/27 due to AEs as the primary reason and 7/27 due to
274 disease progression. In the EP arm, 63.4% (26/41) discontinued treatment, with 13/26 due
275 to AEs as the primary reason and 8/26 due to disease progression. Of the 43 patients who
276 completed the core phase of the study, 41 entered the extension phase (figure 1).
277 The proportions of patients with overall lesion assessment at month 9 being CR, PR, or SD
278 according to RECIST v1.1 (i.e., progression-free) in the P arm, E arm, or EP arm were 16/41
279 (39.0%; 95% CI 24.2–55.5), 14/42 (33.3%; 95% CI 19.6–49.5), and 24/41 (58.5%; 95% CI
280 42.1–73.7), respectively (table 2). As noted in table 2, the minimum number of patients
281 required to be progression free at month 9 in order to consider the treatment as effective
282 was 13 patients for the P arm, 14 patients for the E arm, and 13 patients for the EP arm.
283 Overall lesion response at month 9 was mostly SD among the 3 treatment groups; 34.1%
284 (14/41) in the P arm, 31.0% (13/42) in the E arm, and 48.8% (20/41) in the EP arm.
285 Progressive disease at 9 months was observed in 7/41 (17.1%), 1/42 (2.4%), and 0/41 (0%)
286 patients in the P arm, E arm, or EP arm, respectively. Patients with progressive disease, not
287 assessed, or unknown response at month 9 were classified as non-progression free. The
288 proportions of patients with no tumour assessment performed at 9 months were classified as
289 'not assessed' but were not excluded from the analysis; 18/41 (43.9%), 25/42 (59.5%), and
290 17/41 (41.5%) in the P arm, E arm, or EP arm, respectively. This was mostly due to AEs
291 leading to withdrawal in 3/41 (7.3%), 15/42 (35.7%), and 10/41 (24.4%) of those in the P
292 arm, E arm, and EP arm, respectively, or due to disease progression prior to month 9 tumour
293 assessment in 10/41 (24.4%), 4/42 (9.5%), and 2/41 (4.9%), respectively. Overall, 11/36
294 (30.6%) patients in the P arm, 16/33 (48.5%) in the E arm, and 24/33 (72.7%) in the EP arm
295 experienced some degree of tumour shrinkage (figure 2).

296 The median PFS by investigator-assessed radiological review was 8.51 months (95% CI
297 5.68–not estimable [NE]), 12.48 months (95% CI 5.55–NE), and 11.79 months (95% CI
298 11.10–NE) in the P arm, E arm, and EP arm, respectively (figure 3). The probability of
299 patients remaining event-free (i.e., no objective tumour progression or death from any
300 cause) until 9 months (table 3) was 49.6% (95% CI 31.9–65.1) for those in the P arm, 56.9%
301 (95% CI 38.1–71.9) in the E arm, and 79.2% (95% CI 61.1–89.5) in the EP arm.

302 During the core treatment phase, median patient exposures to long-acting pasireotide in the
303 P arm and everolimus in the E arm were 38.9 weeks (interquartile range [IQR] 20.00–52.14)
304 and 26.9 weeks (IQR 10.43–52.00), respectively. In the EP arm, median patient exposure to
305 long-acting pasireotide was 48.4 weeks (IQR 12.57–52.14) and 49.0 weeks (IQR 12.14–
306 52.14) to everolimus; the median exposure to both drugs combined was 49.0 weeks (IQR
307 12.57–52.14). The median relative dose intensity of long-acting pasireotide was 100% in
308 both the P arm (IQR 97.1%–102.0%) and EP arm (IQR 89.2%–107.1%). The median
309 relative dose intensity of everolimus was 93.6% (IQR 63.0%–100.0%) and 84.1% (IQR
310 53.6%–100.0%) in the E arm and EP arm, respectively.

311 Treatment interruptions or dose reductions occurred in 48.8% (20/41) of patients in the P
312 arm, 66.7% (28/42) of patients in the E arm, 48.8% (20/41) of patients treated with long-
313 acting pasireotide in the EP arm, and 53.7% (22/41) of patients treated with everolimus in
314 the EP arm. The most common reasons for treatment interruptions or dose reductions were
315 ‘as per protocol’ due to emergent safety concerns (95.0% [19/20], 25.0% [7/28], 65.0%
316 [13/20], and 36.4% [8/22] of patients treated with long-acting pasireotide in the P arm,
317 everolimus in the E arm, long-acting pasireotide in the EP arm, and everolimus in the EP
318 arm, respectively) and ‘any other adverse event’ (40.0% [8/20], 82.1% [23/28], 65.0%
319 [13/20], and 100.0% [22/22], respectively).

