Clinical Outcome Assessments (COA) Qualification Program
DDTCOA #000020: The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD)
September 27, 2018 Update

September 27, 2018

To: FDA Clinical Outcomes Assessments Staff
COADDTQualification@fda.hhs.gov

From: Henry Parkman, MD
Dennis Revicki, PhD

Re: ANMS Response Letter to FDA on DDT COA #000020. ANMS GCSI-DD for measurement of severity of gastroparesis in adult outpatients with diagnosed idiopathic or diabetic gastroparesis

This letter responds to the recent August 2, 2018 FDA COA review of our submission dated March 6, 2018, which included our qualitative study report, qualitative study protocol, user manual, psychometric study protocol synopsis, and version of the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD).

We appreciate the statement by the FDA qualification review team (QRT) that we are progressing in the right direction with this important work. We and our society, the American Neurogastroenterology and Motility Society (ANMS), have devoted a significant amount of time and resources in this project that we would like to bring to fruition with an approved patient-reported outcome (PRO) for gastroparesis. Our overall goal is that the ANMS-GCSI is an acceptable endpoint for clinical trials in gastroparesis and would be available to pharmaceutical companies to use in their drug development programs. We started this almost 10 years ago because of our concern with the unmet needs of patients; a qualified PRO symptom endpoint that could be used in such trials, would save time in the drug development process and achieve our goal to enhance the care and meet the needs of our patients. The ANMS GCSI-DD has been developed for its use as a PRO endpoint for clinical trials evaluating new treatments for either diabetic or idiopathic gastroparesis. The ANMS GCSI-DD consists of five core symptoms that are relevant for both diabetic and idiopathic gastroparesis. The ANMS GCSI-DD core symptom composite score as well as their individual symptoms are designed to detect clinical improvement in symptoms of gastroparesis to be used as an acceptable PRO endpoint for clinical trials.

In this letter, we respond to the comments and suggestions made by the FDA QRT to help demonstrate adequate content validity of the ANMS GCSI-DD.

FDA Comment 1 (regarding Submitter Question #1): While many of the patients understood the term "gastroparesis" and correctly identified the associated symptoms, some patients were still not able to clearly indicate that they understood the term "gastroparesis." We recommend you define "gastroparesis" using simpler patient-friendly wording. Based on the patient cognitive interviews, the majority of patients agreed with the following definition: "there is an abnormally delayed emptying of food from the stomach." We suggest providing this definition in parentheses following each time the term "gastroparesis" is used.

ANMS Response: We agree that patients should understand that they have gastroparesis and what this condition entails. In our most recent qualitative research study, 92% (23 of 25 subjects) understood the term 'gastroparesis'. The ANMS GCSI-DD is designed to be given to adult patients with diagnosed gastroparesis as they enter a clinical trial for their symptoms of gastroparesis. Thus, patients will understand that they have this disorder and what it entails as they will have to sign an informed consent which will explain this to get into the study. For a study using the ANMS GCSI-DD, the user manual will be followed that involves going over the ANMS GCSI-DD with the patients prior to their use, during which the term gastroparesis will be explained using the wording for gastroparesis suggested by the FDA that came from the patients in our qualitative study (Study 1) - relating gastroparesis to their abnormally delayed emptying of food from the stomach. In addition, the patients will complete an initial ANMS GCSI-DD with the study coordinator at a study visit to ensure the patient is using it correctly and to address any questions related to the daily diary.

