Psychometric Evaluation of the ANMS Gastroparesis Cardinal Symptom Index – Daily Diary (ANMS GCSI-DD)

Final Protocol

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Protocol Signature Page

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Protocol Date and Version: October 19, 2017; Version 1.0

This protocol with the title, number, and version indicated above has been reviewed and approved by the Evidera Principal Investigator (PI) and Project Manager (PM). This protocol is sponsored by Takeda Pharmaceuticals.

_____ _____
Principal Investigator Date

_____ _____
Project Manager Date

Site Principal Investigator Name: _____

Site Address: _____

_____

_____

I have reviewed the content of this protocol and agree to participate in the study and adhere to all regulations that govern the conduct of this study.

_____ _____
Site Principal Investigator Signature Date

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ANMS	American Neurogastroenterology and Motility Society
CGI-I/ CGI-S	Clinician Global Impression-Improvement / Clinician Global Impression-Severity
CRF	Case report form
CSSR	Clinical Symptom Severity Rating
DM	Diabetes mellitus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSI-DD	Gastroparesis Cardinal Symptom Index Daily Diary
GERD	Gastroesophageal reflux disease
ICC	Intraclass correlation coefficient
ICF	Informed consent form
ID	Identification
IRB	Institutional Review Board
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index
PGI-I / PGI-S	Patient Global Impression of Improvement / Patient Global Impression of Severity
PI	Principal Investigator
PM	Project Manager
PRO	Patient-reported outcome
RA	Research associate
SOP	Standard operating procedure
US	United States

Protocol Synopsis

Parameters	Design
Study Objective	The primary goal of this study is to evaluate the psychometric measurement properties (reliability and validity) of the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) instrument.
Study Design	This is a longitudinal, four-week, observational study consisting of two study visits and at-home diary completion. There are no study drugs or invasive procedures administered as part of this study.
Number and Type of Participants	Up to 70 patients who have been clinically diagnosed with diabetic or idiopathic gastroparesis will be recruited by clinical sites located in the US. Approximately half of participants will be diagnosed with diabetic gastroparesis and the other half with idiopathic gastroparesis. Sites will be encouraged to recruit a diverse sample of participants in regards to age, gender, and race/ethnicity. Up to 10 males will be targeted for overall enrollment across all sites.
Participant Inclusion Criteria	Participants meeting all of the following criteria will be eligible for the study: 1. Adult men and women aged 18 to 85 years, inclusive; 2. BMI ≥18 and ≤ 35kg/m^2 ; 3. Have experienced symptoms of diabetic or idiopathic gastroparesis (e.g., postprandial fullness, nausea, vomiting, upper abdominal pain and early satiety) (at least intermittently) for at least 6 months prior to screening as assessed by a physician; 4. Diagnosis of gastroparesis with documented delay in gastric emptying according to local clinical criteria; 5. Gastroparesis from either idiopathic or diabetic etiologies; 6. Available to attend two in-person study visits; 7. Able and willing to complete a diary for approximately 4 weeks at home; 8. Able and willing to provide written informed consent prior to participation in the study; 9. Able to speak and read English; and <u>Special inclusion for patients with diabetic gastroparesis:</u> 10. Has diabetes mellitus (DM) with HBA1c <11 %.
Participant Exclusion Criteria	Participants meeting any of the following criteria will not be eligible for the study: 1. Prior history of gastric surgery, including but not limited to gastrectomy, gastric bypass, gastric banding, pyloroplasty, vagotomy, or fundoplication, which has manipulated the natural anatomy of the stomach; 2. Known secondary causes of gastroparesis including but not limited to Parkinson's Disease, cancer, viral illness, or connective tissue diseases; 3. History of intrapyloric botulinum toxin injection within 3 months of Screening or currently has functioning implantable electric stimulator; 4. Have a history of clinically significant endocrine, GI (including motility disorder, intestinal obstruction, inflammatory bowel disease), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases; 5. Predominant symptom is epigastric pain, diffuse abdominal pain, or pain associated with bowel movement; 6. Has a history of anorexia nervosa or bulimia; 7. Previous history of bezoars; or 8. Patient has any clinically relevant condition that in the opinion of the investigator/coordinator, would interfere with completing the study including, but not limited to visual problems, severe mental illness or cognitive impairment.
Recruitment Methods	Up to 10 clinical sites will be recruited, contracted, and trained by Evidera to identify, screen, and

Parameters	Design
	recruit up to a total of 70 eligible participants. Trained clinical site staff members will identify participants based on their clinical records and will use IRB-approved recruitment materials to assess interest and confirm eligibility. If participants are eligible and interested in participating, the site staff will schedule them for an in-person Baseline visit. Efforts will be made by sites to recruit a diverse sample of participants with respect to age, gender, race/ethnicity, and diabetic or idiopathic gastroparesis diagnosis.
Data Collection Methods	The site will be responsible for all day-to-day study-related activities including conducting the study visits, submitting all case report forms (CRFs) to Evidera, responding to queried CRFs, and providing payment to all study participants. Data collection for each participant will consist of two in-person visits to the clinic (Baseline = Visit 1 and Week 4 = Visit 2) and daily at-home paper diary completion for four weeks to evaluate test-retest reliability and validity of the ANMS GCSI-DD. Participants will go to the clinic for their Baseline Visit to participate in informed consent procedures and complete patient-reported outcome (PRO) instruments. Sites will instruct participants on how to complete the daily diary. Clinicians will assess relevant clinical measures after the participants complete the PROs. Following Visit 1, participants will be asked to complete the paper ANMS GCSI-DD daily for four weeks at home. Lastly, participants will return to the clinic for Visit 2 (approximately 30 days after the Baseline visit) for follow-up PRO and clinician assessments. Clinical staff will check completed questionnaires for any missing data at Visit 2. Visit 1 is expected to last about 60 minutes, and Visit 2 is expected to last about 30 minutes. Clinic staff will be responsible for making reminder calls for the visits.
Measures	Inclusion/Exclusion Form, ANMS GCSI-DD, Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM), Patient Global Impression of Severity (PGI-S), Patient Global Impression of Improvement (PGI-I), Patient-rated bloating severity item, PROMIS Global scale, Sociodemographic Form, Clinical Symptom Severity Rating (CSSR), Clinician Global Impression-Severity (CGI-S), Clinician Global Impression-Improvement (CGI-I), and Clinical Form.
Protection of Human Subject Rights	Prior to research study activities, the study protocol and clinical sites will be approved by an Institutional Review Board (IRB). All participants will provide written informed consent prior to participation in the study. The purpose of the research study will be fully explained to participants and participants will be informed that their participation is voluntary and confidential.
Data Management	A DataFax data collection system will be developed and tested by Evidera and utilized for all participant demographic, clinical, and PRO data. The system will be programmed to capture out-of-range values, inconsistent responses, and data quality issues. DataFax data will be exported to SAS for statistical analyses.
Statistical Analyses	Analyses will include item characteristics, test-retest reliability, internal consistency reliability, concurrent validity (correlation with other measures), and known groups validity in diabetic and idiopathic gastroparesis patient populations. Item characteristics will be assessed at baseline. Test-retest reliability will be assessed from Baseline to Week 2 and Baseline to Week 4 in a stable population. Internal consistency reliability, concurrent validity, and known groups validity will be assessed at Baseline and at 4 weeks. The Sociodemographic Form and Clinical Form will be used to characterize the patients. Descriptive statistics (e.g., n, mean, standard deviation, or frequency) will be used to characterize the sample in terms of sociodemographic and clinical characteristics.

1.0 Background and Introduction

Gastroparesis is a condition of delayed gastric emptying when no mechanical obstruction is present. Patients can experience a variety of symptoms, including early satiety, nausea, vomiting, and abdominal pain. Gastroparesis of unknown etiology accounts for the largest number of cases, but is also frequently associated with diabetes, and may occur after various types of gastrointestinal surgeries. Gastroparesis-related symptoms are associated with impairments in health-related quality of life and interfere with activities of daily living. There are few approved treatments for gastroparesis; additionally, there is no reliable, valid, and comprehensive daily patient-reported outcome (PRO) measure for gastroparesis to evaluate the effect of treatment on patient symptoms.