320 Grade 1/2 treatment-emergent AEs with a frequency of $\geq 10\%$ in at least one treatment group
321 are summarised in table 4. Grade 1/2 AEs were reported in all patients in all treatment arms.
322 The most common grade 1/2 AEs, regardless of drug relationship, reported in the P arm and
323 the EP arm were hyperglycaemia (43.9% [18/41] and 82.9% [34/41], respectively), diarrhoea

324 (39.0% [16/41] and 75.6% [31/41]), and weight decreased (43.9% [18/41] and 56.1%
325 [23/41]). A higher incidence of grade 1/2 stomatitis (61.9% [26/42]) was reported for patients
326 treated in the E arm vs the P arm, which was consistent with the established safety profile of
327 everolimus; the incidence of grade 1/2 stomatitis was lower (31.7% [13/41]) in patients
328 receiving combination therapy in the EP arm. The most common grade 3 treatment-
329 emergent AEs reported in the P arm were increased gamma glutamyltransferase (12.2%
330 [5/41]) and dyspnoea (9.8% [4/41]); in the E arm were hyperglycaemia (16.7% [7/42]) and
331 stomatitis (9.5% [4/42]); and in the EP arm were hyperglycaemia (24.4%, [10/41]), diarrhoea
332 (17.1%, [7/41]), and fatigue (9.8%, [4/41]) (table 4). Grade 4 treatment-emergent AEs
333 occurred in 12.2% (5/41) of those in the P arm, 19.0% (8/42) in the E arm, and 9.8% (4/41)
334 in the EP arm. A complete listing of all grade 3 and 4 treatment-emergent AEs is provided in
335 the appendix (p 3).

336 The most common grade 1/2 AEs with a suspected relationship to treatment with long-acting
337 pasireotide (P arm; EP arm) were diarrhoea (36.6% [15/41]; 22.0% [9/41]), hyperglycaemia
338 (41.5% [17/41]; 7.3% [3/41]), and weight loss (19.5% [8/41]; 2.4% [1/41]); for everolimus (E
339 arm; EP arm), they were stomatitis (61.9% [26/42]; 22.0% [9/41]) and diarrhoea (38.1%
340 [16/42]; 22.0% [9/41]); and for the combination treatment they were hyperglycaemia (65.9%
341 [27/41]), diarrhoea (46.3% [19/41]), and asthenia (19.5% [8/41]) (appendix, pp 8-13). A
342 complete listing of all grade 3 and 4 AEs with a suspected relationship to treatment are
343 provided in the appendix, pp 8-13.

344 Adverse events requiring study dose adjustment or interruption regardless of study treatment
345 relationship were reported in 24.4% (10/41) of patients in the P arm, 52.4% (22/42) of
346 patients in the E arm, and 61.0% (25/41) patients in the EP arm. Treatment-emergent
347 serious AEs occurred in 39.0% (16/41) of patients in the P arm, 42.9% (18/42) of patients in
348 the E arm, and 31.7% (13/41) of patients in the EP arm. Eleven patients died during the core
349 12-month treatment phase or up to 56 days after the last study treatment exposure date:
350 2/41 (4.9%) in the P arm, 6/42 (14.3%) in the E arm, and 3/41 (7.3%) in the EP arm. In the P
351 arm, one patient died of disease progression and one died due to pneumonia. Neither death

352 was suspected to be related with pasireotide treatment. In the E arm, five deaths were not
353 considered related to study drug: two due to disease progression and one each due to
354 respiratory failure, pneumonia, and cardiac failure. One patient died of acute kidney injury
355 associated with diarrhoea, which was considered related to everolimus therapy. In the EP
356 arm, one death due to disease progression was not considered related to study drug. One
357 patient died from diarrhoea and urinary sepsis which was suspected to be associated with
358 everolimus and one patient died due to acute renal failure and also respiratory failure. For
359 the latter patient, acute renal failure was not suspected to be related with study treatment,
360 while respiratory failure was suspected to be related to everolimus.

361

362 **Discussion**

363 To our knowledge, LUNA is the first prospective, randomised clinical trial dedicated
364 specifically to patients with advanced carcinoid tumours of the lung and thymus,
365 demonstrating the feasibility of conducting clinical trials in this rare NET subpopulation.
366 Results of the current phase 2 study suggest that long-acting pasireotide, everolimus, or
367 combination therapy with both agents is associated with antitumour activity, as the null
368 hypothesis was rejected for all three treatment arms. The 2-year extension phase of this trial
369 is ongoing, with all patients who benefited from treatment at 12 months; mature data on PFS
370 will be available when the extension phase of the trial is completed.