FDA Comment 2 (regarding Submitter Question #1): Additionally, the concept of "bloating" is not assessed in the current version of the ANMS GCSI-DD; however, most patients in your qualitative studies endorsed bloating as an important symptom. It is unclear whether patients consider bloating a separate symptom from post-prandial fullness or whether patients are using the term "bloating" to describe post-prandial fullness. Based on your qualitative research with patients, provide justification for why "bloating" is not included in the current version of the ANMS GCSI-DD, even as an exploratory item. We recommend further exploration of an item asking about "bloating." Although not required, it is important to determine whether patients are experiencing bloating as a unique symptom of their gastroparesis and whether this concept is relevant when interpreting meaningful within-patient improvement in symptoms within the context of a drug development program for gastroparesis.
ANMS Response: In a past teleconference with the FDA on February 5, 2014 regarding the ANMS GCSI-DD, we outlined our reasoning for not using bloating in the ANMS GCSI-DD: "From our studies, we have switched the core symptoms by substituting postprandial fullness for bloating. This is to improve face validity of the ANMS GCSI-DD. Bloating is more commonly used to describe symptoms in irritable bowel syndrome and small intestinal bacterial overgrowth, disorders that can also occur in patients with gastroparesis. Postprandial fullness is correlated to bloating severity (a past study of ours showed r=0.67). In some studies, postprandial fullness, but not bloating, is correlated with impaired gastric emptying (Hasler et al 2011 and Parkman 2018). In patients with gastroparesis, early satiety severity is correlated with postprandial fullness. However, early satiety is a symptom associated with impaired proximal gastric accommodation, whereas postprandial fullness is a symptom associated with impaired antral contractility (provide reference)." Thus, we suggested to remove bloating from the ANMS GCSI-DD because bloating may be due to other gastrointestinal conditions and is less proximal to the experience of gastric emptying. This was agreed upon with the FDA during our teleconference.
However, in response to this request by the FDA, we agree to follow the FDA's suggestion to include bloating as an exploratory item in the ANMS GCSI-DD. This will be used in the upcoming Takeda Phase 2 trial data to collect more information to see if this is an important unique symptom of their gastroparesis and whether this concept is relevant when interpreting meaningful within-patient improvement in symptoms within the context of a drug development program for gastroparesis. We will capture the bloating symptom at the time the patient fills out the ANMS GCSI-DD. We will use the wording that previously underwent content validity studies. See appendix A (ANMS GCSI-DD 20180910a containing the exploratory bloating item). This is in line with the planned assessment of bloating in the upcoming Takeda Phase 2 study that was approved by the FDA.

FDA Comment 3 (regarding Submitter question 2): The terms "normal-sized meal" and "healthy person" in the early satiety item are ambiguous and were interpreted differently by patients in your qualitative studies. In addition, patients were not able to follow the instructions for this item consistently and sometimes substituted the term "normal-sized meal" with "regular meal" and the term "healthy person" with "normal person." Furthermore, patients had differing opinions on the content of a typical

meal as well as the quantity of each item in a meal. Also, these two characteristics were not applied consistently among patients. This variation becomes more apparent with idiopathic vs. diabetic gastroparesis as patients with diabetes typically reported following a more stringent diet. Based on the qualitative data you have provided, the approach to measuring early satiety will need to be revised. We acknowledge there is variation in how patients adjust their meal schedule and content to manage their symptoms. Therefore, you may wish to consider asking patients about whether they are able finish their "planned meal."

ANMS Response: This has been discussed with the FDA in the past and the modifiers presently used were added at the suggestion of the FDA to explain to the patients that the meal size refers to the meal size for a normal, healthy person, such as others at the dining table, and does not refer to the patient's current or planned meal size. For the vast majority of patients, this was not an issue. In our recent qualitative study, 96% (24 of 25) of participants understood the content of this item, and 88% (22 of 25) provided comments consistent with understand of a 'normal sized meal'. This understanding was based on observations of family and friends when dining. This item was considered relevant in 100% (25 of 25) participants. This questionnaire will be used for treatment trials for gastroparesis. The plan for the use of the ANMS GCSI-DD for a treatment study is to describe the PRO measure to the patient at the beginning of the study when the daily diary is reviewed with the patient and these terms will be described, as outlined in the user manual: the term refers to the size of a normal meal for a normal, healthy person. Regarding the suggestion to use the term "their planned meal", we do not agree with this. Many of these patients purposefully eat a smaller meal or are on a gastroparesis diet that instructs the patients to eat a smaller meal size.

