PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Randomized Phase II Trial of CAPTEM or FOLFIRI as SEcond-line Therapy in NEuroendocrine CArcinomas and Exploratory Analysis of Predictive Role of PET/CT Imaging and Biological Markers (SENECA Trial): A Study Protocol
AUTHORS	Bongiovanni, Alberto; Liverani, Chiara; Pusceddu, Sara; Leo, Silvana; Di Meglio, Giovanni; Tamberi, Stefano; Santini, Daniele; Gelsomino, Fabio; Pucci, Francesca; Berardi, Rossana; Lolli, Ivan; Bergamo, Francesca; Ricci, Sergio; Foca, Flavia; Severi, Stefano; Ibrahim, Toni

VERSION 1 - REVIEW

REVIEWER	Pia Österlund Tampere university hospital; Finland
REVIEW RETURNED	31-Oct-2019

GENERAL COMMENTS	This clearly is a good and important initiative. It needs minor revision. Editorial work should have been better before submission! I have read it in the order it has been written. Some points have been clarified later. The primary endpoint as a composite score with disease control rate and selected grade 3-4 toxicity needs to be defined correctly from the abstract onward. Look at a few papers with composite endpoints and take example of their way of expressing things. Some suggestions below. The text needs clarification about what patients have been treated and are treated. Missing references etc are seen also which shows that this has been prepared in a hurry. The language is fair but not splendid (if you have a native English speaker as a friend as them to read it). COMMENTS BY ROW Row: 53: efficacy and safety cannot be the primary endpoint. The primary endpoint needs to be OS or PFS (possibly response rate) and the others included in secondary endpoints. Row 62-63: All analysis will be performed separately, this needs to be clarified, does this mean for FOLFIRI group and CapTem separately or for lung and GI NECs or what does this refer to. 63 for each group Row 65: Whys is treatment duration limited to 6 months. Row 96: grade (G)3 NECs -> grade (G) 3 NECs = Editorial work to

	be done before acceptance for publication, Row 95-99: Clarify if the new 2017 WHO grading will be used or the old i.e. is G3 NETs included or just NECs? Add this throughout. Rows 100-103: The references are missing for etoposide + platinum. Sorbye et al is probably the best reference for this sentence and change accordingly. Row 106: Given the rarity of this disease , prospective clinical data _> Given the rarity of this disease, prospective clinical data. = Editorial work to be done before acceptance for publication, Row 109: add in Grades here, this is probably not Gr NECs but G1-2 I presume and this is a fully different disease entity compare with yours. A good and necessary passage but you need to show the reader this is different. Same thins on row 111, 112 and 115. Rows 116-129 needs addition of patient population studied i.e. grade or more elaboation on Ki-67. Row 149: you could add in survival rate at 1 or 2 years. Then results should be also per G1 (if any)/G2 (if any)/ G3 Ki-67<50 / G3 Ki-67>50 or does this refer to NEC G3s only? You can prove whatever by taking in nice G2 patients as opposed to >50% aggressive disease. Small editorial comment where is 50 included ≥ or ≤. Row 150-152: you cannot claim longer survival and prove it with survival rates at 18 months. Change it to improved survival with higher survival rates at 18 months. Row 156-158: here you need to define the NECs more clearly and what WHO is used as the basis and whether NET G3s are included or excluded (you fins it on row 189 but not before this). Same comment as in the abstract. You cannot study efficacy and safety as primary endpoint in this study. Make the others routine secondary endpoints. The biomarkers could preferably be exploratory endpoints or secondary endpoints. Row 179: why is a suboptimal halved leucovorin dose used? The regular dosing is 400mg/m2 is d/l-leucovorin is used. The time limitation to limit to 12 cycles needs to be clarified throughout. Row 188: the maximum of 6 cycles need to be clarified throughout. When you have a disease where patients are kept alive with medication and you have no cumulative toxicity then it is not very wise to stop a efficient treatment. I have had patients ongoing for nearly five years with temcap for this indication and thereafter had metastasectomy with curative intent and still going strong nearly 3 years later. Row 195: how common is CAPOX or FOLFOX versus Car/Cis+etoloposide in Italy, if known then an estimate of the patient population. Row 199-200: no known hypersensitivity to capecitabine or temozolamide? Row 224: the major limitation of this study is this 3 month tumour evaluation interval which makes this study very poor as efficacy is

