Dear Editor-in-Chief,

Please find the attached, revised version of our manuscript:

Title: “First prospective European study for the feasibility and safety of magnetically controlled capsule endoscopy in gastric mucosal abnormalities”

Running title: Szalai et al. Robotically controlled magnetic capsule endoscopy

We are grateful to the reviewers for the detailed and helpful comments to help in further clarification of the manuscript. We are hereby sending a revised version of the manuscript with the modified, yellow-highlighted text.

We hereby provide point-by-point responses to the comments of the reviewers.

Response to Reviewer 1
Reviewer’s code: 00001114

Thank you so much for your useful, critical review and positive comments. Please, find our reflections and corrections:

„My comments to Authors: MATERIALS AND METHODS 1. The authors should explain if the small bowel included the duodenum. “

Yes, the visualization of the duodenum, including the duodenal bulb and descending and inferior horizontal part of the duodenum, was possible with MCCE as well. We added this explanation into the methods section as follows:

“After transpyloric passage, first we depicted the duodenal bulb, then from the descending and inferior horizontal part of the duodenum, we visualized the ampulla of the Vater by tilting the capsule camera upwards to facilitate the retrograde view.”

„Results 1. The protocol explained visualization of the distal esophagus as Station 0. However, there were no results regarding the distal esophagus. I wonder how this magnetic
CE could visualize the distal esophagus and evaluate reflux esophagitis and Barrett's esophagus. “

Yes, it is possible to visualize the distal esophagus in most of our patients, but the analysis of these results, including GERD and Barrett esophagus was not the scope of the present study; therefore, we deleted the station 0 from the study protocol explanation.

“Discussion 1. The authors showed a modified MRI machine that moved a MACE system by Olympus did not spread worldwide due to high cost. The authors should comment on the cost problem of this magnetic CE and related system.”

The cost of an MRI system is relatively high, and it is well-known in the medical industry. Our present paper is not aiming to focus on cost-benefit analysis, since our inclusion criteria for patient selection was a small bowel capsule indication, and gastric study was only an additive procedure. The cost of a magnetic capsule is comparable to other small bowel capsule endoscopes available in the industry. Therefore, we changed this section as follows: “In 2011, Olympus was the first to introduce a modified MRI machine prototype that moved a MACE system which allowed the operator to successfully guide the capsule in a chosen spatial direction inside the stomach after drinking water. However, the adoption of this diagnostic procedure did not spread worldwide and get medical acceptance (6)”.

“Minor comment 1. Page 12, stops functioning due to the battery shutting down.→"stops" seems to be in the wrong tense.

Thank you for your comment. We corrected this as follows: “The examination ended when the capsule arrives at the colon or stops functioning due to the low battery.”

Reply to the Reviewer 2
Reviewer’s code: 03476311

“The authors showed magnetically controlled capsule endoscopy in gastric mucosal abnormalities.”

Thank you so much for your useful, critical review and positive comments. Please, find our reflections and corrections as follows:

“This trial is considered to be impressive, but I have some Questions. 1) Before the study, the author performed urea breath test, and revealed Helicobacter pylori positivity in 29.5% of patients. However, there was no description about Helicobacter pylori in the
results. To what extent was it possible to identify the presence or absence of Helicobacter pylori infection from the capsule endoscopy image?"

First, we realized, that due to some technical problems on the data analysis, we have significantly more data on HP UBT tests in the presented patient population. Fortunately, this had no significant effect on the results. However, we wanted to keep it precise and corrected the Table 2

<table>
<thead>
<tr>
<th>13C UREA BREATH TEST</th>
<th>All cases</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of performed tests</td>
<td>110 (38.7%)</td>
<td>56 (50.1%)</td>
<td>54 (49.1%)</td>
</tr>
<tr>
<td>Positive</td>
<td>36 (32.7%)</td>
<td>16 (44.4%)</td>
<td>20 (55.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>74 (67.3%)</td>
<td>40 (54%)</td>
<td>34 (46%)</td>
</tr>
</tbody>
</table>

The visual diagnosis of the presence of Helicobacter pylori (HP) with standard white light endoscopy (WLI) has a relatively low accuracy, especially in population with a low pretest probability. Moreover, WLI endoscopy correlates poorly with histopathological findings of HP induced gastritis too. Recently, low quality retrospective studies proposed the theory, that with the application of a special electronic chromoendoscopy, linked color imaging (LCI), diffuse reddish appearance of the mucosa in the gastric body and fundic glands correlates with the presence of HP. ([Endosc Int Open. 2016 Jul; 4(7): E800–E805.])