FDA Comment 4 (regarding submitter question #3): Patients were not able to consistently distinguish between the "Severe" and "Very Severe" response options. We recommend this be further explored to determine whether the response options can be further refined (e.g., potential removal of the "Very Severe" option).

ANMS Response: In prior versions of the GCSI-DD, the descriptors were none, very mild, mild, moderate, severe, very severe. We used item response theory (IRT) analysis to assess the use of these descriptor categories; the results of these analyses indicated that the "very mild" category was not needed and seldom selected, and sometimes miss-ordered with the 'mild' response. However, the IRT analysis supported the use of the very severe category: the "severe" and "very severe" response options were differentiated and we did not identify any miss-ordering between these two response categories and these findings were further confirmed in a recent psychometric analysis (see Tables 3 and 5 in Appendix C). These IRT analyses indicated that there was good model fit for the five ANMS GCSI-DD items, and that the responses for 'severe' and 'very severe' were differentiated and thus helpful for patients. The FDA Guidance on Gastroparesis in 2015 also suggests including both severe and very severe descriptors.

In the recent qualitative study (Study 1), participants were asked about their understanding to the current response scale for each of symptom severity items, and 96% to 100% reported understand the response scale and 79% to 91% reported that the "none to very severe" scale was meaningful.

Thus, we respectively suggest keeping the response items as none, mild, moderate, severe, very severe. The IRT analysis can be repeated based on the Takeda Phase 2 trial data to provide additional support for the item response levels.

FDA Comment 5: The amount of within-patient change that patients would consider clinically meaningful (both in terms of improvement as well as worsening of symptoms) was not clearly defined based on the patient responses. After establishing content validity of the ANMS GCSI-DD, we recommend you include (in a quantitative study) multiple patient global anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the ANMS GCSI-DD from the patient perspective. The anchor scales should be assessed at comparable time points as, but completed after, the ANMS GCSI-DD. We recommend you include at least the following

anchor scales to generate a threshold (or range of thresholds) for within-patient improvement that represents a meaningful amount of change in your target population:

- Static, current state global impression of severity (PGIS) scale
- Patient global impression of change (PGIC) scale

ANMS Response: These are good suggestions, and we plan on conducting analyses to evaluate sensitivity to changes in clinical status and to identify responder definitions. We plan on including the PGIS and PGIC scales in future quantitative Phase 2 studies. For the PGIS scale, we plan to also include a "very severe" category analogous to our symptom severity scale. For the PGIC scale, we plan to extend the range by including the more conventional "very much better" and "very much worse" categories. The definition of a clinically meaningful response will be based on the psychometric and longitudinal analyses based on the PGIS and PGIC anchors. We intend to use phase 2 clinical trial data to define the clinically meaningful within-patient score change and to determine responder definitions.

FDA Comment 6 (Regarding Submitter Question #4): It is premature to determine whether the proposed ANMS GCSI-DD would be acceptable as a "well-defined" primary, co-primary, or secondary endpoint in a phase 2 or 3 trial for the evaluation of treatments for gastroparesis. Additional information is needed to demonstrate there is content validity for the ANMS GCSI-DD, and further work is needed to define clinically meaningful within-patient change in scores. Please refer to our responses to the questions above as well as our "Additional QRT Comments" below.
The utility of this instrument for an individual drug development program will need to be discussed with the FDA within each individual program.
ANMS Response: In this letter, we address the comments made by the FDA. The changes in wording are relatively minor, and are driven primarily by the results of the current qualitative research study in patients with gastroparesis. Thus, we believe we have a questionnaire that demonstrates excellent content validity to use to capture symptom severity in patients with gastroparesis. We plan to use the ANMS GCSI-DD in phase 2 clinical trials to define the clinically meaningful within-patient score change and to define responder definitions. The "clinically meaningful within-patient score change" will be assessed using global anchor scales in each study that uses the ANMS GCSI-DD to ensure the interpretation of meaningful change is fit for purpose for that study and the particular population enrolled.

