SEIGLA™ MEDICAL

#200-0004 Rev 02

Plan, LiquID Guide Catheter Extension Safety Study

☒Plan
☐Report

Approved:

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Date: 09 May 2022

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Date: 9 MAY 2022

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Abstract:
The purpose of this study is to provide initial clinical evidence to establish the safety and performance of the LiquID Guide Catheter Extension in support of post-market clinical follow-up (PMCF) the device for use in PCI.

Revisions

Rev	Date	Description
01	03Mar2022	Initial Release
02	09MAY2022 CRS	Made cardiac enzymes optional to align with standard of care myocardial infarction diagnosis, added additional GDPR data privacy information, added Clinical Trial Agreement wording, changed "patient" and "subject" terminology to "participant" to align with EU terminology

Plan, LiquID Guide Catheter Extension Safety Study

Protocol: 200-0004, Revision 02
Date: 09 May 2022

Sponsor:
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CONFIDENTIALITY STATEMENT

Protocol: 200-0004

I have read this protocol and agree to conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

Site Principal or Lead Investigator's Signature Date

Name of Site Principal/Lead Investigator (Typed or Printed)

Site Name (Typed or Printed)

Protocol: 200-0004

I have read this protocol and agree to conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

The LiquID Guide Catheter Extension conforms to the general safety and performance requirements apart from the aspects covered by the clinical investigation and with regard to those aspects, every precaution has been taken to protect the health and safety of the participant.

09 May 2022
Sponsor Signature Date

John Schultz
Name of Sponsor Contact (Typed or Printed)

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1.0 REVISION HISTORY

Revision #	*Date*	*Description*
01	28 February 2022	Initial release
02	09 May 2022	Made cardiac enzymes optional to align with standard of care myocardial infarction diagnosis, added additional GDPR data privacy information, added Clinical Trial Agreement wording, changed "patient" and "subject" terminology to "participant" to align with EU terminology

2.0 SYNOPSIS

Study Sites	Up to 10 study sites will participate in this study
Study Objective	Demonstrate the safety and performance of the LiquID Guide Catheter Extension
Study Device	LiquID Guide Catheter Extension (LiquID)
Study Design	Single arm, open label, historically controlled, multicenter study evaluating the primary safety and performance endpoints
Study Duration	The study is expected to take approximately 6-9 months to enroll. Follow-up will consist of evaluation through patient discharge and a 7-10 day phone follow-up to assess for adverse events.

Primary Endpoint	In-hospital major adverse cardiac events (MACE), defined as any of the following events that occur within 48 hours post-procedure, or through patient discharge, whichever occurs first:
	• Device-caused events including:
	  ○ Target vessel dissection
	  ○ Longitudinal stent deformation
	  ○ Proximal collar stent stripping
	• Cardiac death
	• Stroke
	• Peri-procedural myocardial infarction (MI) based on participant symptoms, ECG changes and/or SCAI definition[1] (if cardiac enzymes are available)
	
	The primary endpoint for each patient in the Safety Population is the presence/absence status for any MACE as defined above.

Primary Performance (Effectiveness) Endpoint	Device Oriented Clinical Outcome (DOCE), defined as successful deployment and retrieval of the LiquID device without any device deficiencies or where use of the LiquID device directly leads to a MACE, target vessel dissection, longitudinal stent deformation or proximal collar stent stripping.
Inclusion Criteria Participants must be:	1. scheduled for non-emergent, percutaneous coronary procedure in which the use of a guide catheter extension is anticipated 2. able to provide informed consent to participate in the study

