Atrial Fibrillation Algorithms Clinical Validation Study

099-25141, 09 April 2021

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09 April 2021

Atrial Fibrillation Algorithms Clinical Validation Study

Sponsor:	**Apple Inc.**
Protocol Number	099-25141
Version and date:	[redacted] **– 09 April 2021**
Compliance Statement:	This study will be conducted in accordance with this protocol, ICH GCP Guidelines, and the applicable regulatory requirements (21 CFR Parts 50, 54, 56, and 812). The conduct of the study will be approved by the appropriate Institutional Review Board (IRB) of the respective Investigational site. Safety assessments (adverse events) for this study will be conducted in accordance with ISO 14155-1 (2011).

[redacted]

		[redacted]

INVESTIGATOR APPROVAL PROTOCOL SIGNATURE PAGE

Protocol: 099-25141
Title: Atrial Fibrillation Algorithm Clinical Validation Study

Amendment: NA

I confirm that I have read and understood this study protocol and attached appendices and will conduct this study in compliance with the protocol, all statements regarding confidentiality, local regulations, International Council for Harmonization Good Clinical Practice E6 (ICH-GCP), and United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Parts 50 [protection of human subjects], 54 [financial disclosure by clinical investigators], 56 [informed consent and Institutional Review Board (IRB) requirements], 812 [Investigational Device Exemptions]).

With my signature, I agree to:

(i) Conduct the investigation in accordance with the investigator's agreement with CRO, the investigational plan, applicable provisions of 21 CFR Part 812 and other Food and Drug Administration (FDA) regulations, and conditions of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

Reviewed and Approved by:

[redacted]

[redacted]

[redacted]

SYNOPSIS

Study Title	Atrial Fibrillation Algorithm Clinical Validation Study
Protocol Version	[redacted]
Protocol Date	09 April 2021
Study Design	Prospective, multi-center, non-significant risk study
Key Inclusion Criteria	**All cohorts:** • Age 22 or older • Able to read and understand a written informed consent form (ICF) • Willing and able to participate in the study procedures • Able to communicate effectively with and follow instructions from the study staff • Must meet additional binning based on demographics • Able to wear the wrist device for duration of study participation **Cohort 1:** No known history of atrial fibrillation (AF) **Cohort 2 (Aggressor Rhythm Cohort):** No known history of atrial fibrillation (AF) and active diagnosis of at least one of the following: • Frequent premature atrial contractions (PACs) • Frequent premature ventricular contractions (PVCs) • Supraventricular tachycardia (SVT) • Non-sustained ventricular tachycardia (NSVT) **Cohort 3 (Non-permanent AF cohort):** Known diagnosis of paroxysmal, persistent, or chronic AF at time of screening (confirmed by electronic medical record (EMR) or self-report) **Cohort 4:** Subjects with known diagnosis of permanent AF at time of screening (confirmed by EMR or self-report)
Key Exclusion Criteria	All cohorts: • Physical disability that precludes safe and adequate testing • Mental impairment resulting in limited ability to cooperate

	• Known uncontrolled medical conditions, such as (but not limited to) significant anemia, important electrolyte imbalance and untreated or uncontrolled thyroid disease • Open wound(s) on the wrist and/or forearm • Tattoos, large moles, or scars on the wrist at the wrist device location • Medical history, or physical assessment finding that makes the subject inappropriate for participation according to the Investigator • Skin conditions on either wrist that would preclude subject from wearing a wristband on either wrist • Known allergy or significant sensitivity to medical adhesives, isopropyl alcohol, or electrocardiogram (ECG) patch • Participation in a previous study that used a wrist-worn sensor device with a simultaneous ECG reference patch • Subjects with implanted cardiac devices such as a Pacemaker or an automated Implantable Cardioverter - Defibrillator
Study Objective	The objective of this study is to collect data to evaluate the performance of the investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms.
Endpoints	**Primary Endpoints:** **IRNF:** • Sensitivity of the irregular rhythm notification for the identification of persons with AF by 13-day ambulatory ECG, with AF defined as at least 30 seconds of AF by ambulatory ECG. • Specificity of the lack of irregular rhythm notification for the identification of persons without AF by 13-day ambulatory ECG, with AF defined as at least 30 seconds of AF by ambulatory ECG

	AFBF: • Weekly AF burden estimate defined as the percentage of time a subject is in Atrial Fibrillation during wrist device wear over the prior 7 consecutive days **Secondary Endpoints:** **IRNF:** • Notification-level positive predictive value (PPV) with AF by ambulatory ECG at the time of any tachogram comprising the notification. • Tachogram-level performance (Sensitivity, Specificity, false positive rate (FPR), PPV, negative predictive value (NPV)) for tachograms comprising alerts. • Tachogram-level performance (Sensitivity, Specificity, FPR, PPV, NPV) for all generated tachograms. **AFBF:** • Sensitivity, specificity, positive predictive value, and negative predictive value of tachograms for the identification of AF by ambulatory ECG • Day-specific AF burden estimate defined as the percentage of time a subject is in Atrial Fibrillation during a specific day of the week • Four-hour segment-specific AF burden estimate defined as the percentage of time a subject is in Atrial Fibrillation during a specific four-hour segment of a day
Test Device	Investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms
Study App	Investigational Study App
Reference Device	Cardea SOLO Wireless ECG Patch (K123217)
Study Procedures	Screening will include the following: • A brief physical assessment, performed either virtually, or in person following Sponsor approval The following information will also be collected at screening: age, gender, race and ethnicity, occupation, diagnosed medical conditions, medications, allergies, visual assessment of general appearance and skin, body measurements and assessments (height, weight, BMI),

	assessment of tattoos, moles, scars on wrist (both), and skin tone assessment on Fitzpatrick scale. Day 1: • This visit can be done remotely, or in person following Sponsor approval. This visit should be no more than 14 days after screening • Two (2) wrist devices of the same series and configuration will be assigned to each subject (one for daytime wear and one for wear during sleep) at random from the set of wrist device series/configurations included in this study. Two iPhones will also be assigned to each subject. • The single-lead ambulatory ECG patch will be affixed to the subject's upper torso per manufacturer's instructions and using standard procedures. • Skin tone assessment on the Fitzpatrick scale will be confirmed. Day 5 (+ 2 days): • This visit can be done remotely, or in person following Sponsor approval • Study staff will be in contact with the subject to execute replacing the subject's ECG patch. • The ECG patch will be returned to study staff for download Day 13 (± 2 days), or end of 2nd ECG patch wear period, if less than 13 ± 2 days: • This visit can be done remotely, or in person following Sponsor approval • Subjects will be asked to report any study procedure-related adverse events (AEs) that occurred during the previous period of up to 13 days (± 2 days), or during the ECG patch wear periods if less than 13 ± 2 days. • The subject's ECG patch will be removed. The ECG patch data will be returned to the study staff for processing and adjudication. The investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms (test devices) will be run *post-hoc* on the sensor dataset to generate tachograms and notification. The performance of each test device will be determined based upon adjudication of concurrent data from the reference device.

Duration of Study Participation	• Up to 13 ± 2 days, or until the end of the 2nd ECG patch wear period, if less than 13 ± 2 days
Total Number of Study Subjects Enrolled	• A total of n=235 to 627 subjects across the following 4 cohorts are targeted for enrollment in this study as follows: • n=78 (Cohort 1: No Known Diagnosis of AF) • n=67-85 (Cohort 2: Aggressor Rhythm Cohort) • n=54-394 (Cohort 3: Non-permanent cohort, Paroxysmal, Persistent or Chronic AF) • n=36-70 (Cohort 4: Permanent AF) Additionally, there will be a sub-study of approximately 40 participants prior to the pivotal study starting, which would bring the total sample size to 667. The sub-study participants are a separate cohort and will not be included in any of the endpoint analyses for the pivotal study (see section 3.1 *Study Design - Overview)*.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation	Explanation
ADE	Adverse device effect
AE	Adverse event
AF	Atrial fibrillation
AFB	Atrial fibrillation burden
AFBF	Atrial fibrillation burden feature
AFL	Atrial flutter
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular reciprocating tachycardia)
BMI	Body mass index
CFR	Code of Federal Regulations
CIED	Cardiovascular implantable electronic device
CRO	Contract research organization
EAS	ECG Patch Analysis Set
ECG	Electrocardiogram
eCRF	Electronic case report form
EMR	Electronic medical record
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FPR	False positive rate
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRB	Institutional Review Board
IRNF	Irregular rhythm notification feature

Abbreviation	Explanation
ISO	International Organization for Standardization
LOA	Limits of Agreement
mm	millimeter
N or n	number
N/A	Not applicable
NAS	Notification Analysis Set
NPV	Negative predictive value
NSR	Normal sinus rhythm
NSVT	Non-sustained ventricular tachycardia
PAC	Premature atrial contraction
PAF	Paroxysmal atrial fibrillation
PPAS	Per-protocol analysis set
PPG	Photoplethysmography
PPV	Positive predictive value
QC	Quality control
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SR	Sinus rhythm
SVT	Supraventricular tachycardia
UADE	Unexpected adverse device effect
US	United States

1. INTRODUCTION

1.1. Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and when left untreated, is a leading cause of morbidity and mortality from stroke, heart failure and myocardial infarction (Ben Freedman, 2015; Moran, 2016). Data from the Framingham Heart Study indicates that by age 40 years, lifetime risk for developing AF is 1 in 4 (Lloyd-Jones, 2004). AF is also a growing public health problem with prevalence projected to triple between 2010 and 2050, with an estimated 12.1 million diagnosed cases in 2030 in the United States (US) alone (Colilla, 2013).