371 To date, the clinical investigation of exclusive pulmonary NET patient populations have been
372 limited to small retrospective studies.^{9,17-19} Subgroup analyses of mixed NET populations
373 have also been conducted, with everolimus being the most studied drug in the setting of lung
374 NETs.^{8,20} In the current study, the patient population enrolled had relatively aggressive
375 tumours; 68.5% of patients were classified as having AC, 67.7% were post first-line therapy,
376 and 100% had documented disease progression within the previous year according to
377 RECIST v1.1 criteria. Functional disease was present in 22.6% (28/124) of patients; this is
378 an interesting additional finding as this is the first and largest prospective clinical trial

379 conducted exclusively in this patient population. A recent retrospective US population-based
380 analysis of patients diagnosed with well-differentiated grade 1 or 2 NET of the lung or other
381 respiratory organ between 2000-2011 (from the Surveillance, Epidemiology, and End
382 Results-Medicare database) revealed that carcinoid syndrome was present in 8·0%
383 (83/1044), 7·9% (19/239), and 15·3% (30/196) of localised, regional, and distant stage
384 disease.²¹ Previous estimates of carcinoid syndrome in lung carcinoids have been much
385 lower (2%) and carcinoid syndrome is rare in thymic carcinoids.²² Other functional
386 syndromes observed in thoracic carcinoids include Cushing syndrome, caused by ectopic
387 adrenocorticotrophic hormone production, with an incidence of 2% in bronchial carcinoids and
388 up to 50% in thymic carcinoids, and acromegaly, which occurs rarely in both bronchial and
389 thymic carcinoids and is caused by ectopic growth hormone–releasing hormone.²²

390 The ‘conservative’ 9-month timepoint was selected to assess the primary endpoint in this
391 study in order to minimise bias; this timepoint was considered to be acceptable based on the
392 clinical experience and known biological behaviour of lung NET at the time of study design.
393 In addition, uncertainties surrounding the management of pulmonary NET with these novel
394 agents, along with the unknown rate and evolution of functioning syndromes in this NET
395 subpopulation, were taken into account.

396 Treatment guidelines as of 2016 recommend everolimus as a first-line therapy for
397 progressive, advanced lung carcinoids.⁴ The efficacy of everolimus in non-functional well-
398 differentiated NET of GI and lung origin was recently established in the RADIANT-4 trial.⁷ A
399 subgroup analysis of patients with lung NET in RADIANT-4 showed a median PFS of 9·2
400 months with everolimus vs 3·6 months with placebo by central review, and a median PFS of
401 13·8 months with everolimus vs 3·5 months with placebo by investigator assessment.⁸ In
402 addition, an exploratory analysis of the RADIANT-2 trial reported a median PFS of 13·6
403 months with everolimus and long-acting octreotide vs 5·6 months with long-acting octreotide
404 in patients with low or intermediate grade lung NET and carcinoid syndrome.²⁰ In the current
405 study, the median PFS of patients with functional or non-functional thoracic carcinoids
406 treated with everolimus alone and in combination with long-acting pasireotide was 12·5 and

407 11·8 months, respectively. This confirms the efficacy of everolimus that was demonstrated in
408 the lung subgroup of the RADIANT-4 study.

409 Long-acting pasireotide has previously been investigated in clinical trials of patients with
410 advanced, grade 1 or 2 NET, primarily in patients with primary tumours of the small intestine
411 or pancreas, with a median PFS of 11·0–11·8 months reported for monotherapy.^{12,13,23} In this
412 study of patients with lung or thymic carcinoids, the median PFS of patients treated with
413 long-acting pasireotide monotherapy was 8·5 months and the combination of everolimus and
414 long-acting pasireotide was associated with a median PFS of 11·8 months. In the phase 2
415 COOPERATE-2 study, the addition of long-acting pasireotide to everolimus did not
416 significantly improve median PFS vs everolimus in patients with non-functional pancreatic
417 NET (16·8 vs 16·6 months, respectively; hazard ratio 0·99; 95% CI 0·6–1·5, p=0·49).

418 However, combined treatment with everolimus and long-acting pasireotide demonstrated a
419 trend toward a higher objective response rate—20·3%, vs 6·2% treated with everolimus
420 monotherapy.²³

