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For Submission of Study Documents

Study Title:	Acetaminophen Interferent Evaluation of the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System (CP-013)
NCT Number:	NCT06560177
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Acetaminophen Interferent Evaluation of the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System

Protocol Number: CP-013

Investigational Device: The Biolinq MicroArray Intradermal Continuous Glucose Biowearable System

Study Sponsor: Biolinq, Inc.

Study Contacts:

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Version Number: 0

Version Date: August 6, 2024

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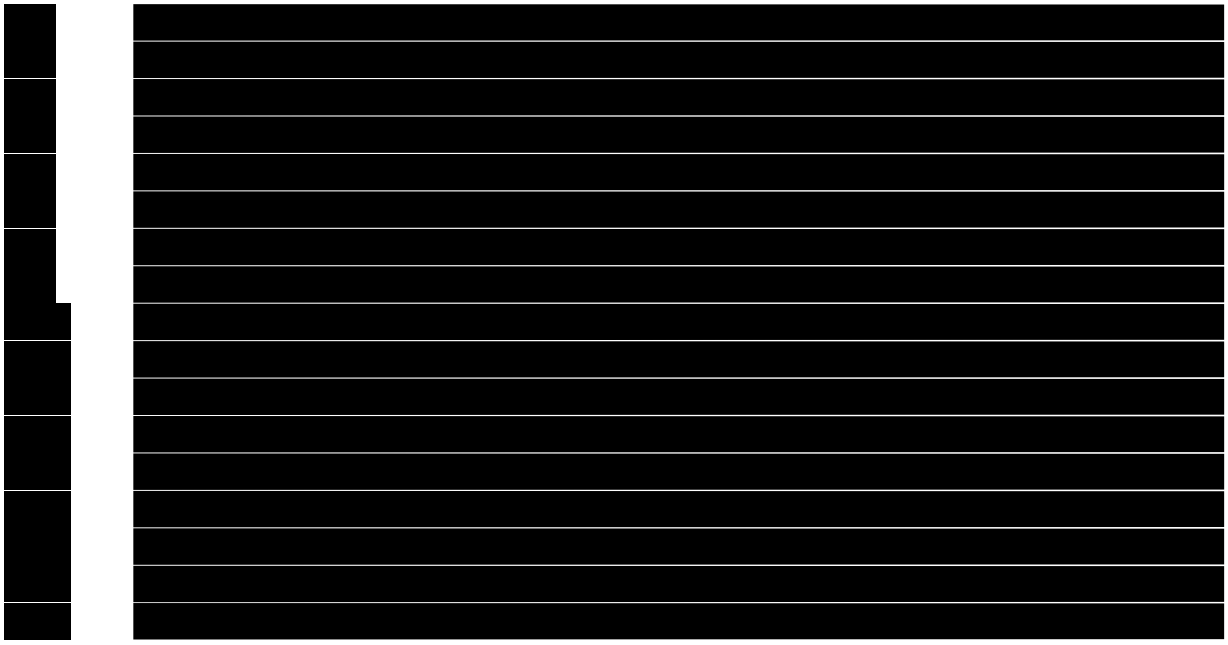

2 PROTOCOL SIGNATURE PAGE

Protocol Title: Acetaminophen Interferent Evaluation of the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System

Protocol Number-Version: CP-013, Version 0

Protocol Date: August 6, 2024

Sponsor: Biolinq, Inc.

The undersigned have read and understand the Protocol specified above and agree on its content. I/we agree to conduct this study in accordance with applicable FDA regulations, including parts 11 (Electronic records; electronic signatures), 50 (Protection of human subjects), 54 (Financial disclosure by clinical Investigators), and 56 (Institutional Review Boards), of CFR Title 21. Investigators shall also conduct this study in accordance with any IRB requirements and local laws.

_____ _____

Investigator Signature Date

_____

Investigator Name

_____

Name of Institution

3 ABBREVIATIONS

Table 1 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AFE	Analog Front End
APAP	N-acetyl-para-aminophenol *(commonly known as acetaminophen or paracetamol)*
ARD	Absolute Relative Difference
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitor/Monitoring
CRF	Case Report Form
DKA	Diabetic Ketoacidosis
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycosylated Hemoglobin
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
IMU	Inertial Measurement Unit
IV	Intra Venous
LA	Laboratory Analyzer
MARD	Mean Absolute Relative Difference
mg/dL	Milligrams per deciliter
NFC	Near Field Communication
OCT	Optical Coherence Tomography
PCB	Printed Circuit Board
PI	Principal Investigator
POC	Point of Care
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMBG	Self-Monitoring Blood Glucose
SOA	Schedule of Activities
YSI	YSI 2300 STAT PLUS Analyzer
UADE	Unanticipated Adverse Device Effect
US	United States

4 PROTOCOL SYNOPSIS

Table 2 Protocol Synopsis

Title:	Acetaminophen Interferent Evaluation of the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System
Study Sponsor:	Biolinq, Incorporated
Investigational Device:	Biolinq System: Biolinq MicroArray Intradermal Continuous Glucose Biowearable System
Reference Device:	FDA-cleared Laboratory Analyzer (LA) • YSI STAT PLUS 2300 Glucose and L-Lactate Analyzer (Yellow Springs, Ohio)
Comparator Devices:	FDA-cleared Self-monitoring blood glucose (SMBG) meter and Continuous Glucose Monitoring (CGM) [redacted]
Design:	Open label, prospective, observational, single-site, and single-arm This study is designed to be a Non-Significant Risk study with no deliberate manipulation of glucose in subjects with diabetes.
Objective:	The primary objective of the study is to evaluate the interference effect of acetaminophen (APAP) on the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System during [redacted]
Study Population	Otherwise, healthy adult subjects (≥ 18 years old) with diabetes.
Number of Subjects:	Up to 35 subjects enrolled [redacted]
Number of Centers:	One (1) investigational center in the United States will participate in the study.
Estimated Duration:	[redacted]

Primary Endpoint:	[redacted]
Safety Analyses:	• Overall adverse device effect rate • Individual adverse device effect rates
Observational Analyses:	• [redacted]
Sample Size Statistical Rationale:	[redacted]
Inclusion Criteria:	Individuals may be included in the study if they satisfy all the following: <u>General</u> 1. ≥ 18 years old. 2. Willing and able to provide written signed and dated informed consent. <u>Diabetes History and Health</u>