Clinical Exclusion Criteria Participants must not have:	1. evidence of ongoing ST-elevation myocardial infarction (STEMI) or STEMI treatment for late presentation STEMI with index admission (stabilized acute coronary syndrome allowed) 2. left ventricular ejection fraction <20% 3. required intervention in a saphenous vein graft 4. an intolerance or known allergy to medications/contrast expected to be used during the procedure or during hospital stay 5. had a cardiac intervention within two weeks of the procedure 6. renal insufficiency (serum creatinine of > 2.3 mg/dl) 7. active gastrointestinal bleeding 8. an active infection or fever (>37.8° C) that may be due to infection 9. significant anemia (hemoglobin < 8.0 mg / dl) 10. severe uncontrolled systemic hypertension (systolic press. > 240 mm Hg within the past month) 11. a severe electrolyte imbalance 12. congestive heart failure (NYHA Class IV) 13. presented with an acute coronary syndrome where serum troponin concentrations have not been demonstrated to be declining prior to the scheduled procedure (within the past two weeks) 14. uncontrolled diabetes (> 2 serum glucose concentrations of > 350 mg/dl within the past 7 days) 15. participation in an investigational protocol 16. unwillingness or inability to comply with any protocol requirements 17. angina, or ischemia caused by occluded artery 18. other clinical conditions, that in the opinion of the investigator significantly compromise the ability to perform a safe and/or effective procedure
Vulnerable Population Exclusion Criteria Participants must not be:	1. under 18 years old 2. pregnant or nursing 3. immuno-compromised 4. over 89 years old 5. incapacitated, mentally compromised or otherwise incapable of understanding and/or providing informed consent (including emergency situations)
Data Collection	**Screening** *a.* Demographics (e.g., age, sex, race) *b.* Documentation of disease-related characteristics *c.* Previous and current treatments for disease *d.* Baseline (pre-procedure) cardiac enzymes **Procedure** *a.* Duration (1st sheath in, to the last sheath out/participant leaving cath lab) *b.* Device-Oriented Clinical Outcome (DOCE) *c.* Procedure-Oriented Clinical Outcome (POCE) *d.* Device deficiencies/malfunctions *e.* Adverse events/adverse device effects *f.* Procedure usability data **Follow-up (48 hours/patient discharge & 7-10 day phone call)** *a.* Assessment for adverse events/adverse device effects *b.* Cardiac enzymes at 1 hour (±15 min) and 4-6 hours post-procedure

Sample Size	Based on historical data regarding the event rate in the safety outcome[2,3,4,5], an exact binomial calculation was used to estimate sample size with the following assumptions[6]: • Wilson score 95% confidence level (CL) for study MACE incidence rate, i.e. 1-sided $\alpha = (1\text{-CL})/2 = 0.025$ • True underlying MACE incidence rate = 0.02 (2% MACE rate) • Delta factor = 0.08, i.e., the goal is to reject 0.10, or a 10% MACE incidence rate, at a 1-sided p of 0.025 significance level A sample size of 85 evaluable participants is proposed based on the above assumptions. In order to reject a true MACE incidence rate of 10% at a 1-sided α level of 0.025, at most 3 out of 85 participants (3.5%) can have MACE in the study. The actual α level is 0.0245 if the true MACE incidence rate is 10%; the power is 0.91 if true MACE incidence rate is 2%. Assuming a 10% attrition rate, 95 participants will be enrolled.
Study Committees	Due to the relatively small size of the study, no study committees will be used but an independent medical monitor cardiologist will be used to adjudicate events and provide safety oversight for the study.

3.0 INTRODUCTION

3.1 Background

Cardiovascular disease (CVD), including coronary heart disease (CHD), is a common ailment caused by the accumulation of atherosclerotic plaque in the arteries of the body. According to the European Heart Network[7], CVD causes 3.9 million deaths in Europe (1.8 million in the EU) and accounts for 45% of all deaths in Europe (37% in the EU). The total prevalence of CHD in the United States is 6.7% in adults over 20 years of age with a prevalence of myocardial infarction (MI) of 3.0%.[8] CHD may be impacted by factors such as family history (inherited/genetic component), diet, physical activity level, stress (lifestyle components), and regular medical screenings and/or follow-up (awareness/maintenance components).

Procedure History

The most common treatment of CHD is percutaneous coronary intervention (PCI), typically with stent placement, occurring at rates of 95-386/100,000 of the general population in the EU. Coronary artery bypass graft (CABG) surgery also remains a treatment option but typically for more complex procedures. Its use has been declining in recent years (18-73/100,000) as new tools and techniques emerge in PCI.[8] Among these new tools is a category called guide catheter extensions. These include devices such as the Guideliner (Teleflex), the Guidezilla (Boston Scientific), and the Telescope (Medtronic).

Device History

The LiquID 061 and LiquID 071 Guide Catheter Extensions (LiquID) are new, unique guide extension devices that optimize compatibility by working with a wider range of sizes of both guide catheters and therapeutic delivery catheters.

3.2 Alternative Treatments and Methods

As mentioned above, other guide catheter extension devices are already on the market in the EU, so those devices may be used as an alternative. Procedures may also be performed without the use of guide catheter extensions. Procedures that cannot be treated via PCI may be treated with CABG procedures.

3.3 Rationale for Procedure/Device

The wider range of device compatibility of LiquID potentially allows guide catheter extension device use in a wider range of clinical conditions (e.g., vessel size, tortuosity, etc.)

3.4 Previous Clinical Experience

This study will be the first clinical use of the LiquID devices.