Early detection and treatment of patients with AF minimizes the risk of sequelae of thromboembolism including >60% reduced risk of stroke (Moran, 2016; Omboni, 2016). However, many affected with AF are unaware they have this dysrhythmia due to a number of factors including lack of symptoms, or experience only mild symptoms that they do not attribute to a disease (Moran, 2016). As a result, asymptomatic patients are 3 times as likely to have sustained an ischemic stroke prior to diagnosis than those with symptoms (Ben Freedman, 2015; O'Neal, 2016). These findings raise concerns and have prompted several variations of screening programs to detect patients with asymptomatic AF to prevent an embolic event (Ben Freedman, 2015; Moran, 2016). While systematic and opportunistic screening programs have demonstrated increased rates of detection when compared to detection during routine clinical practice, such screening programs are not yet widely implemented (Moran, 2016). Additionally, AF may be paroxysmal (PAF or intermittent AF) and therefore missed by recording a single in-clinic electrocardiogram (ECG). This is especially true for those patients with intermittent symptoms. Holter devices are commonly used for ambulatory 24-hour ECG monitoring in at-risk patients, but have limited sensitivity for the detection of new AF (Brachmann, 2016).

Once diagnosed with AF, the condition of AF can affect individual patients with different degrees of burden. AF burden itself can be defined as the percentage time a person is in AF during a specified time period. AF burden has been traditionally estimated through monitoring devices such as Holter devices, implantable loop recorders, or implantable pacemakers and defibrillators. AF burden, moreover, is a strong area of focus in medical research on its impact on outcomes and management. One recent study (Go, 2018) identified 3-fold higher risk of stroke in patients with the highest burden compared to those with low burden. For non-stroke outcomes, AF burden has been a focus of research interest as a potential predictor of other events such as heart failure, mortality, and other cardiac-related outcomes (Chen, 2018).
Although established guidelines do not currently utilize AF burden alone to drive clinical decision making, for many patients, AF burden can have a negative impact on daily life due to symptoms and impact on their cardiovascular health. Indeed, quality of life is of great importance in patients with AF and often a primary goal in optimization of their health after prioritizing stroke prevention. Patients can have a wide range of symptoms while in AF, from palpitations, tiredness, low energy, and other manifestations to complete absence of symptoms. For those patients with symptoms, the degree of AF burden can be correlated with their quantity of symptoms, and therefore have great impact on their quality of life. A number of clinical interventions are utilized to manage AF and its symptoms, including rate control medications, antiarrhythmics, and nonpharmacologic strategies such as catheter ablation. Outside of clinical

interventions, recent data suggests that patients can pursue lifestyle modifications such as weight loss, exercise, improved sleep, and stress management to manage AF burden; as an example, recent guidelines by the AHA/ACC/HRS now recommend, as a Class I indication, lifestyle interventions for overweight persons with AF (January, 2019).

Recent guidelines and professional society consensus documents highlight the importance of enhancing patient knowledge of AF (January, 2019; Lane, 2015). Given that mobile devices permit ways to frequently monitor patients in an outpatient setting, our hypothesis is that use of the test device can facilitate both the identification of AF in the undiagnosed users as well as provide valuable information regarding AF burden estimates for users with known diagnosis of AF.

1.2. Device Description

The Investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms are software-based medical devices.

The IRNF 2.0 algorithm analyzes background data opportunistically collected by the integrated optical sensors on a compatible Apple Watch (wrist device) to identify and notify users of irregular rhythm suggestive with AF.

The AFBF 1.0 algorithm also analyzes background data opportunistically collected by the integrated optical sensors on a compatible Apple Watch (wrist device) and estimates the proportion of time a user is in an AF rhythm as compared to other rhythms; these results can be displayed and accessed by the user on a compatible iPhone.

1.3. Study Rationale

This clinical study is being conducted to evaluate the performances of investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Feature Burden (AFBF) 1.0 algorithms (test devices).

1.4. Risk/Benefit Assessment

There may be risks or discomforts associated with participating in this study. No significant risks or permanent side effects are anticipated. Precautions will be taken to minimize risks; however, there may be risks that are not yet known about. Subjects will be encouraged to talk to study staff if they experience any injuries, side effects, or discomfort while or as a result of participating in this study.

- Subjects may experience slight to moderate discomfort associated with attachment and removal of adhesive electrodes used for ECG patches. The risk will be minimized by using medical-grade disposable electrodes and by leaving them attached to the skin only for the limited study duration. Even with these precautions, temporary skin irritation may still occur.
- Subjects may experience rash from the ambulatory ECG monitor or from the wrist device band.
- Subjects may experience slight to moderate discomfort associated with wearing the wrist device, such as pressure related muscle tenderness.

2. STUDY OBJECTIVES, ENDPOINTS, AND HYPOTHESES

2.1. Study Objective

The objective of this study is to collect data to evaluate the performance of the investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms.

2.2. Study Endpoints

Primary Endpoints:

IRNF:

- Sensitivity of the irregular rhythm notification for the identification of persons with AF by 13-day ambulatory ECG, with AF defined as at least 30 seconds of AF by ambulatory ECG.
- Specificity of the lack of irregular rhythm notification for the identification of persons without AF by 13-day ambulatory ECG, with AF defined as at least 30 seconds of AF by ambulatory ECG.

AFBF:

- Weekly AF burden estimate, defined as the percentage of time a subject is in Atrial Fibrillation during wrist device wear over the prior 7 consecutive days

Secondary Endpoints:

IRNF:

- Notification-level positive predictive value (PPV) with AF by ambulatory ECG at the time of any tachogram comprising the notification.
- Tachogram-level performance (Sensitivity, Specificity, false positive rate (FPR), PPV, negative predictive value (NPV)) for tachograms comprising alerts.
- Tachogram-level performance (Sensitivity, Specificity, FPR, PPV, NPV) for all generated tachograms.

AFBF:

- Sensitivity, specificity, positive predictive value, and negative predictive value of tachograms for the identification of AF by ambulatory ECG.
- Day-specific AF burden estimate defined as the percentage of time a subject is in Atrial Fibrillation during a specific day of the week.
- Four-hour segment-specific AF burden estimate defined as the percentage of time a subject is in Atrial Fibrillation during a specific four-hour segment of a day.

Study Hypotheses

IRNF:

The primary endpoint hypothesis associated with the IRNF is:

Data from subjects in Cohorts 1, 3, and 4 will be used to test this hypothesis.

The secondary endpoint hypothesis associated with the IRNF compares the tachogram-level false positive rate (FPR) of the test device to that of the predicate device to determine if the test device algorithm FPR is non-inferior) to that of the predicate device using all tachograms generated only from subjects in Cohort 2 (Aggressor Rhythm Cohort).

AFBF:

The primary endpoint hypothesis associated with the AFBF is:

The secondary endpoint hypotheses associated with the day-specific and four-hour segment-specific endpoints are listed below, respectively:

[redacted] Additional information on the simulation methodology is contained in Section 6.2.3 and the SAP.

3. STUDY DESIGN

3.1. Overview

This is a prospective, non-significant risk study. The study protocol will undergo review and approval by an Institutional Review Board (IRB) prior to recruitment or enrollment of study subjects.

Written, informed consent will be obtained from all subjects before any protocol-directed procedures are performed. All potential subjects will participate in a screening visit, and if eligibility is confirmed, subjects may begin study participation.

Subjects will be given two separate wrist devices for use in the study – one wrist device will be worn during waking hours, the other wrist device will be worn overnight such that the subject is not wearing multiple wrist devices at one time. Subjects will wear a wrist device simultaneously with a single-lead ambulatory ECG patch for up to 13 days (± 2 days), or until the end of the 2nd ECG patch wear period, if less than 13 ± 2 days, during regular daily life to enable the collection of a single sensor dataset for each subject. The 1st ECG patch will be replaced after 5 days (+2 days). The wrist device will collect accelerometer data continuously and photoplethysmography (PPG) data when the user is still during their daily life use. The study duration will be for up to 13 days (± 2 days). The ECG patch will be returned and assessed for presentation of AF and other arrhythmias.