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	3. Diagnosis of diabetes (Type 1, 2 or LADA) 4. Weigh at least 110 lbs (50 kilograms). 5. Be otherwise in good health, as determined by a medical care professional. 6. Willing to refrain from Acetaminophen (APAP) use for 72 hours prior to Biolinq application and for the duration of the study the duration of study enrollment (except for as administered In-Clinic). <u>Device and Glucose Assessments – Willing to:</u> 7. Wear one (1) Biolinq Biowearable following the application procedure on the volar forearm for up to 3 days. 8. Wear one (1) commercial CGM ([redacted]) on the abdomen for up to 3 days per approved labeling. 9. Participate in one (1) In-Clinic session lasting up to 8 hours of blood draws (anticipated up to 10 hours on site). 10. Perform up to five (5) fingersticks a day with the SMBG device provided during non-in-clinic days. 11. Avoid immersing study devices into water (e.g., no hot tub, SCUBA diving).
Exclusion Criteria:	Individuals with any of the following will be excluded: <u>General</u> 1. Current participation in another investigational study protocol. (If a subject has recently completed participation in another drug study, the subject must have completed that study at least 30 days prior to being enrolled in this study.) *Note*: Subjects will not be excluded if enrolled in another observational trial, wherein the subject is in the follow-up phase and no tests/procedures impacting the subject's health are required. Subjects will be excluded if they have been previously enrolled in this study. 2. Work for, are family members with, or live with someone that works for the sponsor or competitor diabetes-related company (includes social media influencers or bloggers). 3. In the investigator's opinion, any reason that may lead to subject non-compliance with study requirements or confound study data. <u>Health</u> 4. Currently taking Hydroxyurea or chronic use of a medication containing acetaminophen in the last 30 days. 5. Known allergy to medical grade adhesives, acrylic, latex, or isopropyl alcohol. 6. Known contraindication to taking the In-Clinic recommended oral dose of APAP (e.g., cirrhosis, chronic heavy ethanol use, breast feeding). 7. Have dermatological conditions that preclude wearing Biolinq Biowearables (e.g., extensive psoriasis, recent burns, severe sunburn, extensive eczema, extensive scarring, dermatitis herpetiformis, skin lesions, erythema, infection, or other conditions at the discretion of the investigator). 8. For subjects of child-bearing potential, pregnant or not practicing an acceptable form of birth control during the study. 9. Hematocrit measurement via point-of-care (POC) or laboratory testing that is less than the applicable below-mentioned value: a. Male: 36.0% b. Female: 33.0%

	10. Have donated blood, had significant blood loss, or participated in a study with significant blood sampling (420 cc or more) within 56 days prior to study enrollment or plan to participate in such activities during study wear. 11. Required or scheduled to have diathermy, X-ray, MRI, or CT during study wear. 12. In the investigator's opinion, the subject has a history of concomitant medical condition that could interfere with the study participation or present a risk to the safety and welfare of the subject or study staff. Such historical conditions include but are not limited to: a. Syncope in past 6 months b. Severe hypoglycemia (loss of consciousness, seizure, or emergency medical technician assistance within the past 6 months) c. Diabetic ketoacidosis (DKA) requiring hospital admission in the past 6 months d. Coagulopathy e. Chronic infectious disease (e.g., HIV/AIDS, Hepatitis B or C) f. End stage renal disease and currently managed by dialysis or anticipating initiating dialysis during the study wear period g. History of congestive heart failure
Methodology:	**Consent and Screening:** Subjects are considered enrolled after signing and dating an Institutional Review Board (IRB) approved informed consent form (ICF). Screening activities must be completed within 30 days prior to the Biolinq application and include eligibility criteria, vitals, demographics, medical history review, Fitzpatrick Skin assessment, pregnancy testing (as applicable), A1c and hematocrit tests. Subjects who meet the study eligibility criteria will be scheduled for Biolinq Biowearable application. Screen failures must exit the study and reasons for exit are documented. Subjects who do not complete screening activities within 30 days are still eligible to participate in the study but must be reconsented and re-screened. **Device Applications (Day 1):** A POC pregnancy re-test is required if the previous test is greater than 3 days prior to application day. [redacted] **Home Use (Non-in-clinic Day):**

Subjects will be asked to perform up to five (5) SMBG fingersticks on all days after Device Application Day when not attending an in-clinic day. The recommended timing of these samples is as follows: 1 for fasting morning, 3 at 1-hour post-meal, and 1 at bedtime.

In-Clinic Day with Removal Visit (Day 3):

All subjects will participate in one (1) in-clinic session [redacted] of the device intended wear period. Subjects are required to bring all devices to the visit.

Subjects will arrive at the clinic for the observational in-clinic session lasting up to 10 hours (8 hours of active blood draws). [redacted].

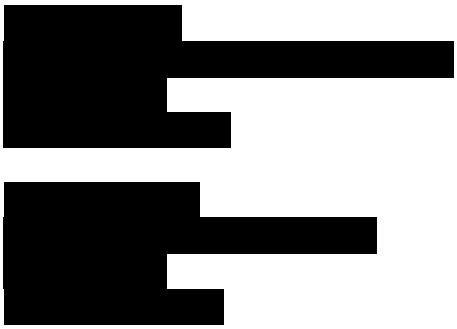
The YSI STAT PLUS 2300 Glucose and L-Lactate Analyzer will be used to measure glucose values (reference data) for all blood draws during the in-clinic session. Measurements will be made at 15 ± 7-minute intervals throughout the in-clinic session. An SMBG fingerstick on the same arm as the Biolinq Biowearable will be taken every at every 30- minute intervals corresponding to every other blood draw for comparative purposes. No glucose manipulations/challenges will be performed. Additional or more frequent blood draws or fingersticks may be performed as per investigator or designee discretion for monitoring/treating hypoglycemia or hyperglycemia.

[redacted]