The American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) is the first instrument to provide valid, reliable, and standardized data on the patient-reported symptoms of gastroparesis and the effect of treatment, and is intended for use as a primary or secondary endpoints in clinical trials. Given the variability in the symptomatic experience over time in this patient population, five core symptoms are monitored in the ANMS GCSI-DD (i.e., nausea, vomiting, early satiety, postprandial fullness, and upper abdominal pain). In addition, to improve patient recall in reporting symptoms, the ANMS GCSI-DD is completed as a daily diary.

The ANMS GCSI-DD was originally developed based on concept elicitation focus groups and qualitative interviews, and was refined through a process of cognitive interviews—all with representative patients from the target gastroparesis population. Based on the requirements of the Food and Drug Administration (FDA) PRO guidance (2009), the recent FDA guidance on gastroparesis (2015), and the FDA feedback to date during the qualification guidance of the ANMS GCSI-DD, a qualitative interview study was recently conducted to generate additional support for the content validity of the revised ANMS GCSI-DD. The qualitative phase of research was conducted in a manner that was conclusive with respect to concept elicitation, and that sufficient cognitive interviews were conducted to ensure that comprehension of the instructions, items, and response scales were acceptable.

As Takeda's TAK-906 clinical trial program will include a finalized version of the ANMS GCSI-DD, additional psychometric evaluation evidence is needed to further evaluate and confirm the measurement properties of the daily diary prior to implementation in Takeda's clinical trial program. Specifically, the data from this proposed standalone psychometric study would aim to provide sufficient supportive evidence of the reliability (i.e., internal consistency, test-retest) and validity (i.e., concurrent, known groups) of the ANMS GCSI-DD, and provide insight into responsiveness and potential responder definitions for determining clinically meaningful improvements in gastroparesis-related symptoms.

2.0 Objective

The objective of this study is to evaluate the psychometric measurement properties of the ANMS GCSI-DD.

3.0 Methods

3.1 Study Design Overview

This is a longitudinal, four-week, observational study consisting of two study visits (Baseline and Week 4) and at-home diary completion for four weeks. There are no study drugs or invasive procedures administered as part of this study. Up to 10 clinical sites will screen and recruit the patient population for the study, and potential study patients will be identified through medical chart review or during a regularly scheduled office visit. Standardized, institutional review board (IRB)-approved recruitment materials will be used by sites to screen potential participants and track enrollment into the study. Once eligible and interested participants have been identified, site staff may schedule the Baseline visit (Visit 1).

Up to 70 total participants will complete one in-person study visit at Baseline (Visit 1). Following Visit 1, participants will be asked to complete the ANMS GCSI-DD and bloating severity item daily for four weeks at home. Participants will return to the clinic for a Week 4 visit (Visit 2), approximately 30 days after the Baseline visit, for follow-up PRO and clinician assessments. Site staff will check completed questionnaires for any missing data at Visit 2. Visit 1 is expected to last about 60 minutes, and Visit 2 is expected to last about 30 minutes. Site staff will be responsible for making reminder calls prior to both visits.

3.2 Participant Inclusion/Exclusion Criteria

3.2.1 Inclusion Criteria

Participants must meet ALL of the following criteria to be considered for enrollment into this study:

1. Adult men and women aged 18 to 85 years, inclusive;
2. BMI ≥18 and ≤ 35kg/m^2 ;
3. Have experienced symptoms of diabetic or idiopathic gastroparesis (e.g., postprandial fullness, nausea, vomiting, upper abdominal pain and early satiety) (at least intermittently) for at least 6 months prior to screening as assessed by a physician;
4. Diagnosis of gastroparesis with documented delay in gastric emptying according to local clinical criteria;
5. Gastroparesis from either idiopathic or diabetic etiologies;
6. Available to attend two in-person study visits;
7. Able and willing to complete a diary for approximately 4 weeks at home;
8. Able and willing to provide written informed consent prior to participation in the study;
9. Able to speak and read English; and

Special inclusion for patients with diabetic gastroparesis:

10. Has diabetes mellitus (DM) with HBA1c <11 %.

3.2.2 Exclusion Criteria

Participants will not be eligible for inclusion in this study if any of the following criteria apply:

1. Prior history of gastric surgery, including but not limited to gastrectomy, gastric bypass, gastric banding, pyloroplasty, vagotomy, or fundoplication, which has manipulated the natural anatomy of the stomach;
2. Known secondary causes of gastroparesis including but not limited to Parkinson's Disease, cancer, viral illness, or connective tissue diseases;
3. History of intrapyloric botulinum toxin injection within 3 months of Screening or currently has functioning implantable electric stimulator;
4. Have a history of clinically significant endocrine, GI (including motility disorder, intestinal obstruction, inflammatory bowel disease), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases;
5. Predominant symptom is epigastric pain, diffuse abdominal pain, or pain associated with bowel movement;
6. Has a history of anorexia nervosa or bulimia;
7. Previous history of bezoars; or
8. Patient has any clinically relevant condition that in the opinion of the investigator/coordinator, would interfere with completing the study including, but not limited to visual problems, severe mental illness or cognitive impairment.

3.3 Recruitment Procedures

3.3.1 Recruit and Train Clinical Site Staff

Evidera will recruit and train 5-10 clinical sites to assist with participant recruitment. Evidera scientific staff will conduct training sessions with each of the participating clinical sites via teleconference to discuss study-related details, such as study objectives, inclusion/exclusion criteria, recruitment procedures, study visit procedures, etc. The training session will last approximately one hour. If the site principal investigator (PI) is unable to attend the session, it is expected that the trained site coordinator will review the training slides with the PI. All clinical site team members, including the site PI, will sign and return a training log to Evidera upon completion of the training. Copies of the training documents will be maintained at both Evidera and the clinical sites.

3.3.2 Participant Screening, Recruitment, and Scheduling

Trained clinical site staff will be responsible for identifying potential participants by reviewing patient charts and patient databases, and/or speaking to patients during their scheduled office visit. All potentially eligible participants will be screened for study eligibility (either over the telephone or in person) by site staff using a standardized recruitment screening script (Appendix A) to ensure the study is presented in a consistent manner, and that participants meet all pre-specified entry criteria. The script instructs the clinical site staff to ask participants about any inclusion/exclusion criteria that cannot be confirmed from the patient's medical chart/record. Sites will also be responsible for completing an Eligibility Form (Appendix B) for each patient they screen, which must be reviewed and signed by the site PI or designee.

A recruitment tracking log (Appendix C) will be maintained by each site to document the recruitment process and track participant eligibility and/or refusal to participate. The site will send the log to Evidera (via either fax or e-mail) on a weekly basis, or more frequently (as required by Evidera), to keep the Evidera project team apprised of their recruitment and scheduling efforts. If a patient is eligible and interested in participating, the site staff will schedule the patient for a Baseline visit (Visit 1) to take place at the clinical site. The site staff will call the participants to remind them of the appointment 1-2 days prior to their scheduled Baseline visit.

3.3.3 Participant Recruitment Targets

Approximately 70 participants will be recruited across 5-10 clinical sites treating participants with diabetic or idiopathic gastroparesis in the United States (US). Across all sites, approximately half of participants will be diagnosed with diabetic gastroparesis, and the other half will be diagnosed with idiopathic gastroparesis; up to 10 males will be targeted for overall enrollment across all sites. Efforts will be made by sites to recruit a diverse cross-section of participants in terms of both sociodemographic (e.g., race/ethnicity) and clinical characteristics. Overall recruitment will be monitored by Evidera, and Evidera will provide sites with information on the status of enrollment targets on a regular basis. Sites will be notified when enrollment quotas are met.

3.4 Data Collection Procedures

After the initial screening process, eligible and consented participants will attend two study visits: Baseline (Visit 1) and Week 4 (Visit 2). Prior to completing any study-related activities at the baseline visit, a clinic site staff member will obtain written informed consent from each participant, as described later in Section 8.2.

