The Jewel IDE Study

A Clinical Evaluation of the Jewel™ P-WCD in Subjects at High Risk for Sudden Cardiac Arrest

("JEWEL")

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with good clinical practice by adherence to 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 54, 21 CFR Part 56, and 21 CFR Part 812)

The protocol, informed consent/research authorization form(s), recruitment materials, and all patient materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study, if required by the IRB. In addition, all changes to the consent form will be IRB-approved; the IRB will determine whether new consent needs to be obtained from subjects who provided consent using a previously approved consent form.

1. PROTOCOL SUMMARY

1.1 Synopsis

Title:	The Jewel IDE Study: A Clinical Evaluation of the Jewel P-WCD in Subjects at High Risk for Sudden Cardiac Arrest. ("JEWEL")
Study Description:	Multi-center, prospective, single arm study of the Jewel Patch-Wearable Cardioverter Defibrillator (P-WCD) System in patients at high risk for Sudden Cardiac Arrest.
Objective:	To demonstrate the safety and clinical effectiveness of the Jewel P-WCD.
Endpoints:	**Primary Effectiveness Endpoint:** To demonstrate an observed inappropriate shock rate of no more than 2.0 inappropriate shocks per 100 patient-months. **Primary Safety Endpoint:** To demonstrate an observed rate of subjects experiencing a clinically significant cutaneous Adverse Device Effects (ADE) of <15%. **Secondary Endpoints:** • To observe successful conversion of at least one shockable rhythm with a salvo of up to five (5) shocks. • To observe a compliance rate of subjects wearing the Jewel of greater than 14.1 average hours per day during a prescription wear period.
Study Population:	A total of 290 analyzable adult subjects in the United States at risk for sudden cardiac arrest who are not candidates for or who refuse an implanted defibrillator. Specifically, subjects: a. with a measured left ventricular ejection fraction (LVEF) less than or equal to 40% (as assessed within the last 30 days prior to enrollment) AND identified as presenting with a diagnosis of an acute myocardial infarction (AMI), ischemic cardiomyopathy (includes congestive heart failure NYHA Class I – III), non-ischemic cardiomyopathy, or myocarditis; OR b. who have a temporary or long-term contraindication to receiving an ICD, who have had an ICD removed, or who refuse an ICD. OR c. whose ICD implantation is delayed due to COVID-19 infection or exposure-related risks.
Sites, Geographies:	Subjects will be enrolled at up to 60 participating sites in the United States.
Study Intervention:	**Jewel Patch Wearable Cardioverter Defibrillator ("Jewel") System** The Jewel is a P-WCD applied directly to a patient's torso in an anterior-apical monitoring vector. The Jewel is worn continuously, 24-hours per day, for up to 8-days per Patch Unit, for the duration of the prescription period.
Total Study Duration:	18 months
Subject Participation Duration:	Individual subject participation will be determined by their Investigator but will not exceed 180 days.

1.2 Schema

Screening

- Obtain Informed Consent
- Screen potential subjects by Inclusion and Exclusion Criteria
- Demographics, Medical History, COVID-19 status obtained and documented

Subject Training and Enrollment

- Subject receives Device Training and Placement Accessory Fitting
- Subject places initial Jewel under guidance (Subject is now considered enrolled)
- Subject returns home with the Jewel and an Adhesive Electrode Patch and Battery Unit ("Patch Unit"). NOTE: Element Science may contact the Subject to provide additional training related to the device, product support, and/or information related to the subject's participation in the study at later timepoints.

Prescription Period – as prescribed by Investigator

- Day 2 Phone Call: Follow-up by Element Science to assess any subject support needs.
- Exchange 1- Exchange 4 Follow Up: Office Visit, Telemedicine Visit, or Phone Call: (the first 4 times the subject removes a Jewel and replaces the Patch Unit) collect Patch Unit replacement information/compliance, assessment of patient status, determine if patient needs assistance, training, or supplies from Element Science, determine if new or changes to Adverse Events (AE), medical information, medications; subject completes experience questionnaire. Optional: photographs of device placement.
- Exchange 5 Follow Up through end of prescription period: Office Visit, Telemedicine Visit, or Phone Call: collect Patch Unit replacement information/compliance, assessment of patient status, determine if patient needs assistance, training, or supplies from Element Science, determine if new or changes to AE(s), medical information, medications.