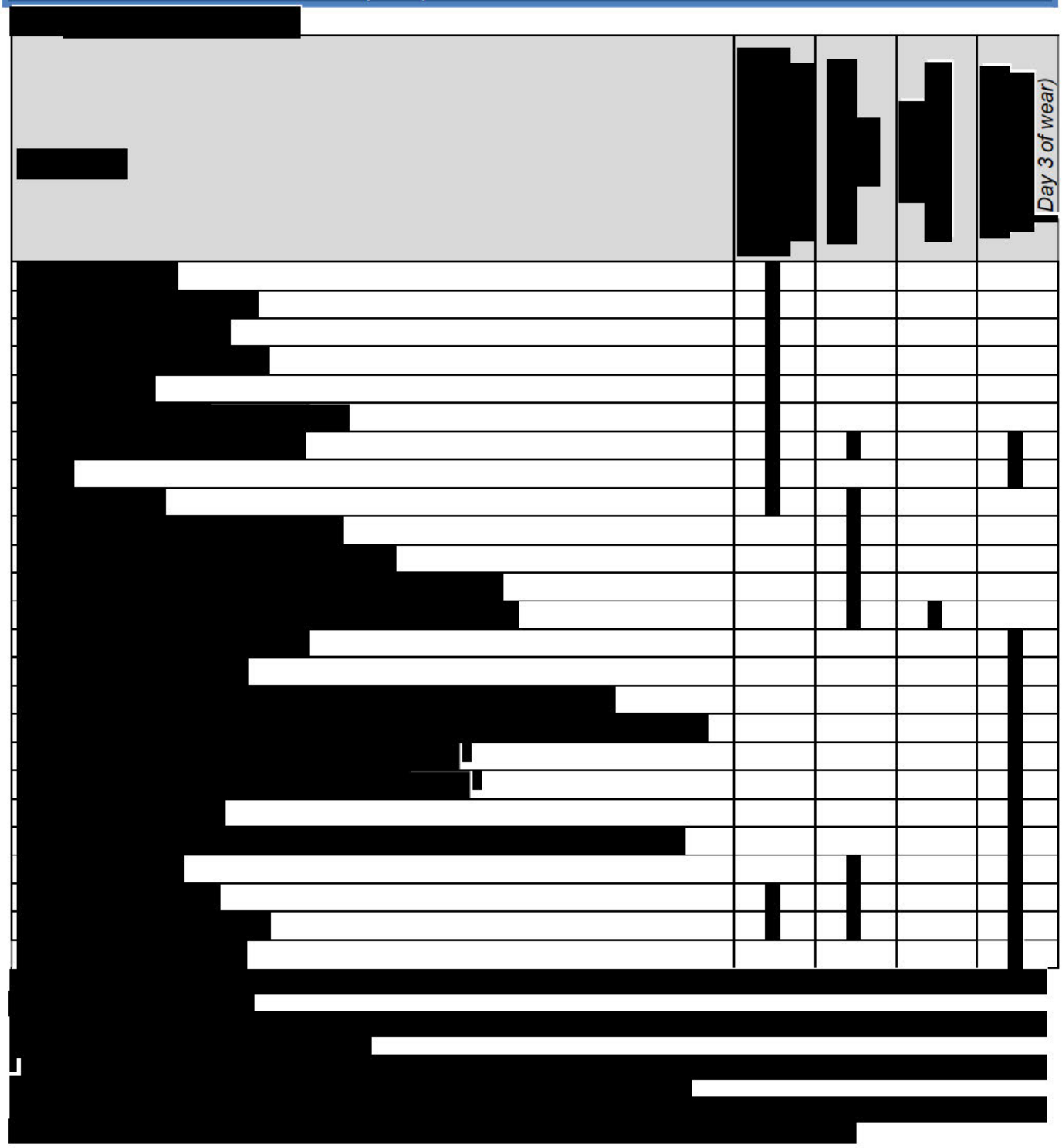
Investigators or designated staff will monitor subjects for safety during an in-clinic session. Appendix 1 – In-Clinic Guidelines will be provided as guidance, but the investigator or designee will maintain final discretion for any in-clinic procedures and methods used based on their medical expertise and training. Fast-acting carbohydrates, glucagon, and ketone testing kits will be available at clinical sites for safety of subjects. Subjects will be discharged at the end of the in-clinic day according to investigator discretion (recommended discharge guidelines provided in Appendix 1 – In-Clinic Guidelines).

Device Removal (After In-Clinic Discharge)

Device removal will occur after completion of the scheduled In-Clinic. [redacted]

	Adverse Event, Protocol Deviation and Device Observation Assessments: After consent and through study exit, each subject will be monitored for any new onset and/or worsening of adverse events regardless of the relatedness to the investigational device, procedure, protocol deviations, or device observations. Adverse events will be followed through resolution. If the investigator deemed the event is stable and requires no additional follow-up, then the subject may exit the study. Protocol Deviations and Device Observations will be documented and reported as applicable. **Study Exit:** Subjects may exit the study after screen failure, if Biolinq Biowearable fails prior to end of wear period, or at subject completion of protocol after device removal and resolution of any ongoing adverse events. Subjects lost-to-follow-up may exit after at least three (3) attempts to contact the subject have been documented. Subjects may also exit study at any time with their withdrawal of consent or an investigator decision to withdraw the subject for cause. Reason for study exit for each subject must be documented.
Sponsor and Contact Information:	Biolinq, Incorporated 10260 Sorrento Valley Road San Diego, California 92121 

5 SCHEDULE OF ACTIVITIES (SOA)



6 INTRODUCTION

Early generations of FDA-approved Continuous Glucose Monitoring (CGM) Systems relying on electrochemical sensors have been subject to varying degrees of interference from several medications and nondrug compounds[4-9]. This interference occurs when the specific electrochemical methodology to measure interstitial glucose is

influenced by substances that can shift the measured glucose in one direction or the other[10, 11]. As CGM technology progressed and non-adjunctive use indications became the goal, new generations of CGM Systems have demonstrated resistance to various interferents.[1, 12, 13]

One of the commonly evaluated interferents, acetaminophen (APAP), also known as paracetamol in many countries, is a widely used non-opioid pain-relieving and fever-reducing agent[14]. [redacted].

The primary objective of the study is to evaluate the interference effect of acetaminophen (APAP) on the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System. For the purposes of the study, the maximum recommended adult dose for any 6-hour period will be evaluated[2]. Because APAP reaches peak concentration in the blood within 90 minutes (with a half-life of 1.5-2.5 hours)[3], [redacted]

[redacted]

7 STUDY MATERIALS

7.1 BIOLINQ MICROARRAY INTRADERMAL CONTINUOUS GLUCOSE BIOWEARABLE SYSTEM

[redacted]

The reportable glucose range for the sensor is between 70 mg/dL and 400 mg/dL. The device does not have any audible or vibratory alerts or alarms.

A summary of clinical studies conducted by Biolinq with the current version Biolinq MicroArray Intradermal Continuous Glucose System is provided in a Report of Prior Investigations.

7.1.1 SYSTEM OVERVIEW

The Biolinq MicroArray Intradermal Continuous Glucose Biowearable System consists of multiple components broadly categorized as follows:

i. Biolinq Microarray Sensor
ii. Biolinq wearable
iii. Biolinq applicator

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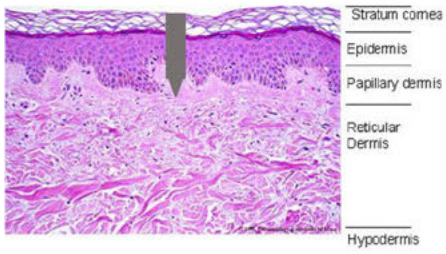
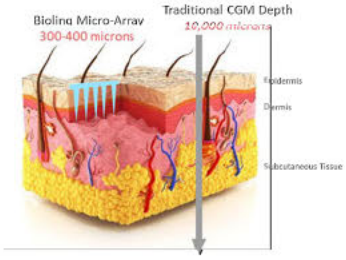
The Biolinq sensor consists of a sterile microarray sensor stack assembly that resides in the upper strata of the reticular dermis to measure interstitial glucose. The sensor is directly connected to a wearable that is adhered to the skin and is applied using the Applicator assembly. The Biolinq System measures and reports glucose information for up to five (5) days. The Biolinq System is designed to measure glucose levels for up to five (5) days. The wearable applied may also contain non-medical device designated off the shelf-components that capture actigraphy and environmental information to transfer to secondary display devices. [redacted]