3.4.1 Baseline Visit (Visit 1)

After informed consent is obtained, the following questionnaires will be completed by the participant at the scheduled baseline visit:

- Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM)
- Patient Global Impression of Severity (PGI-S)

- PROMIS Global Scale
- Sociodemographic Form

The order in which the PRO instruments are administered will be consistent from site to site. Specifically, the PAGI-SYM will be completed first, followed by the PGI-S, PROMIS Global Scale, and lastly, the sociodemographic form.

Participants should be provided with a quiet, private space to complete the self-administered questionnaires. Participants will need to interpret and answer the questionnaires on their own. When the participant has completed the questionnaires, the site staff will ensure that there are no missing responses prior to the participant leaving the site.

Next, the site staff will instruct/train the participant in how to complete the ANMS GCSI-DD and patient-reported bloating severity item at home, and will emphasize that the measures must be completed every evening after dinner until they return for Visit 2. The site will ascertain the best method for sending follow-up reminders to complete the daily measures; participants will be provided with the option of receiving phone calls, text messages, or e-mail reminders from the site on a regular basis. The site staff may tentatively schedule the participant's Week 4 visit (Visit 2) during the Baseline visit (Visit 1).

Lastly, the clinical site staff (PI or designee) will be responsible for completing the following measures at the Baseline visit (Visit 1) for each participant:

- Clinical Symptom Severity Rating (CSSR)
- Clinician Global Impression-Severity (CGI-S)
- Clinical form

3.4.2 Daily Assessments

Starting on the evening of the baseline visit, participants will complete the ANMS GCSI-DD and patient-reported bloating severity item every day at home for four weeks (approximately 28 days) until Visit 2. The daily assessments are anticipated to take five minutes or less to complete each evening. Sites will make follow-up reminders to the participants on a weekly basis to remind them to complete the diary every day. The site staff member will also be responsible for scheduling or confirming the participant's Week 4 visit, if not already scheduled at the Baseline visit. Approximately two days before each of the participant's follow-up visits, the clinical staff will call participants as a reminder about the visit, and will remind them to bring their completed daily assessments with them to the follow-up visit.

3.4.3 Week 4 (Visit 2)

All participants will be asked to return approximately 28 days (± 7 days) after Baseline for Visit 2. Site staff will be responsible for reviewing the participant's daily assessments for completion.

During the four-week follow-up visit, the following questionnaires will be completed by the participant:

- PAGI-SYM
- PGI-S
- Patient Global Impression of Improvement (PGI-I)
- PROMIS Global Scale

At the four-week follow-up visit, the PRO instruments will be administered in the same order as that used at the Baseline visit. Participants should be provided with a quiet, private space to complete the self-administered questionnaires. Participants will need to interpret and answer the questionnaires on their own as best they can, with limited guidance from the site coordinator. When the participant has completed the questionnaires, the site staff will ensure that the participant has completed all questionnaires, and that there are no missing responses prior the participant leaving the site. Visit 2 is expected to last approximately 30 minutes.

Lastly, the clinical site staff (PI or designee) will be responsible for completing the following measures at Visit 2:

- CSSR
- CGI-S
- Clinician Global Impression-Improvement (CGI-I)
- Clinical Form (if patient is diabetic)

Table 1 below displays the visit schedule and forms to be administered at and between the study visits.

3.4.4 Participant Remuneration Schedule

Participants may be remunerated, up to $200 total for completing the study, in the form of a prepaid, reloadable debit card. Specifically, participants who complete the Baseline visit will receive $50 at the end of the Baseline Visit. Participants will also receive $25 per week of at-home diary completion, for up to $100 for daily diary completion. Lastly, participants who successfully complete Visit 2 will receive $50. This payment schedule is reflected below in Table 1.

Table 1. Study Visit Procedures and Assessments

Measure	Completed at Screening Prior to baseline	Completed at Baseline (Visit 1)	Completed Daily at home between Visit 1 and Visit 2 28 days	Completed at Week 4 (Visit 2) 28 ± 7 days
Recruitment Screening Script[1]	x			
Inclusion/Exclusion Form[1]	x			
Informed Consent[1,2]		x		
PAGI-SYM[2]		x		X
PGI-S[3]		x		X
CSSR[3]		x		X
PROMIS Global Scale[2]		x		X
Sociodemographic Form[2]		x		
CGI-S[3]		x		X
Clinical Form[3]		x		X[5]
ANMS GCSI-DD[2]		X[4]	x	
Patient-rated bloating severity item[2]		X[4]	x	
CGI-I[3]				X
PGI-I[2]				X
Participant Remuneration	-	$50	$25 per week	$50

[1] Site staff-completed

[2] Patient-completed

[3] Clinician-completed

[4] ANMS GCSI-DD and bloating severity item completion will start with the evening of the baseline visit

[5] Clinical form completed at Visit 2 only if participant is diabetic

4.0 Description of Measures

4.1 Participant-completed Measures

4.1.1 Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM)

The PAGI-SYM (Appendix D) was developed to assess gastrointestinal symptoms in patients with gastroesophageal reflux disease (GERD), dyspepsia, and gastroparesis. The instrument includes 20 symptom questions on heartburn, regurgitation, bloating, nausea, early satiety, post-prandial fullness, upper abdominal pain, and lower abdominal pain. The recall period is the past two weeks and response options range from 0=None to 5=Very Severe.

4.1.2 Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Improvement (PGI-I)

The PGI-S is a one-item questionnaire designed to assess a patient's impression of disease severity. This questionnaire includes a four-point Likert scale ranging from 1 (Normal, not at all ill) to 4 (Severely ill) and is based on a patient's current symptoms. Like the PGI-S, the PGI-I is also a one-item questionnaire, and is based on a five-point Likert scale ranging from 1 (Very much improved) to 7 (Very much worse). The PGI-I was designed to assess if a patient's symptoms improved. The PGI-S and PGI-I can be found in Appendix E.

4.1.3 PROMIS Global Scale

The PROMIS Global Scale (Hays et al. 2009; Appendix G) is a self-administered global scale that includes 10 items representing physical health, pain, fatigue, mental health, social health, and overall health. Items are assessed on either a five-point response scale ranging from 1 (poor/not at all/none/never) to 5 (excellent/completely/very severe/always) or an 11-point Likert type scale where the response to the question ranges from 0–10, where 0 = "No pain" and 10 = "worst imaginable pain."

4.1.4 Sociodemographic Form

Participants will complete a brief sociodemographic form (Appendix H) that includes questions about participant age, gender, ethnicity, living situation, employment, and education. This information will be used for descriptive purposes.

4.1.5 ANMS GCSI-DD

The ANMS GCSDI-DD (Appendix K) is a daily diary that consists of six symptom questions based on the original Gastroparesis Cardinal Symptom Index, with revisions based on interactions with the FDA. The ANMS GCSI-DD includes a 24-hour recall period, and is intended for daily administration. Items included in the ANMS GCSI-DD include severity assessments of nausea, early satiety, post-prandial fullness, upper abdominal pain, and vomiting, and an overall assessment of gastroparesis symptom severity. The severity of gastroparesis symptoms is assessed using a five-point Likert scale (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe). Vomiting is assessed based on frequency (episodes of vomiting) over the past 24 hours.

4.1.6 Patient-reported Bloating Severity Item

The bloating item is a standalone item (located in Appendix K) from the original GCSI-DD. This item refers to bloating as "feeling like you need to loosen your clothes" and asks patients to rate the severity of their bloating over the past 24 hours on a five-point Likert scale (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe). This item is included within the daily diary, as it is intended for daily administration in the study; however, it is not included in the composite score.

4.2 Site-completed Measures

4.2.1 Clinical Symptom Severity Rating (CSSR)

A CSSR form will be completed by the clinical site study staff at the Baseline visit to capture information on overall severity of gastroparesis symptoms and severity ratings on selected symptoms (i.e., nausea, abdominal distension, bloating, early satiety, vomiting, and abdominal pain) (Appendix F). Severity will be rated on a 0 (none) to 4 (very severe) scale (Revicki et al. 2003).