4.0 STUDY OVERVIEW

4.1 Study Design

The study is a non-randomized, open label study at up to 10 clinical sites. The sites identified are anticipated to be the following:

- Royal Edinburgh, Morningside Pl, Edinburgh EH10 5HF, United Kingdom– Dr. Peter Henriksen
- Golden Jubilee National Hospital, Agamemnon St, Clydebank G81 4DY, United Kingdom – Dr. Mitchell Lindsay
- St. George's Hospital, Blackshaw Rd, London SW17 0QT, United Kingdom – Dr. Simon Wilson
- University Hospitals Bristol, Trust Headquarters, Marlborough St, Bristol BS1 3NU, United Kingdom – Dr. Tom Johnson
- Spire Cardiff Hospital, Glamorgan House, Croescadarn Rd, Pontprennau, Cardiff CF23 8XL, United Kingdom – Dr. Tim Kinnaird
- Mater Private Hospital, Eccles St, Dublin 7, D07 WKW8, Ireland – Dr. Robert Byrne
- Galway University Hospital, Newcastle Rd, Galway, H91 YR71, Ireland – Dr. Darren Mylotte
- Ziekenhuis Oost-Limburg, Schiepse Bos 6, 3600 Genk, Belgium – Prof. dr. Jo Dens
- Additional sites to be determined

Up to 95 participants will be enrolled but enrollment will be stopped as soon as data from 85 clinical procedures using the LiquID devices are obtained.

4.2 Study Objectives

The purpose of this study is to provide initial clinical evidence to establish the safety and performance of the LiquID Guide Catheter Extension in support of post-market clinical follow-up (PMCF) the device for use in PCI.

4.2.1 Primary Endpoint

In-hospital major adverse cardiac events (MACE), defined as any of the following events that occur within 48 hours post-procedure, or through participant discharge, whichever occurs first:

- Device-caused events including:
  - Target vessel dissection
  - Longitudinal stent deformation
  - Proximal collar stent stripping
- Cardiac death
- Stroke
- Peri-procedural myocardial infarction (MI) based on participant symptoms, ECG changes, or SCAI definition[1] (if cardiac enzymes are available)

The primary endpoint for each participant in the Safety Population is the presence/absence status for any MACE as defined above.

4.2.2 Secondary Endpoints

Device Oriented Clinical Outcome (DOCE), defined as successful deployment and retrieval of the LiquID device without any device deficiencies or where use of the

LiquID device directly leads to a MACE, target vessel dissection, longitudinal stent deformation or proximal collar stent stripping.

5.0 STUDY POPULATION

5.1 General Considerations

Patients who are scheduled for percutaneous intervention to treat coronary artery disease who do not have significant comorbidities that might confound outcomes will be considered for enrollment in this trial. Due to the short follow-up and relatively inclusive selection criteria in this trial, recruitment for this trial should be straightforward.

Up to 95 participants will be enrolled in the trial in order to generate data for 85 cases in which the LiquID devices are used clinically. A participant is considered enrolled when they meet study enrollment (all inclusion and no exclusion) criteria and have signed informed consent. All enrolled participants will be assigned a study ID consisting of a 2-digit site number and a 3-digit sequential participant number (e.g., 01-005).

5.2 Informed Consent

The process for obtaining informed consent will be subject to requirements specific to each clinical site but in general the patient will be approached by study site personnel about potential participation in the study. A copy of the informed consent form will be provided to the patient for their review. The patient will be given time to consider participation in the study and will be provided the opportunity to ask questions of regarding their participation in the trial. No indirect forms of informed consent will be allowed in this study, including but not limited to consent provided by a legal representative, spouse, legal guardian, or other advocate in the event that the patient cannot provide informed consent directly. The patient must sign the informed consent form. For patients that do not speak the local language a translated consent form may be provided at some participating sites. Alternatively, a translator may be provided to explain the study and the consent process as allowed by local regulations and/or clinical site policy.

5.3 Inclusion Criteria

Participants must be:

1. scheduled for non-emergent, percutaneous coronary procedure in which the use of a guide catheter extension is anticipated
2. able to provide informed consent to participate in the study

5.4 Clinical Exclusion Criteria

Potential participants must not have:

1. evidence of ongoing ST-elevation myocardial infarction (STEMI) or STEMI treatment for late presentation STEMI with index admission (stabilized acute coronary syndrome allowed)
2. left ventricular ejection fraction <20%
3. required intervention in a saphenous vein graft

4. an intolerance or known allergy to medications/contrast expected to be used during the procedure or during hospital stay
5. had a cardiac intervention within two weeks of the procedure
6. renal insufficiency (serum creatinine of > 2.3 mg/dl)
7. active gastrointestinal bleeding
8. an active infection or fever (>37.8° C) that may be due to infection
9. significant anemia (hemoglobin < 8.0 mg / dl)
10. severe uncontrolled systemic hypertension (systolic press. > 240 mm Hg within the past month)
11. a severe electrolyte imbalance
12. congestive heart failure (NYHA Class IV)
13. presented with an acute coronary syndrome where serum troponin concentrations have not been demonstrated to be declining prior to the scheduled procedure (within the past two weeks)
14. uncontrolled diabetes (> 2 serum glucose concentrations of > 350 mg/dl within the past 7 days)
15. participation in an investigational protocol
16. unwillingness or inability to comply with any protocol requirements
17. angina, or ischemia caused by occluded artery
18. other clinical conditions, that in the opinion of the investigator significantly compromise the ability to perform a safe and/or effective procedure