[redacted]

[redacted]





[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2 OTHER STUDY DEVICE/MATERIALS

7.2.1 COMMERCIAL CONTINUOUS GLUCOSE MONITORING (CGM)

[redacted]

7.2.2 SELF-MONITORING BLOOD GLUCOSE (SMBG)

[redacted]

7.2.3 LABORATORY ANALYZER (LA)

During the In-Clinic Day, the FDA-cleared laboratory analyzer (LA) machine (YSI 2300D STAT PLUS Analyzer (Yellow Springs, Ohio)) will be used to measure venous sample glucose concentrations. Venous samples will be drawn according to a pre-specified protocol schedule and per the In-Clinic Guidelines located in Appendix 1 – In-Clinic Guidelines.

8 POTENTIAL RISKS AND BENEFITS

8.1 STUDY DEVICE RISKS

[redacted]

[redacted]

8.2 STUDY RISKS

[redacted]

Study Risk	Mitigation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Study Risk	Mitigation
[redacted]	• [redacted]

The Principal Investigator, or designee, will be responsible for determining whether an adverse device effect (ADE) is anticipated or unexpected. An ADE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9 RATIONALE FOR THE STUDY DESIGN

A separate study was designed and conducted to support a separate safety and effectiveness (pivotal) of the BLINQ device under the 21 CFR Part 812 IDE Regulation. This is a separate non-significant risk study to evaluate the effect of acetaminophen interferents to the Biolinq biowearables [redacted]

To help obtain comparisons across different glucose ranges without glucose manipulation, Biolinq will enroll both insulin-using and non-insulin-using persons with diabetes. The reference device selected to match the investigational device performance evaluated in the pivotal study is the YSI 2300D Stat Plus Glucose Lactate Analyzer (YSI 2300d).

10 STUDY OBJECTIVES

10.1 PURPOSE OF STUDY

The primary objective of the study is to evaluate the effectiveness of the Biolinq MicroArray Intradermal Continuous Glucose Biowearable System in preventing acetaminophen's interference effect on glucose sensing. [redacted]

10.2 PRIMARY PERFORMANCE ENDPOINTS

The interference effect of the Biolinq Biowearable to reference (YSI) is evaluated with a single maximum acetaminophen (APAP) dose of 1g (1000 mg). The primary endpoint is defined as

- [redacted]

10.3 DEVICE SAFETY

Safety of the Biolinq System will be characterized by the:

- Overall adverse device effect rate
- Individual adverse device effect rates

11 STUDY POPULATION

To help obtain potential varying glucose ranges (occurring without any deliberate glucose manipulation) in the study, the study will enroll subjects outside the intended commercial population of non-insulin-users.

11.1 INCLUSION CRITERIA

Individuals may be included in the study if they satisfy all the following:

General

1. ≥ 18 years old.
2. Willing and able to provide written signed and dated informed consent.

Diabetes History and Health

3. Diagnosis of diabetes (Type 1, 2 or LADA)
4. Weigh at least 110 lbs (50 kilograms).
5. Be otherwise in good health, as determined by a medical care professional.
6. Willing to refrain from Acetaminophen (APAP) use for 72 hours prior to Biolinq application and for the duration of the study the duration of study enrollment (except for as administered In-Clinic).

Device and Glucose Assessments – Willing to:

7. Wear one (1) Biolinq Biowearable following the application procedure on the volar forearm for up to 3 days.
8. Wear one (1) commercial CGM ([redacted]) on the abdomen for up to 3 days per approved labeling.
9. Participate in one (1) In-Clinic session lasting up to 8 hours of blood draws (anticipated up to 10 hours on site).
10. Perform up to five (5) fingersticks a day with the SMBG device provided during non-in-clinic days.
11. Avoid immersing study devices into water (e.g., no hot tub, SCUBA diving).

11.2 EXCLUSION CRITERIA

Individuals with any of the following will be excluded:

General

1. Current participation in another investigational study protocol. (If a subject has recently completed participation in another drug study, the subject must have completed that study at least 30 days prior to being enrolled in this study.) Note: Subjects will not be excluded if enrolled in another observational trial, wherein the subject is in the follow-up phase and no tests/procedures impacting the subject's health are required. Subjects will be excluded if they have been previously enrolled in this study.
2. Work for, are family members with, or live with someone that works for the sponsor or competitor diabetes-related company (includes social media influencers or bloggers).
3. In the investigator's opinion, any reason that may lead to subject non-compliance with study requirements or confound study data.

Health

4. Currently taking Hydroxyurea or chronic use of a medication containing acetaminophen in the last 30 days.
5. Known allergy to medical grade adhesives, acrylic, latex, or isopropyl alcohol.
6. Known contraindication to taking the In-Clinic recommended oral dose of APAP (e.g., cirrhosis, chronic heavy ethanol use, breast feeding).
7. Have dermatological conditions that preclude wearing Biolinq Biowearables (e.g., extensive psoriasis, recent burns, severe sunburn, extensive eczema, extensive scarring, dermatitis herpetiformis, skin lesions, erythema, infection, or other conditions at the discretion of the investigator).
8. For subjects of child-bearing potential, pregnant or not practicing an acceptable form of birth control during the study.

9. Hematocrit measurement via point-of-care (POC) or laboratory testing that is less than the applicable below-mentioned value:
   a. Male: 36.0%
   b. Female: 33.0%
10. Have donated blood, had significant blood loss, or participated in a study with significant blood sampling (420 cc or more) within 56 days prior to study enrollment or plan to participate in such activities during study wear.
11. Required or scheduled to have diathermy, X-ray, MRI, or CT during study wear.
12. In the investigator's opinion, the subject has a history of concomitant medical condition that could interfere with the study participation or present a risk to the safety and welfare of the subject or study staff. Such historical conditions include but are not limited to:
    a. Syncope in past 6 months
    b. Severe hypoglycemia (loss of consciousness, seizure, or emergency medical technician assistance within the past 6 months)
    c. Diabetic ketoacidosis (DKA) requiring hospital admission in the past 6 months
    d. Coagulopathy
    e. Chronic infectious disease (e.g., HIV/AIDS, Hepatitis B or C)
    f. End stage renal disease and currently managed by dialysis or anticipating initiating dialysis during the study wear period
    g. History of congestive heart failure

12 STUDY DESIGN

12.1 DESIGN SUMMARY

The study will be an open label, prospective, observational, single-site, and single-arm non-significant risk study conducted in the United States.