421 The most common grade 1/2 AEs with a suspected relationship to treatment with long-acting
422 pasireotide monotherapy or everolimus and long-acting pasireotide were diarrhoea (36·6%
423 and 46·3%) and hyperglycaemia (41·5% and 65·9%). Most AEs were manageable through
424 dose modification or interruption, with no new safety signals being reported in this study. The
425 safety profiles observed in the monotherapy and the combination treatment arms were
426 similar to that of previous studies,^{8,11,24} indicating the feasibility of combination therapy with
427 long-acting pasireotide and everolimus. Although discontinuations due to AEs and dose
428 modifications were frequently reported, the median relative dose intensity remained high in
429 all treatment groups. Hyperglycaemia has been observed as an AE in other studies with
430 everolimus and pasireotide monotherapy, albeit at lower frequencies.^{8,11} The high levels of
431 hyperglycaemia reported in a phase 1 study²⁴ and in our study of everolimus and long-acting
432 pasireotide in combination, appears to indicate an additive effect, highlighting the importance
433 of close monitoring of fasting serum glucose. Achievement of optimal glycaemic control
434 before initiation of therapy is required.²⁵ Hyperglycaemia is, however, manageable in the

435 context of a multidisciplinary centre, thus avoiding the need for treatment discontinuation,
436 particularly in patients responding to treatment.²⁵ The everolimus dose may be reduced to 5
437 mg/day or interrupted until the fasting serum glucose has normalized, as per the protocol
438 used in this study; however, considering the high number of treatment interruptions (52·4%)
439 or dose reductions (61·1%) due to AEs in this study, it is difficult to state definitively whether
440 hyperglycaemia will be manageable in all patients without exploratory analyses of the dose-
441 exposure relationship. A limited number of deaths in this study were classified as drug-
442 related per investigator review, but based on the analysis of causes of death, close
443 observation is recommended for patients undergoing treatment for pulmonary function, as
444 well as cardiac and kidney function, especially in case of dyspnoea with normal lung imaging
445 or associated diarrhoea or diabetes.

446 This study has a number of limitations. The small size and lack of a placebo control arm
447 limits the comparisons, and the conclusions of the study should be considered exploratory.
448 No subanalyses of efficacy by primary site (lung vs thymus), carcinoid subtype (TC vs AC),
449 Ki-67 index (high vs low), or median time from radiological disease progression at baseline
450 were performed, which may have provided useful information in this rarely studied
451 population. However, these subanalyses were not appropriate, given the small sample size
452 and imbalance between groups (eg, only 8 patients with thymic carcinoids), or were not
453 possible due to the lack of recorded time from disease progression at baseline or Ki-67
454 indices for each patient. Ki-67 indices were not reported for each patient because the
455 pathologic assessment in this study was based on the 2004 WHO classification of tumours
456 of the lung and thymus, which did not include Ki-67.¹⁵ It would have been unethical to select
457 patients based on Ki-67, since the 2004 WHO classification was the only clinical method
458 recognized by regulatory authorities for the classification of thoracic NET at the time of
459 enrolment. Another limitation of the study is that only 43/124 (34·7%) patients completed the
460 12-month core treatment phase. However, the completion and discontinuation rates were
461 consistent across the treatment groups (figure 1). For the primary endpoint, a single-stage

462 Fleming design was employed for each treatment arm; this design has no provision for early
463 termination if the observed response rate is unacceptably low. Furthermore, for the primary
464 endpoint (progression-free rate at 9 months), ideally a Kaplan-Meier analysis should be
465 employed rather than the responder and non-responder analysis that was performed in this
466 study. In this study, it was not appropriate to alter the primary endpoint to a Kaplan-Meier
467 analysis after patients had been recruited because the sample size was determined based
468 on the responder and non-responder analysis. The handling of missing data, such as
469 patients with a missing tumour assessment at 9 months being classified as non–progression
470 free, may have led to an underestimation of tumour response rates included in the analysis
471 of the primary endpoint. However, exclusion of these patients from the primary endpoint
472 analysis would have led to bias in the results by selecting patients who likely had improved
473 outcomes. In addition, the lack of blinded central radiological review of tumour response may
474 have introduced bias in the assessment of response.

475 In summary, the treatment of patients with advanced carcinoid tumours of the lung and
476 thymus with long-acting pasireotide alone or in combination with everolimus showed
477 preliminary evidence of efficacy and an acceptable safety profile. Further studies would be
478 needed to confirm the antitumour efficacy of combination therapy consisting of an SSA with
479 everolimus in this subset of patients with NET. Future research may improve prognostic
480 stratification, identify predictors of response, and determine the anti-secretory impact of the
481 treatment combination of an SSA with everolimus in the thoracic NET setting. While beyond
482 the scope of this study, the process toward personalized and precision medicine will be a
483 priority over the next two decades.