	the primary endpoint, PFS is not a reliable in this study (it would have been somewhat reliable in G1 or G2 NETs). In GEP G3s even 2 months is a long interval, especially in second line, 6 weeks would have been the preferred interval. Could you do an amendment, because this is crucial and the study is a very splendid initiative? Row 228 onwards: for 10 pages I have been commenting the endpoints. So please add in these endpoints in the manuscript starting from the abstract.Is the disease control rate at 12 weeks analyzed in the intention to treat population, i.e. is a patient still analysed if not getting any therapy (which I hope it is). Row 232: the toxicity is not defined as an endpoint! You cannot have 20% in the statistical analysis as the endpoint when you have told us nothing how you are going to use the CTC version 4.03. grade 3-4 toxicity (exclusion of neutropenia, anemia, thrombocytopenia, PPE or not any? how about baseline neurotoxicity which is present in all having received oxaliplatin based and many with carbo/cis? Row 234: Secondary endpoints are the evaluation of sholud the end of the sentence be crossed or not? = Editorial work to be done before acceptance for publication Row 235-237: Calculated from start of treatment, usually calculated from date of randomization if a randomized study in question. Row 241: Here you mention QoL assessment for the first time. If performed actively in all patients this is a important secondary endpoint that deserves to be mentioned clearly If performed "half-heartedly" then you should not mention it at all. The repetition of QoL assessment timepoints should be mentioned as it is included in statistics later on. Row 243: intent.. Crossing over of text = Editorial work to be done before acceptance for publication Row 242: you need to define baseline PET timing as written now it's immediately before initiation of second line therapy. At the time of mCRC diagnosis. After first line or whenever prior to initiation of this therapy? Row 257: this research was done without patient involvement... You probably mean that this research is done with patients (or you use dummies as patients?), but the research plan was performed without patient involvement? Row 265: this is relevant and ok apart from the not toxic on row 272 (even though it fulfills these criteria still nearly 100% of the patients will have toxicity. Rewrite tolerable or safety profile acceptable. Row 279: are these the criteria for toxicity that are added into the 20 or 40% relevance level?Is it per patient level or per cycle? Define clearly. Row 302: add in the Sorbye et al paper here (reference 22) as it shows a lot of prognostic biomarkers but not the fancy ones. But there are valid markers for the clinician. Hopefully you will register these things from your patients to be able to show the demographics and prognostic baseline factors well enough. Take also a look at Sorbye et al Ann Oncol 2007 for demographic factors to publish

	(relevant though published for mCRC). Row 312: morphology refers to what? Small or large cell histology? To my knowledge this has not been mentioned as a stratification factor but only Ki-67% and GEP or lung? Row 313: well differentiated NET means G1 or G2 (which is not under study here if I have understood correctly), not G3 high versus low ki-67%, which everything i poorly differentiated NECs. Row 317: Medicines Agency)- approved -> Medicines Agency) approved. = editorial work...

REVIEWER	STEFANO CRIPPA San Raffaele Scientific Institute, Milan, Italy
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	Currently there are no FDA/EMA (Food and Drug Administration/European Medicines Agency) approved second-line therapeutic options for patients with metastatic NECs. There are vailable few reports on a heterogeneous treatment-options based mainly on retrospective data in small cohorts of patients. The SENECA study is a randomized phase 2 trial comparing CAPTEM or FOLFIRI as second-line therapy in neuroendocrine carcinomas of the lung or GI/pancreas (primary aim). The secondary aims were to correlate the serum miRNA profile and primary mutational status of MEN1, DAXX,ATRX and RB-1 with prognosis and outcome and to investigate the prognostic and predictive role of Ki-67 score and FDG- and 68Ga-PET/CT. Authors will include patients with histological diagnosis of G3 neuroendocrine carcinoma (GEP-NEC and lung NEC) and Ki-67 >20%; all patients must have a progression following a first line, platinum-based chemotherapy. Major comment: NEC (WHO G3) is currently defined by a mitotic count > 20 mitoses/10 HPF and/or Ki67 index > 20. However this category is heterogeneous and may include: -morphological poorly-differentiated NEC: they are characterized by a high ki67 index, usually more than 50%-60%, and they include smal-cell and large-cell tumors. By a clinical standpoint these tumors are aggressive, and they are associated with dismal prognosis (median survival 6-12 months). -morphological well-differentiated NEC:these tumors are well-differentiated NETs by a morphological point of view but they have a mitotic count > 20 mitoses/10 HPF and/or Ki67 index > 20%. They are also defined as "NET G3 tumors". By a clinical standpoint, these tumors have an improved survival compared to morphological PD-NEC (please see Crippa S. Surgery. 2016;159:862–871; Basturk O. Am J Surg Pathol. 2015;39:683–690; Vélayoudom-Céphise FL. Endocr Relat Cancer. 2013;20:649–657) Platinum-based chemotherapy can be more effective for PD-NEC with high ki67 index, but less effective for those with WD morphology. Do Authors think that platinum-based chemotherapy will be the most appropriate strategy in all the patients included in this study? Do you think that sub-analysis in the two above mentioned categories could be appropriate?