4.2.2 Clinician Global Impression-Severity (CGI-S) and Clinician Global Impression-Improvement (CGI-I)

The CGI-S is based on observed and reported symptoms, behavior, and function on a four-point scale ranging from 1 (Normal, not at all ill) to 4 (Severely ill). The CGI-S has a seven-day recall period, and the score reflects the average severity level across the seven days (Busner & Targum 2007). The CGI-I is also observer-reported and uses a seven-point scale ranging from 1 (Very much improved) to 7 (Very much worse). Unlike the CGI-S, the CGI-I compares the patient's overall condition from baseline to the study visit. The CGI-S and CGI-I can found in Appendix I.

4.2.3 Clinical Form

Sites will complete a clinical form for each participant upon enrollment (Appendix J) at the baseline visit and again at Visit 2 (if the participant is diabetic). The clinical form collects information about the patient's diagnosis, treatment history, and comorbid conditions. The clinical data will be used to describe the sample and assist with interpreting results.

5.0 Responsibilities

5.1 Clinical Site Personnel Responsibilities

Site staff participating in this study are required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice (GCP) guidelines and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a research study. Evidera staff will prepare a study binder and develop training materials for assistance with study implementation. The study binder will include all relevant materials needed to implement the study, which will include the protocol, training materials, recruitment logs, recruitment screening scripts, data collection materials, standard operating procedure (SOP) documentation, Evidera contact information, and IRB correspondence and approvals.

Sites will identify a primary site staff member who will be responsible for screening and recruiting participants. A backup site staff member will also be identified to provide coverage for the primary site staff member during times of unavailability. Evidera will be available to answer questions from clinical sites during the study. Throughout the study, Evidera will have regular contact with the investigator/site coordinator at each site. These contacts will include periodic telephone calls to provide information and support to the site investigational team.

Primary site responsibilities are summarized below:

- Submit site applications to the IRB with assistance from Evidera
- Participate in a one-hour telephone and web-based training session conducted by Evidera, which will focus on recruitment procedures and goals to ensure targets are met
- Identify potentially eligible participants in accordance with target recruitment goals, and screen participants using IRB-approved materials
- Provide weekly recruitment updates to Evidera using the Screening and Recruitment Log
- Schedule interested and eligible participants for study visits
- Obtain written informed consent from patients prior to the start of any study-related procedures
- Conduct study visits with participants
- Train and remind participants to complete daily assessments
- Follow Adverse Event (AE) reporting procedures outline in this protocol
- Maintain participant confidentiality and secure data storage
- Ensure the accuracy and completeness of all case report forms (CRFs)
- Submit site and participant-completed CRFs to Evidera via DataFax
- Respond to DataFax and other queries from Evidera
- Remunerate study participants at the end of each study visit
- Conduct site close-out procedures upon completion of the study

5.2 Evidera Responsibilities

Evidera is responsible for the implementation of the study, including overseeing participant recruitment through clinical sites, data analysis, and report writing. The Evidera Principal Investigator (PI), Project Manager (PM), and designated Research Associates (RAs) will oversee all of these activities. Throughout the study, Evidera personnel will have regular telephone and/or e-mail contact with the investigator and/or site staff member at each site to provide information and support to the site investigational team. Evidera study personnel are available via telephone and e-mail during normal business hours in the event that the site investigational team needs information, clarification, or advice.

Detailed Evidera responsibilities are summarized below:

- Contract directly with clinical sites
- Develop and provide clinical sites all necessary study materials, including study protocol with questionnaires, participant informed consent forms (ICFs), and final DataFax CRFs needed for the study procedures
- Assist sites with IRB submission and reviewing site IRB applications

- Conduct a telephone and web-based training session for site staff members prior to the start of the recruitment process to review the protocol, with specific focus on recruitment procedures and recruitment targets
- Track participant recruitment efforts across all sites
- Track participant enrollment and study visit completion status across all sites
- Provide payment to the sites to remunerate participants
- Conduct quality control of CRFs (both site- and participant-completed) sent into the DataFax system, including distribution of queries to sites for resolution
- Collect and manage CRF data
- Analyze quantitative study data and develop a final report
- Lead study close-out procedures with the help of clinical site staff

6.0 Data Management and Quality Control

All study-related scripts, forms, and measures will be provided to the sites to guide participant recruitment and study visit procedures. All study-related documents will be maintained in locked, secured areas separate from any participant-identifying information. Sites will be responsible for sending (i.e., FTP or faxing) all completed paper-and-pencil administered CRFs to Evidera within 24 hours of completion via DataFax, which is a Part 11 compliant data management optical character recognition system. Once received at Evidera, CRFs will be reviewed by Evidera staff for completeness and discrepancies. All quantitative data collected (e.g., sociodemographic/clinical information and data from the participant- and clinician-completed measures) will be reviewed/corrected by two separate reviewers after OCR creates the initial data records.

Evidera will prepare the data verification guidelines regarding out-of-range values, inconsistent responses, and data checks, and will be responsible for subsequent data entry per these guidelines. Discrepancy queries will be submitted to the site on a regular basis by Evidera for clarification and resolution. Sites are expected to respond to queries within two working days of query receipt. Prior to conducting analysis on the final SAS-ready dataset, additional data verification analyses will be performed. The data will be imported into SAS® statistical software version 9.1.3 or higher (SAS Institute Inc.; Cary, NC) to perform the psychometric evaluation according to the methods described below.

Extensive procedures for the careful and complete collection of data will be implemented by Evidera. Site coordinators will be trained by Evidera prior to initiating participant contact. Evidera will monitor the participant recruitment and data collection process, and be available for consultation regarding study implementation, participant recruitment, study visits, and any other questions throughout this process.

7.0 Data Analysis and Statistical Considerations

This section serves as a brief description of the planned statistical analyses. A detailed statistical analysis plan, including table shells, will be developed prior to database lock and data analysis.

7.1 Sample Size

A sample size of 60-70 participants is targeted for the planned analyses. This sample size is sufficient for further confirming the psychometric characteristics of the ANMS GCSI-DD, and is comparable to the sample size in a previous psychometric study on the daily diary (Revicki et al., 2012).

7.2 Descriptive Analysis

Descriptive statistics will be reported for the demographic and clinical characteristics at Baseline. This will include calculations of summary values, such as the frequency, mean, median, range, standard deviation, etc. of variables.

7.3 Item Analysis

Item frequency and distributions will be examined for the ANMS GCSI-DD, including the bloating item, at the Baseline visit. Weekly average item change scores from Baseline to Week 4 (Visit 2) will also be examined.

7.4 Psychometric Evaluation of the ANMS GCSI-DD

7.4.1 Reliability

Essential to PRO questionnaires is good reliability (i.e., low random measurement error). Reliability will be assessed by evaluating the internal consistency and test-retest reliability of the ANMS GCSI-DD.

7.4.1.1 Internal Consistency Reliability

Internal consistency reliability will be assessed, using the Cronbach's alpha coefficient, to examine the extent to which individual items within each measure are related to each other and with the scale as a whole. Cronbach's coefficient alpha will be calculated for the ANMS GCSI-DD total score. Cronbach's coefficients alpha can range from 0 to 1. A low alpha (<0.70; Hays & Revicki 2005; Nunnally & Bernstein 1994) indicates that items in an instrument are not sufficiently related to form a scale. These analyses will be conducted using a random day selected during the first 7 daily diary days in the study from the Baseline visit.

7.4.1.2 Test-retest Reliability

Pearson product-moment correlations, intraclass correlation coefficients (ICCs), and paired t-test comparisons will be calculated for Baseline to Week 2 and Week 4 (Visit 2) scores in a stable gastroparesis population. The ICC will be computed for the average weekly ANMS GCSI-DD total score. An ICC >0.70 is considered acceptable. The stability of scores will be further investigated by examining individual raw scores and median scores across the two assessment timepoints.