484 **Research in context**

485 **Evidence before this study**

486 We searched PubMed/MEDLINE for published reports on clinical trials in lung and thymic
487 neuroendocrine tumours (NET), with 'lung', 'thymic' or 'thymus', 'NET', and 'carcinoid' as our
488 primary search terms, limiting our findings to include studies evaluating the treatment of
489 lung/thymic NET or carcinoid tumours. We did not limit our search by date, but only
490 searched for articles published in English. We identified no prospective clinical trials
491 specifically investigating the treatment of advanced lung/thymic NET or carcinoids. However,
492 prospective studies (e.g., RADIANT-2 and RADIANT-4) in mixed NET populations and small
493 retrospective studies focusing on lung/thymic NET were identified. A subgroup analysis of
494 the RADIANT-4 trial was presented at the ENETS 13th Annual Conference in 2016, and
495 reported a clinically meaningful improvement in median progression-free survival (PFS)
496 following treatment with everolimus in patients with advanced, progressive, well-
497 differentiated, non-functional lung NET. The findings of a subgroup analysis of RADIANT-2
498 also reported an improvement in median PFS following treatment with everolimus plus
499 octreotide long-acting repeatable. These exploratory subgroup analyses highlight the
500 potential benefit of combination therapy with a somatostatin analogue (SSA) and everolimus.

501

502 **Added value of this study**

503 Preclinical data suggest that the SSA pasireotide may be associated with more potent
504 antiproliferative effects than octreotide, thus providing the rationale for combining long-acting
505 pasireotide with everolimus. To our knowledge, LUNA is the first prospective, randomised,
506 phase 2 clinical trial investigating an exclusive population of patients with advanced
507 carcinoid tumours of the lung and thymus. Patients were randomised to treatment with long-
508 acting pasireotide, everolimus, or a combination of the two agents. Our study indicates that
509 long-acting pasireotide with or without everolimus provides preliminary evidence of
510 antitumour activity, may improve PFS, and has an acceptable safety profile. Following
511 confirmation of superiority in phase 3 testing, combination of an SSA with everolimus may be

512 useful in the treatment of patients with advanced lung/thymic carcinoid tumours and
513 demonstrates the feasibility of conducting clinical trials in this rare NET subpopulation.

514

515 **Implications of all the available evidence**

516 Prospective clinical data on lung/thymic carcinoid tumours are limited. The results of this
517 randomised trial indicate that combination therapy of an SSA with everolimus would need
518 further clinical investigation in this rare subset of patients with NET. Additional well-designed,
519 adequately powered, randomised controlled clinical trials are required to expand on these
520 findings and establish the efficacy and safety of this treatment strategy.

521

522 **Contributors**

523 MS was the Clinical Trial Head. PF, GG, MS, KÖ, and EB were responsible for designing the
524 study. GG was responsible for trial management. WM, VD, CL-B, CG, HG, JDC, NR, GG,
525 KÖ, and EB participated in patient recruitment/inclusion. MPB, TM, JM, CDC, HL, AB, WB,
526 CG, HG, MT, JDC, and GG participated in data collection/acquisition. PF, WM, JM, HL, GG,
527 NS, MS, and EB performed the data analyses. PF, MPB, TM, WM, WB, VM, GG, NS, MS,
528 and EB interpreted the data. PF, MS, and EB conducted the literature search. GG was the
529 trial's statistician. KÖ performed a statistical evaluation. PF, WM, JM, WB, VM, NR, GG, MS,
530 KÖ, and EB wrote the manuscript. All authors reviewed and approved the final manuscript.

531

532 **Declaration of interests**

533 PF reports other fees from Novartis, during the conduct of the study; other fees from
534 Novartis, Merck, Ipsen, Pfizer, and Lexicon, outside the submitted work. TM reports personal
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549

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555

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- 633
- 634
- 635

Table 1: Baseline demographics and disease characteristics (full analysis set)

	P arm (n=41)	E arm (n=42)	EP arm (n=41)	All patients (N=124)
Age, years				
<65	21 (51.2%)	18 (42.9%)	24 (58.5%)	63 (50.8%)
≥65	20 (48.8%)	24 (57.1%)	17 (41.5%)	61 (49.2%)
Median	64	66	61	64
IQR	51–69	61–73	56–69	56–70
Sex				
Female	15 (36.6%)	19 (45.2%)	13 (31.7%)	47 (37.9%)
Male	26 (63.4%)	23 (54.8%)	28 (68.3%)	77 (62.1%)
Race				
Caucasian	40 (97.6%)	42 (100%)	40 (97.6%)	122 (98.4%)
Black/African American	1 (2.4%)	0	0	1 (0.8%)
Asian	0	0	1 (2.4%)	1 (0.8%)
Other	0	0	0	0
ECOG performance status				
0	28 (68.3%)	24 (57.1%)	27 (65.9%)	79 (63.7%)
1	11 (26.8%)	17 (40.5%)	14 (34.1%)	42 (33.9%)
2	2 (4.9%)	1 (2.4%)	0	3 (2.4%)
Histological grade*				
Typical	14 (34.1%)	12 (28.6%)	13 (31.7%)	39 (31.5%)
Atypical	27 (65.9%)	30 (71.4%)	28 (68.3%)	85 (68.5%)
Primary site of cancer				
Lung	38 (92.7%)	39 (92.9%)	39 (95.1%)	116 (93.5%)
Thymus	3 (7.3%)	3 (7.1%)	2 (4.9%)	8 (6.5%)
Functional status of tumour				
Functional	12 (29.3%)	7 (16.7%)	9 (22.0%)	28 (22.6%)
Non-functional	29 (70.7%)	35 (83.3%)	32 (78.0%)	96 (77.4%)
Current metastatic extent†				
Liver	30 (73.2%)	34 (81.0%)	31 (75.6%)	95 (76.6%)
Bone	32 (78.0%)	15 (35.7%)	22 (53.7%)	69 (55.6%)