The study will target enrollment of subjects with varying diagnoses of AF, normal sinus rhythm, and other rhythms with a goal to generate a dataset with AF burdens that span from 0% to 100%. Target recruitment bins of AF burden for subjects in Cohorts 3 and 4 will be monitored during the study using only data collected from the ambulatory ECG patch to ensure minimum data collection in each; study enrollment of Cohort 3 and 4 subjects will continue until minimum enrollment targets of low AF burden and high AF burden are achieved (as defined in Section 4.2). Because of anticipated discrepancies between self-reported type of AF and the amount of AF burden measured via ECG patch, for purposes of analysis, the final Cohort assignment will be determined based on the AF burden measured via ECG patch.

The investigational Irregular Rhythm Notification Feature (IRNF) 2.0 and Atrial Fibrillation Burden Feature (AFBF) 1.0 algorithms (test device) will be run *post-hoc* on the sensor dataset to generate tachograms and notifications. The performance of each test device will be determined based upon adjudication of concurrent data from the reference device.

A sub-study cohort of approximately 40 subjects will be enrolled prior to the start of the clinical validation (i.e., pivotal) study. These subjects will follow the same study procedures outlined in this protocol. However, no data from this cohort will contribute towards the performance evaluation of the test device algorithms. This sub-study is primarily intended to provide assurance that all of the data collection, evaluation, and data transfer tools are performing as intended prior to the start of the clinical validation study. Subject accountability, demographic, and safety data will be summarized and reported for this cohort.

3.2. Required Equipment

3.2.1. Sponsor-Provided

The Sponsor will provide the study sites with sufficient wrist devices, iPhones, and ECG patches to complete the study. Subjects will be instructed to return all equipment to the CRO at the end of the study. Site staff will use accountability log for traceability to sponsor provided devices, equipment.

3.2.2. Contract Research Organization (CRO)-Provided

The CRO will provide the necessary supplies for return of study equipment following subject use.

No specific packaging of the study equipment is required, as this study is non-interventional and will temporarily dispense study equipment to subjects.

3.2.3. Storage and Handling Procedure

All study equipment, including reference devices, will be stored in normal room temperature/humidity/pressure conditions with no exposure to direct sunlight or heat source throughout the study. The storage area should be secure with restricted access.

3.2.4. Accountability

Wrist device and reference device ID numbers used for each subject will be recorded in the source documents. All study equipment (excluding equipment listed in 3.2.5 below) will be returned to the CRO at the end of the study.

3.2.5. Investigational Study Site-Provided

The Investigational study site will provide the following:

- Space and technology available to screen and enroll subjects via telehealth visit and/or in person visits following Sponsor approval.

3.3. Qualification Criteria for US Board-Certified Cardiologists

Reviewers of 1-lead ECG data must be US board-certified medical doctors specialized in cardiology.

Curriculum vitae and medical license will be collected for each US board-certified medical doctor specialized in cardiology.

3.4. Randomization and Blinding

Subjects in this study will not be randomized to any treatment regimens but will be randomly assigned a specific wrist device series/configuration ([redacted]) by enrollment cohort using a 1:1 randomization ratio.

US board-certified cardiologists will be blinded to the subjects' past medical history, IRNF notifications, and AF burden results from the AFBF algorithm during the assessment and

adjudication of ECG patch data. Adjudication of ECG strips corresponding to tachograms will also be performed blinded to all other ECG patch data and adjudications. Adjudicators will be instructed to review ECGs independently and separately of each other and not to confer about diagnoses.

[redacted]

3.5. Duration of Subject Participation

Subjects will participate in a screening visit and, if eligible, will participate in the study for up to 13 days (± 2 days).

4. STUDY POPULATION

4.1. Subject Recruitment

Subject recruitment will abide by the guidelines of the IRB and the investigational site(s). Recruitment will continue until enrollment requirements are met, including reaching the targeted number of subjects completing the study procedures with adequate data collection. A subject will be considered enrolled if he/she has signed a consent form and participant has passed all screening criteria.

Investigators will keep a record, i.e. subjects screening log, of subjects who are entered into the study. Each subject must meet all the inclusion criteria and none of the exclusion criteria for this study at the time of screening and study participation. The Sponsor must approve any changes to the target distribution of subjects in writing prior to enrollment.

4.2. Study Cohorts and Target Population

The study will include 4 cohorts of subjects:

- Cohort 1 will include subjects with no known history of AF*
- Cohort 2 (Aggressor Rhythm Cohort) will include subjects with no known history of AF*, but with history of frequent premature atrial contractions (PACs), frequent premature ventricular contractions (PVCs), supraventricular tachycardia (SVT), or non-sustained ventricular tachycardia (NSVT)
- Cohort 3 (non-permanent AF) will include subjects with known history of paroxysmal, persistent, or chronic AF*
- Cohort 4 (permanent AF) will include subjects with permanent AF.

* History of AF encompasses the 2 years prior to participation in study screening procedures.

For all cohorts, the following age, gender, and race/ethnicity enrollment targets will be adhered to during subject recruitment:

- A minimum of 10% of subjects will be enrolled the age category of <55 and a minimum of 20% in of the age categories of 55 to 64, and ≥65 years.
- At least 40% of subjects in Cohort 1 will be female and at least 40% male. At least 20% of subjects in each of Cohorts 3 and 4 will be female and at least 20% will be male.
- At least 10% of subjects in Cohort 1 will be non-Caucasian. In Cohorts 3 and 4 as a combined group, at least 10% of subjects will be non-Caucasian.

The incidence of AF is known to increase with age, male gender, and White race (Benjamin, 2019). These recruitment targets are also consistent with the subject population observed in the Apple Heart Study, which is representative of the intended use population (Turakhia, 2019).

Table 1 identifies the estimated number of subjects targeted for enrollment. A minimum of [redacted] subjects will be enrolled in Cohort 2.

Table 1: Targeted Number of Enrolled Subjects Per Cohort

Cohort 1 (NSR)	Cohort 2 (Aggressor Rhythm Cohort)	Cohort 3 (non-permanent AF)	Cohort 4 (permanent AF)
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NSR = normal sinus rhythm

While subjects will be recruited based upon known inclusion/exclusion criteria including history of arrhythmia, there is uncertainty on whether the presentation of that rhythm will present and occur during study based on the natural temporal variability of heart rhythms. Thus, study enrollment will continue until minimum targets based on rhythm presentation during study is achieved across all cohorts; enrollment may cease after minimum targets are achieved.

Enrollment for Cohort 1 will continue until the target number of enrolled subjects are achieved as in Table 1.

Enrollment for Cohort 2 will continue until minimum numbers of subject enrolled complete the study with presentation of aggressor rhythms as determined by ECG patch are reached, as specified in Table 2A.

Enrollment in Cohorts 3 and 4 will continue during the study until minimum targets of burdens are achieved as in Table 3B. Atrial fibrillation burden for each subject in the self-reported enrollment Cohorts 3 and 4 will be determined from the ambulatory ECG Patch reference device after subjects complete and/or terminate from the study. A final AF cohort assignment will be determined based on this adjudicated AF burden measurement. Enrollment for Cohort 4 will continue until minimum numbers with ≥95% AF burden as determined by ECG patch are reached.

Table 3B identifies the minimum number of subjects in Cohorts 3 and 4 required to exhibit the level of AF burden as determined by ECG patch after the subject completes and/or terminates from the study:

Table 2A: Cohort 2 Minimum Aggressor Rhythm Targets

Presence of Aggressor Rhythm on ECG Patch
[redacted]

Table 3B: Cohort 3 and 4 Minimum AF Burden Targets

Total AF burden >0% to <95%	AF burden >0% to 33%	AF burden >33% to <95%	AF burden ≥95% to 100%
[redacted]	[redacted]	[redacted]	[redacted]

4.3. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be enrolled:

1. Able to read, understand, and provide written informed consent

2. Willing and able to participate in the study procedures as described in the consent form
3. Be 22 years of age and older
4. Able to communicate effectively with and follow instructions from the study staff
5. Able to wear the wrist device for duration of study participation
6. For Cohort 1, have no known medical history of AF
7. For Cohort 2, have no known medical history of AF and active diagnosis of at least one of the following arrhythmias within the past 2 years:
    a. Frequent PACs, defined as at least 1% of total beats of atrial ectopic beats by 24-48 hour Holter, ambulatory ECG monitor, or implantable loop recorder) OR evidence of such by 12-lead ECG.
    b. Frequent PVCs, defined as at least 1% of total beats of ventricular ectopic beats by 24-48 hour Holter, ambulatory ECG monitor, or implantable loop recorder OR evidence of such by 12-lead ECG.
    c. SVT, which will include atrial tachycardia, atrioventricular nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia by 12-lead ECG or 24-48 hour Holter, ambulatory ECG monitor, or implantable loop recorder,
    d. NSVT, defined as three or more consecutive ventricular beats at a rate of at least 100 beats per minute and lasting no more than 30 seconds, by 12-lead ECG or 24-48 hour Holter, ambulatory ECG monitor, or implantable loop recorder
8. For Cohorts 3 and 4, have a known diagnosis of AF at the time of screening (confirmed by electronic medical record (EMR) or self-report) and have had a recent episode of AF, or confirmed AF on ECG, in the past 12 months
9. For Cohort 4, have a known diagnosis of permanent AF at the time of screening (confirmed by EMR or self-report) and have had a recent episode of AF, or confirmed AF on ECG, in the past 12 months
10. Meet additional binning based on demographics.