FDA Comment 7 (Regarding Submitter Question 5):
The Study 2 protocol synopsis is lacking sufficient detail for us to provide comment. Please submit the Study 2 protocol in its entirety, including your statistical analysis plan, preliminary scoring algorithm, description of how missing data will be handled, etc.
The statistical analysis plan should describe in detail the methods that will be used to examine item characteristics, test-retest reliability, internal consistency reliability, concurrent validity, and known-groups validity. It should clearly specify which subjects and timepoints will be included for each analysis. Additionally, provide justification for the sample size and describe how the stable patient population will be defined. We also recommend that you perform a factor analysis to examine the dimensionality of the ANMS GCSI-DD.
ANMS Response: In the prior submission, we submitted the protocol synopsis of study 2. We attach (as appendix 2) the detailed study protocol and statistical analysis plan for Study 2: Psychometric Evaluation of the ANMS Gastroparesis Cardinal Symptom Index – Daily Diary (ANMS GCSI-DD).
Our prior work with the ANMS-GCSI-DD has shown that all items fit into a single factor suggesting a single unidimensional score can be used (See Table 5 in Appendix C). Recent confirmatory factor analysis of a sample of 70 patients with either diabetic or idiopathic gastroparesis demonstrated good model fit for the single factor solution (CFI=0.96; RMSEA=0.15; SRMR=0.034, See Table 2 in Appendix C).

FDA Comment 8: We continue to have concerns with item #5, which asks about the concept of vomiting and how to count vomiting events. We recommend you consider inclusion of the following language for this item: "Please record the number of times you vomited (threw up, with food or liquid coming out of your mouth), and count each time something came out of your mouth as its own vomiting event. For example, if you have not vomited during the past 24 hours, record zero vomiting events (times). If you vomited three times, even during the same episode (e.g., toilet visit), record three vomiting events (times)."

ANMS Response: The wording we used in the ANMS GCSI-DD on vomiting episodes was previously suggested by the FDA (see FDA comment letter dated October 18, 2016 for DDT 000020). The patients understood this item content and the instructions. In our recent qualitative study, 92% (23 of 25) understood the instructions and the item content for vomiting. The remaining two participants reported difficulty in tracking vomiting episodes since they often experienced more than 30 episodes per day. The plan for the use of the ANMS GCSI-DD for a treatment study is to describe the instructions and item content to the patient at the beginning of the study when the daily diary is reviewed with the patient and these terms will be described, as outlined in the user manual.

FDA Comment 9: We recommend asking all patients to complete the diary before bedtime and to ask patients to record symptoms based on the past 24 hours.

ANMS Response: In the current qualitative study, 100% (25 of 25) of the participants reported understanding the main instructions for completing the daily diary. The plan for the use of the ANMS GCSI-DD for a treatment study is to describe the questionnaire to the patient at the beginning of the study when the questionnaire is reviewed with the patient and these terms will be described, as outlined in the user manual. We will describe that this should be filled out in the evening usually before bedtime. We suggest not including before bedtime, because some patients might have abnormal sleep patterns (working late shifts, late night activities), that might result in the patient completing the symptom diary the next day.

FDA Comment 10: We continue to have concerns with the concept of "upper abdominal pain." In your qualitative studies, patients described "upper abdominal pain" in a variety of ways – sharp, dull, due to gas, full, etc. and the pain was in varying locations in the abdomen. Based on your qualitative research, we recommend you consider asking patients about "abdominal pain" in general rather than specifying "upper" abdominal pain. Also, confirm whether patients are experiencing distinct abdominal pain that is separate from post-prandial fullness.

