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CLINICAL STUDY PROTOCOL: HTX-100-403

Protocol Title:	A Phase 4, Open-Label Safety Study of Repeat Doses of SUSTOL in Adult Subjects Receiving Chemotherapy
Brief Title:	Phase 4, Open-Label Safety Study of SUSTOL
Test Product:	SUSTOL® (granisetron) extended-release injection, for subcutaneous use
Phase of Development:	4
Sponsor:	Heron Therapeutics, Inc. 4242 Campus Point Court, Suite 200 San Diego, CA 92121 1-858-251-4400
Medical Monitor:	[redacted]
Medical Project Leader:	[redacted]
Protocol Version:	Version 1 23 August 2021

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SPONSOR SIGNATURE

Protocol Title:	A Phase 4, Open-Label Safety Study of Repeat Doses of SUSTOL in Adult Subjects Receiving Chemotherapy
Protocol Number:	HTX-100-403

This protocol Version 1 has been reviewed and approved by the Sponsor.

The electronic signature is appended.

[redacted]

INVESTIGATOR AGREEMENT

CLINICAL STUDY PROTOCOL: HTX-100-403

TITLE: A Phase 4, Open-Label Safety Study of Repeat Doses of SUSTOL in Adult Subjects Receiving Chemotherapy

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. I will conduct the study as outlined herein.

I will provide copies of the protocol, the approved local label, and all other information on the study drugs and study devices that are furnished to me by the Sponsor to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the test product and the conduct of the study.

I agree to keep records on all subject information (ie, medical records, source documents, case report forms, and informed consent statements), study drug shipment and return forms, and all other information collected during the study in accordance with local regulations and national Good Clinical Practice (GCP) regulations and guidelines.

Principal Investigator: _____

Address: _____

Signature: _____

Date (DD Month YYYY): _____

PROTOCOL SYNOPSIS

NAME OF SPONSOR:	Heron Therapeutics, Inc.
NAME OF TEST PRODUCT:	SUSTOL® (granisetron) extended-release injection, for subcutaneous use
NAME OF ACTIVE INGREDIENT:	granisetron
PROTOCOL NUMBER:	HTX-100-403
PHASE OF DEVELOPMENT:	4
PROTOCOL TITLE: A Phase 4, Open-Label Safety Study of Repeat Doses of SUSTOL in Adult Subjects Receiving Chemotherapy	
STUDY SITES: Up to 25 sites in the United States (US).	
STUDY OBJECTIVES: Primary: To characterize the potential impact of subject-reported injection-site reactions (ISRs) on activities of daily living (ADL) in adult subjects with cancer administered SUSTOL.	
BACKGROUND AND RATIONALE FOR THE STUDY: SUSTOL (granisetron) extended-release injection, for subcutaneous (SC) use, is a 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist (RA) approved by the US Food and Drug Administration (FDA) and is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. A total of 2,226 subjects were exposed to SUSTOL in the 10 studies that compose the clinical development program. Of these, 1,131 subjects with cancer received the SUSTOL 10 mg recommended dose in the Phase 2 and Phase 3 studies. ISRs were the most common adverse reactions reported in SUSTOL-treated patients following a single dose of SUSTOL 10 mg in 2 randomized, active-controlled Phase 3 studies. ISRs occurred in 37% (175/468) of patients in the initial Phase 3 study, Cycle 1 only, and 62% (281/456) of patients in the second Phase 3 study. The higher proportion of subjects with ISR adverse reactions in the second Phase 3 study was likely attributable to the use of a subject daily diary in addition to Investigator reporting, whereas in the initial Phase 3 study, ISRs were reported by the Investigator only. The ISR manifestations included pain, erythema, mass/nodule, swelling/induration, and bleeding. Most ISRs were mild-to-moderate in severity in both studies. Serious ISRs were reported in 2 subjects (1 event each of injection site hemorrhage and injection site infection). Discontinuation due to ISRs (pain and erythema) occurred in 1 subject in the initial Phase 3 study. Overall, data collected during clinical development and during postmarketing surveillance in the US show no evidence of an increased risk of serious ISRs associated with the use of SUSTOL. The purpose of this study is to characterize the potential impact of subject-reported ISRs following injection of SUSTOL on ADL, including physical, social, and work/household activities.	
METHODOLOGY: This is a repeat-dose, single-arm, open-label study that will evaluate the potential impact of subject-reported ISRs on ADL in adult subjects receiving SUSTOL for prevention of chemotherapy-induced nausea and vomiting (CINV) for up to 4 sequential cycles of chemotherapy (MEC or AC combination regimen). Subjects will be screened for study eligibility up to 21 days prior to receiving the first dose of SUSTOL. Subjects who meet eligibility requirements will be enrolled and receive SUSTOL (administered 10 mg SC) per the US prescribing information (USPI) on Cycle 1 Day 1, and on Day 1	

of up to 3 subsequent cycles. SUSTOL will be administered in combination with dexamethasone at least 30 minutes before the initiation of chemotherapy.

The occurrence, severity, and potential impact of subject-reported ISRs on ADL will be evaluated using an electronic patient-reported outcome (ePRO) Daily Injection Site Reaction Assessment (DISRA). After each SUSTOL injection, subjects will complete the ePRO DISRA daily for 14 days, whether an ISR is observed or not. Spontaneous data collection will be allowed in the ePRO DISRA for any ISRs that begin after 14 days. If an ISR is reported, the subject will complete the ePRO DISRA daily until the ISR resolves, with resolution defined as no symptoms reported.

Using the ISR categories and ADL domains listed below, the ePRO DISRA will collect the presence or absence of ISRs, the severity of each ISR (0-10 scale, with 0 indicating no pain/bleeding/itching/or swelling, and 10 indicating worst possible pain/bleeding/itching/or swelling), and the perceived impact of the ISR on the subject's ADL (0-10 scale, with 0 indicating no interference and 10 indicating extreme interference) using the following ISR categories and ADL domains:

ISRs:

- Pain.
- Bleeding.
- Itching.
- Swelling.

ADL domains:

- Physical.
- Social.
- Work/household.

Subjects will return to the study site on Day 8 and Day 15 after each SUSTOL injection for safety assessments. At each site visit, site staff will use the clinician-reported outcome (ClinRO) Clinical Assessment of Injection Site Reactions (CAISR) to assess the following:

The presence or absence of any ISR-related:

- Nodule.
- Erythema.
- Ecchymosis.
- Hematoma.
- Infection.
- Ulceration.
- Necrosis.

The size of:

- Nodules.
- Erythema.
- Ecchymosis.

- Hematomas.

As part of the ClinRO CAISR, ISR-associated healthcare resource utilization (eg, emergency room [ER], urgent care, unscheduled clinic visit) and intervention (surgical or other) will be recorded. All ClinRO ISRs reported will be followed at weekly unscheduled visits through resolution (defined as no signs observed) or until deemed no longer clinically significant in the opinion of the Investigator. All serious adverse events (SAEs) and all treatment-emergent adverse events (TEAEs) that led to discontinuation of SUSTOL treatment or withdrawal from the study will be collected from signing of the informed consent form (ICF) through the Final Follow-Up Visit, which will occur 28 days after the last SUSTOL dose.

NUMBER OF PLANNED SUBJECTS: Approximately 300 subjects will be enrolled and administered SUSTOL.

STUDY POPULATION:

Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is able to provide voluntary, written, informed consent to participate in this study and must be able to fully understand the study requirements.
2. Is willing and able to comply with all testing and requirements defined in the protocol.
3. Is 18 years of age or older at Cycle 1 Day 1.
4. Has cancer, is scheduled to receive MEC or AC regimen as defined by antiemetic treatment guidelines (Hesketh 2020) (National Comprehensive Care Network [NCCN] *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]) is anticipated to require at least 4 cycles of chemotherapy, and is prescribed SUSTOL for CINV prevention.
5. Is entering the first cycle of their current chemotherapy regimen.
6. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Has a life expectancy of >6 months.
8. Is able to receive standardized doses of dexamethasone as required in SUSTOL USPI for the prevention of emesis.
9. Subjects of childbearing potential (defined as premenopausal and capable of becoming pregnant) must meet all of the following criteria:
    a. Is not pregnant and not planning on becoming pregnant during the study. Subjects of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before SUSTOL administration.
    b. Not lactating.
    c. Is practicing abstinence; or is in a monogamous relationship with a partner who cannot impregnate the subject (eg, is surgically sterile); or agrees to use double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities in the event of sexual activity from the Screening Visit through 30 days after the last dose of SUSTOL.

Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Has hypersensitivity to granisetron, any component of SUSTOL, or any other 5-HT_3 RAs.

2. Has received SUSTOL previously.
3. Has severe renal impairment (creatinine clearance [CL_{cr}] <30 mL/min).
4. Has symptomatic primary or metastatic central nervous system (CNS) disease.
5. Has participated in an interventional clinical study within 30 days of Cycle 1 Day 1.
6. In the opinion of the Investigator, has other physiological, psychological, behavioral, and/or other medical conditions that would interfere with participation in a clinical study, such as:
   a. Clinically significant electrolyte disturbance, including but not limited to: uncorrected hypokalemia/hyperkalemia, hypomagnesemia, or hypocalcemia.
   b. Clinically significant cardiac disease including but not limited to: uncontrolled angina, myocardial ischemia or infarction within 6 months, congestive heart failure, myocarditis, or dyspnea on exertion.

STUDY DRUG: Study drug is defined as SUSTOL (test product).

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION:

SUSTOL 10 mg will be administered subcutaneously on Day 1 of each chemotherapy cycle. SUSTOL should not be given not more frequently than once every 7 days. In subjects with moderate renal impairment (CL_{cr} of 30 to 59 mL/min), SUSTOL should not be administered more frequently than once every 14 days. SUSTOL will be supplied by the Sponsor and administered per the approved SUSTOL USPI.

CONTROL PRODUCT, DOSE, AND MODE OF ADMINISTRATION: Not applicable.

PROTOCOL-SPECIFIED MEDICATION(S):

Other CINV Prevention Medications:

CINV prevention may include dexamethasone (intravenous [IV] or oral), neurokinin-1 (NK_1) RAs, and olanzapine, in accordance with antiemetic treatment guidelines (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]).