12.2 DURATION OF PARTICIPATION

[redacted]

12.3 ESTIMATED STUDY DURATION

[redacted]

12.4 STUDY CENTERS

One (1) investigational center in the United States will participate in the study.

13 STUDY ENROLLMENT

13.1 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects may be recruited through various IRB-approved advertising methods including but not limited to digital campaigns, available Investigator treatment databases, print, radio, and the like. All advertising materials will be pre-approved by the reviewing IRB prior to implementation.

13.2 INFORMED CONSENT

To protect the rights, safety, and welfare of subjects, the study is conducted in accordance with the 21 CFR 50, Protection of Human Subjects. The Principal Investigator or designee, as delegated by Principal Investigator on site delegation of authority log, will explain the study nature, overview, purpose, objectives, expected participation duration, study activities, risks of study participation, alternative treatment, participation benefit, study sponsor, cost for participation, new information sharing, medical cost coverage if he/she gets hurt, stipend amounts, confidentiality, and IRB contact information. Subjects will be given ample time to consider their voluntary participation in the study and to ask questions. Potential subjects may take a copy of the IRB approved Informed Consent Form (ICF) home to review with family and friends prior to deciding on whether to participate in the study.

Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the Informed Consent Form will be offered to the participants for their records. The informed consent process will be conducted and documented within the IRB approved Informed Consent Document, with required signatures obtained, before the participant participates in any study activities. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.3 ENROLLMENT

Subjects who sign the IRB approved ICF will be considered “Enrolled” in this study.

13.4 SCREENING

- [redacted]

[redacted]

14 STUDY PROCEDURES

14.1 DEVICE APPLICATION VISIT/STUDY TREATMENT START

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.2 HOME USE

[redacted]

- [redacted]

[redacted]

[redacted]

14.3 IN-CLINIC DAY WITH DEVICE REMOVAL

[redacted]

14.3.1 ADMISSION

[redacted]

14.3.2 VENOUS BLOOD DRAW, CAPILLARY FINGERSTICK AND INTERFERFERENT TIMING

[redacted]

- [redacted]

[redacted].

14.3.3 DIABETES MANAGEMENT

[redacted]

14.3.4 DISCHARGE

[redacted]

14.3.5 DEVICE REMOVAL

[redacted]

- [redacted]

14.3.6 STUDY EXIT

[redacted]

15 DESCRIPTION OF SAFETY EVALUATION

15.1 DEFINITIONS OF ADVERSE EVENTS (AE)

An adverse event means any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the Biolinq MicroArray System. This definition includes events related to the Biolinq MicroArray System as well as events related to the procedures involved. All suspected adverse events will be assessed and monitored by the Principal Investigator, or designee, and recorded in the appropriate source worksheet and transcribed to Case Report Form.

15.1.1 ADVERSE DEVICE EFFECT (ADE)

An adverse device effect is an adverse event related to the use of the Biolinq MicroArray System.

15.1.2 SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or Biolinq, it results in any of the following outcomes:

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

15.1.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An UADE is not expected to occur; however, an unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by – or associated with – the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (including documents such as the protocol, the Informed Consent Form, and other study-related documents), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

An Unanticipated Adverse Device Effect (UADE) is a serious adverse device effect that has not been previously identified in nature, severity or degree of incidence in the investigational plan (including documents such as the protocol, the informed consent form, and other study-related documents).

15.2 SEVERITY OF ADVERSE EVENTS

All adverse events will be classified by the Principal Investigator or designee. The following guidelines will be used to describe severity.

- **Mild** – Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
- **Moderate** – Discomfort severe enough to cause interference with usual activities, requiring treatment but not extended hospitalization or intensive care for the subject.
- **Severe** – Incapacitating, causing inability to do work or usual activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment, requiring additional hospitalization or intensive care (prolonged hospitalization).

15.3 RELATIONSHIP OF ADVERSE EVENT TO THE STUDY DEVICE

The Principal Investigator, or designee, will assess all adverse events (AEs) and determine their relation to the Biolinq MicroArray System. The Principal Investigator, or designee, will use his/her clinical judgment to examine and evaluate the adverse event based on an examination of the subject and the temporal relationship with the use of the device. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to administration of the study device and cannot be explained otherwise.
- **Probably Related** –The AE has a strong temporal relationship to use of the investigational device and another etiology is unlikely.
- **Potentially Related** – The AE has a strong temporal relationship to the use of the investigational device and an alternative etiology is equally or less likely compared to the potential relationship to the investigational device.
- **Unlikely to be related** – The AE has minimum or no temporal relationship to use of the investigational device and/or a more likely alternative etiology exists.
- **Not Related** – The AE is completely independent of the investigational device and is due to an underlying disease state or concomitant medication or therapy not related to the study device.

All device-related irritation will be recorded. Post-removal follow-up may be requested until resolution in the case of any ongoing adverse events.

15.4 ADVERSE EVENT REPORTING

Any AE not considered an SAE, occurring during the study will be documented by the Principal Investigator or designee on the appropriate source worksheet, entered into the Electronic Data Capture system, and reported to the Sponsor within 30 days of the occurrence of the adverse event. All adverse events (mild, moderate, and severe) will be reported in the final Clinical Study Report.

15.4.1 SERIOUS ADVERSE EVENT (SAE) REPORTING

Any SAE, including death, that may occur during a clinical study must be reported immediately (within 24 hours of awareness) to Biolinq, Inc. Clinical Affairs personnel will document details and Clinical Affairs management's assessment of the SAE in a timely manner. The Sponsor contacts are listed on the protocol title page.

15.4.2 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) REPORTING

During the review of a reported SAE, if the PI, or designee, determines the severity or extent of the event was not cited in this protocol or the report of prior investigations, and the event was classified as at a minimum, possibly related to the device, the event will be documented as an UADE.

If the event is classified as an UADE, the PI or designee must notify their IRB and Biolinq will notify the FDA, reviewing IRBs, and other participating Investigators, as applicable, within ten (10) working days of the original SAE notification.

If it is determined that the UADE presents an unreasonable risk to subjects, Biolinq will terminate all investigations or parts of investigations presenting that risk as soon as possible, but not later than 5 working days after such determination is made and not later than 15 working days after Biolinq first receives notice of the original SAE. Biolinq will not resume a terminated study without IRB and FDA approval, as applicable.

15.5 DEVICE OBSERVATION REPORTING

A Device Observation (DO) is defined as any suspected inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, misuse or use errors, or inadequacy in information supplied by the Sponsor.

Site will document Device Observations on source documents and CRFs at each occurrence and notify sponsor. All applicable DOs will be recorded on the Investigational Product Accountability log.

16 STATISTICAL ANALYSIS & METHODS

16.1 ANALYSIS COHORTS

Analysis cohorts for the study are prospectively defined and are described in the following subsections.

