AURORA HEALTH CARE, INC.

PROTOCOL TITLE: Pilot study for the efficacy and tolerability of Senokot-S® in the treatment of diabetic gastroparesis

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This protocol was designed and developed by Aurora Healthcare, Inc. It is intended to be used only in conjunction with institution-specific IRB approval for study entry.

I. Background and Significance

Diabetic gastroparesis can be a difficult-to-treat complication of longstanding diabetes that can significantly compromise quality of life in those affected. Today there is only one medication approved by the FDA for the indication of diabetic gastroparesis and it has received a black box warning due to potential for severe neurological side effects. There are other medications that have found some success in the treatment of diabetic gastroparesis, but they also have the potential for serious side effects, and some are only available through a special use program.[1]

II. Specific Aim

The aim of the study is to evaluate the efficacy of the stimulant laxative Senokot-S® for the treatment of diabetic gastroparesis. Senokot-S, and its metabolites, are thought to produce peristalsis, drive intra-luminal fluid and electrolyte shifts, and have an irritant effect on the gut mucosa[2,3]. These complex physiologic mechanisms appear may sufficiently promote stomach emptying, and thereby reduce or eliminate the severity of gastroparesis symptoms. In this open label study, participants will be randomized into high and low dose groups to assess for ideal dosing and tolerability. It is the overall goal of this study to select the most promising dose-strength for the treatment of mild through severe gastroparesis.

(c) Study End Points

a. Primary Endpoint

i. Modified GCSI-DD: Subjects will complete the modified Gastroparesis Cardinal Symptom Index-Daily Diary (mGCSI-DD)[4,5]. The mGCSI-DD is a validated patient reported outcome (PRO) instrument with excellent test-retest reliability, and will be used as the primary instrument to assess for efficacy in this study.

ii. Questions on the mGCSI-DD are a 6-point Likert scale from 0 (none) to very severe (5) that address: nausea, retching, vomiting, stomach fullness, ability to finish a normal-sized meal, feeling excessively full after meals, loss of appetite, bloating, external assessment of stomach size, upper abdominal pain or discomfort.

b. Secondary Endpoint

i. Breakthrough medication use: Defined as the change in the frequency of use of breakthrough medication, which is the medication that has been previously prescribed on an as-needed basis to manage symptoms.

Any change in frequency of use of breakthrough medications will be used as a secondary endpoint to assess for efficacy in the study.

ii. Bowel habits: Subjects will self report bowel habits during the baseline week and through the study period on the same questionnaire form. Since Senokot-S functions primarily as a mild bowel stimulant any significant change in bowel habits will help to assess for tolerability in this study.

IV. Study Design

The Phase II study design will be an open label, pre- and post-treatment assessment, prospective study. Sixty (60) study participants will be recruited over a 5-month period at a single site. Participants will be randomized into two treatment groups, a high- and low-dose, and will take medication dosed orally, twice daily or once daily at night.

V. Experimental Design, Methods, and Study Procedures

a. Initial Identification of Potential Study Subjects Gastroenterologists who have agreed to refer their patient with diabetic gastroparesis for this study will make the initial contact with those patient (study inclusion/exclusion criteria will be provided to these physicians for ready reference). If the patient is interested in participating in the study the gastroenterologists will secure the patient's verbal permission to provide their name and contact information (phone or e-mail) to Dr. Gose or another member of the study team. The study team member will contact the patient and arrange a time to meet with them to explain the study and to answer any questions the potential subject may have.

b. **Screening Visit** The screening visit will include reviewing the participants' complete medical history after reviewing and obtaining informed consent. Data from the participant's medical history will be abstracted from the electronic medical record (EMR) and will be securely stored with other study-related data. Participants will be given the mGCSI-DD questionnaire and instructed on its use. At this visit participants will start recording their week of baseline scores by filling out a separate mGCSI-DD questionnaire and Breakthrough Medication Use and Bowel Habits documentation form daily.

c. **Visit 1** will occur 1 week after the screening visit. Participants will return with their mGCSI-DD baseline week of scores. They will be sequentially randomized (1:1) into either the high (8.6/50mg of senna/docusate taken by mouth twice daily) or low (8.6/50mg of senna/docusate taken by mouth once every night) dose study group. To reduce potential subject bias and placebo effect, participants will not be informed as to which dose of study medication they are randomized. They will be given their study medication and their 28-day mGCSI-DD questionnaire sheets, along with a pre-printed return envelope for use after completing their month of treatment in the study. They will be instructed to decrease use of any previously prescribed breakthrough medication as can safely be tolerated. Examples of these medication may include prokinetics such as Reglan (metoclopramide), erythromycin, or domperidone; anti-emtics such as Zofran (ondansetron), or Compazine (prochloperazine); or analgesics such as tramadol,

hydrocodone, or oxycodone. They will also be instructed to resume any breakthrough medication use as previously prescribed at the completion of the study and to continue routine follow ups with their care providers.

Subjects will be instructed to immediately contact the Principal Investigator if they experience episodes of significant diarrhea or rectal bleeding.

Participants may be notified by phone at the end of their study period to verify data or request missing data.

VI. Risks

Senokot-S side effects. Known side effects of Senokot-S include diarrhea, nausea or vomiting, stomach pain, rectal bleeding, gas, abdominal bloating, and potential for allergic reaction such as skin rash. There have been safety concerns in the past about potential complications from long term use of stimulant laxatives like Senokot-S, such as cathartic colon, increased incidence of colorectal cancer, and liver disease. Several recent studies and reviews refute those previous conclusions and suggest long-term use of mild stimulant laxatives is likely safe when needed[3,6,7]. Senokot-S is listed as pregnancy category C by the FDA.
Women with child bearing potential will be required to use an effective form of birth control while participating in this study.