4.4. Exclusion Criteria

Subjects who meet any of the following criteria may not be enrolled:

1. Physical disability that precludes safe and adequate testing
2. Mental impairment resulting in limited ability to cooperate
3. Known uncontrolled medical conditions, such as (but not limited to) significant anemia, important electrolyte imbalance and untreated or uncontrolled thyroid disease
4. Open wound(s) on the wrist and/or forearm
5. Tattoos, large moles, or scars on the wrist at the wrist device location
6. Skin conditions on either wrist that would preclude subject from wearing a wristband on either wrist

7. Known allergy or sensitivity to medical adhesives, isopropyl alcohol, wristbands, or ECG patch
8. Medical history or physical assessment finding that makes the subject inappropriate for participation according to investigator(s)
9. Participation in a previous study that used a wrist-worn sensor device with a simultaneous ECG reference patch
10. Implantable cardiac devices such as a Pacemaker or Implantable Cardioverter Defibrillator
11. Clinically significant hand tremors, as judged by the investigator
12. Acute illness including COVID and other respiratory illnesses
13. Subjects with known history of AF on rhythm control medications with history of complete AF rhythm control (i.e history of zero AF burden) will be excluded from Cohorts 3 and 4

Subjects enrolled into Cohort 2 can be on rate control medications.

4.5. Subject Discontinuation

Subject participation in the study is voluntary and the subject has the right to withdraw at any time. Subjects also may be withdrawn from the study without their consent.

Reasons for possible subject discontinuation may include:

- Adverse event
- Death
- Protocol deviation
- Withdrawal of consent
- Investigator discretion
- Termination of the study
- Device malfunction
- Lost to follow-up
- Other

Sites will notify Sponsor of the reason(s) for subject discontinuation. Site investigators must also report this to their respective IRBs, as defined per their IRB procedures.

4.6. Subject Follow-up

A follow-up visit will be conducted at Study Day 13 (± 2 days), or after the conclusion of the 2nd ECG patch wear period, if less than 13 ± 2 days, during which the subject will return the wrist devices and ECG patch to the site. Following the completion of procedures at this visit, the subject's participation in the study will be concluded.

5. STUDY PROCEDURES

Table 4 outlines the procedures to be conducted and the information to be collected during the study.

Table 4: Schedule of Events

Study Procedure	Screening	Study Day 1 Visit	Study Day 5 (+2 days) Visit	End of Study Visit*
Informed Consent	X			
I/E Criteria Assessment	X			
Medical History including allergies	X			
Demographic information (age, gender, race/ethnicity, occupation)	X			
Medications	X			
Physical examination (will include at a minimum visual inspection of general appearance and skin)	X			
Body Measurements and Assessments (anthropometrics) (height, weight, BMI; may be self-reported)	X			
Wrist/Hand Assessment (tattoos, moles, scars, skin tone assessment on Fitzpatrick scale)**	X	X		
Distribution of 2 wrist study devices to subject		X		
Application of ECG patch to subject's upper torso		X		
Replacement of ECG patch			X	
Collection of 2 wrist study devices from subject				X
Removal of ECG patch from subject				X
Collection of all AEs encountered during the study		X	X	X

* End of study visit is on Day 13 (± 2 days), or after the conclusion of the 2nd ECG patch wear period, if less than 13 ± 2 days.
**Skin tone assessment on Fitzpatrick scale confirmed on Study Day Visit 1.

5.1. Screening

Informed consent will be obtained before any study protocol-directed procedures are performed. After the signing of informed consent, the subject will be evaluated for eligibility according to the study inclusion/exclusion criteria (Section 4.3 and Section 4.4). This visit will be conducted remotely; in-person, on-site visits can occur only if approved by Sponsor.

During screening, the following should be obtained on each subject:

- Age
- Gender
- Race and ethnicity
- Diagnosed medical conditions
- Medications
- Allergies
- Occupation
- Visual assessment of general appearance and skin
- Body measurements and assessments (height, weight, BMI)*
- Skin tone assessment on Fitzpatrick scale
- Assessment of tattoos, moles, scars on wrist (both)

*Body measurements may be self-reported if the screening visit is conducted virtually.

5.2. Study Day 1

Subjects will report for the Day 1 visit at their scheduled date and time, which may be the same day as the screening visit if conducted in-person, on-site, but in no case more than 14 days after the screening visit. No special preparation for this visit is required. If eligibility is confirmed after completion of all screening procedures, subjects may begin study participation following the screening. This visit will be conducted remotely; in-person, on-site visits can occur only after Sponsor approval.

All subjects may take their normal medications on the day of the study and may eat normally prior to this visit.

Skin tone assessment on the Fitzpatrick scale will be confirmed at this visit.

5.2.1. Data Collection Study Equipment Set up

The following procedures will be performed for each study subject at study participation:

Two wrist devices of the same series/configuration will be assigned to each subject for the study. The first wrist device will be worn during the day for daytime data collection. The second wrist device will be worn during the night for nighttime data collection during sleep. The wrist devices are to be charged while not being worn.

1. Instruct the subject to choose his/her preferred wrist to wear the wrist device. The wrist device can be worn on whichever side the subject prefers unless there is a skin condition on one wrist as noted above in the exclusion criteria, in which case, the wrist device must be worn on the non-affected wrist. Record the chosen wrist. If the subject does not have a side preference or skin condition on one wrist, the wrist device will be placed on the left wrist.
2. The subject will be asked to put the wrist device on his/her wrist (as indicated in 1). The wrist device should be fitted tightly enough that it does not move when the hand/wrist is shaken.
3. Ask user to adjust band tightness for a snug fit and adjust as needed.

An ECG patch will be self-applied to the upper torso of the subject on Day 1 and Day 5 (+2 days) of the study. Self-application of ECG patch may be performed with aid of instructions via televideo. If the visit is occurring on site, the study staff may assist with the patch placement.

5.3. Study Days 1-13

Subjects will continue to wear the wrist devices and patch as directed during normal daily activities for up to 13 (± 2) days. This includes pressing a button on the patch to confirm that the patch is still working properly. Follow up calls or telehealth video calls may be made to the subject as needed throughout the home use period. Subjects will be advised to not swim or do activities that will cause excessive sweating.

5.4. Study Day 5

Subjects will remove the 1st ambulatory ECG patch on study Day 5 (+2 days). A 2nd ECG patch will be self-applied to the subject. If the visit is occurring on site, the study staff may assist with the patch placement. The 1st patch will be returned to study staff. This visit will be conducted remotely; in person on-site visits can occur only after Sponsor approval.

5.5. End of Study Visit

Thirteen days (±2 days) after the initial study visit, or after the conclusion of the 2nd ECG patch wear period, if less than 13 ± 2 days, subjects will have a follow-up visit to be exited from the study. Wrist devices, study phones and the second ECG patch will be returned to the CRO. Following the completion of procedures at this visit, the subject's participation in the study will be concluded. This visit will be conducted remotely; in-person, on-site visits can occur only after Sponsor approval.

5.5.1.1. Study Procedures

The following study procedures will be performed at this visit/contact:

1. Subjects will be asked to report any study procedure-related adverse events (AEs) that occurred during the previous 13 days (±2 days), or during the ECG patch wear periods if less than 13 ± 2 days.
2. The subject's second ECG patch will be returned to staff. ECG patch data will be downloaded by study staff for processing and adjudication (Section 5.5.2).

5.5.1.2. Wrist Device Data Processing

Wrist device, including accelerometer data and PPG signals, will be uploaded by the subject at home.

Procedures for data analysis based on the data collected via the wrist device are described in Section 6.1.