Information pertaining to the statistical analysis methods using these cohorts is provided in the subsequent sections.

16.1.1 ENROLLED COHORT

The Enrolled Cohort includes all subjects who sign the study IRB approved informed consent. Analyses pertaining to screening eligibility, safety, and protocol compliance prior to the Biolinq application, and study exit will be performed using the Enrolled Cohort.

16.1.2 TREATED COHORT (ANALYSIS POPULATION)

All enrolled subjects who have undergone device application will be included in all analyses. All data that is collected during the study will be included in the analysis. [redacted]

16.2 STATISTICAL METHODS FOR SAFETY OUTCOME

Overall and individual adverse events are summarized for safety outcome by frequency and percentage. In addition, the number of AEs, ADEs, SAEs, SADEs, and UADE and percentage of Subjects with events are summarized. A by-Subject listing of adverse events will also be provided in the study report.

16.3 METHOD DEFINITIONS FOR PERFORMANCE METRICS

[redacted]

- [redacted]

16.5 JUSTIFICATION OF SAMPLE SIZE

[redacted]

16.6 OBSERVATIONAL ANALYSES

[redacted]

16.7 SUBGROUP ANALYSES

[redacted]

16.8 STATISTICAL METHODS FOR SCREENING, BASELINE, PROCEDURAL AND STUDY EXIT DATA

[redacted]

16.9 OTHER STATISTICAL CONSIDERATIONS

[redacted]

17 DATA MANAGEMENT PLAN

17.1 CASE REPORT FORMS (CRFS)

Investigators are responsible for delegating personnel to complete the appropriate case report forms for each subject enrolled in the study. The CRFs should be completed within 5 working days of study visit or the day data is received. The Investigator must sign for data accuracy and completeness contained on each CRF. Biolinq will provide training and instructions to each investigational site on how to properly complete these CRFs.

17.2 SOURCE DOCUMENTS

Source documents refer to the records on which clinical observations are first recorded. Original source documentation must be maintained at the investigational site to substantiate data entered on the CRFs. Source documentation must be made available by the investigational site so that information entered on CRFs is verified and facilitates monitoring by Biolinq or its authorized representative. Source documents must also be made available to any regulatory agency in the event of an inspection so that the integrity of study data may be verified.

The Sponsor will provide sample source worksheets to help with the collection of information for transfer to the EDC System. Sample source worksheets may be revised by site to match workflow or site requirements provided that all required data is collected. In cases where no original source data otherwise exists, a source document worksheet provided by the site or sponsor may be used to establish a source record. To minimize data-related errors, considerations should be taken to avoid duplicative generation of source documentation. All source documents must be signed and dated by a qualified individual generating the record and/or investigator when applicable.

17.3 DATA MANAGEMENT

A 21 CFR Part 11 compliant electronic data capture (EDC) system will be used for data collection in the study. User Acceptance Testing will be performed to validate each eCRFs utilized in the study prior to its use and all subsequent updates. Data is entered into the EDC system by trained delegated personnel as indicated on the Delegation of Responsibilities Log and on its appropriate electronic case report forms (eCRFs). The eCRFs must be completed or updated to reflect the latest data on each Subject participating in the study. The Investigator or authorized Sub-investigator electronically signs the eCRFs testifying data entry accuracy and completeness.

No study document should be destroyed without prior written agreement between Biolinq and the investigational site. If an investigational site is no longer enrolling Subjects or following any enrolled Subjects, an investigator may transfer custody of study records to Biolinq providing a notice of such transfer is given within 10 working days.

The investigational site must maintain study documentation on paper or electronic file for each Subject file. If additional study documentation is required for submission to Biolinq, it must be redacted to remove the Subject's name or other Subject identification, and the Subject's unique identification code inserted prior to being sent to Biolinq.

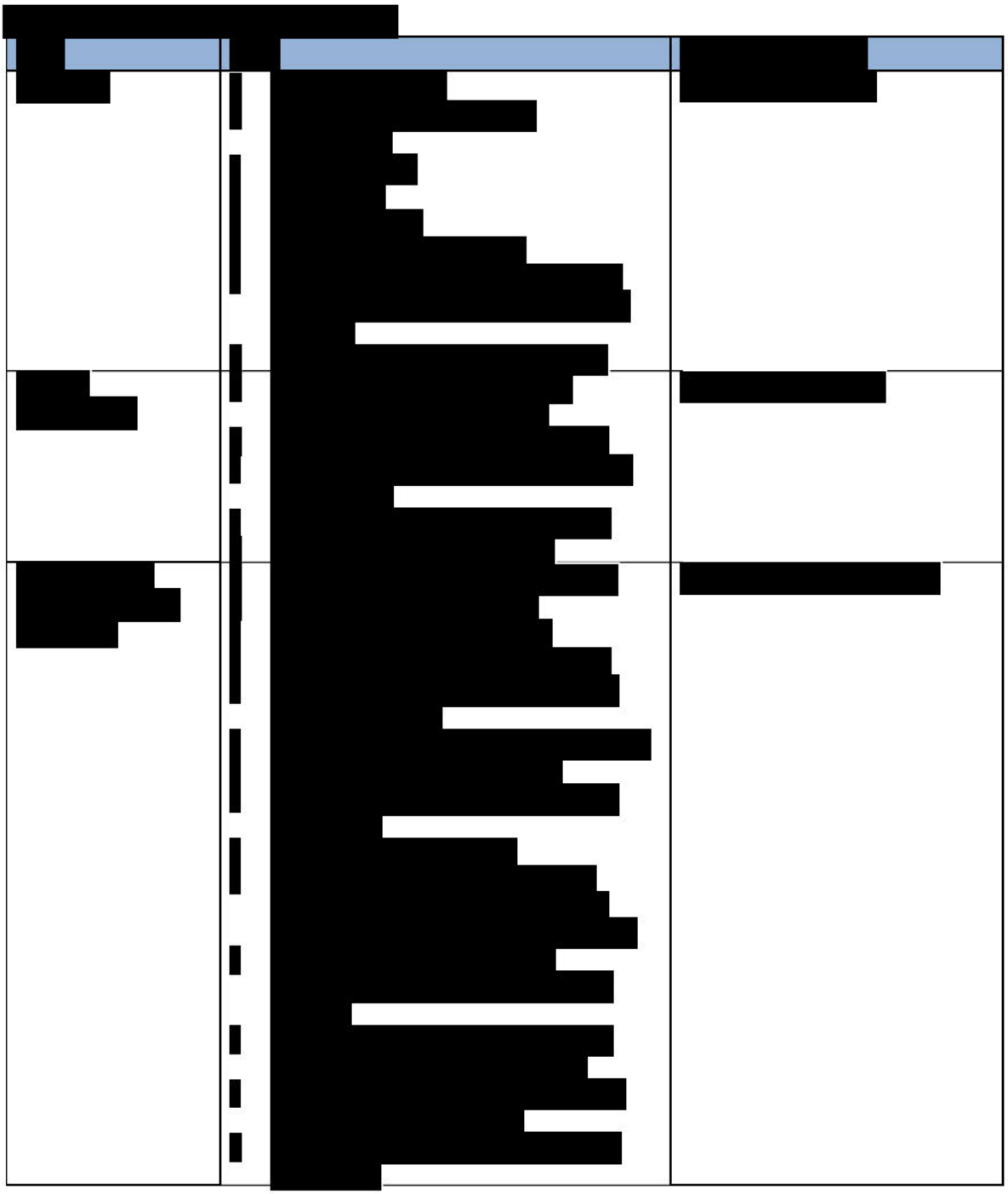
In the Subject file, information should include corresponding follow-up dates, data noted on Table 8, and reasons for early withdrawal from the study if applicable or study exit after activity completion per protocol. It must be possible to verify subject consent to participate in the study, inclusion, and exclusion criteria in the study from the Subject file. These documents should identify the Subject. Evaluation of these records should be documented as necessary, signed, and dated by the Investigator. All data recorded on the eCRFs must be in the Subject's source data.