In our study we found no correlation between the HP status and the activity and type of gastritis observed on MCCE as follows, but not included this into the Table 2, since it would be relevant in another publication, focusing HP status and gastritis on MCCE.

<table>
<thead>
<tr>
<th>HP status</th>
<th>N</th>
<th>HP positive</th>
<th>%</th>
<th>HP negative</th>
<th>%</th>
<th>X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30</td>
<td>7</td>
<td>23%</td>
<td>23</td>
<td>77%</td>
<td>0.9775</td>
<td>0.3228 NS</td>
</tr>
<tr>
<td>Minor proximal gastritis</td>
<td>19</td>
<td>9</td>
<td>47%</td>
<td>10</td>
<td>53%</td>
<td>1.529</td>
<td>0.2163 NS</td>
</tr>
<tr>
<td>Minor antral gastritis</td>
<td>19</td>
<td>4</td>
<td>21%</td>
<td>15</td>
<td>79%</td>
<td>1.0322</td>
<td>0.3096 NS</td>
</tr>
<tr>
<td>Active, erosive antral gastritis</td>
<td>15</td>
<td>6</td>
<td>40%</td>
<td>9</td>
<td>60%</td>
<td>0.3129</td>
<td>0.5759 NS</td>
</tr>
<tr>
<td>Proximal erosive gastritis</td>
<td>22</td>
<td>7</td>
<td>32%</td>
<td>15</td>
<td>68%</td>
<td>0.0069</td>
<td>0.9338 NS</td>
</tr>
<tr>
<td>Pangastritis (proximal and antral)</td>
<td>4</td>
<td>3</td>
<td>75%</td>
<td>1</td>
<td>25%</td>
<td>0.5</td>
<td>0.4795 NS</td>
</tr>
<tr>
<td>Total HP tested patients</td>
<td>110</td>
<td>36</td>
<td>33%</td>
<td>74</td>
<td>67%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


To clarify more precisely the association between HP positivity and gastric mucosal abnormalities on MCCE, we added the following text into the results:

An UBT test revealed Helicobacter pylori (HP) positivity in 32.7% of cases. (Table 2). No significant association with HP status and the type (proximal or distal), or the severity (minimal or active, erosive) of the gastritis described on MCCE results were depicted.

"2) The author described that approximately 8–10 dl of clean water consumed by all patients within 10 minutes to distend the stomach properly. Water ingestion may be repeated as needed to enhance gastric distension during examination. Observing the great curvature of the stomach usually requires considerable insufflation. The image in Figure 9 seems to be slightly inadequately stretched in both the normal endoscopic image and the capsule image. How do we think about it?"

Yes, you are right, since the gastric MCCE procedure through all stations last about 20 minutes, repeated 2-4 dl water ingestion is needed to distend enough the corpus and the gastric body, and maintain gastric distension during the study, which is mainly depending on the speed of gastric emptying. In fact, we agree that on Figure 9, gastric distension could be considered inadequate both on the MCCE and on the gastroscopy picture; therefore, we selected a video segment of MCCE to upload as the Reviewer 3 suggested, to demonstrate both detailed mucosal visibility and sufficient gastric distension could be achieved on MCCE. We also agree with you that adequate gastric distension should be considered as an important quality parameter on both MCCE and gastroscopy since it may lead to miss the diagnosis of diffuse gastric cancer (linitis plastica).

"3) The authors described that it is possible to observe the stomach with minimal invasiveness, but considering that the examination takes an average of 50 minutes and that it is necessary to drink water, if the stomach examination is performed alone, upper endoscopy is performed. Is it really less invasive?"

We are sorry to say, but we could not agree with your comment on the invasiveness of gastroscopy versus MCCE. First, the gastric transit time was 50 minutes, but the active MCCE examination times on average 20 minutes, which is quite similar to a standard, high-quality gastroscopy procedure with its 10-15 minutes long examination time. During MCCE procedure and capsule maneuvering, the patient feels nothing, especially no discomfort or
pain. In our opinion, only swallowing a capsule endoscopy and drinking water might be considered as a non-invasive or minimal invasive procedure as compared to the invasive gastroscopy. Gastroscopy is an invasive procedure where to achieve patient comfort in most of the cases a propofol or midazolam sedation is necessary. We asked some of our patients who had previously gastroscopy without sedation and MCCE as well, and all of them would choose MCCE as a next screening procedure.