5.5.2. Adjudication of ECG Data

5.5.2.1. ECG Patch

IRNF

ECG Patch Diagnosis (Primary Endpoint)

ECG patch data will be reviewed and adjudicated by the [redacted] Each ECG patch will be reviewed by a cardiac technician. The cardiac technician will review each ECG recording in its entiret [redacted] The cardiac technician will be instructed to review ECG patches independently and separately of each other and not to confer about diagnoses. All cardiac technicians will be blinded to subject cohort and IRNF notifications. [redacted] After the cardiac technician has completed their assessment of an ECG patch, the following procedure will be followed by US Board-Certified Cardiologists:

a) Each of the cardiac technician's ECG patch assessments will be reviewed by a Cardiologist who did not perform the initial assessment. ("Over-reader"). At no time may an over-reader who performed the initial assessment of the ECG patch, over-read their own assessment.

b [redacted]

c) If the over-reader determines the cardiac technician's assessments are consistent, they will approve the results and electronically sign the case without changes.

d) If the over-reader determines the cardiac technician's assessments require amendment, the over-reader will make the required changes and approve the results and electronically sign the case. All changes will be automatically tracked in a 21CFR11 compliant audit trail.

e) After the over-reader has completed their over-read, the results will be quality controlled [redacted]

ECG Strip Diagnosis (Secondary Endpoints)

ECG strips will be identified from the ECG patch for the period of time corresponding to each tachogram that was selected for analysis. [redacted] ll adjudicators will be blinded to cohort and IRNF notifications. [redacted]

AFBF

ECG AF Burden Measurement (Primary Endpoint)

ECG patch data will be reviewed and adjudicated by the [redacted] Each ECG patch will be reviewed by a cardiac technician. The cardiac technician will review each ECG recording in its entirety [redacted]
The cardiac technician will be instructed to review ECG patches independently and separately of each other and not to confer about diagnoses. All cardiac technicians will be blinded to cohort and IRNF notifications. After the cardiac technician has completed their assessment of an ECG patch, the following procedure will be followed by US Board-Certified Cardiologists:

a) Each of the cardiac technician's ECG patch assessments will be reviewed by a Cardiologist who did not perform the initial assessment. ("Over-reader"). At no time may an over-reader who performed the initial assessment of the ECG patch, over-read their own assessment.

[redacted]

c) If the over-reader determines the cardiac technician's assessments are consistent, they will approve the results and electronically sign the case without changes.

d) If the over-reader determines the cardiac technician's assessments require amendment, the over-reader will make the required changes and approve the results and electronically sign the case. All changes will be automatically tracked in a 21CFR11 compliant audit trail.

[redacted]

ECG Strip Diagnosis (Secondary Endpoint)

ECG strips will be identified from the ECG patch for the period of time corresponding to each tachogram that was selected for analysis. [redacted] Strips will be reviewed by 2 independent US

Board Certified Cardiologist adjudicators for a strip diagnosis (Section 5.5.2.1.1). If there are any differences in adjudication decisions, the strip in question will be sent to a third adjudicator for final decision. Adjudicators will be instructed to review ECGs independently and separately of each other and not to confer about diagnoses. All adjudicators will be blinded to cohort and AFBF information. [redacted]

5.5.2.1.1. Rhythm Diagnoses

The diagnosis of the rhythm will fall into one of five categories:

1. Sinus Rhythm
2. Atrial Fibrillation (AF)
3. Atrial Flutter (AFL)
4. Other irregular rhythms (examples include sinus rhythm with frequent PACs, sinus rhythm with frequent PVCs, SVT, VT/VF)
5. Unreadable as defined that a diagnosis cannot be made as the strip is not adequate for reading

The diagnosis will be made via the following logic flow (in sequential order):

1. If the ECG strip contains at least 10 seconds of continuous atrial fibrillation, then it will be classified as “Atrial fibrillation.” Any atrial fibrillation with PACs or PVCs will be classified as “Atrial fibrillation”, with the note of PACs or PVCs be added to the comments section.
2. Otherwise, if 6 or more of the sub-strips cannot be interpreted (e.g. due to noise or artifacts), then the strip will be classified as “Unreadable.”
3. Otherwise, if the ECG strip contains a non-AF arrhythmia, then it will be classified as “Other arrhythmia”. This includes:
   - Supraventricular Tachycardia (includes atrial tachycardia, AVNRT, AVRT)
   - Sinus rhythm with PACs
   - Sinus rhythm with PVCs
   - Sinus rhythm with junctional beats
   - Sinus arrhythmia
   - Ventricular tachycardia (sustained or nonsustained)
   - Heart Block (includes 2nd or 3rd degree HB)
4. Otherwise, the ECG will be classified as “Sinus rhythm”

6. STATISTICAL ANALYSIS

6.1. Dataset Generation

Subjects will wear wrist devices with specially configured study software to enable the collection of a single sensor dataset for each subject. The subjects' sensor datasets will be used as the common source of data for this study to which the algorithms will be applied in a *post-hoc* fashion.

For evaluation of the IRNF, the algorithm software will collect accelerometer data continuously and PPG data when the user is still, which is when it would be possible for a tachogram for either the predicate or test algorithms to be collected. The platform and device algorithms for the test and predicate devices will be run on the sensor dataset to generate tachograms and notifications. The performance of the test device will be compared to the performance of the predicate device according to the pre-specified analyses as outlined below.

For the AFBF, the platform algorithm will be applied to reflect the tachogram sampling strategy that will be implemented in the final, finished product. The algorithm parameters associated with minimum requirements to produce the 7-day AF burden measurement will be finalized prior to database lock. The AFBF algorithm will be run on the subjects' sensor datasets to estimate the 7-day average AF burden and identify AF episodes. Additionally, the algorithm will be applied to the set of tachograms generated via the IRNF 2.0 algorithm and compared to the corresponding ECG strips adjudicated by US Board Certified Cardiologists. The AFBF analyses will be performed on all subjects in Cohorts 3 and 4.

6.2. Statistical Methodology

For all of the IRNF statistical analyses, atrial fibrillation (AF) and atrial flutter (AFL) will be treated as a single category of "AF". For all of the AFBF statistical analyses, atrial fibrillation (AF) will be considered its own unique category (i.e., atrial flutter will not be included as part of the detection of AF episodes).

6.2.1. Randomization Methodology

A summary of the randomization methodology applied in this study is outlined below. Additional details may be found in the study Statistical Analysis Plan (SAP).

Wrist Device Assignments

Subjects will be randomly assigned to wear two wrist devices [redacted] from the same series/configuration. A pre-determined block randomization schedule will be generated for each enrollment cohort and subjects will be assigned sequentially to either a [redacted]

IRNF

[redacted]

[redacted]

To assess overall tachogram performance, a least burdensome approach will also be used [redacted]

[redacted]

[redacted]

AFBF

[redacted]

6.2.2. Primary Endpoint Analysis

IRNF

Two separate tables will be generated for subject-level data cross-classified by the test device and the predicate device results as presented below for the data collected on all subjects in Cohorts 1 and 3, and 4. One table will be diagnosis of at least one AF episode of at least 30 seconds present on the ECG patch (Table 5) to assess sensitivity and the other table will be no AF episodes present on ECG patch (Table 6) to assess specificity per the ECG patch diagnosis definition presented in Section 5.5.2.1. AF will be defined as any AF of at least 30 seconds duration by ambulatory ECG patch report. A concordant notification is defined as ≥ 30 seconds of AF present on ECG patch as determined by AF onsets/offsets + cardiac technician overread during the time period defined by the first and last tachograms comprising the alert. A discordant

notification is defined as a notification that is not concordant. Each subject can be represented once and in only one of the cells of the tables below.

Table 5: Diagnosis of ≥1 AF Episode Present on ECG Patch

Test Device (IRN 2.0)		Predicate Device (IRN 1.0)		
		≥1 Notification		No Notifications
		≥1 Concordant	All Discordant	--------
≥1 Notification	≥1 Concordant	a	b	c
	All Discordant	d	e	f
No Notifications	--------	g	h	i

By defining N1 as the sum of all subjects in Table 5 above, the sensitivity of the test device will be estimated as (a+b+c)/N1 and the sensitivity of the predicate device will be estimated as (a+d+g)/N1.

Table 6: No AF Episodes Present on ECG Patch

Test Device (IRN 2.0)		Predicate Device (IRN 1.0)		
		≥1 Notification		No Notifications
		≥1 Concordant	All Discordant	--------
≥1 Notification	≥1 Concordant	------	------	------
	All Discordant	------	r	s
No Notifications	--------	------	t	u

By defining N2 as the sum of all subjects in Table 6 above, the specificity of the test and predicate devices will be estimated as (t+u)/N2 and (s+u)/N2, respectively.

Usable wrist device data that aligns with and corresponds to the time interval during which the ECG patch is worn will be used for this analysis. [redacted]

Only subjects in Cohorts 1, 3, and 4 will be included in the primary endpoint analysis. [redacted]

[redacted]

AFBF

A single weekly AF burden estimate will be recorded for both the test device and the ambulatory ECG Patch reference method for all subjects contributing usable data in Cohorts 3 and 4. [redacted]

[redacted]

[redacted]

The primary endpoint hypothesis associated with the AFBF algorithm is:

[redacted]

[redacted]

[redacted] The results will also be graphically displayed on a Bland-Altman Plot.