7.4.2 Validity

Validity of an instrument refers to the extent to which an instrument measures the construct it is intended to measure (Hays & Revicki 2005). Validity will be evaluated by assessing both concurrent and known groups validity. Criterion for validity assessments, for example concurrent validity, will use the Pearson's product-moment and Spearman's rank correlation coefficients. A correlation coefficient >0.3 indicates moderate convergent validity, whereas a correlation coefficient >0.5 indicates strong convergent validity.

7.4.2.1 Concurrent Validity

Concurrent validity will be evaluated by assessing the level of association between scores on a questionnaire and scores from comparator questionnaires that measure related and unrelated constructs, respectively. Concurrent validity will be assessed using Baseline and Week 4 (Visit 2) data. Spearman's rank correlation coefficients will be calculated between ANMS GCSI-DD scores and the PAGI-SYM, PGI-S, PROMIS Global Scale, and patient-rated overall gastroparesis symptom severity item (from the ANMS GCSI-DD). Correlations between the scores on the ANMS GCSI-DD and CSSR/CGI-S scores will be evaluated using Spearman rank correlation coefficients.

7.4.2.2 Known-groups Validity

Known-groups validity, or discriminant validity, is the extent to which scores from an instrument are distinguishable from groups of subjects that differ by a key indicator. The known-groups validity of the ANMS GCSI-DD will be assessed at Baseline and at Week 4 (Visit 2) by comparing patients on PGI-S and CGI-S defined groups at baseline and visit 2. Analysis of variance will be used to compare differences among patient and clinician defined severity groups (i.e., none, mild, moderate, severe). We will also compare mean weekly ANMS GCSI-DD total and item scores between IG and DG groups using t-tests.

8.0 Ethical and Regulatory Considerations

8.1 Institutional Review Board (IRB) Approval

In accordance with ethical practice and with the requirements of most peer-reviewed journals, IRB approval will be obtained to comply with human subject research requirements prior to initiation of any study procedures. Evidera will prepare and submit all materials for IRB approval, including the study protocol, consent forms, and data collection tools. For sites that use a central IRB, Evidera will assist sites in the preparation of documents for IRB submission. For sites that require local IRB approval, Evidera will assist with the IRB submission and provide templates as needed.

8.2 Informed Consent Procedures

All participants will provide written informed consent prior to participating in the study. The person administering consent at the clinical site will explain the study and the procedures required (time commitment, information collected, and questionnaires administered), risks/benefits, confidentiality, and remuneration to the participant. Participants will be informed that participation in the study is voluntary, and that they may refuse to participate or withdraw at any time without penalty and without giving up

any benefits to which they are otherwise entitled. Participants will be told that should, they choose not to participate in all or any parts of the study, their current or future treatment will not be affected. Additionally, participants will be assured of the confidential nature of study participation. Lastly, participants will be provided with a copy of their signed consent form describing the study, visit procedures, compensation, risks, and benefits.

8.3 Potential Risks and Benefits

This study involves the collection of patient- and clinician-completed measures for informational purposes only. There are no known risks to participants, and the study does not involve the use of an investigational drug or device. During or following the research study, patients may become more aware of how they feel about their condition and how their condition may affect certain aspects of their lives. Likewise, clinicians may become more aware of their patients' conditions and experiences. Participants will be free to share their questions or concerns during or in between study visits. The elements of federal regulations pertaining to consent procedures, disclosure of potential risks and benefits, and participant confidentiality will be strictly observed.

There will be no direct benefit to the patient. It is hoped that this project will help finalize a daily diary for gastroparesis symptoms that can be used for clinical care and for the evaluation of new agents to treat this disorder. This information could then be used to develop and evaluate new treatment approaches that improve clinical outcomes and PROs for future patients who need treatment for gastroparesis.

8.4 Alternative Treatments

This is not a treatment study protocol. The alternative is not to participate.

8.5 Participant Confidentiality

All data collected in this study will be strictly confidential in accordance with local, state, and federal law. Personnel from the following organizations may examine the research study records: Evidera, Takeda, clinical site, regulatory agencies (e.g., the FDA), and an IRB. Study staff from both the clinical site and Evidera will be instructed to maintain complete confidentiality of all collected data. All consent procedures and study visits will take place in a quiet and private space at the sites to ensure participant confidentiality. The report generated from the study will not contain any participant-identifying information.

Staff will retain participant screening and recruitment materials that contain participant-identifying information in a secure, locked area. At the time of enrollment, participants will be assigned unique participant identification (ID) numbers. Only the unique participant ID number and participants' initials will be recorded on participant questionnaires. The unique ID assigned will be used to track the participants throughout the study. Signed ICFs will be maintained by the site in a locked, limited-access file cabinet, separate from the study files and participant CRFs.

8.6 Safety Monitoring

The study does not involve the use of any Takeda investigational or marketed drug or device; therefore, no adverse drug reactions or AE reporting is expected. If evidence emerges from study documentation of the occurrence of an AE or adverse reaction involving a Takeda Pharmaceutical Company product, such information will be reported to the local Drug Safety Unit (e.g., MedWatch Form [Appendix L]) within 24 hours of the site becoming aware of the event.

In the event an AE or other reportable safety information (as defined by Takeda Pharmaceutical Company) involving a Takeda Pharmaceutical Company product, the appropriate information must be reported to Takeda Pharmaceutical Company's drug safety department in accordance with Takeda Pharmaceutical Company's policies and procedures outlined in STND-PV-006 for non-interventional studies. This section covers studies where there is primary data collection from healthcare professionals or patients.

At a minimum, the FDA MedWatch Form will include the following elements: identifier (e.g., participant ID), drug name (brand name or generic name/active ingredient), AE description, and contactable reporter. If the participant offers additional information, the FDA MedWatch safety report may include the medical diagnosis, or a medically recognized term in the opinion of the treating physician, along with the circumstances leading to the onset of the event. Also, if applicable, the form may indicate the start date, stop date for the event/condition, seriousness (e.g., if it required hospitalization), severity (mild, moderate, severe), outcome, any concomitant medications, and all underlying comorbidities. The condition/event will be reported as soon as possible, but no later than one business day following discovery of the event. The timeframe for AE collection starts after the ICF is signed and ends upon conclusion of the study visit (i.e., participant receipt of remuneration).

8.7 Records Retention

All records will be retained for a minimum of two years on site and an additional five years off site after completion of the study, as directed by Takeda (or Evidera). Subsequent to this time period of seven years, or if an appropriate and adequate place to store such records is not available for the specific timeframe indicated above, the site must contact Evidera (or Takeda) for the appropriate process forward.

9.0 References

Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*. 2007;4(7):28-37.

Food and Drug Administration. Gastroparesis: Clinical Evaluation of Drugs for Treatment. Guidance for Industry. July 2015. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455645.pdf. Accessed on May 5, 2017.

Food and Drug Administration. Guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. Federal Register. 2009;74(235):65132-65133.

Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res*. 2009;18(7):873-880.

Hays RD, Revicki DA. Reliability and validity, including responsiveness. In: Fayers PM, Hays RD, eds. *Assessing Quality of Life in Clinical Trials*. 2nd ed. New York: Oxford University Press; 2005:25-39.

Nunnally JC, Bernstein IH. *Psychometric Theory*. 3rd ed. New York: McGraw-Hill; 1994.

Revicki DA, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther*. 2003;18(1):141-150.

Appendix A. Recruitment Screening Script

Participant ID: _____ Participant Initials: _____ Date: ____/____/____

RECRUITMENT SCREENING SCRIPT

(This screening script can be administered via telephone or in-person)

Instructions: Clinic staff will use this screening script to introduce the study to each potential participant to ensure that the study is introduced consistently. Please complete the entire screening script for each potential participant so that all reasons for ineligibility can be documented.

[If screening over the phone, first confirm that you are speaking with the correct individual/the target participant.]