17.4 DEVICE DATA DOWNLOAD

[redacted]

17.5 DATA COLLECTION

[redacted]



Visit	Data	Collection Period
[redacted]	[redacted]	[redacted]

18 ETHICAL CONSIDERATIONS

18.1 STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with ISO 14155:2020 Clinical Investigation of medical devices for human subjects – Good clinical practice, International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or 21 CFR Part 812).

The study will also be conducted in accordance with the Declaration of Helsinki (1964).

18.2 PROTOCOL APPROVAL AND AMENDMENTS

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/ Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

All revisions and/or amendments to the protocol and informed consent must be approved in writing by the Sponsor, the appropriate IRB, and regulatory body, as appropriate.

19 REPORTS

The Investigator or designee is responsible for completing the source worksheets and Case Report Forms (CRFs) in the Electronic Data Capture (EDC) system, as applicable. The Sponsor and Investigator will submit any progress or safety reports that the IRB or applicable regulatory authorities may require, including any final close-out reports.

20 MONITORING

Monitoring will be conducted by trained and experienced clinical professionals in accordance with Bioliq's standard operating procedures. Monitors will evaluate study conduct and documentation on an ongoing basis to ensure that

the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

20.1.1 PROTOCOL DEVIATIONS

The Investigator or designee is required to conduct the study in accordance with the protocol, the Study Agreement, and all applicable local and national regulations. A protocol deviation exists when a requirement in the protocol is not followed. All protocol deviations must be reported to the Sponsor using the appropriate source worksheet and entered into the Electronic Data Capture (EDC) system.

All protocol deviations that have the potential to affect the reliability or integrity of the study data will be reported to the sponsor and evaluated by the Principal Investigator, or designee, and Sponsor. Any protocol deviations that have the potential to adversely affect the health and safety of study subjects, adversely affect the reliability and integrity of the data, constitute a breach of subject confidential information, constitute a deviation from the IRB requirements for the study or constitute a failure to adhere to local, state, or federal regulations must be reported to the IRB and the FDA as required.

21 STUDY TERMINATION

Each subject's participation in the study will be terminated following the completion skin site evaluations after device removal, or when all adverse events have been resolved or deemed as ongoing but stable. The study will be terminated for a subject if they become acutely ill during the study.

Prior to sensor removal, the subject may voluntarily withdraw at any point in the study or the investigator and/or Sponsor may determine it is in the best interest of the subject to be terminated from the study. The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate source worksheet and entered into the Electronic Data Capture (EDC) system

The clinical study in its entirety will be considered complete upon completion of a final Clinical Study Report and per Biolinq's standard operating procedures.

22 INVESTIGATOR RESPONSIBILITES

The Investigator's signature on this protocol confirms that Investigator is familiar with all sections of the protocol and agrees to conduct this study in accordance with the provisions of the protocol and applicable regulations. The Investigator must sign this protocol prior to commencement of any study-related activities (e.g., screening).

Investigator and designees are responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care. The Investigator and designees are also responsible for obtaining IRB approval prior to study start and the written informed consent of each subject before he/she participates in this study. The informed consent must comply with FDA regulations and be approved by the IRB.

Other Investigator and designee responsibilities include ensuring completion of appropriate source worksheets, and entry into the Electronic Data Capture (EDC) system per the study timelines discussed in this protocol, the site initiation visit and subsequent monitoring visits. In certain circumstances Investigators or designee must report serious adverse events to the Sponsor and reviewing IRB as soon as made aware (without a delay that cannot be justified).

Investigator or designee will retain study records until the latter of the following: 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator or designee when these documents no longer need to be retained.

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23 SPONSOR RESPONSIBILITES

Biolinq, Inc. is the Sponsor of this study. The Sponsor is responsible for selecting qualified Investigators and providing them with the information needed to conduct the investigation properly. The Sponsor will ensure proper monitoring of the investigation and that IRB and FDA approvals have been obtained prior to the Investigator or designee commencing study-related activities. The Sponsor is also responsible for ensuring that the reviewing IRBs and FDA, if applicable, are promptly informed of significant new information.

23.1 CONFLICT OF INTEREST POLICY

This study is sponsored by Biolinq as part of the commercial development of the Biolinq MicroArray System. The Principal Investigator(s) is not an employee of Biolinq and any disclosable financial arrangement will be documented as appropriate on a financial disclosure form and reported to IRB as required. The Informed Consent process will be conducted by the Principal Investigator(s) or designee.

23.2 STUDY RECORDS

This study will be conducted in accordance with Biolinq's standard operating procedures. All clinical study sites will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

23.3 INVESTIGATIONAL DEVICE ACCOUNTABILITY

Designated staff will maintain appropriate records of each device intended for the clinical study. (e.g., record of the subject device assignments, such as serial number of the device, subject ID, expiration dates, and date which the device was applied to/removed from subjects). At the conclusion of the study, the devices may undergo post-study investigation, as applicable. After processing, the devices will be cleaned, disposed of, and/or documented per appropriate regulations. The commercially available CGM used for the study will be transported, stored, and disposed of according to the instructions for use provided with the packaging. Designated staff will keep records of the serial and/or lot numbers, subject ID, and dates of insertion and removal of study-assigned devices.

23.4 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical study staff at the site under the supervision of the Principal Investigator, or designee, at that site. The Principal Investigator, or designee, is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Study data collection may be through paper source and/or electronic data capture (EDC) format, per current Sponsor processes. As applicable, hard copies of the study visit Case Report Forms may be provided for use as source document worksheets for recording data for each participant enrolled in the study. In addition, electronic data will be downloaded from the Biolinq System, commercial CGM, and glucometers, and will be maintained per sponsor guidelines. Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data, if applicable, will be entered into the subject-specific study binders or EDC system, as applicable.