4) About how much does it cost to perform the procedure? Is the cost realistic?
Thank you for the question. However, our present paper is not aiming to focus on cost-benefit analysis, the cost of a magnetic capsule and the system is comparable to other small bowel capsule endoscopy capsule and systems available in the industry. The cost of the robotic magnetic controller machine and operation table is currently business secret, since the final prize of the new mobile controller panel has not been communicated to public, but we can give you a private information that it will be similar to a complete HD endoscopy system, including the processor, monitor, and one gastroscope. Therefore, we believe that the MCCE cost is realistic, and would be a cost-effective alternative in the near future, in patients with high gastric cancer risk.

5) Number of the figure is considered to many. Fig 15,16 should be changed to Table. Table 4 is not Table style but Figure.

Thank you for your comment. We corrected as recommended.

Response to Reviewer 3
Reviewer’s code: 03729702

This is an interesting study demonstrating the feasibility and safety of the Ankon MCCE system in the western population, and it describes the detailed procedure of MCCE with figures. Some major and minor points need to be corrected.
Thank you so much for your useful and critical review, and positive comments. Please, find our reflections and corrections as follows:

# The diagnostic yield of major and minor pathologies from stomach and small bowel should be compared with other studies from similar populations to demonstrate the Ankon MCCE system’s feasibility.
Thank you for your suggestion. We included the following text in the final part of the discussion with a new citation:
There is no similar study in the literature, as we performed a complete upper GI capsule examination, including the stomach and the small bowel with the same capsule endoscope during MCCE. Denzer et al. published a blinded, prospective trial from two French centers with the Intromedic manually controlled magnetic capsule endoscopy (MACE). A total of 189 patients were enrolled into this multicenter study. Lesions were defined as major (requiring biopsy or removal) or minor ones. The final gold-standard was unblinded conventional gastroscopy with biopsy, under sedation with propofol. Twenty-three major lesions were found in 21 patients and in this population, the capsule accuracy was 90.5% as compared to gastroscopy. Of the remaining 168 patients, 94% had minor and mostly multiple lesions; the capsule accuracy was 88.1%. All patients preferred MACE over gastroscopy.


Also, transit time and the rate of incomplete investigation should be compared. These comparisons can be presented in the discussion section. In addition, I wonder about the result of comparison of gastric transit time between the cases with successful transpyloric transit by the magnet (41.9%) and others.

Thank you for your comment, we put the following section into the discussion:

One of the risk factors of incomplete SB capsule endoscopy is a prolonged gastric transit time, which could be considered as a limitation of our combined gastric and small bowel study protocol. In our patient population, the average gastric transit time with magnetic transpyloric, manual control was 26 minutes. In contrast, in those cases where the magnetic transpyloric control failed, after examining the stomach, we left the capsule to propel through the pylorus by spontaneous peristaltic activity. In these patient groups, the average gastric transit time took 1 hour and 9 minutes. In 10 cases out of 18 incomplete SB studies caused by battery low energy, this event occurred in 3 patients with manual magnetic passage and in 7 patients with spontaneous transpyloric passage.


„# The magnetic manipulation of the capsule can be significantly affected by abdominal obesity or height. I think the height, weight, and BMI should be presented in Table 1. „

As the fixed part of the navigation capsule system, the investigation table has a maximum workload capacity of 135 kg, we did not examine a heavier or extreme obese patients. According to our experience with more than 1000 MCCE examinations, magnetic navigation has not been influenced in any obese people of this weight range. In our patient population, the mean BMI was 26.5 kg/m². Furthermore, no correlation was found between the frequency of MCCE detected gastric abnormalities and BMI status. We added the BMI data on the Table 1.
"#. In Table 3, is this proportion calculated per subject? It would be better to understand the meaning of the diagnostic yield by presenting the N numbers like Table 2. "

"#. The diagnostic yield presented in Table 3 is different from the value shown in the Result (e.g., total diagnostic yield 81.9% in table vs. 82.3% in result section). "

Thank you for these comments, we double checked and corrected the data, we added the numbers (N) and we changed this section and Table 3 as follows:

"The diagnostic yields for detecting any abnormalities in the stomach and SB with MCCE were 81.9%: 68.6% for minor pathologies and 13.3% for major pathologies. 25.8% of the abnormalities were found in the SB, and 74.2% were in the stomach. The diagnostic yield for stomach/SB was 4.9%/8.4% for major pathologies and 55.9%/12.7% for minor pathologies (Table 4)."