Hello, this is [NAME] from <<name of clinical site>>. [If phone screening say, "Am I speaking with (patient name)?"]

I want to discuss a new research study with you for which you may qualify. Our office is participating in a study to help assess a questionnaire about gastroparesis. Gastroparesis is condition in which the stomach is unable to adequately empty itself. We are asking people, like you, if they would like to be part of a study which would involve two in-person visits to our office along with completing a brief diary at home in between those two visits. The study only involves completing questionnaires; there is no drug or medication being administered as part of this study.

If you are eligible and want to participate, you will be asked to provide written consent at your first study visit and then complete a few questionnaires. The first visit is expected to last about 60 minutes. At that visit, you would be given a daily diary to take home and complete at home every night for about 4 weeks, until your second and final visit to our office. The daily diary takes less than 5 minutes to complete. At the second (and final) visit, you will also be asked to come in and return your daily diary and then complete additional questionnaires. This last visit is expected to take about 30 minutes.

For your participation and time, you will receive up to $200 for completion of the full study ($50 after completion of the first visit, $25 per week of at-home diary completion, and $50 after completion of the second visit). This money will be provided in the form of a pre-paid debit card as compensation for your time.

Participating in this study is completely voluntary. Whether you decide to participate or not, your medical care will NOT be affected. You will be free to withdraw from the study at any time. All questionnaires you fill out during both visits will have a unique participant identification number and not your full name.

After hearing this information, would you be interested in participating in the study?

If the patient is <u>not</u> interested, then thank for their time and terminate.

If the patient is interested, proceed: To find out if you are eligible for this study, I need to ask a few health-related questions. You don't have to answer any question you don't want to answer. Your answers will be recorded, but your information will only be used for the purposes of this study. If you have any questions, you can contact someone from the study at [*insert contact information*]. Do I have your permission to proceed? (Record: YES/NO) *(Refer to ELIGIBILITY FORM and ask about criteria that could not otherwise be determined through medical chart review.)*

If the patient is not eligible, state: I'm sorry, but based on your responses we will not be able to include you in the study. Thank you for your interest and for taking the time to speak with me today.

If the patient is eligible: Based on the answers that you just gave me, you are eligible to participate in this study!

Would [TBD date, time] (or what dates/times) for a first visit work for you? As a reminder, the first visit will last about an hour. ***(Record scheduled interview time below).*** What is the best telephone number for me to use when calling to confirm your visit date/time? I may also call if we need to reschedule you for any reason. If you would like to cancel the study visit or need to reschedule, please call (site contact) at (telephone number).

NOTE TO SITE: DO NOT SEND THIS INFORMATION TO EVIDERA, TO BE RETAINED AT THE SITE FOR INTERVIEW SCHEDULING PURPOSES

Participant Name: _____ Phone: _____

Potential Ranges of Dates/Times of Baseline Visit (Visit 1):

_____

Potential Ranges of Dates/Times of Week 4 Visit (Visit 2; 28 days ± 7 days after Baseline):

_____

Do you have any questions? [*Answer any questions*] Thank you very much for your time. Have a nice day!

Screener Name: _____

Screener Signature: _____ Date: _____

Appendix B. Eligibility Form

Please review the participant's eligibility through chart review and/or in-person participant discussion before scheduling the Baseline visit. Check YES or No for each of the following criteria and send the completed form to Evidera:

INCLUSION CRITERIA	YES	NO
1. Adult man or woman aged 18 to 85 years, inclusive;	☐	☐
2. BMI ≥18 and ≤ 35kg/m^2;	☐	☐
3. Have experienced symptoms of diabetic or idiopathic gastroparesis (e.g., postprandial fullness, nausea, vomiting, upper abdominal pain and early satiety) (at least intermittently) for at least 6 months prior to screening as assessed by a physician;	☐	☐
4. Diagnosis of gastroparesis with documented delay in gastric emptying according to local clinical criteria;	☐	☐
5. Gastroparesis from either idiopathic or diabetic etiologies;	☐	☐
6. Available to attend two in-person study visits;	☐	☐
7. Able and willing to complete a diary for approximately 4 weeks at home;	☐	☐
8. Able and willing to provide written informed consent prior to participation in the study;	☐	☐
9. Able to speak and read English; and	☐	☐
Special inclusion for patients with diabetic gastroparesis: 10. Has diabetes mellitus (DM) with HBA1c <11 %.	☐	☐

If **ANY** of the above answers are **NO**, the patient is **NOT ELIGIBLE** for participation in this study. ***Do not proceed any further with this patient***.

If **ALL** of the above items are **YES**, continue by checking YES or NO for each of the following criteria, assessed through chart review or in-person screening:

EXCLUSION CRITERIA	YES	NO
1. Prior history of gastric surgery, including but not limited to gastrectomy, gastric bypass, gastric banding, pyloroplasty, vagotomy, or fundoplication, which has manipulated the natural anatomy of the stomach;	☐	☐
2. Known secondary causes of gastroparesis including but not limited to Parkinson's Disease, cancer, viral illness, or connective tissue diseases;	☐	☐
3. History of intrapyloric botulinum toxin injection within 3 months of Screening or currently has functioning implantable electric stimulator;	☐	☐
4. Have a history of clinically significant endocrine, GI (including motility disorder, intestinal obstruction, inflammatory bowel disease), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases;	☐	☐
5. Predominant symptom is epigastric pain, diffuse abdominal pain, or pain associated with bowel movement;	☐	☐
6. Has a history of anorexia nervosa or bulimia;	☐	☐
7. Previous history of bezoars; or	☐	☐
8. Patient has any clinically relevant condition that in the opinion of the investigator/coordinator, would interfere with completing the study including, but not limited to visual problems, severe mental illness or cognitive impairment.	☐	☐

If **ANY** of the above answers are **YES**, the patient is **NOT ELIGIBLE** for participation in this study. ***Do not proceed any further with this patient.*** If **ALL** of the above answers are **NO** please continue.

I have reviewed the eligibility criteria above, and find that the participant fulfills the criteria for this study.

Site Investigator or Designee Signature	Date

Appendix C. Screening and Recruitment Log

RECRUITMENT TRACKING LOG (EVA-20216-01): SITE XXX

Please e-mail or fax to Evidera every Tuesday

(Attn: Kellie Washington – email: Kellie.Washington@evidera.com; fax: 301-654-9864)

Screening ID	Participant Initials	Age	Gender	Ethnicity	Diabetic or Idiopathic Gastroparesis Classification *(Reminder: Aim for 50% in each group)*	Screen Date	Eligible/ Ineligible/ Declined	If Ineligible, Record Criteria*	Baseline (Visit 1) Date and Time if Scheduled	Week 4 (Visit 2) Date and Time if Scheduled (28 days ± 7 days from Baseline)
Example 001-001	JAD	32	M	Native Am.	□ Diabetic □ Idiopathic	10/20/2017	Eligible	N/A	10/23/2017 11:30 AM	11/20/2017 3:00 PM
Example 001-002	SRD	65	F	Asian	□ Diabetic □ Idiopathic	10/25/2017	Ineligible	Inclusion 3, Exclusion 1	N/A	N/A
001-001					□ Diabetic □ Idiopathic					
001-002					□ Diabetic □ Idiopathic					
001-003					□ Diabetic □ Idiopathic					
001-004					□ Diabetic □ Idiopathic					

Appendix D. Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM)

UBC 0xx Participant Page 1 of 2

UBC # 036 Plate # 007 Visit # 002

Participant ID ☐☐ ☐☐☐ Participant Initials ☐☐☐ (F M L) Date Completed ☐☐ (mm) ☐☐ (dd) 20☐☐ (yyyy)

Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM)

