Dear Editor,

Re: MS 28479-revision

Please find our reply to the comments given by your reviewer.

The following comments were raised by the reivewer.

This manuscript presents stable gastric pentadecapeptide BCP157, along with NOS-blockade, L-NAME, and NOS-substrate L-argnine application would favorably define the esophagogastric anastomosis healing, esophagitis and gastric defects healing and rescued sphincter pressure. Although this study was well designed and evaluated, there are a few points as described below to be clarified. Major revision 1. The control rats underwent esophagogastric anastomosis showed severe necrosis along the anastomosis in Fig 7, 8, while the effect of BCP157 was more clarified. However, is there the problem of surgical procedure for severe necrosis along the anastomosis in controls? Moreover, is the illustrative microscopic presentation anastomotic suture removal? Minor revision 1. A focus does not match Fig. 9 in controls, to look at the blood vessel?

We appreciate the general positive attitude of the reviewer.
To the specific comments, see our reply

Major revision 1. The control rats underwent esophagogastric anastomosis showed severe necrosis along the anastomosis in Fig 7, 8, while the effect of BCP157 was more clarified. However, is there the problem of surgical procedure for severe necrosis along the anastomosis in controls? Moreover, is the illustrative microscopic presentation anastomotic suture removal?

We appreciate that this reviewer finds that the effect of BPC 157 is suitably clarified. However, considering the controls (if his/her question is correctly understood), we have to emphasize that we carried out the surgical procedure at the exactly same way in all animals, which were randomized. Thus, we have to exclude any possibility for mistake done in the methodology that could influence subsequent outcome. Thereby, the severe necrosis along the anastomosis in controls is direct consequence of the general failure of the healing of the anastomosis such as gastroesophageal anastomosis. And, not need to emphasize, these control data are in full agreement with the generally known problems with gastroesophageal anastomosis in the experimental studies (see, i.e., Cui Y, Urschel JD, Petrelli NJ. Esophagogastric anastomoses in rats--an experimental model. J Invest Surg. 1999 Sep-Oct;12(5):295-8.
Cui Y, Urschel JD.Esophagogastric anastomotic wound healing in rats. Dis Esophagus. 1999;12(2):149-51.)and vice versa, these results are in concern with our data obtained in our

previous studies with other gastrointestinal anastomoses (Klicek R, Kolenc D, Suran J, Drmic D, Brcic L, Aralica G, Sever M, Holjevac J, Radic B, Turudic T, Kokot A, Patrlj L, Rucman R, Seiwerth S, **Sikiric P**. Stable gastric pentadecapeptide BPC 157 heals cysteamine-colitis and colon-colon-**anastomosis** and counteracts cuprizone brain injuries and motor disability.J Physiol Pharmacol. 2013 Oct;64(5):597-612.
Sever M, Klicek R, Radic B, Brcic L, Zoricic I, Drmic D, Ivica M, Barisic I, Ilic S, Berkopic L, Blagaic AB, Coric M, Kolenc D, Vrcic H, Anic T, Seiwerth S, **Sikiric P**. Gastric pentadecapeptide BPC 157 and short bowel syndrome in rats.Dig Dis Sci. 2009 Oct;54(10):2070-83.
Vuksic T, Zoricic I, Brcic L, Sever M, Klicek R, Radic B, Cesarec V, Berkopic L, Keller N, Blagaic AB, Kokic N, Jelic I, Geber J, Anic T, Seiwerth S, **Sikiric P**. Stable gastric pentadecapeptide BPC 157 in trials for inflammatory bowel disease (PL-10, PLD-116, PL14736, Pliva, Croatia) heals ileoileal **anastomosis** in the rat.Surg Today. 2007;37(9):768-77.).
Likewise, we have to emphasize (a point clearly stated in the Materials and methods) that no removal of the suture was neither perfomed or seen. Thus, the illustrative microscopic presentation is not presentation of the anastomotic suture removal, but the failed healing by itself.

Minor revision 1. A focus does not match Fig. 9 in controls, to look at the blood vessel?

Acknowledged. The Fig. 9 is now improved.

In conclusion, we hope that you will find our arguments to adequately respond to the suggestions given by the reviewer.

Sincerely

Predrag Sikiric, MD, PhD

Professor