23.5 CONFIDENTIALITY AND PRIVACY

The Sponsor and Investigator must treat Subjects' identity as confidential. Subjects must not be identified in any publicly released reports of the study. All records are kept confidential to the extent provided by national or local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records that are required to be maintained by the Investigator, including but not limited to, medical records. Regulatory agencies also maintain the right to review records pertinent to the study. Unless required by law, the sponsor and investigator must report de-identified data to secure subject confidentiality.

24 REFERENCES

1. Calhoun, Peter & Johnson, Terri & Hughes, Jonathan & Price, David & Balo, Andrew. (2018). Resistance to Acetaminophen Interference in a Novel Continuous Glucose Monitoring System. Journal of Diabetes Science and Technology. 12. 193229681875579. 10.1177/1932296818755797.
2. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin*. 2012;28(4):499-516.
3. Critchley JA, Critchley LA, Anderson PJ, Tomlinson B. Differences in the single-oral-dose pharmacokinetics and urinary excretion of paracetamol and its conjugates between Hong Kong Chinese and Caucasian subjects. J Clin Pharm Ther. 2005;30(2):179-184.
4. Basu A, Slama MQ, Nicholson WT, et al. Continuous glucose monitor interference with commonly prescribed medications: a pilot study. *J Diabetes Sci Technol*. 2017;11(5):936-941.
5. Basu A, Veettil S, Dyer R, Peyser T, Basu R. Direct evidence of acetaminophen interference with subcutaneous glucose sensing in humans: a pilot study. *Diabetes Technol Ther*. 2016;18(suppl 2):S243-S247.
6. Maahs DM, DeSalvo D, Pyle L, et al. Effect of acetaminophen on CGM glucose in an outpatient setting. *Diabetes Care*. 2015;38(10):e158-e159.
7. Dexcom. Dexcom G5 mobile continuous glucose monitoring system user guide. San Diego, CA: Dexcom, Inc; 2016. Available at: https://s3-us-west-2.amazonaws.com/dexcompdf/LBL013990-REV003-G5-Mobile-User-Guide-NA-Android-US.pdf (accessed January 17, 2024).
8. Medtronic. MiniMed 670G system user guide. Northridge, CA: Medtronic Minimed; 2016. Available at: https://www.medtronicdiabetes.com/sites/default/files/library/download-library/user-guides/MiniMed%20670G%20System%20User%20Guide.pdf (accessed January 17, 2024).
9. Abbott. FreeStyle Libre Flash glucose monitoring system: User's manual. Alameda, CA: Abbott Diabetes Care Inc; 2017. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150021C.pdf (accessed January 17, 2024).
10. Zhang Y, Hu Y, Wilson GS, Moatti-Sirat D, Poitout V, Reach G. Elimination of the acetaminophen interference in an implantable glucose sensor. *Anal Chem*. 1994;66(7):1183-1188.
11. Heinemann L. Interferences With CGM Systems: Practical Relevance? Journal of Diabetes Science and Technology. 2022;16(2):271-274. doi:*10.1177/19322968211065065*
12. Denham D. Effect of Repeated Doses of Acetaminophen on a Continuous Glucose Monitoring System with Permselective Membrane. J Diabetes Sci Technol. 2021 Mar;15(2):517-518. doi: 10.1177/1932296820948544. Epub 2020 Aug 29. PMID: 32865043; PMCID: PMC8256057.
13. Dexcom, Dexcom G6 Continuous Glucose Monitoring System User Guide, 2020 (LBL014003 Ver 11). San Diego, CA.
14. Gerriets V, Anderson J, Nappe TM. Acetaminophen. 2023 Jun 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29493991.
15. Fitzpatrick, T.B., The Validity and Practicality of Sun-Reactive Skin Types I Through VI. Archives of Dermatology, 1988. 124(6): p. 869-871.
16. Fitzpatrick skin phototype. [cited 2020 23 March]; Available from: https://www.arpansa.gov.au/sites/default/files/legacy/pubs/RadiationProtection/FitzpatrickSkinType.pdf.
17. D. Liu, E. Moberg, M. Kollind, P.-E. Lins a, U. Adamson and I. A. Macdonald . Arterial, arterialized venous, venous and capillary blood glucose measurements in normal man during hyperinsulinaemic euglycaemia and hypoglycaemia. Diabetologia (1992) 35:287-290.
18. WE Clutter, DM Bier , SD Shah & PE Cryer: Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J. Clin. Invest. 66: 94-101, 1980.
19. JD Best & JB Halter: Release and clearance rates of epinephrine in man: Importance of arterial measurements. J. Clin. Endocrinol. Metab. 55: 263-268, 1982.
20. DE Matthews, G Pesola & RG Campbell: Effect of epinephrine upon amino acid and energy metabolism in humans. Am. J. Physiol. Endocrinol. Metab. 258: E948-E956, 1990.
21. Iqbal, A. and S. Heller, Managing hypoglycaemia. Best Pract Res Clin Endocrinol Metab, 2016. 30(3): p. 413-30.
22. Siperstein, M.D., Diabetic ketoacidosis and hyperosmolar coma. Endocrinol Metab Clin North Am, 1992. 21(2): p. 415-32.
23. Kitabchi, A.E., et al., Hyperglycemic crises in adult patients with diabetes. Diabetes Care, 2009. 32(7): p. 1335-43.

24. Fayfman, M., F.J. Pasquel, and G.E. Umpierrez, Management of Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Med Clin North Am, 2017. 101(3): p. 587-606.

25 APPENDIX: IN-CLINIC GUIDELINES

25.1 PURPOSE

To outline guidelines for performing an In-Clinic Day including an interferent challenge to assess performance of the Biolinq System relative to a commercial CGM, an SMBG meter and an FDA-cleared glucose laboratory analyzer (LA)

25.2 IN-CLINIC OBJECTIVE

The primary objective of an In-Clinic Day is to safely obtain sufficient data to support the primary efficacy endpoint (Biolinq Biowearable vs. YSI assessment) as relative to interference effect. Commercially available comparator devices (CGM and SMBG) will also be evaluated for reference analysis during an In-Clinic Day.

25.3 RESPONSIBILITIES

The investigator and investigator's staff or qualified designees are responsible for:

- Inserting intravenous catheter(s) for each subject
- Monitoring subjects for safety, including blood glucose levels
- Obtaining blood samples as outlined in this document
- Providing meal options to subjects
- Providing interferent (APAP) doses and measurement of APAP levels

The Principal investigator shall maintain final discretion for any In-Clinic procedures and methods used based on their medical expertise and/or training.

25.4 SAFETY MEASURES

[redacted]

[redacted]

[redacted]

[redacted]