	I think that the inclusion of patients with heterogeneous tumors (PD-NEC vs WD-NEC) can be a limitation of the study. In the Methods the inclusion criteria did not clearly specify if Authorsm will include both WD and PD-NEC

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
This clearly is a good and important initiative. It needs minor revision. Editorial work should have been better before submission! I have read it in the order it has been written. Some points have been clarified later. The primary endpoint as a composite score with disease control rate and selected grade 3-4 toxicity needs to be defined correctly from the abstract onward. Look at a few papers with composite endpoints and take example of their way of expressing things. Some suggestions below. The text needs clarification about what patients have been treated and are treated. Missing references etc are seen also which shows that this has been prepared in a hurry. The language is fair but not splendid (if you have a native English speaker as a friend as them to read it).
Reply: Many thanks for the suggestions. All the corrections made in the text on the basis of the reviewers' comments are indicated in blue. The paper has also been revised by a native English speaker.

COMMENTS BY ROW
Row: 53: efficacy and safety cannot be the primary endpoint. The primary endpoint needs to be OS or PFS (possibly response rate) and the others included in secondary endpoints.
Reply: We would like to explain the reasoning behind the choice of primary endpoints. Treatment efficacy in our study is measured on the basis of the disease control rate at 12 weeks. Whilst we agree with the reviewer that the primary aim should be based on OS or PFS, we felt that, given the aggressiveness of the disease, DCR would be a more useful measure of efficacy, as recently reported in other studies (Battle trial). Furthermore, OS and PFS were pre-planned secondary endpoints in our work.

Row 62-63: All analysis will be performed separately, this needs to be clarified, does this mean for FOLFIRI group and CapTem separately or for lung and GI NECs or what does this refer to.
Reply: As suggested, we have specified in the text that all of the analyses will be performed separately for each treatment group (lines 62-63).

63 for each group
Reply: This has been corrected.

Row 65: Whys is treatment duration limited to 6 months.
Reply: We decided to limit both treatments to 6 months for reasons of safety.

Row 96: grade (G)3 NECs -> grade (G) 3 NECs = Editorial work to be done before acceptance for publication.
Reply: This has been corrected (line 96).

Row 95-99: Clarify if the new 2017 WHO grading will be used or the old i.e. is G3 NETs included or just NECs? Add this throughout.
Reply: The SENECA study was activated in 2016 and we used the classifications available at that time (2010 for GEP NENs and 2015 for lung NRNs). This information has been added to the Materials

and Methods section (lines 194-195). The protocol will be amended shortly with the 2017 and 2019 classifications.

Rows 100-103: The references are missing for etoposide + platinum. Sorbye et al is probably the best reference for this sentence and change accordingly.
Reply: The reference in question has been added (ref. no. 6, line 102).

Row 106: Given the rarity of this disease , prospective clinical data _> Given the rarity of this disease, prospective clinical data. = Editorial work to be done before acceptance for publication,
Reply: The has been corrected (line 106).

Row 109: add in Grades here, this is probably not Gr NECs but G1-2 I presume and this is a fully different disease entity compare with yours. A good and necessary passage but you need to show the reader this is different. Same things on row 111, 112 and 115.
Reply: The clinical studies cited refer to neuroendocrine carcinoma. This has been clarified in the text (page 6, lines 125-126).

Rows 116-129 needs addition of patient population studied i.e. grade or more elaboration on Ki-67.
Reply: As requested, more details have been added (lines 111,121 and 125-126).