Lung	15 (36.6%)	13 (31.1%)	20 (48.8%)	48 (38.7%)
Cervical/thoracic lymph nodes	14 (34.1%)	15 (35.7%)	9 (22.0%)	38 (30.6%)
Pleura	2 (4.9%)	2 (4.8%)	6 (14.6%)	10 (8.1%)
Other‡	28 (68.3%)	24 (57.1%)	27 (65.8%)	79 (63.7%)

637

638 Data are n (%) unless otherwise stated. P arm=long-acting pasireotide treatment arm. E
639 arm=everolimus treatment arm. EP arm=everolimus and long-acting pasireotide treatment
640 arm. ECOG=Eastern Cooperative Oncology Group. IQR=interquartile range. *Reconciled
641 rates. During the randomisation process, seven patients were misstratified by the
642 investigational sites with respect to histologic grade. †Including individual sites with more
643 than 10% involvement in at least one treatment group. ‡Including skin, thyroid, kidney,
644 adrenal glands, testis, ovary, breast, ascites (malignant), peritoneum, para-aortic abdominal
645 lymph nodes, pancreas, spleen, brain, bone marrow, abdomen lymph node, paravertebral
646 lymph node, subcutaneous lesions, supraclavicular lymph nodes, mediastinum, lung nodes,
647 left supraclavicular adenopathy, right retrocrural lymph node, or soft tissue on anterior
648 abdominal wall.

Table 2: Proportion of patients progression-free at month 9 (full analysis set)

	P arm (n=41)		E arm (n=42)		EP arm (n=41)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Overall lesion response at month 9*						
CR	0	0.0%– 8.6%	0	0.0%– 8.4%	0	0.0%– 8.6%
PR	1 (2.4%)	0.1%– 12.9%	1 (2.4%)	0.1%– 12.6%	1 (2.4%)	0.1%– 12.9%
SD	14 (34.1%)	20.1%– 50.6%	13 (31.0%)	17.6%– 47.1%	20 (48.8%)	32.9%– 64.9%
PD	7 (17.1%)		1 (2.4%)		0	
Unknown†	1 (2.4%)		2 (4.8%)		3 (7.3%)	
Not assessed‡	18 (43.9%)		25 (59.5%)		17 (41.5%)	
Discontinued before Month 9	20 (48.8%)		24 (57.1%)		16 (39.0%)	
Progression-free rate at month 9§	16 (39.0%)	24.2%– 55.5%	14 (33.3%)	19.6%– 49.5%	24 (58.5%)	42.1%– 73.7%
Minimum number of progression- free patients to reject H_{0ll}	13		14		13	

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm. EP arm=everolimus and long-acting pasireotide treatment arm. CI=confidence interval. CR=complete response. PR=partial response. SD=stable disease. PD=progressive disease.

*Overall lesion response at month 9 is the investigator-reported overall lesion response at the week 36 visit. The 95% CI for the responses are computed using an exact binomial method. †If progression is not documented and one or more lesions have not been assessed or have been assessed using a different method from baseline, then the overall lesion response at month 9 is 'unknown'. ‡If a patient does not have any tumour assessments made in the study day 211-294 window, then the overall lesion response at month 9 is 'not assessed'. §The progression-free rate at month 9 is defined as the proportion of patients with overall lesion assessment at month 9 being CR, PR, or SD according to Response Evaluation Criteria in Solid Tumours, version 1.1. Patients with missing or unknown month 9 assessment and with CR, PR, or SD at any of the following assessments at month 11 or 12 are considered as progression free at month 9. || H_0 : a progression-free rate $\leq 20\%$ is the null hypothesis on the progression-free rates at month 9. The minimum number of progression-free patients to reject H_0 is calculated according to the Fleming single-stage design.