For subjects receiving MEC, the recommended dexamethasone dosage is 8 mg IV on Day 1. For subjects receiving AC combination chemotherapy regimens, the recommended dexamethasone dosage is 20 mg IV on Day 1, followed by 8 mg orally, twice a day, on Days 2, 3 and 4. If SUSTOL is administered with an NK_1 RA, see the prescribing information of the NK_1 RA for the recommended dexamethasone dosage.

For subjects who cannot continue to take dexamethasone after the first cycle, an NK_1 RA must be used. If SUSTOL is administered with dexamethasone and an NK_1 RA, review the prescribing information of the NK_1 RA for the recommended dexamethasone dosage.

The Sponsor will not supply the other protocol-specified medications.

DURATION OF TREATMENT: The total study duration is anticipated to be approximately 3 years.

The total duration of study participation for each subject from Screening through the Final Follow-Up Visit will be approximately 20 weeks.

STUDY ASSESSMENTS:

Safety Assessments

- ePRO DISRA.
- ClinRO CAISR.

- TEAEs (evaluated by the clinician using the Common Terminology Criteria for Adverse Events [CTCAE] toxicity grade categories) that:
  - Led to discontinuation of SUSTOL treatment.
  - Led to withdrawal from the study.
- SAEs (evaluated by the clinician using the CTCAE categories).

STUDY ENDPOINTS:

Primary Endpoint

- Proportion of subjects with a subject-reported ISR composite dichotomous (0 or 1) score of 1 defined as follows:
  - ISR of pain, itching, or swelling with a severity ≥7 **AND** ADL impact of ≥7 in any ADL domain (physical, social, work/household).

    OR
  - ISR of bleeding with ADL impact of ≥7 in any ADL domain (physical, social, work/household), **AND** 1 of the following:
    - severity ≥7 and 4 to 6 bandage changes per day **OR**
    - ≥7 bandage changes per day **OR**
    - urgent care/ER visit

Other Endpoints

- Proportions of subjects with ISR-related SAEs and ISR-related TEAEs that led to discontinuation of SUSTOL treatment or withdrawal from the study.
- Proportions of subjects with SAEs and TEAEs that led to discontinuation of SUSTOL treatment or withdrawal from the study, of any cause.
- Proportions of subjects with ISRs that led to delay of chemotherapy treatment.
- Proportion of subjects with a subject-reported ISR for each ISR category by maximum severity, by cycle and overall.
- Proportion of subjects with a subject-reported ISR by highest level of impact on each ADL domain, by cycle and overall.
- Proportion of subjects with an ISR requiring healthcare utilization.
- Proportion of subjects with an ISR requiring intervention (surgical, other).
- Mean duration (days) of each subject-reported ISR, by cycle and overall.
- Mean maximum size of each clinician-reported ISR, by cycle and overall.
- Proportion of subjects with a subject-reported ISR pain severity ≥7 AND presence of each or any of ClinRO CAISR signs (nodule, hematoma, erythema, ecchymosis, infection, ulceration, or necrosis).

STATISTICAL METHODS:

Determination of Sample Size

Approximately 300 subjects will be enrolled, with approximately 100 subjects anticipated to experience an ISR that may potentially impact subject ADL.

Safety Analyses

Safety will be evaluated by analysis of the ePRO DISRA and ClinRO CAISR and by the incidence, severity, and relationship to SUSTOL of specific adverse events (AEs) (SAEs and TEAEs resulting in study or SUSTOL discontinuation). Continuous data will be presented using descriptive statistics: number of subjects, mean, SD, median, minimum, and maximum. Categorical data will be summarized by the number and percent of subjects.

No formal interim analyses are planned.

SCHEDULE OF EVENTS

	Screening	Treatment Cycle (Repeat for up to 4 cycles)			Final Follow-Up Visit[c]	ET Visit[d]
		Baseline Day 1 Visit	Day 8 Visit[a,b]	Day 15 Visit[b]		
Assessment **Time Window**	**≤21 days**		**±1 day**	**±1 day**		
Obtain informed consent	X					
Serum hCG test[e]	X					
Urine pregnancy test[e,f]		X				
Assess/confirm eligibility	X	X[g]				
Medical history	X					
Demographics	X					
ECOG performance status[h]	X	X			X	X
Physical examination	X					
Vital signs[i]	X	X				
Hematology and serum chemistry tests	X	X[j]				
Administer SUSTOL[k]		X				
Administer chemotherapy		X				
SAEs and specified TEAEs[l]	- - -

Abbreviations: CAISR, Clinical Assessment of Injection Site Reactions; ClinRO, clinician-reported outcome; DISRA, Daily Injection Site Reaction Assessment; eCL_{cr}, estimated creatinine clearance; ECOG, Eastern Cooperative Oncology Group; ePRO electronic patient-reported outcome; ET, early termination; hCG, human chorionic gonadotropin; ISR, injection-site reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] If an ISR is noted in the ClinRO CAISR, Day 8 assessments are to be repeated weekly as an unscheduled visit until the ISR is resolved or until deemed no longer clinically significant in the opinion of the Investigator. During clinic visits, it is recommended that the ePRO DISRA is reviewed by site staff before the completion of the ClinRO CAISR.

[b] For subjects receiving chemotherapy regimens with a cycle of 7 days, the Day 8 and Day 15 assessments will be conducted on Day 1 of the next cycle(s) prior to receiving chemotherapy, and will evaluate each injection site until 14 days have elapsed after each SUSTOL injection.

[c] 28 days after the last SUSTOL dose.

[d] Subjects who withdraw from the study early will be asked to complete ET procedures.

[e] Subject of childbearing potential only.

[f] Perform urine pregnancy test and confirm negative prior to administering SUSTOL at Day 1 of each cycle.

[g] Cycle 1 only for assessments other than pregnancy test. Perform assessments prior to administering SUSTOL.

[h] It is recommended that the ECOG assessment be completed prior to SUSTOL administration.

[i] It is recommended that vital signs should be collected prior to, or at least 10 minutes after, clinical laboratory tests.

[j] On Day 1 of each cycle, assess eCL_{cr} only using Cockcroft-Gault formula.

[k] The start of study drug administration will be considered Time 0 for all safety assessments.

[l] Assessments for SAEs and TEAEs that lead to discontinuation of SUSTOL treatment or withdrawal from the study will be collected from signing of the informed consent form (ICF) through the Final Follow-Up Visit.

[m] Cycle 1 only.

[n] Subject is to record the presence or absence of ISRs daily for 14 days after each SUSTOL administration whether an ISR is observed or not. Spontaneous data collection will be allowed in the ePRO DISRA for any ISRs that begin after 14 days. If an ISR occurs, subject is to record the ISR(s) in ePRO DISRA daily until resolution.

[o] Record all concomitant medications taken from the time the subject signs the ICF through the Final Follow-Up Visit.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
5-HT_3	5-hydroxytryptamine 3
AC	Anthracycline and cyclophosphamide
ADL	Activities of daily living
AE	Adverse event
ASCO	American Society of Clinical Oncology
CAISR	Clinical Assessment of Injection Site Reactions
CFR	Code of Federal Regulations
CINV	Chemotherapy-induced nausea and vomiting
CL_{cr}	Creatinine clearance
ClinRO	Clinician-reported outcomes
CV	Cardiovascular
CYP	Cytochrome P450
DISRA	Daily Injection Site Reaction Assessment
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ePRO	Electronic patient-reported outcome
ER	Emergency room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEC	Highly emetogenic chemotherapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFU	Instructions for Use
ISR	Injection-site reaction
IV	Intravenous(ly)
MEC	Moderately emetogenic chemotherapy
NCCN	National Comprehensive Care Network
NK_1	Neurokinin-1
RA	Receptor antagonist

Abbreviation	Definition
SAE	Serious adverse event
SC	Subcutaneous(ly)
TEAE	Treatment-emergent adverse event
US	United States
USPI	United States prescribing information

Note: Abbreviations defined in the text but not used again in the text are not included in this List of Abbreviations. Abbreviations used only in a table or figure are also excluded from this List of Abbreviations; they are defined in the table or figure footnotes.

1. INTRODUCTION

1.1. Background Information and Study Rationale

Chemotherapy-induced nausea and vomiting (CINV) is a common and debilitating side effect of chemotherapy that can lead to a decreased quality of life and interfere with patients' ability to perform everyday activities (Feyer 2011; Haiderali 2011; Sommariva 2016). CINV can lead to the delay or discontinuation of chemotherapy, and to patient reluctance to eat or drink with resulting nutritional deficits (Van Laar 2015). Without prophylactic therapy, 70% to 80% of all patients receiving chemotherapy would experience CINV (Rangwala 2012).

The 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists (RAs) are the foundation of CINV prevention. To prevent CINV following highly emetogenic chemotherapy (HEC) including anthracycline and cyclophosphamide (AC) combination chemotherapy, antiemetic treatment guidelines from the American Society of Clinical Oncology (ASCO), the National Comprehensive Care Network (NCCN), and Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) recommend at least a 3-drug antiemetic regimen on the day of chemotherapy, which includes a 5-HT_3 RA, dexamethasone, and a neurokinin 1 (NK_1) RA (Hesketh 2017a; MASCC/ESMO 2016) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). The ASCO and NCCN antiemetic treatment guidelines recommended 5-HT_3 RAs for moderately emetogenic chemotherapy (MEC) or HEC include granisetron, ondansetron, palonosetron, and dolasetron (Hesketh 2017b) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). For MEC, antiemetic treatment guidelines vary across therapies; generally, a 2-drug regimen (5-HT_3 RA and dexamethasone) is recommended with or without an NK_1 RA in select patients (Hesketh 2017b; MASCC/ESMO 2016).

SUSTOL® (granisetron) extended-release injection, for subcutaneous (SC) use, is a 5-HT_3 RA that has been approved by the United States (US) Food and Drug Administration (FDA) and is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or AC combination chemotherapy regimens. While oral and intravenous (IV) formulations of granisetron and ondansetron historically have not demonstrated efficacy in the prevention of delayed-phase CINV (>24-120 hours), the efficacy benefit of SUSTOL in the prevention of CINV in both the acute and delayed phases in patients receiving MEC and HEC regimens was demonstrated in 2 large, randomized, double-blind, Phase 3 clinical studies (Raftopoulos 2015a; Raftopoulos 2015b; Schnadig 2016).