5.5 Vulnerable Population Exclusion Criteria

Potential participants must not be:

1. under 18 years old
2. pregnant or nursing
3. immuno-compromised
4. over 89 years old
5. incapacitated, mentally compromised or otherwise incapable of understanding and/or providing informed consent (including emergency situations)

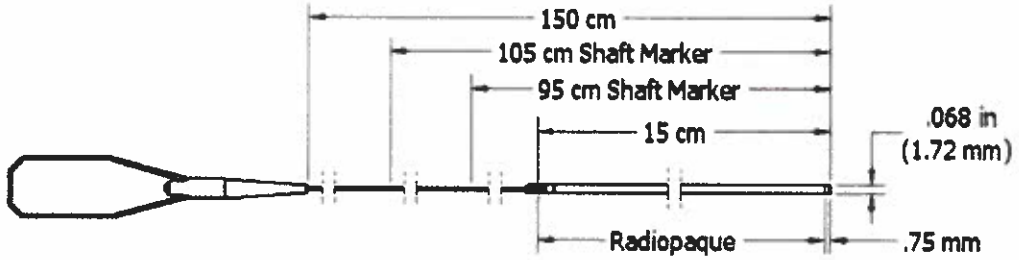
6.0 DEVICE DESCRIPTION

6.1 General Description

The LiquID Guide Catheter Extensions are a single lumen catheter offered in a 6F (LiquID 061) and 7F (LiquID 071) size. The 150cm device has a stainless-steel shaft connected to a 15cm single lumen tube, which is used to extend traditional guide catheters. The 15cm single lumen tube catheter body contains a coil for kink resistance and radiopacity. The single lumen tube catheter body is also silicone coated for lubricity. The device has two

proximal positioning marks located at 95cm and 105cm from the distal tip. The device handle is color coded to match the standard guide catheter color code.

Figure 1: 6F Device Image (.068 in dimension is the outer diameter)



6.2 Intended Use

The LiquID Guide Catheter Extension is intended to be used in conjunction with guide catheters to access discrete regions of the coronary and/or peripheral vasculature, and to facilitate placement of interventional devices.

6.3 Claims and Intended Performance Verification

This study is intended to support claims that the LiquID devices are safe and effective for their intended use.

6.4 Number of Devices

Most procedures will require one device per case but occasionally an additional device may be required. It is conservatively estimated that 1.3 devices per case will be required for a total of 95 devices used in 85 evaluable cases.

6.5 Device Manufacturer

Seigla Medical, Inc.
7688 5th Street SE
Buffalo, MN 55313

6.6 Principle of Operation

The LiquID devices support the delivery of interventional devices by allowing more distal access of coronary and peripheral arteries. Passing the device beyond the distal tip of the guide catheter and into the vessel improves guide catheter back-up support thus improving the ability to push subsequent devices beyond points of obstruction. In addition, the guide catheter extension may itself cross points of obstruction allowing direct delivery of interventional devices to mid or distal portions of vessel anatomy.

Device operation includes introduction through a previously placed coronary or peripheral guide catheter and into a position within the target vessel using common interventional cardiology techniques. Subsequent devices are delivered in parallel to the LiquID push rod, through the interior lumen of the LiquID catheter body and into the target vessel beyond the distal tip.

7.0 PRE-PROCEDURE EVALUATION

7.1 Pre-Procedure Tests/Data

a. Demographics (e.g., age, gender, race)
b. Documentation of disease-related characteristics
c. Previous and current treatments for disease

8.0 CLINICAL PROCEDURE

All study procedures will be performed according to the study site's standard of care. No special procedures or tests are required for this protocol.

8.1 Device Preparation, Introduction, and Use

The LiquID devices and all other devices to be used in the study procedure will be prepared according to their product instructions for use (IFU).

8.2 Perform Procedure

All study procedures will be performed per the clinical study site's standard of care. Seigla Medical personnel may be present during study procedures, but they are not required to be at all study cases.