Table 3: Progression-free survival per investigator radiological review (full analysis set)

	P arm (n=41)	E arm (n=42)	EP arm (n=41)
Patients, n (%)			
With events	20 (48.8%)	17 (40.5%)	14 (34.1%)
With censorings	21 (51.2%)	25 (59.5%)	27 (65.9%)
Censored at day 1	1 (2.4%)	5 (11.9%)	5 (12.2%)
PFS, months, median (95% CI)	8.5 (5.7–NE)	12.5 (5.6–NE)	11.8 (11.1–NE)
Event-free probability estimate, * % (95% CI)			
3-month	83.6% (67.1%– 92.3%)	91.2% (75.1%– 97.1%)	88.6% (72.4%– 95.5%)
6-month	68.2% (49.8%– 81.1%)	63.5% (44.7%– 77.4%)	85.5% (68.6%– 93.7%)
9-month	49.6% (31.9%– 65.1%)	56.9% (38.1%– 71.9%)	79.2% (61.1%– 89.5%)
12-month	35.9% (18.3%– 53.9%)	50.2% (31.9%– 66.0%)	39.4% (17.0%– 61.2%)

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm. EP

arm=everolimus and long-acting pasireotide treatment arm. PFS=progression-free survival.

CI=confidence interval. NE=not estimable; *Percentage event-free probability estimate is the estimated probability that a patient will remain without objective tumour progression or death from any cause up to the specified timepoint. These estimates are obtained from the Kaplan-Meier survival estimates for all treatment groups; the Greenwood formula is used for confidence intervals of Kaplan-Meier estimates.

Table 4: Treatment-emergent adverse events, regardless of study drug relationship, by preferred term and treatment (safety set)

Preferred term*	P arm (n=41)			E arm (n=42)			EP arm (n=41)		
	Grade 1 or 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1 or 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 1 or 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Total	41 (100.0%)	23 (56.1%)	5 (12.2%)	42 (100.0%)	29 (69.0%)	8 (19.0%)	41 (100.0%)	33 (80.5%)	4 (9.8%)
Hyperglycaemia	18 (43.9%)	3 (7.3%)	0	12 (28.6%)	7 (16.7%)	0	34 (82.9%)	10 (24.4%)	0
Diarrhoea	16 (39.0%)	3 (7.3%)	1 (2.4%)	18 (42.9%)	2 (4.8%)	1 (2.4%)	31 (75.6%)	7 (17.1%)	1 (2.4%)
Stomatitis	2 (4.9%)	0	0	26 (61.9%)	4 (9.5%)	0	13 (31.7%)	2 (4.9%)	0
Weight decreased	18 (43.9%)	0	0	17 (40.5%)	1 (2.4%)	0	23 (56.1%)	3 (7.3%)	0
Asthenia	10 (24.4%)	0	0	12 (28.6%)	1 (2.4%)	0	15 (36.6%)	1 (2.4%)	0
Abdominal pain	13 (31.7%)	1 (2.4%)	0	4 (9.5%)	0	0	5 (12.2%)	0	0
Decreased appetite	10 (24.4%)	0	0	13 (31.0%)	2 (4.8%)	0	12 (29.3%)	2 (4.9%)	0
Cough	6 (14.6%)	0	0	12 (28.6%)	0	0	11 (26.8%)	0	0
Oedema peripheral	7 (17.1%)	0	0	12 (28.6%)	1 (2.4%)	0	10 (24.4%)	1 (2.4%)	0

Anaemia	8 (19.5%)	3 (7.3%)	0	12 (28.6%)	1 (2.4%)	0	8 (19.5%)	2 (4.9%)	0
Dyspnoea	6 (14.6%)	4 (9.8%)	1 (2.4%)	12 (28.6%)	2 (4.8%)	0	3 (7.3%)	2 (4.9%)	0
Rash	1 (2.4%)	0	0	11 (26.2%)	3 (7.1%)	0	5 (12.2%)	0	0
Nausea	10 (24.4%)	0	0	10 (23.8%)	1 (2.4%)	0	8 (19.5%)	0	0
Fatigue	6 (14.6%)	1 (2.4%)	0	7 (16.7%)	1 (2.4%)	0	10 (24.4%)	4 (9.8%)	0
Constipation	9 (22.0%)	0	0	6 (14.3%)	1 (2.4%)	0	0	0	0
Thrombocytopenia	0	0	0	9 (21.4%)	1 (2.4%)	0	7 (17.1%)	0	0
Pyrexia	7 (17.1%)	0	0	7 (16.7%)	1 (2.4%)	0	6 (14.6%)	0	0
Headache	7 (17.1%)	0	0	5 (11.9%)	0	0	6 (14.6%)	0	0
Back pain	7 (17.1%)	1 (2.4%)	1 (2.4%)	6 (14.3%)	0	0	4 (9.8%)	0	0
Diabetes mellitus	7 (17.1%)	3 (7.3%)	0	3 (7.1%)	0	0	5 (12.2%)	3 (7.3%)	0
Blood alkaline phosphatase increased	7 (17.1%)	1 (2.4%)	0	2 (4.8%)	1 (2.4%)	0	2 (4.9%)	1 (2.4%)	0
Dysgeusia	4 (9.8%)	0	0	4 (9.5%)	0	0	7 (17.1%)	0	0
Pruritus	2 (4.9%)	0	0	2 (4.8%)	0	0	7 (17.1%)	0	0
Hypertriglyceridaemia	3 (7.3%)	0	0	7 (16.7%)	0	0	5 (12.2%)	1 (2.4%)	0