Ineffective treatment of diabetic gastroparesis. Since this medication has not yet been studied in the treatment of diabetic gastroparesis it is possible that symptoms of the disorder may worsen. The common symptoms of diabetic gastroparesis include nausea, vomiting, postprandial fullness, early satiety, and abdominal pain.

Loss of confidentiality. It is expected that this risk will be low because of numerous safeguards that will be in place, including standard data management procedures with Aurora Health Care.

VII. Benefits

A successful outcome in the proposed study will have immediate implications by reducing the symptoms of diabetic gastroparesis. Such a result will address the significant unmet need by providing a safe, inexpensive pharmacological therapy for a difficult to treat chronic disorder. These findings would allow patients to reduce or eliminate intake of the only FDA-approved therapeutic medication, Reglan®, which has a black box warning and unfavorable side-effect profile. These known potential benefits are highly likely to outweigh the potential risks of the intervention in this study.

VIII. Study Population

Inclusion Criteria:

- Age 18-75 years, male and non-pregnant, non-lactating females
- Diagnosis of type 1 or type 2 diabetes mellitus
- Clinical diagnosis of diabetic gastroparesis

Exclusion Criteria:

- Diagnosed idiopathic gastroparesis
- A history or inflammatory bowel disease, such as Crohn's disease or ulcerative colitis
- A history of bowel obstruction, current unexplained abdominal pain, or undiagnosed rectal bleeding
- Gastrointestinal cancer
- Any active cancer
- Prior gastric surgery
- End-stage heart disease, liver disease, lung disease
- Known or suspected drug abuse
- Any condition requiring use of daily narcotics
- Concurrent usage of mineral oil or products containing mineral oil
- Current or recent (within the last 3 months) usage of Senokot-S, docusate or senna

IX. Recruitment and Screening

Recruitment will occur through care provider referrals. Clinicians will be notified of the study through paper advertisement and posters. Initial screening will be done over the phone or through e-mail at the time of referral and will include a medical record review. Final screening and informed consent will be completed during the formal in person screening visit between the participant and research staff and is expected to take about one to two hours.

X. Privacy Plan

Patients will initially be notified of the potential to be in a research study by a current caregiver. If the patient is agreeable to consideration for the study the research team will be contacted by phone or through e-mail by the clinician with the patient's contact information. The patient will then be contacted by a member of the research team via an institution-based phone or EMR e-mail (based on the patient's preference) for initial screening and to set up a clinic visit for final screening and informed consent.

XI. Data Collection

The data to be collected will include a complete medical history of the participant, mGCSI-DD score forms, medication usage and bowel habits forms. Data will not be shared with any outside institutions.

This research study plans to store and manage the subject lists, demographic information, validated questionnaire, study and breakthrough medication use, and bowel habits datasets in REDCap Cloud, a secure electronic data capture application that is based on Vanderbilt University's REDCap application. Flexible for a variety of types of research, REDCap Cloud provides an intuitive data-entry interface for end users into study-specific data collection forms associated with study events. The application includes real time validation rules and query management, audit trails, and the automated export of study data into statistical programs. The REDCap Cloud platform is compliant with GCP predicate rule requirements and US FDA 21

CFR Part 11 pertaining to the use of electronic records and signatures. Aurora Health Care, Inc. has executed an agreement for use of the application with nearly all research studies conducted at Aurora.

Access to data housed in REDCap Cloud and associated with this research study will be limited to those individuals listed on the IRB approved research study, as well as caregivers from Research Analytics for administrative reasons. Study team members access to the system and the data itself will be limited in accordance with need (i.e., biostatisticians may be limited to simply export the dataset to statistical tools, research coordinators may be limited to entering data, etc.). Overall, limiting access to study team members by need should reduce the risk of accidental disclosure and breach of confidentiality. However, using a cloud-based application may incidentally raise the risk of a breach in confidentiality, and, therefore, Aurora Health Care, Inc. has negotiated strong protections with the vendor in the event of a breach of confidentiality.

XII. Statistical Plan

All category and continuous variables will be described using appropriate descriptive statistics such as frequency, percentage for category variables and mean, standard deviation, median, and range for continuous variables. Pre and post outcomes variables for two groups of patients in the experimental groups will be compared using appropriate parametric and/or non parametric statistical tests. For all statistical tests an alpha level of 0.05 will be used and all statistical analysis will be carried out using SAS version 9.4, SAS Institute, Cary, NC.

XIII. Monitoring Plan

Data monitoring, safety monitoring, and statistical analysis will be done through the research office and principal investigator.

Participants can stop the study at any time for any reason and can resume previous treatments whenever needed. Stopping points will be at the end of the 5 month study period or if a negative trend in mGCSI-DD post-treatment scores is observed.

XIV. Regulatory Requirements

The investigators and all key personnel agree to abide by the determinations of the Aurora IRB, including obtaining documented informed consent prior to inclusion of any individual in this research study. The investigators and all key personnel will comply with reporting requirements as outlined in the Aurora IRB Standard Operating Procedures (SOPs). In addition, investigators will permit access for on-site monitoring by representatives of the Aurora IRB, the Aurora Research Institute Investigator-Initiated Research unit, and the Aurora Research Institute Quality Improvement Program.

XV. References

1 Camilleri, M., Bharucha, A. E. & Farrugia, G. Epidemiology, mechanisms, and management of diabetic gastroparesis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* **9**, 5-12; quiz e17, doi:10.1016/j.cgh.2010.09.022 (2011).

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3 Morales, M. A., Hernandez, D., Bustamante, S., Bachiller, I. & Rojas, A. Is senna laxative use associated to cathartic colon, genotoxicity, or carcinogenicity? *Journal of toxicology* **2009**, 287247, doi:10.1155/2009/287247 (2009).

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