In the SUSTOL development program, a total of 2,226 subjects were exposed to SUSTOL in 10 studies. Of these, 1,131 subjects with cancer received the recommended dose (10 mg) of SUSTOL in the Phase 2 and Phase 3 studies. Injection-site reactions (ISRs) were the most common adverse reactions reported in SUSTOL-treated patients following a single dose of SUSTOL 10 mg in 2 randomized, active-controlled Phase 3 studies. ISRs occurred in 37% (175/468) of patients in the initial Phase 3 study, Cycle 1 only, and 62% (281/456) of patients in the second Phase 3 study. The higher proportion of subjects with ISR adverse reactions in the second Phase 3 study was likely attributable to the use of a subject daily diary (including self-grading of the ISR severity) in addition to Investigator reporting, whereas in the initial Phase 3 study, ISRs were reported by the Investigator only.

The ISR manifestations included pain, erythema, mass/nodule, swelling/induration, and bleeding. Most ISRs were mild-to-moderate in severity in both studies. Serious ISRs were reported in 2 subjects (1 event each of injection site hemorrhage and injection site infection). Discontinuation due to ISRs (pain and erythema) occurred in 1 subject in the initial Phase 3 study. Overall, data collected during clinical development and during postmarketing surveillance in the US show no evidence of an increased risk of serious ISRs associated with the use of SUSTOL.

The purpose of this study is to characterize the potential impact of subject-reported ISRs following injection of SUSTOL on activities of daily living (ADL), including physical, social, and work/household activities.

1.2. Rationale for Study Design, Doses, and Control Groups

This is a repeat-dose, single-arm, open-label study designed to characterize the potential impact of subject-reported ISRs on ADL in adult subjects with cancer administered SUSTOL for the prevention of CINV for up to 4 sequential cycles of chemotherapy (MEC or AC combination regimen). The open-label, uncontrolled study design was chosen to assess the impact of ISRs on ADL because no other CINV prevention product is approved for SC administration that would allow a comparison of ISRs.

This study will use standardized clinical outcome assessments (COAs) including both patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) assessments to evaluate the impact of ISRs on ADL. The rationale for using the electronic PRO (ePRO) Daily Injection Site Reaction Assessment (DISRA) is to enable daily assessment in a subject-friendly format, which would more reliably assess ISR-related symptoms and the impact on ADL, and minimize the recall bias that would occur if information were only collected during site visits. The ClinRO Clinical Assessment of Injection Site Reactions (CAISR) will be provided to ensure consistent collection of information on observed ISR signs objectively assessed by the clinician.

The recommended dosage, administration method, and timing of administration of SUSTOL follow the current US prescribing information (USPI) (SUSTOL USPI 2017).

The primary endpoint for this study is the proportion of subjects with a subject-reported ISR composite dichotomous (0 or 1) score of 1, defined as having an ISR of pain, itching, or swelling with a severity ≥7 and ADL impact of ≥7 in any ADL domain, or an ISR of bleeding with ADL impact of ≥7 in any ADL domain and 1 of the following: severity ≥7 and 4 to 6 bandage changes per day or ≥7 bandage changes per day or urgent care/emergency room (ER) visit. The rationale for this endpoint was that ISRs meeting this definition would constitute a substantial disruption of a person's ability to conduct normal life functions, and would be consistent with the goal of the study to characterize the potential impact of significant ISRs on ADL. The analyses of the other endpoints will further characterize the safety of SUSTOL treatment in this study population.

SUSTOL is indicated in combination with other antiemetics in adults for the prevention of CINV (SUSTOL USPI 2017), including dexamethasone (IV or oral), and NK_1 RAs. For patients receiving AC, antiemetic treatment guidelines recommend a 4-drug regimen of a 5-HT_3 RA (SUSTOL in this study), combined with an NK_1 RA, dexamethasone, and olanzapine (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). For

patients receiving MEC, NCCN antiemetic treatment guidelines recommend 2 options that include SUSTOL: a 3-drug regimen with an NK_1 RA, a 5-HT_3 RA (SUSTOL in this study), and dexamethasone; or a 2-drug regimen of a 5-HT_3 RA (SUSTOL in this study) and dexamethasone (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). Rescue medications for breakthrough CINV are allowed, if they are from a different drug class than those used for prophylaxis.

1.3. Potential Risks and Benefits

1.3.1. SUSTOL

The potential risks and benefits of SUSTOL (granisetron) extended-release injection, for subcutaneous use, are expected to be associated with those of its active ingredient, granisetron, and the delivery system. A summary based on the current prescribing information for SUSTOL for CINV (SUSTOL USPI 2017), including clinical study results and postmarketing experience, is presented in this section.

1.3.1.1. Potential Benefits

SUSTOL is a 5-HT_3 RA. It is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or AC combination chemotherapy regimens.

The efficacy of SUSTOL was demonstrated in two Phase 3 double-blind, randomized, active-controlled studies; one in adult patients treated with MEC and AC-based HEC (Raftopoulos 2015b; SUSTOL USPI 2017) and the other in adult patients treated with HEC (Schnadig 2017).

In the first study, 200 patients received SUSTOL 10 mg SC compared to 206 patients who received 0.25 mg palonosetron IV and 171 AC-based HEC patients received SUSTOL 10 mg SC compared to 156 AC-based HEC patients who received 0.25 mg palonosetron administered IV. All patients received dexamethasone. Complete response was defined as no emetic episodes and no use of rescue medication. Both comparisons in MEC and AC-based HEC patients met the criteria for non-inferiority for both MEC and AC-based HEC for the acute and the delay phases (a lower bound of the 95% CI was greater than -15%).

Table 1: Number and Percentage of Patients Who Achieved Complete Response With MEC or AC-based HEC

Complete Response	SUSTOL 10 mg SC N=200 n (%)	Palonosetron HCl 0.25 mg IV N=206 n (%)	Difference (95% CI) SUSTOL Minus Palonosetron
MEC			
Acute phase (0-24 hours)	166 (83)	183 (89)	-6 (-13, 1)
Delayed phase (>24-120 hours)	137 (69)	144 (70)	-1 (-10, 8)
Complete Response	**SUSTOL 10 mg SC N=171 n (%)**	**Palonosetron HCl 0.25 mg IV N=156 n(%)**	**Difference (95% CI) SUSTOL Minus Palonosetron**
AC-based HEC			
Acute phase (0-24 hours)	120 (70)	99 (64)	6 (-3, 17)
Delayed phase (>24-120 hours)	85 (50)	74 (47)	2 (-9, 13)

Abbreviations: AC, anthracycline and cyclophosphamide; HEC, highly emetogenic chemotherapy; IV, intravenous(ly); MEC, moderately emetogenic chemotherapy; SC, subcutaneous(ly).

In the second study in patients undergoing HEC, 450 patients received SUSTOL 10 mg SC compared to 452 patients who received ondansetron IV. All patients received fosaprepitant, an NK_1 RA, and dexamethasone. Complete response was observed in the late phase in 65% and 57% of HEC patients receiving SUSTOL and ondansetron, respectively (p=0.014).

1.3.1.2. Potential Risks

The safety of SUSTOL 10 mg SC was evaluated in the two Phase 3 studies, in which a total of 924 patients who were undergoing treatment with MEC or HEC received SUSTOL.

SUSTOL is contraindicated in patients with hypersensitivity to granisetron, any of the components of SUSTOL, or any other 5-HT_3 RA. The warnings and precautions in the USPI are ISRs (may occur 2 weeks or more after administration), including infection, bleeding, pain, nodules, swelling, and induration; gastrointestinal disorders; hypersensitivity reactions (may occur 7 days or more after administration); and serotonin syndrome (reported with 5-HT RAs alone but particularly with concomitant use of serotonergic drugs).

The most common adverse reactions (≥3%) following administration of SUSTOL are ISRs, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia, and gastroesophageal reflux. Postmarketing experience of other formulations of

granisetron include reports of bradycardia, chest pain, palpitations, and sick sinus syndrome (Schnadig 2017; SUSTOL USPI 2017).

1.3.1.2.1. Injection Site Reactions

ISRs following administration of SUSTOL occurred in 37% and 62% of patients (1 or more ISR) in Study 1 SUSTOL versus palonosetron (n=468) and Study 2 SUSTOL versus ondansetron (n=463), respectively, with the most common being bruising/hematoma, erythema/redness, mass/nodules, and tenderness/pain. In these 2 studies, 1 serious injection site infection occurred in a subject that had comorbid neutropenia who was hospitalized for an opportunistic skin infection, and recovered (SUSTOL USPI 2017).

Bruising and/or hematomas at the injection site occurred in 426 of 1,131 (38%) patients treated with SUSTOL 10 mg, with a median time to onset of 2 days. Bruising and/or hematomas with a delayed onset (onset 5 or more days following SUSTOL administration) were reported in 175 (15%) patients. Severe bruising or hematoma (eg, >4 cm bruise or hematoma) occurred in 3% of patients. Patients receiving concomitant anticoagulant and antiplatelet medications were at greater risk for severe injection site bruising and hematomas.

Injection site pain and tenderness from patient diaries in Study 2 SUSTOL versus ondansetron (Schnadig 2017), pain with or without tenderness at the injection site was reported by 91 of 456 (20%) patients treated with SUSTOL 10 mg, and an additional 50 of 456 (11%) patients reported tenderness without pain. Severe injection site pain (requiring narcotic pain control or affecting activities of daily living) were observed in 3 of 465 (0.7%) patients. Among all patients who reported pain and/or tenderness with SUSTOL 10 mg in clinical studies, the median duration was 5 days, and pain lasting longer than 7 days occurred in 6% of patients.

Nodules at the injection site occurred in 203 of 1,131 (18%) patients treated with SUSTOL 10 mg. Nodules persisted for a median of 15 days and 73 patients (6%) had nodules with durations longer than 21 days.

Bleeding at the injection site occurred in 4% patients treated with SUSTOL, with 1 patient requiring emergency management. Bleeding for longer than 5 days was reported in 1% of patients.