Vomiting	6 (14.6%)	0	0	4 (9.5%)	0	0	4 (9.8%)	1 (2.4%)	0
Gamma-glutamyltransferase increased	6 (14.6%)	5 (12.2%)	1 (2.4%)	2 (4.8%)	2 (4.8%)	1 (2.4%)	2 (4.9%)	3 (7.3%)	0
Productive cough	0	0	0	3 (7.1%)	0	0	6 (14.6%)	0	0
Chest pain	3 (7.3%)	1 (2.4%)	0	6 (14.3%)	0	0	4 (9.8%)	1 (2.4%)	0
Hypercholesterolaemia	1 (2.4%)	0	0	6 (14.3%)	0	0	5 (12.2%)	0	0
Urinary tract infection	3 (7.3%)	2 (4.9%)	0	2 (4.8%)	0	0	5 (12.2%)	0	0
Hypophosphataemia	1 (2.4%)	0	0	2 (4.8%)	2 (4.8%)	0	5 (12.2%)	1 (2.4%)	0
Mouth ulceration	0	0	0	2 (4.8%)	1 (2.4%)	0	5 (12.2%)	1 (2.4%)	0
Epistaxis	0	0	0	5 (11.9%)	0	0	2 (4.9%)	0	0
Abdominal pain upper	4 (9.8%)	0	0	2 (4.8%)	0	0	3 (7.3%)	0	0
Hypomagnesaemia	4 (9.8%)	0	0	2 (4.8%)	0	0	3 (7.3%)	0	0
Dizziness	4 (9.8%)	0	0	2 (4.8%)	0	0	2 (4.9%)	0	0
Musculoskeletal pain	4 (9.8%)	0	0	1 (2.4%)	0	0	2 (4.9%)	0	0
Musculoskeletal chest pain	4 (9.8%)	0	0	0	0	0	2 (4.9%)	0	0
Muscle spasms	4 (9.8%)	0	0	2 (4.8%)	0	0	1 (2.4%)	0	0

Aspartate aminotransferase increased	4 (9.8%)	0	0	2 (4.8%)	0	0	0	1 (2.4%)	0
Pneumonia	4 (9.8%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	0	0	0	0
Chills	4 (9.8%)	0	0	0	0	0	0	0	0
Hypokalaemia	1 (2.4%)	1 (2.4%)	0	3 (7.1%)	0	0	4 (9.8%)	0	0
Haemorrhoids	1 (2.4%)	0	0	1 (2.4%)	1 (2.4%)	0	4 (9.8%)	0	0
Toothache	1 (2.4%)	0	0	1 (2.4%)	0	0	4 (9.8%)	0	0
Flushing	1 (2.4%)	0	0	0	1 (2.4%)	0	4 (9.8%)	0	0
Pneumonitis	0	0	0	2 (4.8%)	2 (4.8%)	0	4 (9.8%)	2 (4.9%)	0
Dysphagia	0	0	0	4 (9.5%)	2 (4.8%)	0	0	0	0

P arm=long-acting pasireotide treatment arm. E arm=everolimus treatment arm; EP arm=everolimus and long-acting pasireotide treatment arm.

*Presented for those with grade 1 or 2 adverse events occurring with a frequency of $\geq 10\%$ in at least one treatment group.

Figure Legends

Figure 1: Trial profile

*Two patients completed the core phase of the study but did not enter the extension phase: one patient in the P arm due to worsening clinical condition and one patient in the E arm by investigator decision.

Figure 2: Best percentage change from baseline in sum of longest diameters of target lesions (full analysis set)

Percentages are calculated based on n (number of patients included in the analysis).

Contradiction refers to a percentage change in target lesion available, but contradicted by overall lesion response (progressive disease). [†]N is the number of randomised patients; n is the number of patients with valid postbaseline assessments, excluding patients for whom target lesion and overall response is 'unknown'.

Figure 3: Progression-free survival per investigator radiological review (full analysis set)