End of Study Assessment (Visit / Phone Call) – within 14 days of device removal

- Adverse Event Review
- Exit Interview
- Study Exit

1.3 Schedule of Activities (SoA) by the Site

Procedures	Screening	Training & Enrollment (Day 0)	Exchange 1 – Exchange 4	Exchange 5 – end of prescription period	Study Exit Visit (end of prescription ± 14 days)
Informed consent	X				
Demographics	X				
Medical history	X				
Weight & measurements	X				
Eligibility review (IC/EC)	X				
Jewel training		X			
Placement Accessory fitting		X			
Apply device		X	X	X	
Photos of device after application		X	X (optional)		
QOL questionnaire		X			X
Wear experience questionnaire			X		
Occurrence of any shocks/deferrals			X	X	X
Changes to medications, health status			X	X	X
Subject request(s) for assistance, training, or supplies			X	X	
Adverse Event evaluation			X	X	X
Exit Interview					X

2. INTRODUCTION

2.1 Background and Study Rationale

Sudden Cardiac Death (SCD) is sudden, unexpected death often caused by Sudden Cardiac Arrest (SCA), an abrupt loss of heart function with no sign of blood circulation, and is the leading cause of natural death in the US, resulting in about 325,000 adult deaths each year.(1) SCA is most often caused by abnormal heart rhythms called arrhythmias which prevent the heart from adequately pumping blood to the body. Ventricular Fibrillation (VF), which is an erratic, disorganized firing of impulses from the ventricles is the most common life-threatening arrhythmia. Ventricular Tachycardia (VT), in which the ventricles of the heart rapidly contract due to improper electrical activity, can also potentially be life threatening.

While the Implantable Cardioverter Defibrillator (ICD) is typically implanted for long-term prevention of SCA in high-risk populations, there are temporary periods of time when ICD implantation is commonly deferred. Examples include the initial 40 days after myocardial infarction (MI), the initial 90 days after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or after ICD explantation. The WCD has become a viable option to treat these temporary periods of elevated risk for SCA. Patients are typically prescribed to wear a WCD 24 hours a day, 7 days a week for 40 to 90 days or longer until a medical decision is made on whether to implant an ICD.(2)

Time to defibrillation is the single most critical determinant of survival in SCA. Survival rates after VF decrease approximately seven to ten percent with every minute that defibrillation is delayed. (3) While rapid defibrillation with an Automatic External Defibrillator (AED) by nonmedical personnel can improve survival after out-of-hospital cardiac arrest, the time period between arrest and successful resuscitation must be short and the cardiac arrest must be witnessed. The development of a wearable cardioverter defibrillator has provided a new therapy option for patients who are at high risk of SCA, and may require a defibrillation shock without the assistance from a bystander.

The Jewel Patch Wearable Cardioverter Defibrillator is an automatic external cardioverter defibrillator that monitors patients at risk for SCA and provides a therapeutic shock if needed. It is intended to be worn at home or in hospital during temporary periods of time when ICD implantation is commonly deferred.

To date, only one manufacturer has a commercial product approved as a wearable automated external defibrillator. The ZOLL LifeVest WCD is currently available in the United States, Europe, Australia, Israel, Japan, and Singapore.

The clinical efficacy of external defibrillation shock waveforms used in the ZOLL LifeVest WCD and other AEDs has been well studied in the controlled environment of the electrophysiology (EP) lab. For example, with the replacement of monophasic damped sine waveforms with lower energy biphasic truncated exponential waveforms, clinical efficacy was compared by measuring first shock success rate in patients undergoing electrophysiologic testing. (3) With the ZOLL LifeVest WCD, clinical efficacy was also evaluated as part of a routine EP procedure in which ten (10) patients were induced into VF and the LifeVest was used to deliver a single defibrillation shock. (4) In this study, special WCD units were used that were manually charged and discharged by the physician to terminate the VF episode in a relatively short time period (mean duration of 32 seconds per episode).