6.2.3. Secondary Endpoint Analyses

IRNF

The notification-level PPV of AF by ambulatory ECG at the time of any tachogram comprising the notification will be estimated for both the test and predicate device algorithms. The notification-level PPV is defined as the proportion of notifications where at least one of the ECG strip results associated with the spot tachograms that comprise the notification exhibits AF of at least 10 seconds per the ECG strip diagnosis definition presented in Section 5.5.2.1.

Notification-Level PPV = (# of notifications with an adjudicated ECG strip diagnosis of AF of at least 10 seconds for any tachogram comprising the notification) / (# of alert notifications)

For subjects who exhibit a high level (≥ 95%) AF burden, it is expected that a large (100 to 200) number of notifications will be generated in total for both the IRN 1.0 and 2.0 algorithms resulting in >1,000 tachograms per subject in Cohort 4. For these subjects who are permanently in AF, a least burdensome approach will be followed where for all notifications generated from subjects in Cohorts 1 and 3 and randomly selected notifications from subjects in Cohort 4 will be included in this analysis. A corresponding adjudicated ECG strip diagnosis will be determined for all tachograms comprising these notifications.

Because the set of notifications may differ between the test and predicate device algorithms and because multiple notifications may be associated with some subjects, a bootstrap approach will be implemented to obtain 95% two-sided confidence intervals separately for each algorithm's notification-level PPV. The bootstrap sampling will randomly select subjects who have analyzable data with replacement rather than individual data points to account for any correlation structure that might exist within subjects so that confidence limits are corrected for within-subject correlation.

Two tachogram-level analysis results [redacted] associated with the secondary endpoints

of tachogram performance will be reported separately for each device algorithm using tachograms generated by subjects in Cohorts 1, 3, and 4. Separate contingency tables cross-classifying the adjudicated cardiologist diagnoses from ECG strips with the binary classification of tachogram results for test and predicate devices will be presented as outlined in Table 7 below.

Table 7: Cross-Classification Table of Tachogram Results and Adjudicated Cardiologist Diagnoses from ECG Strips

	Adjudicated Cardiologist Diagnosis					
Tachogram Result	SR	AF	Atrial Flutter	Other Irregular Rhythm	Uninterpretable	Total
Irregular	n11	n12	n13	n14	n15	nTI
Not AF	n21	n22	n23	n24	n25	nTN
Total	nSR	nAF	nAFL	nOA	nU	N

Abbreviations: SR = sinus rhythm; AF=atrial fibrillation; AFL=atrial flutter

Tachogram performance for the test and predicate devices will be estimated separately as outlined below because the set of tachograms will differ by device. Two-sided 95% bootstrap confidence intervals will be constructed for each performance metric by randomly selecting subjects who have analyzable data with replacement to account for any within subject correlation of multiple tachograms associated with each subject.

Tachogram Sensitivity = (n12+n13)/(nAF+nAFL)

Tachogram Specificity = n21/nSR

Tachogram False Positive Rate = (n11+n14)/(nSR+nOA)

Tachogram PPV = (n12+n13)/(nTI-n15)

Tachogram NPV = n21/(nTN-n25)

The ECG strips corresponding to all tachograms which comprise each notification for subjects in Cohorts 1, 3 and 4 from the test and predicate device algorithms will be adjudicated and included in the analysis of this secondary endpoint.

[redacted]

[redacted]

AFBF

A tachogram-level analysis associated with the secondary endpoint of tachogram performance for the AFBF will be reported by cross-classifying the binary classification of tachogram results with the adjudicated cardiologist classifications from ECG strips where the SR and Other Abnormal Rhythm adjudications are combined into a single category. [redacted]

Using the notation of Table 7, tachogram performance will be estimated as outlined below from the randomly selected tachograms for all subjects in Cohorts 3 and 4. Two-sided 95% bootstrap confidence intervals will be constructed for each performance metric to account for potential within subject correlation of the multiple tachograms associated with each subject.

- Tachogram Sensitivity = n12/nAF
- Tachogram Specificity = (n21+n23+n24)/(nSR+nAFL+nOA)
- Tachogram PPV = n12/(nTI-n15)
- Tachogram NPV = (n21+n23+n24)/(nTN-n25)

Although the set of tachograms for the AFBF device algorithm will differ from the set of tachograms generated from the test IRNF device algorithm, [redacted] The same tachogram performance analysis of the AFBF device algorithm will be performed as specified above.

The analysis of the day-specific AF burden estimate will be performed to demonstrate that the algorithm provides accurate estimates of AF burden regardless of the set of days included in the analysis using a Monte Carlo simulation based approach. In this approach and at each iteration of the simulation, days will be selected at random (and without replacement) for each subject from the set of days where reference and test device data is available. An AFB measurement will be determined from the test device across the selected days as will the reference AFB measurement for each subject. [redacted]

[redacted]

6.2.4. Safety Analyses

All adverse events (AEs) will be recorded throughout the entire study period, whether they are considered to be related to the study procedures or not. Signs and symptoms of each AE will be described in detail: date of event, description of event, severity, relationship to study procedures, action taken and outcome. AEs will be collected as spontaneously reported by the subjects.

AEs will be coded using MedDRA (latest version). The number of any AEs and the number and percentage of subjects reporting each type of adverse event will be presented by Preferred Term. Multiple occurrences of the same event reported by the same subject will be counted only once.

AE summaries (number of events and incidence) will be presented for all AEs, including the following:

- Serious adverse events (SAEs)
- Study procedure related AEs
- Severe AEs, which are AEs that are rated as Severe in intensity

Study procedure related AEs will include those events classified as possibly or definitely related to the study procedure.

6.2.5. Additional Analyses

Subject accountability, device accountability, medical history, medication, demographic and baseline characteristics will be summarized by final cohort assignment for the reporting of results for the subjects included in the evaluation of the IRNF and AFBF devices. The final cohort assignments for subjects who self-report at the time of screening in Cohorts 1, 3, and 4 will be determined based on their final adjudicated reference ECG results of AF burden as follows:

- Cohort 1: Adjudicated AF Burden via reference ECG of 0%
- Cohort 3: Adjudicated AF Burden via reference ECG of >0% to <95%
- Cohort 4: Adjudicated AF Burden via reference ECG of $\geq$ 95%

The final cohort assignment of subjects who self-report at the time of screening in Cohort 2 will remain Cohort 2. If an adjudicated AF Burden measurement cannot be determined for a subject, the final cohort designation will be the same as the self-reported cohort at the time of screening. The rationale for reporting the results by final cohort designation is to most closely align the reporting of results based on the presentation or absence of AF during the study monitoring period regardless of prior diagnosis.

Additional efficacy analyses are described below.

IRNF

The performance at the person- and notification-level for AF and other arrhythmias (treated as a single combined category) by ambulatory ECG will be analyzed similarly to the corresponding primary and secondary endpoint analyses outlined above for the adjudicated diagnoses of only AF using all available data for subjects in Cohorts 1, 3, and 4. These additional analyses are distinct from the primary and secondary endpoint analyses in that the AF and other arrhythmia categories of diagnoses presented in Section 5.5.2.1 will be combined into a single category for purposes of analysis. In particular, the following performance parameters will be estimated and presented along with their associated 95% confidence intervals.

1. Sensitivity of the IRNF for the identification of persons for AF or other arrhythmias by up to 13-day (±2 days) ambulatory ECG, defined as at least 10 seconds of AF or other arrhythmia by ambulatory ECG
2. Specificity of the lack of IRNF for the identification of persons without AF or other arrhythmias by up to (±2 days) 13-day ambulatory ECG, defined as at least 10 seconds of AF or other arrhythmia by ambulatory ECG
3. Notification-level PPV with AF and other arrhythmias by ambulatory ECG at the time of any tachogram comprising the notification

The false positive rate at the person-level for all subjects in Cohort 2 (Aggressor Rhythm Cohort) will also be reported. Using the notation of Table 6, the FPR for the test and predicate devices will be estimated as (r+s)/N2 and (r+t)/N2, respectively. Two-sided exact binomial confidence intervals associated with the FPRs will also be reported.

The following conditional probabilities computed using the randomly selected tachograms generated from subjects in Cohorts 1, 3, and 4 will be reported separately for the test and predicate devices along with their associated 95% two-sided bootstrap confidence intervals:

- Pr(Device = Irregular | Reference = Other Irregular Rhythm);
- Pr(Device = Not AF | Reference = Other Irregular Rhythm);
- Pr(Device = Irregular | Reference = Uninterpretable);
- Pr(Device = Not AF | Reference = Uninterpretable);
- Pr(Reference = Other Irregular Rhythm | Device = Irregular);
- Pr(Reference = Other Irregular Rhythm | Device = Not AF);
- Pr(Reference = Uninterpretable | Device = Irregular);
- Pr(Reference = Uninterpretable | Device = Not AF).

