DDT COA #000020 **COMMENTS ON SUBMISSION**

ANMS Gastroparesis Symptom Endpoint Working Group
Henry Parkman, MD, henry.parkman@temple.edu
Dennis Revicki, PhD, Ddennis.Rrevicki@evidera.com
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Regarding: the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index Daily Diary (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 review of the materials submitted with your meeting request, dated September 27, 2018. After reviewing the materials and our teleconference discussion held December 3, 2018, the qualification review team (QRT) believes that you may proceed with your psychometric validation study. As you continue with your psychometric validation study, you will need to address our comments either during your validation study or as part of your full qualification package. Should the ANMS GCSI-DD receive a positive qualification decision under the COA DDT Qualification Program, the qualification statement will reflect the specific context of use of the ANMS GCSI-DD for regulatory purposes.

We have the following additional comments and suggestions.

1. We note that your SAP and ANMS GCSI-DD user manual defines the total score of the ANMS-GCSI-DD differently. In your SAP the total score is defined as the sum of nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain scores plus bloating severity, divided by 6; however, page 9 of the user manual defines the total score total as the sum of nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain scores, divided by 5, which is the same scoring algorithm for the ANMS GCSI-DD Core Symptom Composite Score in the SAP. Please correct your SAP to reflect what is in your user manual.

2. We recommend that you conduct the following analyses to inform the missing data scoring algorithm:
   a. <u>At the item level</u>: Randomly replace valid (non-missing) responses with missing responses for an increasing number of items (1 item, 2 items, 3 items, etc.) and evaluate

at which point the daily score becomes unstable (indicated by a large standard deviation (SD) and/or a large deviation from the original daily score computed without missing data).

b. At the form level: Randomly replace valid (non-missing) daily scores with missing daily scores for an increasing number of days (e.g., 1 day, 2 days) and evaluate at which point the overall/average score (per your preliminary scoring algorithm) becomes unstable (indicated by a large standard error and/or a large deviation from the original overall/average score computed without missing data).

3. We acknowledge that the proposed scoring algorithm for the ANMS GCSI-DD is preliminary, but we want to reiterate that there are concerns with capping the vomiting frequency at 4 and with the interpretability of summing the vomiting frequency with the symptom scores. You will need to justify the proposed scoring algorithm using data from EVA-20216-01 and TAK-906-1002.

4. Please clarify if all of the information presented in Table 2 is based on the weekly average score for that item, including the percent missing and the floor and ceiling effects. Is the reported percent of missing data for the ANMS GCSI-DD Endpoint Score, Composite Score, and Total Score based on the proposed missing data rules? Please present additional descriptive statistics on the both the number of missing days and number of missing items for a score. Similar descriptive statistics to those in Table 2 should be presented for weeks 2, 3, and 4 in EVA-20216-01 and week 2 in TAK-906-1002.

5. The proposed confirmatory factor analysis and internal consistency assessment indicate that a random day will be selected from EVA-20216-01 and TAK-906-1002. Clarify whether a random day is selected and if the analysis is conducted using all patient data from that day, or if a separate random day is chosen for each enrolled patient.

6. We have concerns that your sample size of 118 patients (70 patients in EVA-20216-01 and 48 patients in TAK-906-1002) will make it difficult to interpret the proposed IRT analyses.

7. Your proposed analyses for test-retest reliability in trial TAK-906-1002 include the screening period in Time 1 and the treatment period in Time 2. It would be preferable not to compare patients' scores before and after receiving active treatment for assessing test-retest reliability. Instead, we recommend selecting both Time 1 and Time 2 from the screening period. Since there are several ways to compute an ICC, specify how the ICC will be computed. Furthermore, we do not recommend assessing test-retest reliability using a t-test. In addition to the proposed analyses, we recommend presenting scatter plots for the two timepoints.

8. In addition to correlations, we recommend presenting scatter plots to assess convergent validity.

9. Provide additional details in the main text on the ANCOVA model that will be used to evaluate known-groups validity. List the covariates that will be used in the model and the hypothesis tests that will be performed. In addition to the ANCOVA model, we recommend

presenting box plots for the distribution of ANMS GCSI-DD endpoint, composite, total scores, and individual items by each known-group criterion variable.

10. We recommend that patients have stable controlled glucose since episodes of hyperglycemia can delay gastric emptying and uncontrolled glucose may confound the results. We note that you are enrolling patients with HBA1c < 11%, which may allow for inclusion of some patients with poorly controlled glucose. In addition to the information being collected in the "clinical form" (Appendix J of the submission), we recommend that you also capture blood glucose levels during the trial.

Please contact the COA Staff at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000020).

Sincerely,

Elektra J. Papadopoulos -S

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