Row 149: you could add in survival rate at 1 or 2 years. Then results should be also per G1 (if any)/G2 (if any)/ G3 Ki-67<50 / G3 Ki-67>50 or does this refer to NEC G3s only? You can prove whatever by taking in nice G2 patients as opposed to >50% aggressive disease. Small editorial comment where is 50 included ≥ or ≤.
Reply: We only refer to NEC G3, We have modified the text accordingly (line 153).

Row 150-152: you cannot claim longer survival and prove it with survival rates at 18 months. Change it to improved survival with higher survival rates at 18 months.
Reply: The text has been modified accordingly (lines 155-156).

Row 156-158: here you need to define the NECs more clearly and what WHO is used as the basis and whether NET G3s are included or excluded (you fins it on row 189 but not before this). Same comment as in the abstract. You cannot study efficacy and safety as primary endpoint in this study. Make the others routine secondary endpoints. The biomarkers could preferably be exploratory endpoints or secondary endpoints.
Reply: The text has been modified as requested (194-195).
Row 179: why is a suboptimal halved leucovorin dose used? The regular dosing is 400mg/m2 is d/l-leucovorin is used. The time limitation to limit to 12 cycles needs to be clarified throughout.
Reply: Line 183: We prefer to use a dose of 200 mg/m2, as reported in several studies (Tournigand, J Clin Oncol 2004;22:229-237, modified by Taïeb, Ann Oncol 2007;18:498–503 [pancreas]); Dank M. Ann Oncol 2008;19:1450-1457).

Row 188: the maximum of 6 cycles need to be clarified throughout. When you have a disease where patients are kept alive with medication and you have no cumulative toxicity then it is not very wise to stop a efficient treatment. I have had patients ongoing for nearly five years with temcap for this indication and thereafter had metastasectomy with curative intent and still going strong nearly 3 years later.
Reply: We agree with the reviewer comments. However, given that Seneca study is a not sponsored trial, we decided to have a treatment time limit of 6 months.

Row 195: how common is CAPOX or FOLFOX versus Car/Cis+etoloposide in Italy, if known then an estimate of the patient population.
Reply: We do not have this information.In some cases FOLFOX /CapOx is used, as reported by ENETS guidelines. Given the rarity of the tumor, we decided to include patients receiving these treatments in the study.

Row 199-200: no known hypersensitivity to capecitabine or temozolamide? Reply: The use of temozolomide is an exclusion criterion and is now reported in the text (line 204). We have also added that known hypersensitivity to capecitabine is an exclusion criterion (line 205).

Row 224: the major limitation of this study is this 3 month tumour evaluation interval which makes this study very poor as efficacy is the primary endpoint, PFS is not a reliable in this study (it would have been somewhat reliable in G1 or G2 NETs). In GEP G3s even 2 months is a long interval, especially in second line, 6 weeks would have been the preferred interval. Could you do an amendment, because this is crucial and the study is a very splendid initiative? Reply: Whilst we agree with reviewer's standpoint, this is a no profit study and in order to avoid additional costs for diagnostic procedures, we were obliged to use an interval of three months. This is also a requirement of the Italian Medicines Agency.

Row 228 onwards: for 10 pages I have been commenting the endpoints. So please add in these endpoints in the manuscript starting from the abstract.Is the disease control rate at 12 weeks analyzed in the intention to treat population, i.e. is a patient still analysed if not getting any therapy (which I hope it is). A
Reply: As requested, we have inserted the endpoints throughout the text. All of the analyses will be performed in the intention-to-treat population and this has been specified in the text (lines 63 and 243).

Row 232: the toxicity is not defined as an endpoint! You cannot have 20% in the statistical analysis as the endpoint when you have told us nothing how you are going to use the CTC version 4.03. grade 3-4 toxicity (exclusion of neutropenia, anemia, thrombocytopenia, PPE or not any? how about baseline neurotoxicity which is present in all having received oxaliplatin based and many with carbo/cis?
Reply: We decided to include both efficacy and toxicity as primary end-points so that we could also evaluate the impact of treatment on patients' clinical conditions In this way we can assess patients' quality of life. Previous treatment toxicity will be recorded at the baseline evaluation.

Row 234: Secondary endpoints are the evaluation of sholud the end of the sentence be crossed or not? = Editorial work to be done before acceptance for publication
Reply: This has been corrected.

Row 235-237: Calculated from start of treatment, usually calculated from date of randomization if a randomized study in question.
Reply: Patients normally begin treatment a few days after the date of randomization because of the often rapid deterioration of their clinical conditions. For this reason the date of randomization and the date of the start of treatment are similar but does not influence the statistical analysis.