Contingency tables comparing the binary classification of randomly selected tachograms from the test and predicate devices will also be presented for each of the adjudicated cardiologist sub-category classifications of Other Abnormal Rhythm diagnoses presented in Section 5.5.2.1.

Contingency tables comparing the test and predicate device classifications (notification vs. no notifications at the subject-level) with each of the adjudicated cardiologist classifications of diagnoses presented in Section 5.5.2.1 including all sub-categories of the Other arrythmia category will also be presented.

AFBF

A histogram will be produced for the paired differences in the weekly AFB average measurements. Boxplots of the weekly AFBF device measurements for ECG Patch categories of 0%, >0% to 33%, >33% to < 95%, ≥95% will also be displayed.

The paired differences in the weekly AFB average measurements between the AFBF device and ambulatory ECG patch and corresponding two-sided 95% confidence intervals for the average paired difference will be presented for each of the following ranges of ambulatory ECG patch AFB categories:

- 0%
- >0% to 33%
- >33% to < 95%
- ≥95%

The false negative rate will be estimated as the number of subjects with a weekly AFBF device measurements = 0% and a paired ECG patch AFB measurement > 0% divided by the number of subjects with a paired ECG patch AFB measurement > 0%. A two-sided 95% exact binomial confidence interval for the false negative rate will also be reported.

A modified Bland-Altman analysis will be performed using only reference AF burden measurements which are strictly between 0% and 100%. In the analysis, the x-axis will be the reference burden and the y-axis will be the paired differences between the test device and reference method. Estimated limits of agreement and mean bias with associated 95% confidence interval) will be reported. No hypotheses will be tested in this analysis.

Medications (verbatim terms) will also be tabulated and reported.

6.3. Sample Size Determination

IRNF

The approach for sample size determination associated with the IRNF primary endpoint follows that of Zhou et al for the comparison of sensitivity and specificity of paired subject-level data arising from the test and predicate IRNF devices (Zhou 2002). Performance estimates used for the sample size calculations are based on internal engineering data.

[redacted]

Table 8: Sample Sizes for AF Cohorts of Subjects Required for IRNF Evaluation

Cohort	Required for 80% Power	Targeted for Enrollment to Observe AF Rhythm Presentation
Permanent AF (Cohort 4)	[redacted]	[redacted]
Non-Permanent AF (Cohort 3)	[redacted]	[redacted]
Total for AF Cohorts	[redacted]	[redacted]

[redacted]

Table 9: Sample Sizes for Subjects without AF Required for IRNF Evaluation

Cohort	Required for 80% Power	After Correction for Attrition
No Known Diagnosis of AF	[redacted]	[redacted]

Additionally, to assess the secondary endpoint hypothesis H_{02} of the study, an aggressor cohort of subjects with no known history of AF but with a known history of other arrhythmias which may resemble the irregularity of AF (i.e., frequent premature atrial contractions (PACs), frequent premature ventricular contractions (PVCs), supraventricular tachycardia (SVT), or non-sustained ventricular tachycardia (NSVT)) will be enrolled. [redacted]

Table 10: Sample Sizes for Aggressor Subjects without AF Required for IRNF Evaluation

Cohort	Required for 80% Power	After Correction for Attrition and Rhythm Presentation
Aggressor Rhythms	[redacted]	[redacted]

AFBF

The approach for sample size determination follows the approach of Lu et al (Lu, 2016). The power associated with the primary endpoint hypothesis can be estimated as

$$Power = 1 - \Phi\left(\frac{\overline{D} + 1.96S_D - \delta}{se_{LOA}} - z_{\alpha/2}\right) - \Phi\left(\frac{-\overline{D} + 1.96S_D - \delta}{se_{LOA}} - z_{\alpha/2}\right)$$

where Φ(x) is the cumulative density function of the standard normal distribution, $\overline{D}$ is the expected average difference in AF burden measurements between the device and reference method, δ is the maximum allowable difference, $z_{\alpha/2}$ is the cumulative 100($\alpha/2$)% percentile of the standard normal distribution, and se_{LOA} is the standard error of the lower or upper Limit of Agreement defined as $se_{LOA} = S_D$*sqrt[1/n + (1.96^2)/(2*(n-1)] where S_D is the standard deviation of the paired AFB differences.

[redacted]

To summarize, a total [redacted] subjects will be enrolled into the study according to the cohorts below:

- n[redacted] (Cohort 1: No Known Diagnosis of AF)
- n[redacted] (Cohort 2: Aggressor Rhythm Cohort)
- n[redacted] (Cohort 3: Non-Permanent AF)
- n[redacted] (Cohort 4: Permanent AF)

6.4. Significance Level

The primary non-inferiority hypotheses test of sensitivity and specificity and the secondary endpoint non-inferiority comparison of false positive rates for the IRNF will use a one-sided

significance level of 0.025. If non-inferiority is demonstrated, a test of superiority will be performed using the same significance level.

All AFBF analyses will use a two-sided significance level of 0.05.

6.5. Missing Data

Rigorous efforts will be made to ensure all subjects are compliant with the protocol. However, some subjects may drop out prematurely or some planned measurements may not be readable or interpretable. The data analyses will be conducted on all readable and interpretable data. Additional details defining readable and interpretable data may be found in the study Statistical Analysis Plan (SAP).

6.6. Subgroup Analyses

In accordance with the FDA Guidance on the reporting of age-, race-, and ethnicity-specific data, the primary endpoints for both IRNF and AFBF devices will be reported by the following subgroups (data permitting). Some subgroups may be combined depending on data availability.

- Age group (<55; ≥55 to <65; ≥65 years)
- Sex (Male; Female)
- Race (White; Black or African American; Asian; American Indian or Alaska Native; Native Hawaiian or other Pacific Islander)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino)
- Wrist device series/configuration [redacted]
- Fitzpatrick Scale

6.7. Interim Analyses

There are no interim analyses planned in this study.

6.8. Analysis Sets

Full Analysis Set (FAS): All subjects who sign an informed consent and are enrolled into the study. This analysis set will be used to summarize subject and device accountability, demographic and baseline characteristics, and safety data. The data for this analysis set will be presented overall and separately for each of the final cohort designations.

ECG Patch Analysis Set (EAS): [redacted] This analysis set will be used to analyze the IRNF primary endpoint and additional subject-level sensitivity/specificity analyses.

ECG Patch Burden Analysis Set (EABS): All subjects in enrollment cohorts 3 and 4 with paired usable Watch and ECG patch data which provides for a weekly AF burden average measurement. This analysis set will be used to analyze the AFBF primary endpoint data.

Notification Analysis Set (NAS): All subjects with a IRNF 1.0 or IRNF 2.0 notification who have simultaneous, analyzable ECG patch data at the time of the notification. This analysis set will be used to analyze the secondary endpoint and additional notification-level endpoints.

Tachogram Analysis Set (TAS): All subjects with at least one tachogram paired with a readable ECG strip diagnosis. This analysis set will be used to analyze the secondary endpoint and additional tachogram-level endpoints for the IRNF and AFBF algorithms.

Sub-Study Analysis Set: All subjects who sign an informed consent and are enrolled into the sub-study which precedes the clinical validation study. This analysis set will be used to summarize subject accountability, demographic characteristics, and adverse event information.

7. SAFETY PARAMETERS AND ASSESSMENT

7.1. Adverse Events

The definition of adverse events are as follows:

Term	Definition	Reference
Adverse Event (AE)	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 study procedures.	ISO 14155: 2011
Serious Adverse Event (SAE)	Adverse event that 1. Led to death, 2. Led to serious deterioration in the health of the subject, that either resulted in: a. A life-threatening illness or injury, or b. A permanent impairment of a body structure or a body function, or c. In-patient or prolonged hospitalization, or d. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function 3. Led to fetal distress, fetal death or a congenital abnormality or birth defect	ISO 14155: 2011
The Severity of an AE will be categorized as follows:		
Mild	Mild events are those that are tolerated with no disruption of normal daily activity	
Moderate	Moderate events are those that cause sufficient discomfort to interfere with daily activity	
Severe	Severe events are those that incapacitate and prevent usual activity x	

7.1.1. AE/SAE Collection

Any abnormal laboratory findings, abnormal safety assessments, or anticipated day-to-day fluctuations which are associated with a pre-existing disease or condition, are not considered an adverse event unless judged by the investigator to be worsening or more severe than expected. All adverse events must be fully recorded throughout the entire study period, whether they are considered to be related to the study procedures or not. Adverse events will be collected as spontaneously reported by the subjects.

Adverse events should be followed until they are resolved or stabilized (returns to baseline for a pre-existing condition) and followed by a private MD, or the subject is lost to follow-up. In the event of a subject not returning to the clinical unit, the outcome of this event will be recorded as lost at follow up.