8.3 Procedure Data

a. *Procedure Duration*, measured as the time from the introduction of the first sheath into the participant, to the last sheath removed from the participant. If a sheath is left in the participant post-procedure, the procedure time will end when the participant leaves the catheter laboratory (cath lab).
b. *Device Oriented Clinical Outcome (DOCE)*, defined as the successful deployment and retrieval of the LiquID device without any device deficiencies or where use of the LiquID device directly leads to a MACE, target vessel dissection, longitudinal stent deformation or proximal collar stent stripping.
c. *Procedure Oriented Clinical Outcome (POCE)*, defined as DOCE without any device- or procedure-related event (causal or probable) that leads to a MACE.
d. The occurrence of any device deficiencies/malfunctions
e. The occurrence of any adverse events/adverse device effects

9.0 POST-PROCEDURE CARE/STUDY EVALUATIONS

Participant assessments will consist of an evaluation at 48 hours post-procedure or through participant discharge, whichever occurs first, and a follow-up telephone call 7-10 days post-procedure. At those evaluations, the following will be followed/assessed:

9.1 Post-Procedure Tests & Assessments

a. Cardiac enzymes at 1 hour (±15 minutes) and 4-6 hours post-procedure
b. Assess for the occurrence of adverse events/adverse device effects
c. All other participant care post-procedure during the study will be according to the clinical study site's standard of care.

9.2 Participant Care Following the Investigation

Following the participant's involvement in the clinical investigation, there will be no special care provided. Participant care following the investigation will be exactly the same as it would be if they were not in the study.

10.0 STATISTICAL METHODS

10.1 Sample Size Estimation

For the primary endpoint of participant incidence of any MACE, the rates in similar prior studies[2-5] provided information to establish an estimated rate for this study of 2.0%. The exact binomial probability calculation was used to determine the sample size, using the following assumptions[6]:

- 95% confidence level (CL) for study MACE incidence rate, i.e., 1-sided $\alpha = (1\text{-CL})/2 = 0.025$
- True underlying MACE incidence rate = 0.02 (2% MACE rate)
- Sampling delta factor = 0.08, i.e., performance goal to reject =0.10, or 10%, at a 1-sided p of 0.025 significance level

A sample size of 85 evaluable participants is proposed based on the above assumptions. In order to reject a true MACE incidence rate of 10% at a 1-sided α level of 0.025, at most 3 out of 85 participants (3.5%) can have a MACE in the study. The actual α level is 0.0245 if the true MACE incidence rate is 10% and the power is 0.91 if true MACE incidence rate is 2%

Allowing for attrition, including cases in which the study device is not used and participants that are not available for follow-up assessments, up to 95 participants may be enrolled to obtain 85 evaluable cases.

10.2 Analysis Populations

10.2.1 Primary Endpoint (Safety) Population

The population for the primary endpoint will be any participant into whom the study device is introduced, regardless of whether or not it is used as intended.

10.2.2 Secondary Endpoint (Performance) Population

The population for the secondary endpoint will be participants into whom the study device is introduced and used as intended.

10.3 Data Analyses

10.3.1 Statistical Methods

Due to the relatively small size of the study descriptive statistics will be presented for demographics, baseline characteristics, procedure duration and product performance (effectiveness). Continuous variables will be summarized as mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized as frequency and percentages.

10.3.2 Safety Analysis

For the Safety Population, the study primarily aims to rule out a 10% by-participant MACE incidence rate using the upper limit of a 2-sided 95% Wilson score confidence interval (equivalent to a 1-sided 0.025 α level) for the observed MACE incidence rate. To achieve this goal with the proposed sample size, a study incidence rate much lower than 10% needs to be observed in the study. In fact, up to 3 participants with MACE are allowed, which would be a rate of 3.5%. The Wilson score 95% confidence interval for 3/85 = 3.5% is (1.2%, 9.9%). As the upper limit of 9.9% is < 10%, a 10% incidence rate can be ruled out at a 1-sided 0.025 α level.

All MACE occurrences will be descriptively reported. If there are more than three participants with MACE events, the study will be judged as not meeting its primary safety objective.

Additionally, non-MACE adverse events occurring during or after the protocol procedure will be summarized as follows. The number and proportion of participants reporting any given event will be tabulated according to the highest severity reported. Separate tables will be constructed for (a) all reported adverse events (including adverse device effects), (b) protocol procedure/device related adverse events, (c) serious adverse events, and (d) adverse events requiring study device discontinuation.

10.3.3 Performance Analysis

For the Performance Population, the proportion of participants achieving the composite secondary endpoint of Device Oriented Clinical Outcome (DOCE), defined as the successful deployment and retrieval of the LiquID device without any device deficiencies or where use of the LiquID device directly leads to a MACE, target vessel dissection, longitudinal stent deformation or proximal collar stent stripping, will be reported with a 95% confidence interval. In addition, the proportions of (a) participants achieving each component of DOCE, (b) participants achieving POCE, and (c) study device that malfunctioned will be similarly reported.