Infections at the injection site occurred in 0.4% of patients with cancer and 0.2% of healthy subjects in clinical trials. Infections had a median onset of 9 days (range 7 to 16 days) following SUSTOL administration. One patient who was neutropenic at the time of the infection was hospitalized. All patients with infection were treated with antibiotics and had complete resolution.

1.3.1.2.2. Gastrointestinal Disorders

In clinical program in adult patients, 20% of patients treated with SUSTOL 10 mg reported constipation compared to 13% to 15% of patients in the 5-HT_3 RA control arms. Hospitalization due to constipation or fecal impaction was reported in 0.3% of SUSTOL-treated patients.

SUSTOL may mask a progressive ileus and/or gastric distention. This should be particularly considered before use of SUSTOL in patients who have had recent abdominal surgery.

1.3.1.2.3. Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported in granisetron-treated patients who have exhibited hypersensitivity to other 5-HT_3 RAs.

Due to the extended-release properties of the SUSTOL polymer formulation, exposure to granisetron may continue for 5 to 7 days following administration. Hypersensitivity reactions may occur up to 7 days or longer following SUSTOL administration and may have an extended course.

1.3.1.2.4. Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 RAs. Most reports have been associated with concomitant use of serotonergic drugs (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and IV methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 RA alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 RA use occurred in a postanesthesia care unit or an infusion center.

For more information about the potential benefits and risks associated with SUSTOL, refer to the current prescribing information (SUSTOL USPI 2017).

1.3.2. Potential Risks Associated With Other Protocol-Specified Medications

Common, as well as uncommon but severe, adverse drug reactions that are associated with the other protocol-specified medications are listed below. The Investigator should refer to the respective package inserts for detailed information on risks associated with these medications.

1.3.2.1. Dexamethasone

Dexamethasone is not indicated but is part of recommendations for the prevention of CINV (Hesketh 2017b) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]).

Dexamethasone is contraindicated for systemic fungal infections and in patients hypersensitive to components of dexamethasone (Dexamethasone Sodium Phosphate USPI 2020).

Warnings include:

- Hypersensitivity and allergic-type reactions including anaphylaxis.
- Cardio-renal effects including elevation of blood pressure, sodium and water retention, and increased excretion of potassium.
- Endocrine effects including hypothalamic-pituitary adrenal axis suppression.
- Increased susceptibility to infections including fungal infections, latent pathogens, viral infections, and ophthalmic infections.

Precautions include:

- Use with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

- Acute myopathy has been observed in rare cases.
- Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations.

Adverse reaction include allergic reactions, cardiovascular (CV) effects (including cardiac arrest and cardiac arrhythmia), dermatologic effects (including impaired wound healing and thinning of skin), endocrine effects (including hyperglycemia and suppression of growth in children), fluid and electrolyte disturbances (including congestive heart failure and fluid retention), gastrointestinal effects (including elevated liver enzymes and peptic and intestinal perforations), metabolic effects (protein catabolism), musculoskeletal effects (including osteoporosis and vertebral compression fractures), neurological/psychiatric effects (including depression and other psychic disorders), ophthalmic effects (including glaucoma and cataracts), and other effects (including weight gain and abnormal fat deposits).

Refer to the dexamethasone product label for detailed safety information.

1.3.2.2. NK_1 Receptor Antagonists

1.3.2.2.1. Aprepitant and Fosaprepitant

Aprepitant and fosaprepitant are approved for the prevention of CINV. Aprepitant is available as capsules for oral administration (EMEND Oral USPI November 2019) and as an injectable emulsion for IV administration (CINVANTI USPI October 2019). Fosaprepitant is available as an injection for IV use (EMEND IV USPI 2020). Refer to the USPI or equivalent for full prescribing information.

IV aprepitant (CINVANTI®) and IV fosaprepitant (EMEND®) and oral aprepitant (EMEND) are contraindicated for known hypersensitivity to any component of the drug and concurrent use with pimozide.

Warnings and precautions include:

- Drug-drug interactions due to aprepitant's effect as a substrate, weak-to-moderate inhibitor and inducer of cytochrome P450 (CYP) 3A4.
- Hypersensitivity reactions including anaphylaxis (not a warning for oral aprepitant).
- Aprepitant and warfarin decreases international normalized ratio (INR).
- Reduced efficacy of hormonal contraceptives.

Adverse reactions for IV aprepitant (CINVANTI) reported in at least 2% of subjects were headache and fatigue.

Adverse reactions for IV fosaprepitant (EMEND) in at least 2% of subjects were fatigue, diarrhea, neutropenia, asthenia, anemia, peripheral neuropathy, leukopenia, dyspepsia, urinary tract infection, and pain in extremity.

Adverse reactions for oral aprepitant (EMEND) in at least 3% of subjects were fatigue, diarrhea, asthenia, dyspepsia, abdominal pain, hiccups, white blood cell count decreased, dehydration, and alanine aminotransferase increased.

Refer to the respective product labels for detailed safety information.

1.3.2.2.2. Rolapitant

Rolapitant is indicated in adults for prevention of delayed CINV (VARUBI USPI 2018).

Rolapitant is contraindicated for known hypersensitivity to any components of the drug including soybean oil and concurrent use with CYP2D6 substrates with narrow therapeutic index; for example, thioridazine and pimozide.

Warnings and precautions include:

- Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions.
- Increase of CYP2D6 substrates for at least 28 days after rolapitant administration.

Common adverse reactions to rolapitant in patients receiving cisplatin-based HEC greater than or equal to 3% and with incidence for rolapitant exceeding that of the control group include neutropenia, hiccups, and abdominal pain.

Common adverse reactions to rolapitant in patients receiving MEC and combination of AC greater than or equal to 3% and with incidence for rolapitant exceeding the control group include decreased appetite, neutropenia, dizziness, dyspepsia, urinary tract infection, stomatitis, and anemia.

Refer to the rolapitant product label for detailed safety information.

1.3.2.3. Olanzapine

Olanzapine is not indicated but is part of recommendations for the prevention of CINV (Hesketh 2017b) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]).

Olazapine increases the risk of death for elderly patients with dementia-related psychosis. Refer to the SYMBYAX USPI for use of olanzapine with fluoxetine (SYMBYAX USPI 2021).

Warning include increased risk for:

- Suicide.
- Neuroleptic malignant syndrome.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Metabolic changes including hyperglycemia and diabetes mellitus, dyslipidemia, and weight gain.
- Tardive dyskinesia.
- Orthostatic hypotension.
- Leukopenia, neutropenia, and agranulocytosis.
- Seizures.
- Potential for motor and cognitive impairment.
- Anticholinergic effects in subjects with urinary retention, prostatic hypertrophy, constipation, paralytic ileus, or related conditions.

- Hyperprolactinemia.

Precautions include:

- Exercise caution when used with fluoxetine, lithium, or valproate.
- Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment.

Common adverse reactions (>5% and greater than placebo) include postural hypotension, constipation, weight gain, dizziness, personality disorder, and akathisia.

In a Cochrane review with 14 randomized clinical trials including 1,917 patients treated with 5 mg to 10 mg olanzapine in CINV, there was unclear evidence for an olanzapine effect on serious adverse events (SAEs) and a possible increase in somnolence and fatigue (Sutherland 2018).

Refer to the olanzapine product label for detailed safety information.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to characterize the potential impact of subject-reported ISRs on ADL in adult subjects with cancer administered SUSTOL.

3. INVESTIGATIONAL PLAN AND ENDPOINTS

3.1. Description of the Study Design

3.1.1. Overall Study Design

This is a Phase 4, open-label safety study of SUSTOL in adult subjects with cancer receiving MEC or AC combination chemotherapy regimens.

Subjects will be screened for study eligibility up to 21 days prior to receiving the first dose of SUSTOL. Approximately 300 subjects will be enrolled. Subjects who meet eligibility requirements will be enrolled and receive SUSTOL (administered 10 mg SC) per the USPI (SUSTOL USPI 2017) on Cycle 1 Day 1, and on Day 1 of up to 3 subsequent cycles. SUSTOL will be administered in combination with dexamethasone at least 30 minutes before the initiation of chemotherapy.

Safety and other assessments will be conducted per the SCHEDULE OF EVENTS.

The occurrence, severity, and potential impact of subject-reported ISRs on ADL will be evaluated using an ePRO DISRA. During screening and again on Cycle 1 Day 1 prior to initial treatment, all subjects will be trained on the use of the ePRO DISRA. After each SUSTOL injection, subjects will complete the ePRO DISRA daily for 14 days, whether an ISR is observed or not. Spontaneous data collection will be allowed in the ePRO DISRA for any ISRs that begin after 14 days. If an ISR is reported, the subject will complete the ePRO DISRA daily until the ISR resolves, with resolution defined as no symptoms reported. Using the ISR categories and ADL domains listed below, the ePRO DISRA will collect the presence or absence of ISRs, the severity of each ISR (0-10 scale, with 0 indicating no pain/bleeding/itching/or swelling, and 10 indicating worst possible pain/bleeding/itching/or swelling), and the perceived impact of the ISR on the subject's ADL (0-10 scale, with 0 indicating no interference and 10 indicating extreme interference) using the following ISR categories and ADL domains:

ISRs:

- Pain.
- Bleeding (measures of severity also include number of bandage changes and healthcare resource utilization).
- Itching.
- Swelling.

ADL domains:

- Physical.
- Social.
- Work/household.

Subjects will return to the study site on Day 8 and Day 15 after each SUSTOL injection for safety assessments. Note, for subjects receiving chemotherapy regimens with a cycle of 7 days, the Day 8 and Day 15 assessments will be conducted on Day 1 of the next cycle(s) prior to

receiving chemotherapy, and will evaluate each injection site until 14 days have elapsed after each SUSTOL injection. At each site visit, site staff will use the ClinRO CAISR to assess the following:

The presence or absence of any ISR-related:

- Nodule.
- Erythema.
- Ecchymosis.
- Hematoma.
- Infection.
- Ulceration.
- Necrosis.

The size of:

- Nodules.
- Erythema.
- Ecchymosis.
- Hematomas.