ANMS Response: All participants reported understanding the response scale and 90% thought the response scale provided meaningful categories for assessing the severity of upper abdominal pain. In the recent qualitative study, 100% of the participants (25 of 25) understood the content of the upper abdominal pain item, and 96% (24 of 25) could locate or describe upper abdominal pain. Our concern is that the revision to "abdominal pain" may be too non-specific and may result in increased variation in patient's responses to this item, and increased measurement error. For example, lower abdominal pain can be from irritable bowel syndrome which can coexist in patients with gastroparesis.

To address your comment on whether patients are experiencing distinct abdominal pain that is separate from post-prandial fullness - in our qualitative interviews, all 25 patients understood the terminology used for post-prandial fullness. They described this symptom also with terms such as "stuffed" or feeling like there is "too much food" in their stomach. For the upper abdominal pain descriptor, patient pain was above the navel/belly button or near the middle of the stomach and further described the feeling of pain as "sharp," "deep," "dull," "burning," and "uncomfortable." By these interviews, post-prandial fullness was distinct from upper abdominal pain. In addition, based on the Temple data, the correlation between upper abdominal pain and post-prandial fullness is 0.35 in the total sample, 0.31 in IG and 0.42 in DG, suggesting little overlap in the symptom scores.

Thus, we respectively suggest keeping the terminology "upper abdominal pain".

FDA Comment 11: Please submit screenshots from the electronic diary for QRT review.
ANMS Response: We are submitting screen shots of the electronic diary. See appendix E.

FDA Comment 12: As you progress through the qualification process, you should include datasets from Study 2 when you submit your full qualification package (FQP).
ANMS Response: We agree to provide datasets for completed psychometric studies and analyses.

FDA Comment 13: We recommend that you collect information on the clinical characteristics of the patient population, including blood glucose for diabetic patients, since symptoms of gastroparesis and gastric emptying may be impacted by underlying disease states, medication(s), etc.
ANMS Response: We agree. We will capture aspects related to clinical characteristics, medications, and in diabetic patients, representative blood glucose values. For clinical trials, data on additional clinical characteristics will be collected at study visits. This is outlined in the user manual for the ANMS GCSI-DD.

We hope you agree with our current reasoning for our responses. We believe that the ANMS GCSI-DD has adequate content validity and is ready for the next phase – use in our Study 2 Psychometric Evaluation of the ANMS GCSI-DD and then in a phase 2 study to demonstrate patient responsiveness and to determine responder definitions. At this time, we believe it would be helpful to ensure clarity of this and we agree with you in setting up a teleconference to review our responses and hopefully agreement from FDA that the qualitative assessment of the ANMS GCSI-DD is complete, and the next step now is to conduct a quantitative psychometric study (Study 2). This will be helpful so that we can proceed with the further development of this ANMS GCSI-DD. We will set up the teleconference to answer questions, by contacting the Clinical Outcome Assessments Staff at COADDTQualification@fda.hhs.gov and referring to our DDT COA #000020.

We appreciate the FDA's help in progressing this questionnaire towards qualification for use as a PRO.

Sincerely,

ANMS Gastroparesis Symptom Endpoint Working Group
Henry Parkman, MD, henry.parkman@temple.edu
Dennis Revicki, PhD, dennis.revicki@evidera.com

Attachments
Appendix A. ANMS GCSI-DD
Appendix B. User manual for ANMS GCSI-DD. .
Appendix C. IRT analysis
Appendix D1. Study Protocol for Study 2: Psychometric Evaluation of the ANMS Gastroparesis Cardinal Symptom Index – Daily Diary (ANMS GCSI-DD)
Appendix D2. Statistical Analysis Plan for Study 2: Psychometric Evaluation of the ANMS Gastroparesis Cardinal Symptom Index – Daily Diary (ANMS GCSI-DD)
Appendix E. Screen shots of ANMS GCSI-DD.