11.0 RISK ANALYSIS

11.1 Summary of Expected Benefits

It is anticipated that the LiquID devices will provide additional support for other devices (e.g., guidewires, stent delivery systems, etc.) in coronary interventional cases that will optimize ease-of-use and device manipulation.

11.2 Summary of Potential Risks

The LiquID devices are not anticipated to add any incremental risk to interventional procedures. The following adverse events are anticipated adverse events associated with all interventional procedures:

- Access site/groin complications including but not limited to:
  - AV fistula
  - Bleeding
  - Bruising
  - Hematoma
  - Infection
  - Oozing

  - Pain
  - Pseudoaneurysm
- Air embolus
- Allergic reaction to any of the following:
  - Contrast dye
  - Anesthesia anesthetic medications
  - Procedure medications
  - Materials in devices used in procedure
- Apnea
- Arrhythmias
- Arterial perforation
- Atrial septal defect
- Blood loss requiring transfusion
- Blood toxicity
- Chest pain or other symptoms due to or indicative of (but not limited to) any of the following:
  - Angina
  - Discomfort
  - Endocarditis
  - Pericardial effusion with or without cardiac tamponade
  - Pericarditis
  - Pleural effusion
  - Pulmonary edema
- Dissection or thrombosis with or without vessel occlusion
- Fever
- Hypertension/hypotension
- Ischemia
- Infection
- Prolonged procedure time
- Renal insufficiency/failure
- Respiratory failure/hypoxia
- Stroke/transient ischemic attack
- Surgery to recover failed/embolized devices
- Occlusion of coronary artery branch
- Myocardial infarction
- Death
- Pain
- Procedure failure requiring additional intervention/surgery
- Toxicological response
- Vagal reaction
- Valvular damage/insufficiency
- Ventricular failure
- Vessel trauma

11.3 Justification of Clinical Trial Design

The design of the study is commensurate with the risk-benefit profile of the device and the minimal incremental potential risk posed to potential study participants. The size of the trial provides adequate post-market evidence of product safety and performance. Guide catheter extension (GCE) devices are support devices used in interventional procedures that have been established in clinical practice with an acceptable safety and performance profile. The LiquID devices are new GCE that is expected to have similar safety and performance. Therefore, the trial design is such that its results can be easily compared with outcomes from previous GCE devices. The study endpoints were selected based on outcomes from prior clinical studies of GCE devices and in consultation with study investigators. Bias will be minimized by the used of inclusion/exclusion criteria and enrollment of consecutive patients who qualify for the study.

12.0 ADVERSE EVENTS

12.1 Definitions

Adverse Event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the device.

Adverse Device Effect: An adverse event related to the use of the device

Serious Adverse Event: An adverse event that:

- Led to death
- Led to serious deterioration in the health of the participant that resulted in:
  - A life-threatening illness or injury
  - A permanent impairment of a body function
  - In-patient or prolonged hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
- Led to fetal distress, fetal death, or congenital abnormality or birth defect

Serious Adverse Device Effect: An adverse device effect resulting in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect: A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

12.2 Severity

The following categories of adverse device events severity are to be used:

Mild	Easily tolerated by the participant, caused minimal discomfort, and did not interfere with everyday activities;
Moderate	Sufficiently discomforting to interfere with everyday activities;
Severe	Prevents everyday activities.

12.3 Relatedness

The following categories of adverse events causality, both to procedure and device, are to be used (see guidance document[9] for additional details):

Causal	Event is associated beyond reasonable doubt
Probable	Relationship seems relevant and/or cannot reasonably be explained by another cause, but additional information may be obtained
Possible	Relationship is weak but cannot be ruled out completely
Unlikely	Relationship seems not relevant and/or can be reasonably explained by another cause
Not related	Event clearly due to another cause and/or cannot reasonably be shown to be related in any manner

12.4 Reporting Timeline

Adverse events are to be reported on case report forms, typically within two weeks of the event. Serious adverse events must be reported immediately to the Sponsor Vigilance Responsible Person, who can be reached at +1-612-615-9058 or ckugler@seiglamedical.com. Serious adverse events must also be reported to the Ethics Committee according to the Ethics Committee guidelines.

13.0 ETHICS

13.1 Sponsor Statement of Compliance

The Sponsor will conduct the clinical study in accordance with the clinical investigational plan, the ethical practices with their origin in Declaration of Helsinki, the principles of ISO 14155:2011 - Good Clinical Practices (GCP), and applicable regulatory requirements. This trial will not commence until a favorable opinion has been obtained by an appropriate ethics committee, including any conditions imposed by the committee. Insurance will be provided by the Sponsor as required by applicable laws in the countries in which the study is being conducted.