As part of the ClinRO CAISR, ISR-associated healthcare resource utilization (eg, ER, urgent care, unscheduled clinic visit) and intervention (surgical or other) will be recorded. All ClinRO ISRs reported will be followed at weekly unscheduled visits through resolution (defined as no signs observed) or until deemed no longer clinically significant in the opinion of the Investigator.

All SAEs and all treatment-emergent adverse events (TEAEs) that led to discontinuation of SUSTOL treatment or withdrawal from the study will be collected from signing of the informed consent form (ICF) through the Final Follow-Up Visit, which will occur 28 days after the last SUSTOL dose.

3.1.2. Treatment Groups

In this single-arm study, eligible subjects will receive SUSTOL (administered 10 mg SC) per the USPI on Cycle 1 Day 1, and on Day 1 of up to 3 subsequent cycles.

3.1.3. Concomitant Therapy

SUSTOL is indicated in combination with other antiemetics in adults for the prevention of CINV (SUSTOL USPI 2017).

In accordance with antiemetic treatment guidelines and standard of care, dexamethasone should be used as concomitant medication with SUSTOL with or without an NK_1 RA (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). For subjects who cannot continue to take dexamethasone after the first cycle, an NK_1 RA must be used.

For subjects receiving AC combination chemotherapy regimens, SUSTOL should be combined with an NK_1 RA, dexamethasone, and olanzapine (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]); the recommended dexamethasone dosage is 20 mg IV on Day 1, followed by 8 mg orally, twice a day, on Days 2, 3 and 4 (SUSTOL USPI 2017).

For subjects receiving MEC, NCCN antiemetic treatment guidelines recommend 2 options that include SUSTOL: a 3-drug regimen of SUSTOL combined with an NK_1 RA and dexamethasone or a 2-drug regimen of SUSTOL and dexamethasone (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]); the recommended dexamethasone dosage is 8 mg IV on Day 1 (SUSTOL USPI 2017).

If SUSTOL is administered with dexamethasone and an NK_1 RA, review the prescribing information of the NK_1 RA for the recommended dosage of dexamethasone and the NK_1 RA.

Concomitant antiemetics may include the following:

- Dexamethasone.
- Aprepitant.
- Fosaprepitant.
- Rolapitant.
- Olanzapine (AC regimens only).

The recommended dosage of olanzapine per the NCCN and ASCO guidelines is 5 mg to 10 mg daily for 4 days starting on Day 1 of a HEC regimen (ie, AC regimen) (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]).

All other treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the standard of medical care.

MEC or AC combination chemotherapy, dexamethasone (IV or oral), NK_1 RAs, and other antiemetic medications will be supplied by the study site and administered per approved labeling.

3.1.4. Rescue Medications

If subjects require rescue medications for treatment of CINV, antiemetic treatment guidelines recommend prescribing an antiemetic from a different drug class than those used for prophylaxis (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]). Rescue medication cannot include additional SUSTOL or other $5\text{-}HT_3$ RAs, and may include the following:

- Olanzapine (if not given as prophylaxis).
- Lorazepam.
- Dronabinol.
- Nabilone.
- Haloperidol.
- Metoclopramide.

- Scopolamine.
- Prochlorperazine.
- Promethazine.

Rescue medications should be administered per approved prescribing information or per antiemetic treatment guidelines.

The agent, dose, and time of administration for any rescue medication will be recorded in the electronic case report form (eCRF). Rescue medication cannot include additional SUSTOL.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint is the:

- Proportion of subjects with a subject-reported ISR composite dichotomous (0 or 1) score of 1 defined as follows:
  - ISR of pain, itching, or swelling with a severity ≥7 **AND** ADL impact of ≥7 in any ADL domain (physical, social, work/household).

    OR
  - ISR of bleeding with ADL impact of ≥7 in any ADL domain (physical, social, work/household), **AND** 1 of the following:
    - severity ≥7 and 4 to 6 bandage changes per day **OR**
    - ≥7 bandage changes per day **OR**
    - urgent care/ER visit

3.2.2. Secondary Endpoints

3.2.2.1. Other Endpoints

- Proportions of subjects with ISR-related SAEs and ISR-related TEAEs that led to discontinuation of SUSTOL treatment or withdrawal from the study.
- Proportions of subjects with SAEs and TEAEs that led to discontinuation of SUSTOL treatment or withdrawal from the study, of any cause.
- Proportions of subjects with ISRs that led to delay of chemotherapy treatment.
- Proportion of subjects with a subject-reported ISR for each ISR category by maximum severity, by cycle and overall.
- Proportion of subjects with a subject-reported ISR by highest level of impact on each ADL domain, by cycle and overall.
- Proportion of subjects with an ISR requiring healthcare utilization.
- Proportion of subjects with an ISR requiring intervention (surgical, other).
- Mean duration (days) of each subject-reported ISR, by cycle and overall.

- Mean maximum size of each clinician-reported ISR, by cycle and overall.
- Proportion of subjects with a subject-reported ISR pain severity ≥7 AND presence of each or any of ClinRO CAISR signs (nodule, hematoma, erythema, ecchymosis, infection, ulceration, or necrosis).

3.3. Study Duration

The overall duration of the study is anticipated to be approximately 3 years. The total duration of study participation for each subject from Screening through the Final Follow-Up Visit will be approximately 20 weeks.

For regulatory reporting purposes, the end of the study is defined as the date of the last subject's last visit.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. Study Population

Approximately 300 subjects will be enrolled and administered SUSTOL in the study at up to 25 study sites in the US.

4.1.1. Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is able to provide voluntary, written, informed consent to participate in this study and must be able to fully understand the study requirements.
2. Is willing and able to comply with all testing and requirements defined in the protocol.
3. Is 18 years of age or older at Cycle 1 Day 1.
4. Has cancer, is scheduled to receive MEC or AC regimen as defined by antiemetic treatment guidelines (Hesketh 2020) (NCCN *Clinical Practice Guidelines in Oncology, Antiemesis* [December 2020]), is anticipated to require at least 4 cycles of chemotherapy, and is prescribed SUSTOL for CINV prevention.
5. Is entering the first cycle of their current chemotherapy regimen.
6. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Has a life expectancy of >6 months.
8. Is able to receive standardized doses of dexamethasone as required in SUSTOL USPI for the prevention of emesis.
9. Subjects of childbearing potential (defined as premenopausal and capable of becoming pregnant) must meet all of the following criteria:
    a. Is not pregnant and not planning on becoming pregnant during the study. Subjects of childbearing potential must have a negative serum pregnancy test at screening and negative urine pregnancy test before SUSTOL administration.
    b. Not lactating.
    c. Is practicing abstinence; or is in a monogamous relationship with a partner who cannot impregnate the subject (eg, is surgically sterile); or agrees to use double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities in the event of sexual activity from the Screening Visit through 30 days after the last dose of SUSTOL.

4.1.2. Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Has hypersensitivity to granisetron, any component of SUSTOL, or any other 5-HT_3 RAs.
2. Has received SUSTOL previously.
3. Has severe renal impairment (creatinine clearance [CL_{cr}] <30 mL/min).

4. Has symptomatic primary or metastatic central nervous system (CNS) disease.
5. Has participated in an interventional clinical study within 30 days of Cycle 1 Day 1.
6. In the opinion of the Investigator, has other physiological, psychological, behavioral, and/or other medical conditions that would interfere with participation in a clinical study, such as:
    a. Clinically significant electrolyte disturbance, including but not limited to: uncorrected hypokalemia/hyperkalemia, hypomagnesemia, or hypocalcemia.
    b. Clinically significant cardiac disease including but not limited to: uncontrolled angina, myocardial ischemia or infarction within 6 months, congestive heart failure, myocarditis, or dyspnea on exertion.

4.2. Method of Assigning Subjects to Treatment Groups

All subjects who meet eligibility requirements will receive SUSTOL in this single–arm study.

4.2.1. Procedures for Handling Subjects Who Do Not Meet the Study Eligibility Criteria

Subjects who fail to meet the eligibility criteria at Screening or prior to treatment on Day 1 of Cycle 1 will be considered screen failures.

In the event a subject does not meet the eligibility criteria but receives SUSTOL, the subject will be considered a study subject and part of the Safety population. The Investigator should inform the Sponsor immediately. The Sponsor's Medical Monitor and the Investigator will discuss whether the subject may continue on study.

4.3. Blinding

This is an open-label study.

4.4. Subject Withdrawal and Replacement

4.4.1. Subject Withdrawal

Subjects are free to withdraw from the study at any time without prejudice to further treatment. A subject may also be withdrawn from the study by the Investigator or the Sponsor at any time if either determines that it is not in the subject's best interest to continue participation.

Possible reasons for early withdrawal include the following:

- Adverse event (AE).
- Withdrawal by subject.
- Death.
- Lost to follow-up.
- Pregnancy.
- Investigator's decision.

- Sponsor's decision.

The date and the primary reason for early withdrawal will be recorded on the eCRF. At the time of withdrawal from the study, every attempt should be made to complete the Early Termination Visit assessments.

4.4.2. Subject Replacement

Subjects who withdraw early from the study for any reason will not be replaced.

5. STUDY DRUG

All subjects will receive SUSTOL per the approved prescribing information (SUSTOL USPI 2017).

5.1. Description of Study Drug

SUSTOL is a clear, colorless to slightly yellow, viscous liquid that will be provided by the Sponsor in commercially available sterile, single-dose, prefilled syringes containing 10 mg of granisetron (approximately 0.4 mL).

5.2. Packaging and Labeling

SUSTOL will be packaged and labeled by the Sponsor or designee and will be packed and dispatched to comply with shipping and storage conditions. SUSTOL labeling will comply with all applicable national and local laws and regulations.

The SUSTOL kit contains:

- 1 sterile single-dose glass syringe which contains 10 mg granisetron.
- 1 sterile 18G x 5/8" administration needle.
- 2 sodium acetate warming pouches.
- 1 Point-Lok® needle protection device.
- Instructions for Use (IFU), Package Insert, and Medication Guide.

5.3. Storage

Store SUSTOL in the refrigerator at 2°C to 8°C (36°F to 46°F). SUSTOL can be placed back in the refrigerator after being kept at room temperature. SUSTOL can remain at room temperature for a maximum of 7 days.

SUSTOL should be protected from light and should not be frozen.