Possible AEs include the following:

- Skin rash on wrist due to wearing the wrist device;
- Pressure artifacts on wrist due to wearing the wrist-sensor device;

The following occurrences are not to be regarded as AEs:

- Underlying (pre-existing) symptoms or diseases, unless there is an increase in severity or frequency during the course of the investigation;
- Detection of atrial fibrillation or other irregular heartbeat;
- Complaint about wrist device functionality.

7.1.2. SAE Reporting

The site investigator should report all SAEs to the Sponsor as soon as possible but no later than 24 hours of becoming aware of the event. The site investigator should also report the SAEs to their IRB as soon as possible and according to their IRB reporting requirements, but in no event later than 10 working days after the investigator becomes aware of the event. On the date the Site staff became aware that the event met the SAE definition set out in this protocol, the investigator will be requested to complete an AE/ SAE reporting form in the database, in addition to the information on the source documentation. The investigator will conduct further investigation of these events regarding determination of event as a serious adverse event and determination of relatedness of the event to the study. The investigation of these events will be completed and reported to the Sponsor within 15 days of initial report to Sponsor.

7.1.3. Reporting of all other Study Adverse Events

Possible adverse events (non-serious) related to the study will be reported to the Sponsor within 14 business days of being reviewed by the investigator. The investigator will conduct further investigation of these events regarding determination of event as a serious adverse event and determination of relatedness of the event to the study. The investigation of these events will be completed and reported to the Sponsor within 30 days of initial report to the Sponsor.

7.2. Safety Plan

The clinical staff is responsible for the ongoing safety and well-being of the subjects during study participation. Management of all medical complications arising during the course of the research study will be managed by the investigator as deemed appropriate. A medical monitor will be available for consultation related to subject safety and adverse events. All incidental findings identified during screening will be referred at the investigator's discretion to the appropriate additional care in accordance with current standard of care. This can include removal of the study-associated devices, as well as other measures as required. Even if a study-associated device is removed prior to the specified duration, data may be used if of suitable quality.

7.3. Overview of study suspension and termination criteria

The research study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information regarding the safety or performance of the study becomes available in such a way that the research study is deemed unsafe or ineffective;
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety;
- Failure to meet expected enrollment goals;
- Administrative reasons.

8. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

8.1. Institutional Review Board

IRB approval for the protocol, ICF, and any subject-facing materials will be obtained by the site investigator at each Investigational site prior to study commencement. The IRB approval letter must be received at the investigational site prior to starting the study, and a copy must be provided to the Sponsor. No changes will be made to the Protocol, ICF, or subject-facing materials without appropriate approvals, including the IRB's and the Sponsor's approval.

Until study completion, the site investigator will inform/advise his/her IRB of the study progress, per their IRB requirements. Further, any amendments to the protocol, ICF, and/or subject-facing materials will be submitted to and approved in writing by the IRB prior to implementation.

The submitted documents will include but are not limited to:

a. The final protocol
b. IRB application forms
c. ICF

The study will not begin unless the IRB gives a favorable opinion of the study.

8.2. Informed Consent

All information about the study, including information about the subjects, and the ICF, is prepared and used for the protection of the human rights of the subject according to International Council for Harmonisation (ICH) GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from each subject participating in this study after adequate explanation of the aims, methods, and objectives of the study and before undertaking any study-related procedures.

The ICF, prepared by the investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IRB and be acceptable to the Sponsor.

The ICF must provide subjects with information about the nature, significance, implications, potential risks, and basic procedures of participation in the study, consistent and in accordance with the study protocol version approved by the relevant IRB. The ICF must be written in a language fully comprehensible to the prospective subject. Subjects must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The subject and the study staff explaining the study and with whom the subject discusses the informed consent will sign and date the ICF; this can be done remotely by using the remote consenting capabilities in the electronic system. A copy of the signed and dated ICF will be retained by the subject and the original will be filed in the investigator file unless otherwise agreed. New information will be provided in written form to the subject.

8.3. Record Keeping

This study will be conducted in accordance with GCP guidelines. Study documents should be retained until at least 2 years after the last approval of marketing application in an ICH region and until there are no pending or contemplated-marketing applications in an ICH region. If there are no local laws, sites should retain files for 5 years after completion of the study. Records include informed consent, protocols, and electronic case report forms (eCRFs).

8.4. Confidentiality and Privacy

Subject privacy will be protected by the participating investigators, their staff, and the Sponsor and its agents. The study protocol, documentation, data, and all other information collected or generated in the study will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. Compliant with Health Insurance Portability and Accountability Act of 1996 (HIPAA) guidelines as applicable, only certified copies of coded data will be sent from the study site to the cardiology reviewers. Under no circumstances, except when legally required or permitted by applicable law, will any healthcare provider of any enrolled subject be allowed to receive specific outcome data for that subject directly from the study team for that subject.

8.5. Protocol Adherence

The protocol must be read thoroughly in its entirety and instructions followed exactly. Any deviations should be agreed on by Sponsor and the investigator and reported to IRB as per their reporting guidelines, with the appropriate written and approved protocol amendments made to reflect the agreed upon changes. Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action taken. Actions taken for the well-being of a subject may occur before the Sponsor is notified.

8.6. Collection and Management Responsibilities

Data will be collected using eCRFs in a validated system. The Sponsor or designee will supply the eCRFs. All eCRFs should be completed by designated, trained personnel, as appropriate. All changes or corrections to the eCRF will be documented via a data correction form (query) with an audit trail and adequate explanation for the revision is required. eCRFs will be signed and dated by the Principal Investigator or his/her designee.

The investigator(s) will permit trial-related monitoring, audits, IRB review and regulatory inspections(s), providing access to data documents. Members of the investigational site team and their designated authorization(s) will be identified in a log.

Access to data collection devices will be controlled and the devices will be used only in the clinical investigation and according to the clinical investigation plan. The investigator or authorized designee will keep records documenting the receipt, use, and return of the study-related data collection devices.

8.7. Study Monitoring

On behalf of the Sponsor, a CRO monitor will contact and visit the investigator(s) at the study site(s) before the entry of the first subject and at predetermined appropriate intervals during the

study until after the last subject has completed the study. The monitor will also perform a study closure visit.

Prior to starting the study, the investigator understands and accepts the obligation to conduct the study according to the Protocol and applicable regulations, and has signed the investigator agreement. In accordance with ICH GCP guidelines, the investigators must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol, including the safety and well-being of subjects, and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (i.e., the various study records, ICFs, eCRFs, other subject records, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the subjects with the entries on the eCRF (i.e., source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved in a reasonable period of time. Contact information for the study monitor is located in the investigator file. Representatives from the Sponsor may also contact and visit the investigators and monitor data during the study.

8.8. Data Quality Assurance and Quality Control

The Sponsor or designee will perform internal quality management of study conduct, and data collection, documentation and completion. Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to study staff for clarification/resolution.

8.9. Use of Information

All information concerning the study-associated devices, equipment, and the Sponsor is considered confidential information. The information developed during the conduct of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of the test device as described in this protocol. This information may be disclosed as deemed necessary by the Sponsor to allow the use of information derived from this clinical study and to ensure complete and thorough analysis. The investigator is obligated to provide the Sponsor with complete study results and all data developed in this study.

Independent analyses and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of the Sponsor. Written permission to the investigator will be contingent on the Sponsor's review of the statistical analysis and/or manuscript, and will provide for nondisclosure of the Sponsor's confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties at least 30 days prior to submission. This will enable all parties to protect proprietary

information and to provide comments based on information that may not yet be available to other parties.

This confidential information shall remain the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor and shall not be used except in the performance of this study.

8.10. Study Record Retention

All data collected or derived from this research study will remain the property of the Sponsor.

Any and all correspondence relating to this research study, for example with the Sponsor or the IRB, should be kept in the appropriate file folders at the CRO. Records of research study subjects' source documents which pertain to the research study must be kept on file at the CRO.

Records must be maintained according to ICH GCP guidelines and according to what is stated in section 8.3.

8.11. Study Termination and Site Closure

The Sponsor and the investigators reserve the right to terminate the study or participation in the study, respectively, at any time. Both parties will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigators will assure that adequate consideration is given to the protection of the subjects' interests.

The Sponsor reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- Evidence has emerged that, in the opinion of the Sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical;
- The stated objectives of the study are achieved;
- The development of the test device is discontinued.

Regardless of the reason for termination, all data available for subjects at the time of discontinuation of follow up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented.

8.12. Completion of the Study

The investigator(s) agree to provide financial disclosure forms and to complete this study in satisfactory compliance with the protocol and all applicable regulatory requirements within the timeframe allotted in the financial contract. Delays in the completion and/or reporting of the study beyond this time must be mutually agreed upon in writing by both the investigator and the Sponsor.

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