<table>
<thead>
<tr>
<th>Diagnostic yield</th>
<th>Major</th>
<th>Minor</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>38 (13.3%)</td>
<td>195 (686%)</td>
<td>233 (81.9%)</td>
</tr>
<tr>
<td>Gastric</td>
<td>14 (4.9%)</td>
<td>159 (55.9%)</td>
<td>173 (60.8%)</td>
</tr>
<tr>
<td>SB</td>
<td>24 (8.4%)</td>
<td>36 (12.7%)</td>
<td>60 (21.1%)</td>
</tr>
</tbody>
</table>

"#. I wonder about the total observation time and duration from the pylorus to the last image in 17 cases of incomplete investigations due to the shutdown of MCCE battery.

The whole study population had a mean small intestine transit time of 3 hours and 46 minutes, compared to a mean period of 6 hours and 19 minutes for the incomplete investigation patient population. It is worth mentioning that in only one patient, the capsule was shut down within two hours, likely owing to a manufacturing battery defect. To clarify more of the details of these incomplete SB investigations, we summarized the data on the following Table 6.

Table 6 Distribution of different types of transpyloric transit in complete and incomplete SB studies

<table>
<thead>
<tr>
<th>Transpyloric transit</th>
<th># Cases</th>
<th>Mean total transit time</th>
<th>Mean gastric transit time</th>
<th>Mean SB transit time</th>
<th>Mean total transit time with magnet by automatic protocol</th>
<th>Mean total transit time with magnet manually</th>
<th>Mean total transit time without magnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>284</td>
<td>5:48:35</td>
<td>0:47:40</td>
<td>3:46:22</td>
<td>56 (19.7%)</td>
<td>63 (22.2%)</td>
<td>165 (58.1%)</td>
</tr>
<tr>
<td>Incomplete studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The capsule depleted (&gt;5h)</td>
<td>18 (6.3%)</td>
<td>7:13:41</td>
<td>0:52:35</td>
<td>6:19:51</td>
<td>2</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>The capsule depleted (&lt;5h)</td>
<td>10 (3.5%)</td>
<td>9:12:09</td>
<td>0:46:05</td>
<td>8:26:04</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>The capsule depleted (&gt;5h)</td>
<td>3 (1%)</td>
<td>2:23:25</td>
<td>0:24:09</td>
<td>1:51:22</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
The patient requested to terminate 3 (1%).

The capsule stopped because of a disease 2 (0.7%).

“#. UBT test seems to be performed for adjusting the diagnostic yield of gastric lesions, so it would be better to present and compare the diagnostic yield of gastric ulcer or gastritis according to the H. pylori infection status.”

Thank you for your comment, as we have responded it more detailed above:

In our study, we found no correlation between the HP status and the observed activity and type of gastritis on MCCE as follows, but not included into the Table 2, as it would be relevant in another publication, focusing HP status and gastritis on MCCE.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>HP positive</th>
<th>%</th>
<th>HP negative</th>
<th>%</th>
<th>X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>30</td>
<td>7</td>
<td>23%</td>
<td>23</td>
<td>77%</td>
<td>0.9775</td>
<td>0.3228 NS</td>
</tr>
<tr>
<td>Minor proximal gastritis</td>
<td>19</td>
<td>9</td>
<td>47%</td>
<td>10</td>
<td>53%</td>
<td>1.529</td>
<td>0.2163 NS</td>
</tr>
<tr>
<td>Minor antral gastritis</td>
<td>19</td>
<td>4</td>
<td>21%</td>
<td>15</td>
<td>79%</td>
<td>1.0322</td>
<td>0.3096 NS</td>
</tr>
<tr>
<td>Active, erosive antral gastritis</td>
<td>15</td>
<td>6</td>
<td>40%</td>
<td>9</td>
<td>60%</td>
<td>0.3129</td>
<td>0.5759 NS</td>
</tr>
<tr>
<td>Proximal erosive gastritis</td>
<td>22</td>
<td>7</td>
<td>32%</td>
<td>15</td>
<td>68%</td>
<td>0.0069</td>
<td>0.9338 NS</td>
</tr>
<tr>
<td>Pangastritis (proximal and antral)</td>
<td>4</td>
<td>3</td>
<td>75%</td>
<td>1</td>
<td>25%</td>
<td>0.5</td>
<td>0.4795 NS</td>
</tr>
<tr>
<td>Total HP tested patients</td>
<td>110</td>
<td>36</td>
<td>33%</td>
<td>74</td>
<td>67%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

To clarify more precisely the association of HP positivity and gastric mucosal abnormalities on MCCE, we added the following text into the results:

A UBT test revealed Helicobacter pylori (HP) positivity in 32.7% of cases. (Table 2). No significant association with HP status and the type (proximal or distal), or the severity (minimal or active, erosive) of the gastritis described on MCCE results were depicted.