Row 241: Here you mention QoL assessment for the first time. If performed actively in all patients this is a important secondary endpoint that deserves to be mentioned clearly If performed "half-heartedly" then you should not mention it at all. The repetition of QoL assessment timepoints should be mentioned as it is included in statistics later on.
Reply: This information has been added to the text (lines 231-232).

Row 243: intent.. Crossing over of text = Editorial work to be done before acceptance for publication
Reply: This has been corrected.

Row 242: you need to define baseline PET timing as written now it's immediately before initiation of second line therapy. At the time of mCRC diagnosis. After first line or whenever prior to initiation of this therapy?
Reply: Ga68 PET/CT should be performed < 90 days before randomization. Due to the cost and the no-profit nature of the study, this was not mandatory but is highly recommended.

Row 257: this research was done without patient involvement... You probably mean that this research is done with patients (or you use dummies as patients? but the research plan was performed without patient involvement?
Reply: This is a pre-defined journal statement. It means that patients are not involved in the study design or outcome measures. This has been specified in the text (lines 263-264).

Row 265: this is relevant and ok apart from the not toxic on row 272 (even though it fulfills these criteria still nearly 100% of the patients will have toxicity. Rewrite tolerable or safety profile acceptable.
Reply: The most important toxicities are specified on page 13 (lines 287-289).

Row 279: are these the criteria for toxicity that are added into the 20 or 40% relevance level?Is it per patient level or per cycle? Define clearly.
Reply: The relevant toxicities are already specified in the text (lines 287-289). We are referring to relevant toxicity per patient.

Row 302: add in the Sorbye et al paper here (reference 22) as it shows a lot of prognostic biomarkers but not the fancy ones. But there are valid markers for the clinician. Hopefully you will register these things from your patients to be able to show the demographics and prognostic baseline factors well enough. Take also a look at Sorbye et al Ann Oncol 2007 for demographic factors to publish (relevant though published for mCRC).
Reply: The reference in question has been added at this point in the text (line 299, ref. no. 25). We plan to perform an analysis of the demographic characteristics in the future.

Row 312: morphology refers to what? Small or large cell histology? To my knowledge this has not been mentioned as a stratification factor but only Ki-67% and GEP or lung?
Reply: We will record information on morphology (well differentiated or poorly differentiated tumors) and will amend the study protocol according to the new classifications.

Row 313: well differentiated NET means G1 or G2 (which is not under study here if I have understood correctly), not G3 high versus low ki-67%, which everything i poorly differentiated NECs.
Reply: Please see our previous reply.

Row 317: Medicines Agency)- approved -> Medicines Agency) approved. = editorial work...
Reply: The hyphen is correct and serves to show the link between ‘FDA/EMA’ and ‘approved’.

Reviewer 2

Major comment:
NEC (WHO G3) is currently defined by a mitotic count > 20 mitoses/10 HPF and/or Ki67 index > 20. However this category is heterogeneous and may include:

-morphological poorly-differentiated NEC: they are characterized by a high ki67 index, usually more than 50%-60%, and they include smal-cell and large-cell tumors. By a clinical standpoint these tumors are aggressive, and they are associated with dismal prognosis (median survival 6-12 months).
-morphological well-differentiated NEC:these tumors are well-differentiated NETs by a morphological point of view but they have a mitotic count > 20 mitoses/10 HPF and/or Ki67 index > 20%. They are also defined as "NET G3 tumors". By a clinical standpoint, these tumors have an improved survival compared to morphological PD-NEC (please see Crippa S. Surgery. 2016;159:862–871; Basturk O. Am J Surg Pathol. 2015;39:683–690; Vélayoudom-Céphise FL. Endocr Relat Cancer. 2013;20:649–657)
Platinum-based chemotherapy can be more effective for PD-NEC with high ki67 index, but less effective for those with WD morphology. Do Authors think that platinum-based chemotherapy will be the most appropriate strategy in all the patients included in this study?
Reply: This is a pertinent question. G3 NENs are a hereogenous group of tumors including both NET G3 and NEC G3. Unfortunately, no prospective controlled randomized clinical trials have been performed to date to compare the two different first-line therapeutic strategies. Platinum-based chemotherapy remains the most effective strategy.