The refrigerator at the study site should be in a locked area with restricted access. A temperature log should be maintained to monitor the refrigerator's temperature.

5.4. Preparation

SUSTOL will be prepared per the approved IFU. Do not substitute any of the components from the kit for administration.

Please follow the detailed instructions in the IFU to complete the following steps:

- Bring SUSTOL to room temperature.
- Prepare the syringe.
- Warm SUSTOL to body temperature.

5.5. Study Drug Administration

SUSTOL will be administered per the approved prescribing information and the IFU.

A single dose of SUSTOL 10 mg will be administered subcutaneously on Day 1 of each chemotherapy cycle at least 30 minutes before the start of emetogenic chemotherapy. SUSTOL should not be given not more frequently than once every 7 days. In subjects with moderate renal impairment (CL_{cr} of 30 to 59 mL/min), SUSTOL should not be administered more frequently than once every 14 days.

The start time of study drug administration will be recorded in the eCRF.

Use standard aseptic technique when performing the injection. Administer SUSTOL as a single SC injection in the skin of the back of the upper arm or in the skin of the abdomen at least 1 inch away from the umbilicus. Avoid injecting SUSTOL anywhere the skin is burned, hardened, inflamed, swollen, or otherwise compromised. Topical anesthetic may be used at the injection site prior to administration of SUSTOL. Due to the viscosity of SUSTOL, the time required for injection is greater than most medications administered SC. SUSTOL requires a slow, sustained injection which **may take up to 20 to 30 seconds**. Pressing the plunger harder will NOT expel SUSTOL faster.

For subsequent injections, use the same general area of the body. However, be sure not to inject in the exact same place. Administer new injections at least 1 inch from the previous site.

Alternately, for subjects receiving chemotherapy regimens with a 7 day cycle, the injection site may vary between upper arm and abdomen by treatment cycle, to more easily distinguish injection sites during the 14-day reporting period for each SUSTOL injection.

Please follow the detailed instructions in the IFU to inject SUSTOL.

5.6. Study Drug Compliance

Because SUSTOL is being administered by the Investigator or designee, a lack of treatment compliance is not expected. The dose and volume of administration (complete or partial) will be recorded in the eCRF. All SUSTOL must be administered in accordance with the protocol.

5.7. Study Drug Accountability

SUSTOL provided for this study will be used only as directed in the study protocol. In accordance with Good Clinical Practice (GCP), Investigators are required to maintain accurate and up-to-date records of all SUSTOL units to permit reconciliation. The Investigator or designee must maintain adequate records of distribution, including the date received, number and units received, lot numbers, dispensing, and return or destruction of all SUSTOL units (ie, accountability or dispensing logs).

All SUSTOL records must be readily available for inspection by the site's Clinical Monitor and/or auditor. The Clinical Monitor is responsible for verifying the accuracy of the SUSTOL records at the study site. All returns, disposal, or destruction must be approved by the Sponsor in writing.

6. STUDY PROCEDURES AND ASSESSMENTS

The following sections describe the study procedures and assessments that will be performed during the study. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS table.

6.1. Medical History and Demographics

6.1.1. Medical History

A complete medical history, including surgical history, will be obtained to ensure subjects qualify for the study. Medical history will be obtained through subject interview. In addition, a review of the subject's medical records from their primary care physician is recommended.

6.1.2. Demographics

Demographic information collected will include age, sex at birth, race, and ethnicity.

6.2. Prior and Concomitant Therapy

All medications taken by subjects between 21 days prior to study drug administration through the Final Follow-Up Visit will be recorded in the subject's eCRF. Medications to be recorded include prescription and/or over-the-counter medications (including topical anesthetics, herbal products and vitamins, and cannabinoids).

Concomitant chemotherapy treatment type (MEC or AC combination chemotherapy) will also be collected.

See Section 3.1.3 for further information on concomitant antiemetics and other medications, and Section 3.1.4 for rescue medications.

6.3. Safety Assessments

6.3.1. Adverse Events

SAEs and TEAEs that lead to discontinuation of SUSTOL treatment or withdrawal from the study (Section 8.1.1, Section 8.1.2, and Section 8.3.1), regardless of causality, will be recorded from the time the subject signs the ICF through the Final Follow-Up Visit. TEAEs that are not SAEs or do not lead to discontinuation of SUSTOL treatment or withdrawal from the study will not be collected in the clinical database.

Findings from the ePRO DISRA or ClinRO CAISR will not be recorded as TEAEs unless they meet definition of SAEs or TEAEs lead to discontinuation of SUSTOL treatment or withdrawal from the study.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs after the subject's last study visit and the Investigator considers the event to be possibly related to the study drug, the Investigator must report the SAE to the Sponsor, as described in Section 8.4.1.

6.3.2. Physical Examinations

Scheduled physical examinations will include an evaluation of the following: head, eyes, ears, nose, and throat as well as CV, respiratory, gastrointestinal, neurological, dermatological, and musculoskeletal systems.

Baseline height and weight measurements will be conducted and body mass index (BMI) calculated (Appendix A).

Unscheduled physical examinations may also be performed (the extent of which is to be determined by the Investigator) at any time during the study if indicated by a change in the subject's medical history or condition.

Any abnormal physical examination finding noted after the Screening physical exam must be recorded if it meets the criteria for an SAE or TEAE that leads to discontinuation of SUSTOL treatment or withdrawal from the study.

6.3.3. Vital Signs

Vital sign measurements will include blood pressure, resting heart rate, respiration rate, and body temperature. Subjects should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before measuring vital signs.

Any abnormal vital sign result after the Screening Visit must be recorded if it meets the criteria for an SAE or TEAE that leads to discontinuation of SUSTOL treatment or withdrawal from the study. If so, the abnormal vital sign result must be recorded on an eCRF (scheduled or unscheduled assessment eCRF, as applicable).

6.3.4. ECOG Performance Status

ECOG performance status will be evaluated per Appendix B (Oken 1982).

6.3.5. DISRA

Subjects will use an ePRO DISRA to record the occurrence, severity, and potential impact of subject-reported ISRs on ADL. During screening and again on Cycle 1 Day 1 prior to initial treatment, all subjects will be trained on the use of the ePRO DISRA. At each site visit, site staff will review the ePRO DISRA for subject completion and to determine if any follow-up treatment is required.

Screenshots of the ePRO DISRA are provided the Study Manual.

6.3.6. CAISR

At each site visit, site staff will use the ClinRO CAISR to assess clinical signs of ISRs. It is recommended that the ClinRO CAISR be completed after DISRA review by site staff.

The healthcare provider should collect the following information using the ClinRO CAISR:

- The presence or absence of any ISR-related nodule, erythema, ecchymosis, hematoma, infection, ulceration, or necrosis.
- The size (longest diameter, in cm) of nodules, erythema, ecchymosis, and hematomas.

- Resource utilization (eg, ER, urgent care, unscheduled clinic visit) and intervention (surgical or other) associated with the ISRs.

All ClinRO CAISR ISR signs will be followed at weekly unscheduled visits through resolution (defined as no signs observed) or until deemed not clinically significant, in the opinion of the Investigator. Only ISRs meeting the definition of an SAE or TEAE leading to discontinuation of SUSTOL treatment or withdrawal from the study are to be captured as a TEAE (Section 6.3.1).

A copy of the ClinRO CAISR is provided the Study Manual.

6.3.7. Clinical Laboratory Tests

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology and serum chemistry). A list of clinical laboratory tests and parameters is provided in Table 2. Scheduled hematology and serum chemistry tests will be performed by a local laboratory. Serum and urine samples collected for pregnancy will be tested at the study site. Laboratory tests performed per standard of care may be used if performed within the time window.

Laboratory results will be reviewed by the Investigator. Laboratory values outside of the normal reference range will be evaluated for clinical significance. An abnormal laboratory result, scheduled or unscheduled, that meets the criteria for an SAE or TEAE that leads to discontinuation of SUSTOL treatment or withdrawal from the study must be recorded.

Refer to the Laboratory Manual for detailed instructions on sample collection, processing, and shipping procedures.

Table 2: Clinical Laboratory Tests

Diagnostic Screening/Safety Tests (Study Site):		
Urine Pregnancy test: Human chorionic gonadotropin test (subjects of childbearing potential only) **Serum** Pregnancy test: Human chorionic gonadotropin test (subjects of childbearing potential only)		
Safety Laboratory Tests (Local Laboratory):		
Hematology	**Serum Chemistry**	
Red blood cell count Hematocrit Hemoglobin Mean corpuscular volume Platelet count White blood cell count (with automated differential)	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Direct bilirubin	Gamma-glutamyltransferase Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin Total protein Uric acid

7. GUIDANCE FOR COMPLETING PROCEDURES AND ASSESSMENTS

Study procedures and assessments are described in Section 6. The timing of procedures and assessments is provided in the SCHEDULE OF EVENTS table. The start of study drug administration will be considered Time 0 for all safety assessments.

Unless there is a safety concern, every effort should be made to avoid protocol deviations by completing procedures and assessments according to the protocol guidance. Actual times will be recorded for all events, and events performed outside the specified ranges should be documented as deviations.

During the Screening period, serum pregnancy tests (subjects of childbearing potential only) should be performed and confirmed as negative prior to performing any additional assessments. The definition of a subject of childbearing potential is provided in Section 9.1.

When vital signs and clinical laboratory tests are scheduled at the same timepoint, it is recommended that vital signs should be collected prior to, or at least 10 minutes after, clinical laboratory tests. It is recommended that the ECOG assessment be completed prior to SUSTOL administration. During clinic visits, it is recommended that the ePRO DISRA is reviewed by site staff before the completion of the ClinRO CAISR.

If an ISR is noted in the ClinRO CAISR, Day 8 assessments are to be repeated weekly as an unscheduled visit until resolution or until deemed not clinically significant in the opinion of the Investigator. Other unscheduled visits and assessments should be performed if clinically indicated in the opinion of the Investigator. Except when urgent clinical evaluation is necessary, it is expected that the Investigator will have the subject return for an unscheduled visit rather than directing the subject to a hospital ER. The results of any unscheduled assessments should be recorded on the eCRF.