“#. I recommend to show the real video clip of gastric image investigated by Ankon MCCE.”
Thank you for your advice, we attached a video to our article.

“#. This study did not compare the diagnostic yield with standard EGD. Even though in some aspects, we can compare the diagnostic yield of this study with other studies of similar populations by EGD. However, this is the inherent limitation of the current study, which should be discussed.”

Thank you for your comment, we put the following text into the discussion part:

An inherent limitation of our present study that we performed gastroscopy only in a few patients with major gastric pathologies to accomplish final diagnosis and biopsy; and therefore, we could not assess the accuracy of MCCE in all patients compared to gastroscopy. However, several previous studies demonstrated excellent diagnostic value and high accuracy.

In a recent meta-analysis of Zhang et al., four studies with 612 patients were included, in which the results of blinded MCCE and gastroscopy were compared. MCCE demonstrated a pooled sensitivity and specificity of 91% (95% CI, 0.87–0.93) and 90% (95% CI, 0.75–0.96), respectively. The diagnostic accuracy of MCCE was 91% (95% CI, 0.88–0.94) for assessing gastric diseases.

Use of magnetically controlled capsule endoscopy for the diagnosis of gastric diseases in adults: a systematic review and meta-analysis

Hao Zhang¹, Jingyao Chen², Jianfeng Li², Chumei Huang², Mingzhe Li², Wenhui Wu², Jianlong Jiang²

https://dmr.amegroups.com/article/view/6844/pdf

#. Visibility and identification of landmarks are important factors to consider in accurate examination of stomach using MCCE. You have mentioned in discussion that your previous study using the same system had almost 100% visualization. How were visibility and maneuverability evaluated in the current study? Also, bubbles and mucoid secretions are factors that interfered with visibility. How were these factors managed in your study? „

#. Detection time and maneuverability were dependent on the learning curve of an operator. Although you have used automatized protocol, were there any variations in
examination time along with training and experience? Presenting the learning curve would be very informative to the readers without any experience of Ankon MCE.”

Thank you for these comments, we included the following text into the discussion and the references to the Citations to clarify your critical points and questions:

Visibility and identification of landmarks are important factors to consider in accurate examination of stomach using MCCE. Gastric landmarks and typical stations described in the methods were always forced to achieve during combined automatic and manual maneuvering. For improving the learning curve of our gastroenterologist, we started to train the examinations in a plastic stomach model. In our previously published abstract, we described the improvement of the learning curves with manual magnetic controls both in experts and in trainees (1). In this study, we find significant differences in the examination time of the complete inner surface mapping between trainees and experts, and moreover automatic protocols were faster and equally accurate as experts to achieve a complete inner surface mapping.

The problem how to minimalize bubbles and mucoid secretions is an existing problem in real life studies. To improve visibility, we established a unique preparation process with a combination of bicarbonate, Pronase B, and simethicone combined with a patient body rotation technique (2). Moreover, in our described stations, we rotate our patients from left lateral to supine, then from supine top right lateral, and finally from right lateral to supine position during MCCE study. During this protocol, the gastric mucoid secretions also moving into different parts of the stomach due to the gravity making visible all the landmarks and the majority of the mucosal abnormalities. Application of prokinetics or motilin agonist erythromycin might also be an option in future studies to improve the visibility and reduce gastric lake content.

Szalai, M; Oczella, L; Lovasz, BD; Madacsy, L Surface mapping in plastic gastric model assisted by a robotic autoscan program with a new magnetically controlled gastric capsule endoscopy system compared to manual controlling UNITED EUROPEAN GASTROENTEROLOGY JOURNAL 6 : Suppl. 1 pp. A415-A415. Paper: P0865 (2018)
„Minor comments #. The primary endpoint and secondary endpoint introduced at the last part of the introduction section and the study design section seems to be different, which needs to be matched. „

Thank you for this comment, we harmonized that into the results section of this article.

„#. In discussion session, on 16 page: 2-2 cases & 1-1 cases seems to be typo.”

Thank you, we corrected as recommended:

„Cancer prevalence was highest in the gastric body (3 cases), followed by 2 cases in the cardia and 2 in the antrum, while 1-1 cases were detected in the region of the angulus, in the fundus and in the esophagus. “

We would like to thank you again for the helpful comments.

We do hope that our revised manuscript has merit for publication and could be of interest to the readers of World Journal of Gastroenterology.