Do you think that sub-analysis in the two above mentioned categories could be appropriate?
Reply: We agree with reviewer and will perform a sub-analysis of the two categories, especially from a translational point of view.

I think that the inclusion of patients with heterogeneous tumors (PD-NEC vs WD-NEC) can be a limitation of the study.
Reply: We agree with the reviewer that this is an important issue. We thus calculated the size of the study sample in order to provide clinical information on both subgroups.

VERSION 2 – REVIEW

REVIEWER	Pia Österlund Tampere university hospital, Tampere Finland
REVIEW RETURNED	12-Mar-2020

GENERAL COMMENTS	This paper has significantly improved during revision. I would add in honest statements regarding the scan interval of 12 weeks as Italian standard by regulatory agencies. This is not clearly mentioned in the text. Line 65 and 175: CapTem and FOLFIRI do not have significant cumulative toxicity. You should have consulted an experienced GI oncologist first. Consider revising the protocol to allow longer treatment duration. Most of my patients with long term remission in GEP-NECs have received longer treatment than 6 months, but that in the first-line mostly. Pausing an efficient treatment is not always the best in aggressive cancers, but in lung NECs we have experience with pausing and no clear evidence for continued treatment. In GEPs there are no evidence as far as I know. Then you tell me it is limited to 6 months because of economical issues (temozolamide I presume). You need to clarify this both in

	abstract and text, be honest. Line 230: Write in the time point within 90 days, add in the recommended instead of when possible. There is extra spaces between words at least fifteen times in the body text - they are undelined with two blue lines in the word processor.

REVIEWER	Stefano Crippa IRCCS Ospedale San Raffaele, Milan, Italy
REVIEW RETURNED	20-Mar-2020

GENERAL COMMENTS	The revision is fine

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Reviewer Name: Pia Österlund
Institution and Country: Tampere university hospital, Tampere Finland
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This paper has significantly improved during revision.
Reply: We thank the reviewer for the suggestions received and appreciate the opportunity to improve our protocol.

I would add in honest statements regarding the scan interval of 12 weeks as Italian standard by regulatory agencies. This is not clearly mentioned in the text.
Reply: We have inserted this information into the text (page 10, lines 230-231).

Line 65 and 175:
CapTem and FOLFIRI do not have significant cumulative toxicity. You should have consulted an experienced GI oncologist first. Consider revising the protocol to allow longer treatment duration. Most of my patients with long term remission in GEP-NECs have received longer treatment than 6 months, but that in the first-line mostly. Pausing an efficient treatment is not always the best in aggressive cancers, but in lung NECs we have experience with pausing and no clear evidence for continued treatment. In GEPs there are no evidence as far as I know.

Then you tell me it is limited to 6 months because of economical issues (temozolamide I presume). You need to clarify this both in abstract and text, be honest.
Reply: Some clarification is needed with regard to this point. We are grateful to the reviewer for her advice and will certainly bear it in mind for future protocol revisions. We agree that the duration of treatments in the metastatic setting of NENs, especially neuroendocrine carcinomas, is something of a dilemma. There is a lack of evidence-based recommendations on treatment duration, above all in second line. A fixed duration for treatments would avoid unnecessary exposure to cytotoxic agents and consequent bone marrow reserve depletion.

In the paper by Lamarca et al., TEMCAP maintenance did not seem to influence PFS in metastatic NEN patients. Given the palliative setting of their study and the lack of strong evidence on the efficacy of treatments and their prolongation beyond 6 months in second-line neuroendocrine carcinomas, we prefer to opt for patient safety. If there is proof found of the efficacy of both treatments, a further trial on maintenance therapy vs. fixed treatment duration could be planned in the future. These are the main reasons for our choice.
Like all non sponsored trials, it cannot be denied that the economic aspect has to be taken into consideration when planning a multicentre study and so we understand that this may have been construed as the main reason for our choice of the duration of therapy.

Line 230:
Write in the time point within 90 days, add in the recommended instead of when possible.
Reply: We have modified the text in accordance with the reviewer's request (page 10, lines 232-233).

There is extra spaces between words at least fifteen times in the body text - they are undelined with two blue lines in the word processor.
Reply: The extra spaces have been removed throughout the text.

Reviewer 2

Reviewer Name: Stefano Crippa
Institution and Country: IRCCS Ospedale San Raffaele, Milan, Italy
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The revision is fine
Reply: Thank you.