DDT COA #000020 **COMMENTS ON SUBMISSION**

August 2, 2018

ANMS Gastroparesis Symptom Endpoint Working Group
Henry Parkman, MD, henry.parkman@temple.edu
Dennis Revicki, PhD, Ddennis.Rrevicki@evidera.com
GI Section; Temple University Hospital
3401 North Broad Street; Philadelphia, PA 19140

Re: ANMS GCSI-DD for measurement of the severity of gastroparesis in adult outpatients with diagnosed idiopathic or diabetic gastroparesis.

Dear Drs. Parkman and Revicki:

We have completed our review of your submission dated March 6, 2018, which included your qualitative study report, qualitative study protocol, user manual, psychometric study protocol, and copy of the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD)

After reviewing your submission, the qualification review team (QRT) believes you are progressing in the right direction with this important work. Additional qualitative work is necessary to demonstrate adequate content validity of the ANMS GCSI-DD. Our responses to your specific questions are provided below:

SUBMITTER QUESTION #1

Does the Agency agree that the item content of the ANMS GCSI-DD is consistent with the concepts that emerged from the concept elicitation portion of the Study 1 qualitative interviews and previous qualitative research? If no, what further information is needed?

FDA Response:

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." Per our comments communicated in the March 24, 2017 response letter, 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.

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.

SUBMITTER QUESTION #2

Does the Agency agree that the qualitative data presented provide sufficient evidence that patients understand and interpret in the way intended for all of the ANMS GCSI-DD items and instructions? If no, what further information is needed?

2a. Does the Agency agree that the qualitative data presented provide sufficient evidence that all patients with gastroparesis, through interactions at mealtimes with friends and family members, understand what a 'normal size meal' represents? If no, what further information is needed?

FDA Response:

No, 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."

SUBMITTER QUESTION #3

Does the Agency agree that the qualitative data presented in this package support the response options of the ANMS GCSI-DD? If no, what further information is needed?

FDA Response:
No. 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).

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

Examples of PGIS and PGIC scales are as follows:

Example of a Patient Global Impression of Severity (PGIS) Scale:

Please choose the response below that
best describes the severity of your
<SYMPTOM/OVERALL STATUS/ETC.>
over the past week.

□ None

□ Mild

□ Moderate

□ Severe

Example of a Patient Global Impression of Change (PGIC) Scale:

Please choose the response below that
best describes the overall change in your
<SYMPTOM/OVERALL STATUS/ETC.>
since you started taking the study medication.

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse

SUBMITTER QUESTION #4

Does the Agency agree that there is sufficient qualitative evidence to support the use of the ANMS GCSI-DD as a "well-defined" primary, co-primary, or secondary endpoint in a phase II or III trial for the evaluation of treatments for gastroparesis? If no, what further information is needed?

FDA Response:

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.

SUBMITTER QUESTION #5

The Agency requested to review the study design of Study 2. Attached is the protocol synopsis for Study 2. Does the Agency agree that, as planned, Study 2 will generate necessary data to support the psychometric properties of the ANMS GCSI-DD? If no, what further information is needed?

FDA Response:

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.

We also have the following additional comments and suggestions.

Additional QRT Comments:

1. 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)."

2. We recommend asking all patients to complete the diary before bedtime and to ask patients to record symptoms based on the past 24 hours.
3. 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.
4. Please submit screenshots from the electronic diary for QRT review.
5. As you progress through the qualification process, you should include datasets from Study 2 when you submit your full qualification package (FQP).
6. 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.

If you have any questions or would like to set up a teleconference to answer questions, please contact the Clinical Outcome Assessments Staff at COADDTQualification@fda.hhs.gov. Please refer to DDT COA #000020.

Sincerely,

Michelle Campbell -S
Digitally signed by Michelle Campbell -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001611013, cn=Michelle Campbell -S
Date: 2018.08.02 13:37:56 -04'00'

Lisa M. Soule -S
Digitally signed by Lisa M. Soule -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lisa M. Soule -S, 0.9.2342.19200300.100.1.1=13002 19575
Date: 2018.08.02 13:32:59 -04'00'

Michelle Campbell, PhD, MS for
Elektra Papadopoulos, MD, MPH
Associate Director
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research

Lisa Soule, MD
Associate Director
Division of Gastroenterology and Inborn Error Products (DGIEP)
Office of New Drugs
Center for Drug Evaluation and Research