13.2 Study Financing

The study will be completely funded by the Sponsor, Seigla Medical, Inc. The Sponsor will reimburse the clinical site for work performed in the collection of data for the study. There will be no direct payments to any member of the research team at the clinical site. A Clinical Trial Agreement (CTA) will be executed with each investigational site to include such reimbursement as well as to document sponsor and site obligations and responsibilities during the investigation.

13.3 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), applicable regulatory requirements, and institutional procedures.

13.4 Ethics Committee (EC)

The investigator will undertake the study after a favorable opinion of the protocol and adjunctive materials (e.g., informed consent form) has been obtained from a local EC and a copy of this opinion has been received by the Sponsor.

During the conduct of the study, investigators must submit progress reports to the EC as required and request re-review and approval of the study at least once a year. After the study is concluded, the investigator should notify the EC of this status and prepare a final report for EC review.

13.5 Participant Care After Investigation End, Temporary Halt or Early Termination

Following completion of a participant's participation in the investigation or in the event of a temporary halt to enrollment or early termination of the investigation, study participants will be cared for as standard for their clinical condition. Participants' participation in the investigation will not alter their clinical care following their participation in the study.

13.6 Participant Confidentiality

The participant will receive all information as required by the EU General Data Protection Regulation (GDPR), including the identity of the controller, the clinical research purposes, the fair processing of his data, and all his/her data participants rights. Additional details are listed in the informed consent form.

Only Sponsor personnel with an upfront agreed and approved assigned task on the trial that requires to know the full identity of the participant will have access to data that fully identifies the participant. This consists of personnel supporting clinical cases and monitoring/audit personnel. All other Sponsor personnel working on the trial will only have access to data using the unique participant identification code. All sponsor personnel have been adequately trained on applicable rules and regulations on the protection and confidentiality of personal data. Any unintentional exposure of personal data will immediately be reported by the Sponsor to the clinical site. Any exposed data will be immediately returned to the site or destroyed and the applicable Data Protection Authority (DPA) will be notified of the data breach by the site. The latter will also take every precaution to avoid such personal data breaches in the future.

During this study, the following medical information, results and participant personal data will be collected, processed and sent to the Sponsor:

- Medical history;
- Demographic data (gender, age);
- Treatment data regarding use of the study product;
- Data regarding participant status and/or symptoms;
- Medication taken;
- Results of assessments required per this protocol

The data will be kept in the participant's medical file and portions of the data will be transferred to study Case Report Forms (CRFs) within an Electronic Data Capture (EDC) system. Participant names will not be used but will be replaced by a unique study-specific subject code. Only the Investigator and his/her study team, the trial monitor, auditor and safety data reviewers, who are Sponsor representatives or regulatory inspectors have access to participant identity.

The study team will ensure that participant name and other personal information will never be released outside of the study institution. Study data transmitted to the Sponsor will not contain any combination of elements that might allow participants to be identified with that information alone.

The research team will take every precaution to respect privacy in accordance with relevant legislation and EU Directives on protection of individuals with regard to the processing of personal data. The data in the study database will be pseudo-anonymised, so that a number will be assigned to each participant which will be mapped to identifiable participant details

at each hospital site only. This means that the data in the database is non-identifiable but will permit re-identification by the local site Investigator in case of emergencies and as required to follow-up with the participant. The data for this study may be transferred within and/or outside the EU in line with reporting requirements. For data transferred outside the EU, the data controller must be assured of the legality and privacy safeguards of the transfer and ensure adherence to all other applicable legislative and regulatory requirements including GDPR and Clinical Trial legislation pertaining to such data transfer.

13.7 Medical Monitor

Due to the small size and anticipated rapid enrollment of the study, a Medical Monitor will be responsible for study safety oversight and event adjudication in lieu of a safety committee. The Medical Monitor will be independent of any clinical site. All adverse events will be reviewed by the Medical Monitor. Any participant-level data questions from the Medical Monitor will be forwarded to the sites for resolution via a database query. Any concerns regarding overall study safety, including recommendations for enrollment holds will be immediately forwarded to the Sponsor and will result in a timely meeting with the Sponsor to discuss those concerns. Any such meeting will be documented via meeting minutes.

13.8 Enrollment Interruption/Early Termination

The Sponsor reserves the right to interrupt enrollment in the investigation and/or terminate the investigation at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of events in this or other studies potentially affects the rights, safety, and/or welfare of participants in the investigation
- Enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

Such action will be done in consultation with the Medical Monitor. The Sponsor will provide written notification of this and the trial participants, Ethics Committee and Regulatory Authorities will be promptly informed or notified.

