Dear Editor,

Thank you for considering our article “PRE-TREATMENT CLINICAL FEATURES IN CENTRAL RETINAL VEIN OCCLUSION THAT PREDICT VISUAL OUTCOME FOLLOWING INTRAVITREAL RANIBIZUMAB” for publication in BMC Ophthalmology. We would like to thank the reviewers for their comments. Please see below our responses to each comment. Any changes made throughout the manuscript have been highlighted.

Yours Sincerely,
Reviewer 1: This is an interesting and well-written manuscript. Several recent studies have been published on the same topic. Therefore, the manuscript does not add anything new to the existing literature. References are not adequate.

Our response: We have now referenced recent publications on the current topic in our discussion. We could not find previous studies reporting CWS to predict poorer visual outcome in patients with CRVO undergoing anti-VEGF. We therefore feel our results complement the current literature.

Reviewer 2: Here are some comments for the authors:

Methods need to be further described:

- description of the regimen of treatment (PRN or monthly treatment ?)

Our Response: PRN, we have now amended this in the methods.

- Naïve traitement patients ? You need to specify clearly as some patients had a first ranibizumab treatment several months after the time from presentation

Our Response: all of our patients were treatment naïve; we have now included this in our methods. Few patients failed to attend their initial injection appointment therefore delaying treatment.

Results:

Can you specify the mean number of ranibizumab injections during the 12 months of follow-up ?

Our Response: 4 injections (SD 2) at 12 months follow up. We have not included this in our results section and critiqued this in the discussion. In our earlier use of anti-VEGF in CRVO some patients did not receive 3 injections as a loading dose.

That could explain the inefficiency of ranibizumab
Our Response: This is a fair point, however, our analysis did not show number of injections to influence VA significantly in our cohort.

Discussion:

* Discussion need to be reorganized and shortened.

Our Response: we have now shortened our discussion.

* You should discuss about the pre-treatment clinical features identified in your serie as predictive factors of the final visual outcome and you should refere to others articles already published on this subject.

Our Response: We have now referenced and critiqued our data with recent studies on prognostic features in CRVO

* You don't discuss why ranibizumab is not effective in your serie.

Our Response: This is real world clinical data, there was a broader phenotypic range than in clinical trials, and patients were not adherent to strict monthly FU in our cohort. We have now included this in our discussion.

* Page 8 ligne 12 : You say that « the treatment benefit in ischaemic CRVO has not been proven as patients with significant baseline retinal ischaemia were excluded in the landmark studies. » That is true for CRUISE and BRAVO but not for GALILEO and COPERNICUS. In Galileo and Copernicus, RAPD were not excluded and sub-division of patients (Perfused, Non perfused, Indeterminable) was defined by >/< 10 Disc area of retinal non perfusion on FFA. So these two studies included severe ischaemic CRVO.

Our Response: In the GALILEO and COPERNICUS studies the definition of ‘nonperfusion’ (≥ 10 disc areas of nonperfusion on 7 field FFA) was originally used in the CVOS study in 1995. There are problems with using this method for measuring ischaemia as haemorrhage frequently masks areas of non-perfusion on FFA in the acute phase of the disease and this method only covers one third of the retinal surface. We found it surprising that the baseline BCVA of the perfused and nonperfused groups were almost identical and that the study sponsors did not produce statistical analysis of this subgroup comparison. In addition, the data on numbers of patients with RAPD was not published or presented. We contacted the study sponsors requesting access to these data, but they were not able to release the information. We were told that a ‘small number of patients had pupillary reflex impairment’ but they were unable to specify what type of reflex or the number of patients affected.

In their appraisal in 2014 the NICE committee have also questioned whether the results of GALILEO and COPERNICUS are applicable to patients with ischaemia and or severe ischaemia. For these reasons we still believe that the landmark studies do not accurately portray treatment outcomes for ischaemic CRVO patients. For this paper, however, we have toned our opinion down.
* You want to stop classifying patients into ischaemic and not ischaemic group and to focus on looking at clinical features in CRVO that predict poorer visual outcome from anti-VEGF therapy but finally poorer pre treatment VA and CWS are ischaemia indicators already identified in previous studies

Our Response: We are unable to find any studies demonstrating CWS to be indicator of poorer outcome. We do agree, however, literature now shows Pre-treatment VA and age to predict treatment outcomes. We have included these studies in our discussion.

Finally you should reorganize and shorten your discussion in that way:

* Efficiency of anti-VEGF in RVO
* Difficulty to identify ischaemia and the different technics already known
* Importance to distinguish macular ischemia from global ischemia (CRYSTAL)
* Discussion of predictive factors you identified in your study and comparison with previous study
* Discussion of inefficiency of ranibizumab in your serie
* Discussion of the necessity or not of treatment in ischaemic CRVO
* Conclude with the importance to identify predictive factors of visual outcome to initiate treatment of CRVO

Our Response: We agree this is a more orderly structure to the discussion section. We have adjusted the manuscript accordingly.