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *mark with an "X"* the box that best describes how *severe* the symptom has been during the past 2 weeks. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past two weeks:	None 0	Very Mild 1	Mild 2	Moderate 3	Severe 4	Very Severe 5
1. Heartburn (burning pain rising in your chest or throat) during the day	☐	☐	☐	☐	☐	☐
2. Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	☐	☐	☐	☐	☐	☐
3. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	☐	☐	☐	☐	☐	☐
4. Upper abdominal (above the navel) pain	☐	☐	☐	☐	☐	☐
5. Stomach fullness	☐	☐	☐	☐	☐	☐
6. Loss of appetite	☐	☐	☐	☐	☐	☐
7. Upper abdominal (above the navel) discomfort	☐	☐	☐	☐	☐	☐
8. Bloating (feeling like you need to loosen your clothes)	☐	☐	☐	☐	☐	☐
9. Heartburn (burning pain rising in your chest or throat) when lying down	☐	☐	☐	☐	☐	☐
10. Regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	☐	☐	☐	☐	☐	☐
11. Lower abdominal (below the navel) pain	☐	☐	☐	☐	☐	☐
12. Feeling of discomfort inside your chest during the day	☐	☐	☐	☐	☐	☐

PAGI-SYM
February 11, 2009, v1 Protocol A2-8010-001 Participant initials: _____

UBC # 036 Plate # 007 Visit # 002

Participant ID ☐☐ ☐☐☐ Participant Initials ☐☐☐ (F M L)

Patient Assessment of Gastrointestinal Disorders–Symptom Severity Index (PAGI-SYM)

Please rate the severity of the following symptoms during the past two weeks.	None 0	Very Mild 1	Mild 2	Moderate 3	Severe 4	Very Severe 5
13. Bitter, acid or sour taste in your mouth	☐	☐	☐	☐	☐	☐
14. Lower abdominal (below the navel) discomfort	☐	☐	☐	☐	☐	☐
15. Feeling of discomfort inside your chest at night (during sleep time)	☐	☐	☐	☐	☐	☐
16. Retching (heaving as if to vomit, but nothing comes up)	☐	☐	☐	☐	☐	☐
17. Stomach or belly visibly larger	☐	☐	☐	☐	☐	☐
18. Vomiting	☐	☐	☐	☐	☐	☐
19. Not able to finish a normal-sized meal	☐	☐	☐	☐	☐	☐
20. Feeling excessively full after meals	☐	☐	☐	☐	☐	☐

Appendix E. Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Improvement (PGI-I)

Patient Global Impression of Severity (PGI-S)

How would you rate your severity level of gastroparesis-related symptoms today?

- ☐ Normal, not at all ill
- ☐ Mildly ill
- ☐ Moderately ill
- ☐ Severely ill

Patient Global Impression of Improvement (PGI-I)

Please rate the change in your gastroparesis-related symptoms today, as compared to your gastroparesis-related symptoms 4-weeks ago when you started this study.

- ☐ Very much improved
- ☐ Much improved
- ☐ A little improved
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

Appendix F. Clinical Symptom Severity Rating (CSSR)

Clinician Symptom Severity Rating Form

Rate each symptom, as experienced by the subject, over the last seven days. Mark with an "X" only one box for each symptom.

Physician-rating of Patient Gastroparesis Severity:

	None	Mild	Moderate	Severe	Very Severe
1. Nausea	☐	☐	☐	☐	☐
2. Abdominal distension	☐	☐	☐	☐	☐
3. Bloating	☐	☐	☐	☐	☐
4. Early satiety	☐	☐	☐	☐	☐
5. Epigastric pain	☐	☐	☐	☐	☐
6. Vomiting	☐	☐	☐	☐	☐

Physician-rating of Patient Gastroparesis Severity:

None	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐

Appendix G. PROMIS Global Scale

PROMIS v.1.0 - GLOBAL

Global Items

Please respond to each item by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS v.1.0 - GLOBAL

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

		None	Mild	Moderate	Severe	Very severe
Global08	How would you rate your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst imaginable pain

Appendix H. Sociodemographic Form

Please answer the following questions about YOU.

1. What is your age? _____ years old

2. What is your gender?
   - ☐ Male
   - ☐ Female

3. What is your racial background? *(please check all that apply)*
   - ☐ American Indian or Alaska Native
   - ☐ Asian
   - ☐ Black or African American
   - ☐ Native Hawaiian or Pacific Islander
   - ☐ White
   - ☐ Other race (please specify): _____

4. What is your ethnic background? *(please check one only)*
   - ☐ Hispanic or Latino
   - ☐ Not Hispanic or Latino

5. What is your current marital status? (*Please check only one*)
   - ☐ Single/never married
   - ☐ Married or living in marriage-like relationship
   - ☐ Widowed/separated/divorced/annulled
   - ☐ Other (please specify): _____

6. What is your current living/domestic situation? (*Please check only one*)
   - ☐ Living alone
   - ☐ Living with a partner or spouse, family, or friends
   - ☐ Other (please specify): _____

7. How would you describe your employment status? (*Please check all that apply*)
   - ☐ Employed, full-time
   - ☐ Employed, part-time
   - ☐ Homemaker
   - ☐ Student
   - ☐ Unemployed
   - ☐ Retired
   - ☐ Disabled
   - ☐ Other (please specify): _____

8. What is the highest level of education you have completed? (*Please check only one*)
   - ☐ Elementary/primary school
   - ☐ Secondary/high school/GED
   - ☐ Some college or post-high school education or training
   - ☐ College degree
   - ☐ Postgraduate degree
   - ☐ Other (please specify): _____

Appendix I. Clinician Global Impression-Severity (CGI-S) and Clinician Global Impression-Improvement (CGI-I)

Clinician Global Impression of Severity (CGI-S)

How would you rate the severity level of the patient's gastroparesis-related symptoms today?

- ☐ Normal, not at all ill
- ☐ Mildly ill
- ☐ Moderately ill
- ☐ Severely ill

Clinician Global Impression of Improvement (CGI-I)

Please rate the change in the patient's gastroparesis-related symptoms today, as compared to the patient's gastroparesis-related symptoms 4-weeks ago when the patient started this study.

- ☐ Very much improved
- ☐ Much improved
- ☐ A little improved
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

Appendix J. Clinical Form

CLINICAL FORM

(to be completed by clinical sites via interview with patient and referring to chart)

VISIT 1

1. How long has the participant been a patient in your practice? ____ years ____ months

2. At what age did the patient start having symptoms of gastroparesis: _____ years old

3. Date of gastroparesis diagnosis: _____
   (MM/DD/YYYY)

4. Has the patient had a motility assessment, such as scintigraphy, gastric emptying breath test (GEBT), Smartpill?
   ☐ Yes
   ☐ No

5. How many times in the past year has the patient gone to the emergency room because of gastroparesis?
   _____ times in the past year

6. How many times in the past year has the patient stayed overnight in the hospital due to gastroparesis?
   _____ times in the past year

7. Which best describes the nature of the patient's gastroparesis symptoms? *(check most appropriate answer)*
   ☐ Chronic symptoms, but stable
   ☐ Chronic, but progressive worsening of symptoms
   ☐ Chronic, with periodic exacerbations
   ☐ Cyclic pattern of exacerbations with feeling well in between

8. What best describes the gastroparesis severity?
   - ☐ Mild gastroparesis: Symptoms relatively easily controlled. Able to maintain weight on diet.
   - ☐ Compensated gastroparesis: Moderate symptoms - only partial control with daily medications.
   - ☐ Gastroparesis with gastric failure: Refractory symptoms not under control.
   - ☐ Frequent ER visits, hospitalizations, doctor's visits, not able to maintain nutrition.