14.0 MONITORING RESPONSIBILITIES & PLAN

14.1 Source Documentation

Source documents are original records, or certified copies of original records, that contain clinical findings, observations or other activities in a clinical trial (e.g., hospital records, clinical and office charts, laboratory notes, participant diaries, or evaluation checklists) necessary for the documentation and evaluation of the clinical trial.

Source document worksheets may be used to supplement other medical records but should not be reviewed as the only source. Worksheets must be treated as medical records, that is, signed and dated by the person performing the evaluation.

Photocopies of source documents are acceptable for review only if the original document can be provided upon request. The monitor will check the CRF data points against the source document data points during a monitoring visit.

The Sponsor and Principal Investigator shall maintain the clinical investigation documents as required by the applicable regulatory requirement(s). They shall take measures to prevent accidental or premature destruction of these documents. The Principal Investigator or Sponsor may transfer custody of records to another person/party and document the transfer at the investigation site or at the Sponsor's facility.

14.2 Monitors

Field and monitoring personnel contact information will be provided once field and monitoring personnel are finalized.

14.3 Monitoring Visits

Prior to beginning the study, Sponsor personnel will contact each investigator to discuss the investigational plan and to review the data requirements in detail. The monitor will visit the investigator periodically during the study to monitor progress, verify that all study requirements are completed and answer any questions that may arise. During these visits, the monitor may review the participant records to verify that all records and files are current and to assure compliance with all requirements of this investigational plan.

The monitoring plan will consist of a study initiation visit to train the site on the CIP and case report forms. After the index procedure, a monitoring visit will take place to review the pre-procedure and index procedure forms. A final monitoring visit will take place to review any outstanding items from the previous visit and any follow-up visit forms. This last monitoring visit may or may not be combined with a study close-out visit.

Due to the small size of the study, the low number of site visits required and anticipated rapid enrollment, no frequency of monitoring is specified.

14.4 Publication Policy

The right of individual Investigators to publish trial results with regard to educational and scientific purposes shall not be infringed. Investigators will submit drafts of all manuscripts to the Sponsor prior to submission to ensure accuracy of technical details. Publication of individual results will await the publication of the multicenter study results, however, if the multicenter results are not published within one year, individual site data may be published.

15.0 DATA MANAGEMENT

Data will be collected using an EDC system called Viedoc. This validated database will undergo database-specific testing and verification prior to the entry of clinical data. Data will be entered and monitored from any computer directly into the online database. Embedded edit checks will aid data entry by reducing the number of entry errors due to missing data, incorrect data format, and/or improper data type. In addition, some limited logistical data checks may also be

employed to verify certain data fields. Once the data points are entered, further edit checks will generate queries that will be forwarded to the site for clarification and/or correction. All data entry and/or edits will be tracked by user in the database to ensure data integrity. Once all queries are answered and all data is entered, the online database will be closed.

15.1 Data Retention

Once the database is closed, data will be exported from the database for data analysis. This original export will be maintained according to applicable national regulatory requirements. Data from the clinical database will be retained according to the Sponsor's documentation retention policies. At a minimum, data will be retained as required by national regulations for each country participating in the study.

16.0 CLINICAL INVESTIGATIONAL PLAN (CIP)

16.1 Deviations

Deviations from the CIP, GCP, applicable regulatory requirements, or institutional procedures should be documented. In general deviations are not allowed except to protect the rights, safety or well-being of a participant. Deviations to maintain the scientific integrity of the trial are also allowed with prior approval from the Sponsor. In all cases, the deviations will be reported to the Sponsor as soon as possible if not reported prior to the deviation taking place but no later than 10 days after the deviation has taken place.

Participant non-compliance, which is not within the control of the Investigator and is a participant's right, does not need to be reported unless it impacts study data. Non-compliance issues include, but are not limited to, informed consent not obtained, inclusion or exclusion criteria not met, missed visits due to site oversight, protocol visits conducted outside the defined time period, required testing not completed.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of participants are allowed without prior approval of the Sponsor but shall be documented and reported to the Sponsor and the Ethics Committee as soon as possible but no later than 5 days after the deviation has taken place and/or according to Ethics Committee policy. All deviations will be recorded by the Sponsor and reported to ethics committees according to their reporting requirements.

16.2 Modifications

Modification of the CIP and related documents is not anticipated but in the event it is necessary, the Sponsor will consult with the Investigators to revise the plan or related documents. A record of the revision will be maintained within the plan or other document that will include the revision letter, the date of the revision and a summary of the revision(s). All modifications will be reported to ethics committees and competent authorities as required.

16.3 Final Report

At the conclusion of the trial, or in the event of premature trial termination, a final report of the study results will be generated by the Sponsor. This report will be submitted to all participating sites and the ethics committee within the timeline required by applicable regulations.

17.0 REFERENCES

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