8. SAFETY MONITORING AND REPORTING

Investigators are responsible for the detection, assessment, and documentation of AEs, including SAEs, unanticipated problems, and pregnancies, as detailed in this protocol.

Investigators must review the current SUSTOL prescribing information as well as the current prescribing information for other protocol-specified medications to be aware of the safety-related events that may be anticipated with their use.

8.1. Definition of Safety Parameters

8.1.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered causally associated with the use of the study drug. Any abnormal physical examination finding, laboratory value, vital sign result, or ECG finding that meets the criteria for an SAE or TEAE that leads to discontinuation of SUSTOL treatment or withdrawal from the study must be recorded. A clinical diagnosis, rather than a change in a laboratory analyte or other assessment, should be recorded (eg, anemia rather than low hemoglobin value).

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the condition or indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency or intensity of the condition (eg, abnormal physical examination finding).
- Signs, symptoms, or clinical sequelae of a suspected interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE, unless nonserious or serious sequelae occur).
- The following abnormal laboratory results:
  - Any laboratory abnormality suggestive of a new disease/organ toxicity or a worsening of a pre-existing condition.
  - Any laboratory abnormality that required the subject to have study drug interrupted or discontinued.
  - Any laboratory abnormality that required the subject to receive specific treatment for the laboratory abnormality.
  - Any laboratory abnormality that required further diagnostic investigation and/or follow-up visits (excluding repeat testing to confirm the abnormality).

The following examples are not considered AEs:

- Medical or surgical procedure (eg, endoscopy, appendectomy), although the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) (including laboratory values) present or detected at the start of the study that do not worsen.
- The disease or disorder being studied; or expected progression, signs, or symptoms of the disease or disorder being studied, unless they become more severe or occur with a greater frequency than expected for the subject's condition.
- Transient paresthesia that is considered to be clinically normal (would be expected to occur as a long-acting local anesthetic wears off).

8.1.2. Definition of a Serious Adverse Event

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE (ie, an AE that presented an immediate risk of death from the event as it occurred. This criterion is not intended to include an AE that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following events do not meet the definition of an SAE:

- Hospitalization for the following:
  - Elective treatment of a pre-existing condition that does not worsen from baseline.
  - A standard procedure for study drug administration and routine monitoring of the studied indication not associated with any deterioration in condition.
- Social or convenience admission to a hospital.
- Prolongation of a hospitalization for social or convenience reasons not associated with the occurrence of an AE.

- Hospitalization or an emergency room visit that lasts less than 24 hours and does not meet the criteria of an important medical or a life-threatening event.

According to 21 Code of Federal Regulations (CFR) 812.3(s), an unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.1.3. Definition of Unanticipated Problems

Unanticipated problems are incidents, experiences, or outcomes that meet all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the research protocol and informed consent document approved by the Ethics Committee (EC; includes Institutional Review Boards [IRBs], Independent Ethics Committees [IECs], and Research Ethics Boards [REBs]) and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An unanticipated adverse device effect is defined in Section 8.1.2.

8.2. Classification of Adverse Events

8.2.1. Severity of Adverse Events

The Investigator will assess the severity of each AE based on his/her clinical judgment using one of the following Common Terminology Criteria for Adverse Events (CTCAE) categories:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2.2. Relationship to Study Drug

The Investigator will assess the relationship of each AE to SUSTOL based on his/her clinical judgment. The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

Relationship to study drug will be assessed according to the following guidelines:

- **Possibly related:** The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
- **Unlikely related:** There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

Even in situations in which minimal information is available for initially reporting an SAE, it is important that the Investigator always make an assessment of causality for every event when entering the information into the eCRF or completing the SAE reporting form, in the event electronic data capture (EDC) is not available. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the SAE information accordingly in the eCRF or the SAE reporting form, as applicable.

8.3. Time Period and Frequency for Event Assessment and Follow Up

8.3.1. Adverse Event and Serious Adverse Event Monitoring

All SAEs and all TEAEs that led to discontinuation of SUSTOL treatment or withdrawal from the study will be collected in the clinical database from the time the subject signs the ICF through the Final Follow-Up Visit, which will occur 28 days after the last SUSTOL dose. TEAEs that are not SAEs or do not lead to discontinuation of SUSTOL treatment or withdrawal from the study will not be collected in the clinical database.

For subjects who received study drug, if an Investigator becomes aware of an SAE that occurs after the subject's last study visit and the Investigator considers the event to be possibly related to the study drug, the Investigator needs to report the SAE to the Sponsor as described in Section 8.4.1.

8.3.2. Follow-Up of Events

After the occurrence of an AE, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All AEs documented at a previous visit or contact and designated as ongoing will be reviewed at subsequent visits or contacts.

Nonserious AEs will be followed after the last scheduled study visit until the event resolves, the condition stabilizes, or until the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent).

The Investigator will assess the outcome of each AE using the following categories:

- **Recovered/Resolved:** The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (a device implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- **Recovered/Resolved with sequelae:** The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to SAEs. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved:** At the end of the study, a nonserious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- **Unknown:** The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- **Fatal.**

SAEs will be followed until the event resolves (ie, when the event no longer meets any of the seriousness criteria), the condition stabilizes, or the event is otherwise explained or judged by the Investigator to be no longer clinically significant (unless the subject is lost to follow-up or withdraws consent). The Investigator will ensure that follow-up information provided to the Sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both. New or updated information will be recorded as outlined in Section 8.4.1.

8.4. Reporting Procedures

8.4.1. Reporting Serious Adverse Events to the Sponsor

If the Investigator determines that an event that occurs during the course of this study meets the protocol definition of an SAE (see Section 8.1.2) due to any cause, regardless of relationship to

study drug, he/she must notify the Sponsor by entering the SAE information into the eCRF **within 24 hours of the Investigator becoming aware of the SAE**.

If EDC is not available, the Investigator must complete an SAE reporting form and email it to the Sponsor **within 24 hours of the Investigator becoming aware of the SAE**. The Investigator must also enter the SAE information into the eCRF as soon as possible thereafter.

Email Address: Heron_PV@ubc.com

The following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE.

EDC is the primary method for notification of SAE information. In rare circumstances and in the absence of email capacity, notification by fax or telephone is acceptable, with a copy of the SAE reporting form sent by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the SAE information in the eCRF within the time frames outlined.

If the Investigator does not have all information regarding an SAE, he/she must not wait to receive additional information before notifying the Sponsor of the event. The SAE must be updated when additional information is received using the same process and timelines as for the initial report.

The Investigator must notify the Sponsor by reporting any unanticipated adverse device effect within 24 hours of the Investigator becoming aware of the effect.

8.4.2. Reporting Unanticipated Problems to the Sponsor

If the Investigator determines that an event meets the protocol definition of an unanticipated problem (see Section 8.1.3), he/she must notify the Sponsor by completing an Unanticipated Problem Form and emailing it to the Sponsor **within 24 hours of the Investigator becoming aware of the problem**.

Email Address: Heron_PV@ubc.com

The following information will be included with unanticipated problem reporting:

- Protocol identifying information: protocol title, protocol number, and Investigator's name.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an unanticipated problem.

It is the Investigator's responsibility to report any unanticipated problem to the Sponsor and their EC, as required by local regulations.

8.4.3. Regulatory Reporting Requirements

The Investigator must promptly report all SAEs and unanticipated adverse device effects to the Sponsor in accordance with the procedures detailed in Section 8.4.1. The Sponsor has a legal

responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that serious suspected adverse reactions that are either unexpected or observed with increasing occurrence be reported and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

The Investigator, or responsible person according to local requirements, must comply with requirements related to the reporting of SAEs to the EC.

The Sponsor is responsible for informing ECs, Investigators, and regulatory authorities of any finding that could adversely affect the safety of subjects or affect the conduct of the study. Events will be reported to regulatory authorities in accordance with expedited and periodic reporting requirements.

Investigator letters are prepared according to Sponsor policy and are forwarded to the Investigators as necessary. An Investigator letter is prepared for any suspected adverse reaction that is attributable to study drug, serious, and unexpected. The purpose of the Investigator letter is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

8.4.4. Pregnancy Reporting

Pregnancy is not considered to be an AE; however, any subject who becomes pregnant during the study must be withdrawn from the study immediately. Subjects who become pregnant within 28 days after receiving study drug should also notify the Investigator. The Investigator must attempt to follow the pregnancy to term or termination in order to report on outcome and health status of mother and child.

The Investigator must notify the Sponsor of any pregnancy by completing a Pregnancy Form and emailing it to the Sponsor **within 24 hours after the Investigator becomes aware of the pregnancy**.

Email Address: Heron_PV@ubc.com

8.5. Safety Oversight

An internal, Product Safety and Risk Management Committee will monitor safety data on a periodic basis throughout the study (ie, approximately monthly unless more frequent monitoring is necessary due to high enrollment or safety concern), including regular review of AEs, available laboratory results, and other safety assessment results.

The stopping criteria for suspending enrollment or terminating the study or closing a study site for safety issues are provided in Section 13.5.1 and Section 13.5.2, respectively.

9. OTHER STUDY RESTRICTIONS

9.1. Contraception

A subject of childbearing potential is defined as a premenopausal subject capable of becoming pregnant. This includes subjects on oral, injectable, or mechanical contraception; subjects who are not in a relationship; and subjects whose partners have been vasectomized or have received or are utilizing mechanical contraceptive devices.

Subjects of childbearing potential must use an acceptable form of contraception in the event of sexual activity from the Screening Visit through 30 days after the last SUSTOL administration. Acceptable forms of contraception include double-barrier contraception or an insertable, injectable, transdermal, or combination oral contraceptive approved by applicable regulatory authorities.

10. STATISTICAL CONSIDERATIONS

10.1. General Considerations

All data will be listed by subject. Continuous variables will be summarized using the number of subjects with data (n), mean, SD, median, minimum, and maximum, unless otherwise specified. Categorical variables will be summarized using frequency counts and percentages. Details of all statistical analyses will be described in a separate statistical analysis plan.

10.2. Determination of Sample Size

Approximately 300 subjects will be enrolled, with approximately 100 subjects anticipated to experience an ISR. The sample size is based on anticipation of a 33% rate of ISRs that may potentially impact subject ADL. This rate was estimated from the results of a prospective, randomized, active-controlled, double-blind Phase 3 study that included a patient diary to record ISRs, in which the highest ISR rate associated with a grade reported to interfere with activities was approximately 33% for pain.