9. Please indicate medications/treatments that the participant is currently receiving for gastroparesis. *(select all that apply)*
   - ☐ Prokinetic Agent
   - ☐ Antiemetic Agent
   - ☐ Gastric Antisecretory Agent
   - ☐ Pain Medications
   - ☐ Psychotropic Agent
   - ☐ Diabetes Treatment
   - ☐ Gastric electric stimulation (pacemaker)
   - ☐ Gastric Surgery
   - ☐ Gastrostomy tube (G tube)
   - ☐ Jejunostomy Tube (J tube)
   - ☐ Central line or PICC line
   - ☐ Other (please specify): _____
   - ☐ Not currently taking treatments or medications for gastroparesis

10. Please indicate prior gastrointestinal (GI) specific surgeries that the participant has had:
    - ☐ Fundoplication
    - ☐ Gastrectomy
    - ☐ Gastric banding
    - ☐ Gastric bypass
    - ☐ Gastric electric stimulation (GES)
    - ☐ Jejunostomy (J-tube)
    - ☐ Pyloroplasty
    - ☐ Vagotomy
    - ☐ Other surgery, specify: _____
    - ☐ No prior surgeries

11. Date of most recent upper endoscopy: _____
(MM/DD/YYYY)

12. Does the participant have a history of any of these conditions? *(select all that apply)*
- ☐ Auto-immune disorder
- ☐ Cancer
- ☐ Cardiovascular condition
- ☐ Dyslipidemia/hyperlipidemia
- ☐ Insomnia/sleep problems
- ☐ Liver disease
- ☐ Mood disorder or mental health condition
- ☐ Neurological condition
- ☐ Obesity
- ☐ Respiratory condition
- ☐ Other Gastrointestinal disorder (other than gastroparesis): _____
- ☐ Other (please specify): _____
- ☐ None of the above

13. Does the patient have diabetes?
- ☐ No
- ☐ Yes
- ☐ Unsure

If Yes:

a. Date of diabetes diagnosis: _____
(MM/DD/YYYY)

b. Type of diabetes:

☐ Type 1

☐ Type 2

c. Patient's most recent HgbA1c level:

i. Value: _____

ii. Date: _____

(MM/DD/YYYY)

☐ Level unknown or not available

Visit 2

If patient has diabetes:

1. Patient's most recent HgbA1c level:

i. Value: _____

ii. Date: _____

(MM/DD/YYYY)

☐ Level unknown or not available

I certify that the above information is correct.

Principal Investigator Signature _____ Date _____

Appendix K. ANMS GCSI-DD

ANMS GASTROPARESIS CARDINAL SYMPTOM INDEX – DAILY DIARY

Instructions: These questions ask about symptoms you may have each day. Please complete the daily diary at about the same time every evening.

For each symptom listed below, please mark with an X the box that best describes the worst severity of each symptom during the past 24 hours. Please be sure to answer each question.

	None	Mild	Moderate	Severe	Very Severe
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	☐	☐	☐	☐	☐
2. Not able to finish a normal-sized meal (for a healthy person)	☐	☐	☐	☐	☐
3. Feeling excessively full after meals.	☐	☐	☐	☐	☐
4. Upper abdominal pain (above the navel).	☐	☐	☐	☐	☐
5. Bloating (feeling like you need to loosen your clothes)	☐	☐	☐	☐	☐

The next question asks you to record the number of times vomiting occurred in the last 24 hours. Please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero, if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited three times during the day, record three. If you vomited three times, whether it was during the same trip to the bathroom or three separate trips, record three as the number of episodes of vomiting.

6. During the past 24 hours, how many episodes of vomiting did you have? ____

	None	Mild	Moderate	Severe	Very Severe
7. In thinking about your gastroparesis disorder, what was the overall severity of your gastroparesis symptoms today (during the past 24 hours)?	☐	☐	☐	☐	☐

Appendix L. FDA MedWatch Form

Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

FDA USE ONLY

Triage unit sequence #

FDA Rec. Date

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. **Patient Identifier** — In Confidence

2. **Age** ☐ Year(s) ☐ Month(s) ☐ Week(s) ☐ Days(s)
or Date of Birth *(e.g., 08 Feb 1925)* __ __ – _ _ _ – _ _ _ _

3. **Sex** ☐ Female ☐ Male

4. **Weight** ☐ lb ☐ kg

5.a. **Ethnicity** *(Check single best answer)*
☐ Hispanic/Latino
☐ Not Hispanic/Latino

5.b. **Race** *(Check all that apply)*
☐ Asian ☐ American Indian or Alaskan Native
☐ Black or African American ☐ White
☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

1. **Check all that apply**
☐ **Adverse Event** ☐ **Product Problem** *(e.g., defects/malfunctions)*
☐ **Product Use Error** ☐ **Problem with Different Manufacturer of Same Medicine**

2. **Outcome Attributed to Adverse Event** *(Check all that apply)*
☐ Death *Include date (dd-mmm-yyyy):* __ __ – _ _ _ – _ _ _ _
☐ Life-threatening ☐ Disability or Permanent Damage
☐ Hospitalization – initial or prolonged ☐ Congenital Anomaly/Birth Defects
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. **Date of Event** *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _

4. **Date of this Report** *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _

5. **Describe Event, Problem or Product Use Error**

(Continue on page 3)

6. **Relevant Tests/Laboratory Data, Including Dates**

(Continue on page 3)

7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)*

(Continue on page 3)

C. PRODUCT AVAILABILITY

2. **Product Available for Evaluation?** *(Do not send product to FDA)*
☐ Yes ☐ No ☐ Returned to Manufacturer on *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _

D. SUSPECT PRODUCTS

1. **Name, Manufacturer/Compounder, Strength** *(from product label)*

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

3. **Dose or Amount** / **Frequency** / **Route**
#1
#2

4. **Dates of Use** *(From/To for each) (If unknown, give duration, or best estimate) (dd-mmm-yyyy)*
#1
#2

5. **Diagnosis or Reason for Use** *(indication)*
#1
#2

6. **Is the Product Compounded?**
#1 ☐ Yes ☐ No
#2 ☐ Yes ☐ No

7. **Is the Product Over-the-Counter?**
#1 ☐ Yes ☐ No
#2 ☐ Yes ☐ No

8. **Expiration Date** *(dd-mmm-yyyy)*
#1 __ __ – _ _ _ – _ _ _ _ | #2 __ __ – _ _ _ – _ _ _ _

9. **Event Abated After Use Stopped or Dose Reduced?**
#1 ☐ Yes ☐ No ☐ Doesn't apply
#2 ☐ Yes ☐ No ☐ Doesn't apply

10. **Event Reappeared After Reintroduction?**
#1 ☐ Yes ☐ No ☐ Doesn't apply
#2 ☐ Yes ☐ No ☐ Doesn't apply

E. SUSPECT MEDICAL DEVICE

1. **Brand Name**

2. **Common Device Name** | 2b. **Procode**

3. **Manufacturer Name, City and State**

4. **Model #**	**Lot #**	5. **Operator of Device** ☐ Health Professional ☐ Lay User/Patient ☐ Other
Catalog #	**Expiration Date** *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _	
Serial #	**Unique Identifier (UDI) #**	

6. **If Implanted, Give Date** *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _

7. **If Explanted, Give Date** *(dd-mmm-yyyy)* __ __ – _ _ _ – _ _ _ _

8. **Is this a single-use device that was reprocessed and reused on a patient?** ☐ Yes ☐ No

9. **If Yes to Item 8, Enter Name and Address of Reprocessor**

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates *(Exclude treatment of event)*

(Continue on page 3)

G. REPORTER *(See confidentiality section on back)*

1. **Name and Address**
Last Name: | First Name:
Address:
City: | State/Province/Region:
Country: | ZIP/Postal Code:
Phone #: | Email:

2. **Health Professional?** ☐ Yes ☐ No

3. **Occupation**

4. **Also Reported to:**
☐ Manufacturer/ Compounder
☐ User Facility
☐ Distributor/Importer

5. **If you do NOT want your identity disclosed to the manufacturer, please mark this box:** ☐

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/15) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Food *(including beverages and ingredients added to foods)*

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

Fold Here

Fold Here

The information in this box applies only to requirements of the Paperwork Reduction Act of 1995

The burden time for this collection of information has been estimated to average 40 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed, and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please DO NOT RETURN this form to the PRA Staff e-mail to the left.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (10/15) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

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MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

FORM FDA 3500 (10/15) *(continued)*

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

Page 3 of 3

Back to Form

B.5. **Describe Event or Problem** *(continued)*

Back to Form

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Back to Form

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Back to Form

F. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (continued)*