10.3. Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of study drug. This population will be used for all demographic and safety summaries.

10.4. Statistical Analysis Methods

10.4.1. Disposition and Demographics

The number and percentage of subjects in the safety population will be summarized. Subject disposition, including the number of subjects screened, dosed, and completing the study will be summarized. Screening failures and early study withdrawal will also be summarized.

Subject demographics and baseline characteristics will be summarized for the Safety Population as well.

10.4.2. Safety Analysis

All safety data will be listed. Safety assessments including ePRO DISRA, ClinRO CAISR, SAEs, and TEAEs leading to SUSTOL discontinuation or withdrawal from the study will be summarized for the Safety Population.

10.5. Interim Analysis

No formal interim analyses are planned.

11. QUALITY ASSURANCE AND QUALITY CONTROL

Quality assurance and quality control systems will be implemented and maintained by the Sponsor and its designee(s), as appropriate, following Standard Operating Procedures to ensure that the clinical study is conducted and the data are generated, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation (ICH) E6 GCP guidelines, and applicable regulatory requirements. The accuracy, completeness, and reliability of the study data presented to the Sponsor, however, are the responsibility of the Investigator. The Investigator or designee must record all required data using the prespecified data collection method defined by the Sponsor or its designee.

The study will be monitored regularly by the Sponsor (Section 13.1) and may be audited by the Sponsor (or designee), or inspected by a regulatory authority at any time during the study or after study completion. In the event of an audit or inspection, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the competent authority, or other regulatory authority direct access to all study records. The Investigator will immediately notify the Sponsor of all audits or inspections scheduled by any regulatory authority and promptly forward to the Sponsor copies of any inspection reports received.

12. REGULATORY AND ETHICAL CONSIDERATIONS

12.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before any site may initiate the study in that country.

12.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol and all applicable regulatory requirements in accordance with ICH/GCP and in general conformity with the most recent version of the Declaration of Helsinki.

12.3. Ethics Committee Approval

The Investigator or the Sponsor is responsible for submitting the following documents to the ECs for review and, if applicable, approval: study protocol, ICF(s), Investigator's Brochure, recruitment materials, information about study compensation to subjects, and any information for presentation to potential subjects.

The Investigator is responsible for providing the Sponsor with the written EC approval prior to commencing the study (ie, before shipment of study drug to the site). All amendments to the protocol require review and approval by the EC before the changes to the study are implemented. All changes to the ICF will be approved by the EC; a determination will be made regarding whether previously consented participants need to be re-consented. If any other information previously approved by the EC for presentation to potential subjects is amended during the study, the Investigator is also responsible for ensuring EC review and re-approval.

Study sites must adhere to all requirements stipulated by their respective ECs. This may include, but not be limited to, notifying the EC of serious and unexpected AEs or other local safety reporting requirements, submitting a final status report, or providing a synopsis of the study report upon study completion.

12.4. Informed Consent Process

Note: All references to "subject" in this section refer to the study subject or his/her legally authorized representative.

The Sponsor (or its designee) will provide Investigators with an ICF for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final ICF must be accepted by the Sponsor and approved by the EC. Investigators must provide the Sponsor with an unsigned copy of the final ICF before and after it is approved by the EC. If any new information becomes available that might affect subjects' willingness to participate in the study, or if any amendments to the protocol require changes to the ICF, the Sponsor will provide Investigators with a revised ICF.

Prior to participating in any study-related procedure, each subject must sign and date an EC-approved ICF written in a language the subject can understand. The ICF should be as

nontechnical as practical and understandable to the subject. The ICF must provide the subject with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF details the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. Before informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject.

Once signed, the original ICF will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the subject's case history. All subjects will receive a copy of their signed and dated ICF.

If the ICF is revised during the study and requires the subject to be re-consented, informed consent will be obtained in the same manner as for the original ICF.

12.5. Confidentiality

All information provided by Heron Therapeutics, Inc. and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study and will not be released to any unauthorized third party without prior written approval of the Sponsor. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an EC solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 13.6. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, that contract's confidentiality provisions shall apply rather than this statement; provided, however, that the confidentiality provisions in any written contract shall not be less restrictive than this statement.

The Investigator agrees to comply with all applicable national, state, and local laws and regulations relating to the privacy of a subject's health information. The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA) and in a form satisfactory to the Sponsor.

The subject's contact information will be securely stored at each clinical site for internal use during the study. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected in the subject's eCRF). At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the EC and institutional regulations.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the Sponsor requires that the Investigator permit its monitor or designee's monitor, representatives

from any regulatory authority, the Sponsor's designated auditors, and the appropriate ECs to review the subject's original medical records (source data or documents), including, but not limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 12.4).

13. STUDY ADMINISTRATION

13.1. Clinical Monitoring

The Sponsor (or its designee) is responsible for ensuring the proper conduct of the study. This includes ensuring the subjects' rights and well-being are protected, the conduct of the study is within compliance of an approved protocol and GCPs, and the integrity of the data are accurate, complete, and verifiable from source documentation. During the study, the Sponsor's study monitors will contact the study site via site visits or remote monitoring to review study progress and the eCRF completion and to address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent process and documents, the site's essential documents, subject recruitment procedures, subjects' compliance with the study procedures, source-data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and the quality of data.

13.2. Source Documents and Record Retention

Each study site will maintain study documents and records as specified in *ICH E6, Section 8 (Essential Documents for the Conduct of a Clinical Trial)* and as required by regulatory authorities and institutional requirements. These include, but are not limited to the following: the study protocol, eCRF, delegation of authority log, pharmacy dispensing records, drug accountability logs, AE reports, subject source data (original or certified copies), correspondence with regulatory authorities and ECs, ICFs, monitoring visit logs and records, laboratory certification or quality control procedures, and laboratory reference ranges and reports. Access to study documents and records will be strictly controlled (Section 12.5).

Study documents and records must be retained for at least 2 years after the data have been submitted to a marketing application in the US or until at least 2 years have elapsed since the formal discontinuation of the product. However, these documents must be retained for a longer period if required by applicable regulatory requirements or if agreed to in the Clinical Trial Agreement. It is the responsibility of the Sponsor to inform the site as to when these documents no longer need to be retained.

13.3. Management of Protocol Amendments and Deviations

13.3.1. Protocol Amendments

The protocol cannot be modified except in a formal protocol amendment by the Sponsor.

13.3.2. Protocol Deviations

A protocol deviation is a change, divergence, or departure from the study design or procedures defined in this protocol. The Investigator will notify the EC of any protocol deviations as required by EC guidelines and site requirements. Protocol deviations will be documented at the site and in the Sponsor files.

13.4. Financial Disclosure

The Sponsor has determined that the study is not a Covered Clinical Study and is not subject to 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

13.5. Stopping Criteria: Suspension or Termination of the Study or Closure of a Study Site

13.5.1. Suspension of the Study

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s).

Enrollment in the study will be temporarily suspended if the Sponsor discovers the occurrence of any of the following:

- Two subjects with a non-fatal suspected unexpected serious adverse reactions (SUSAR) at any time during the study.
- Any death for which a clear alternative cause (eg, unrelated to study drug or if in relation to disease progression of the patient's underlying malignant condition) is not readily apparent.

Following a review of the data by the Sponsor, a decision will be made to either resume, modify, or stop the study. If the study is terminated early by the Sponsor, written notification documenting the reason for study termination will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study termination.

13.5.2. Closure of a Study Site

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions arising during the study that indicate that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator(s). Reasons for closing a site include, but are not limited to, the following:

- Failure of the Principal Investigator to comply with the protocol, GCP regulations and guidelines, or local requirements.
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data.
- Insufficiently complete and/or evaluable data.
- Inadequate recruitment of subjects by the Investigator.
- Sponsor decision.

If a study site is closed by the Sponsor, written notification documenting the reason for study site closure will be provided to the Investigator and regulatory authorities. The Investigator will promptly inform the EC and provide the reason(s) for study site closure.

13.6. Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of Heron Therapeutics, Inc.

For clinical interventional studies in patients, Heron will post study results on websites such as https://clinicaltrials.gov/ and https://eudract.ema.europa.eu/ in accordance with FDA and European Union reporting rules. Regardless of study outcome, Heron commits to submit for publication results of its interventional clinical studies according to the prespecified plans for data analysis. Wherever possible, Heron also plans to submit for publication the results of any nonclinical or technology studies while protecting any proprietary information.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Heron has developed a policy for the publication of scientific and clinical data that follows the recommendations of the International Committee of Medical Journal Editors (ICMJE), the Consolidated Standards of Reporting Trials (CONSORT) group, and Good Publication Practice (GPP). A copy of this policy will be made available to the Investigator upon request.

When the study is completed or prematurely terminated, the Sponsor or designee will ensure a Clinical Study Report is written in compliance with ICH E3 (Structure and Content of Clinical Study Reports) and submitted to the regulatory authorities, as required by the applicable regulatory requirement(s). Where required by applicable regulatory requirements, the Investigator signatory will be identified for the approval of the Clinical Study Report. The Investigator will be provided reasonable access to statistical tables, listings, and figures, as well as relevant reports, and will have the opportunity to review the complete study results.

14. REFERENCE LIST

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APPENDIX A. BODY MASS INDEX CALCULATION

Body mass index (BMI) = (Weight in kilograms [kg])/(height in meters [m])^2

Weight in pounds × 0.453592 = weight in kg

Height in inches × 0.0254 = height in m

For example, for a man who weighs 165 pounds and is 71 inches tall:

165 pounds × 0.453592 = 74.8 kg

71 inches × 0.0254 = 1.803 m

BMI = 74.8 kg/(1.803 m × 1.803 m) = 23.01 kg/m^2

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Site staff will complete the Eastern Cooperative Oncology Group (ECOG) Performance Status assessment at Screening, Baseline, Early Termination, and Final Follow-Up Visit. It is recommended that the ECOG assessment be completed prior to SUSTOL administration. Site staff will circle the grade that corresponds to the subject's status at the time of assessment.

Grade	ECOG
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair for more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-655.

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