The Jewel delivers a salvo of up to 5 shocks (150, 162, 162, 162, 162 joules) using a biphasic truncated exponential waveform that is adjusted based on the transthoracic impedance of the patient . In this clinical study, the objective is to demonstrate the safety of the Jewel and to collect efficacy data on termination of potentially lethal arrhythmias, such as life-threatening VT or VF.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

Potential risks include many risks that exist in the patient population being studied (i.e., those at risk for sudden cardiac death). These risks vary in frequency and severity, and include:

- acceleration or induction of atrial or ventricular arrhythmias,
- angina,
- bradycardia,
- death,
- discomfort/pain,
- dizziness,
- fluid accumulation,
- heart block,
- heart failure,
- myocardial infarction,
- myocardial necrosis,
- myocardial trauma,
- non-elective intubation,
- reduced cardiac function,
- shortness of breath,
- stroke,
- syncope,
- tachyarrhythmias, including early, recurrent atrial fibrillation,
- thrombus,
- thromboemboli,
- valve damage,
- vasovagal response, and
- worsening heart failure.

Additional risks from P-WCDs and WCDs, including Jewel, vary in frequency and severity and include:

- Allergic contact dermatitis
- Annoyance
- Arrhythmia, supraventricular
- Asystole
- Bradycardia
- Brain injury
- Burns, thermal
- Cardiac Arrest
- Chest pain
- Death
- Discomfort, distress
- ECG changes
- Electric shock
- Hearing Loss
- Infection, systemic and/or topical
- Injury
- Irritation
- Itching
- Misdiagnosis
- Myocardial Trauma
- Overstimulation
- Pain
- Rash
- Shock, Anaphylactic
- Skin reactions, including but not limited to: discoloration, erosion, inflammation, irritation, tears
- Sudden cardiac death
- Syncope
- Tachycardia
- Urticaria
- Ventricular fibrillation
- Ventricular tachycardia

Of note, the occurrence of inappropriate shocks, which is one of the known risks of using the Jewel and participating in this study, is the primary endpoint of the study.

2.2.2 Known Potential Benefits

The Jewel is an investigational device so it is possible that the subject may not receive any benefit from participating in the study. Subjects taking part in this study are at risk for SCA and are not otherwise candidates for, or refuse an ICD, so participating in the study and using the Jewel may have the potential to convert a life-threatening cardiac rhythm and prevent SCA in this at-risk population. The results of this study may help other people to gain access to the Jewel, which may result in the prevention of SCD.

2.2.3 Assessment of Potential Risks and Benefits

The Jewel has been developed and tested thoroughly to meet the electrical safety standards published by the International Electrotechnical Commission (IEC). The device is battery powered and operates at low levels of electrical current, except when delivering a defibrillation shock. The electrodes are attached to sticky, adhesive pads, which consist of materials that are widely used in commercially available medical adhesives. The patient population being evaluated is at risk for SCA, and the device being tested has the potential to convert life threatening rhythms in this population who would otherwise be dependent on bystanders and emergency medical personnel for administration of a life-saving therapy in a timely fashion. The results of Element Science's simulated human use and preclinical testing, combined with the risk analysis of the Jewel System, indicate that the risk-to-benefit profile of the Jewel is favorable for the patient. With a better patient experience, the Jewel is anticipated to have significantly better compliance, and therefore has potentially greater effectiveness than the current standard WCD, with an equivalent safety profile to the standard WCD.

3. OBJECTIVES AND ENDPOINTS

3.1 Objective

The objective of this study is to demonstrate the safety and clinical effectiveness of the Jewel P-WCD.

3.2 Endpoints

3.2.1 Primary Effectiveness Endpoint

To demonstrate an observed inappropriate shock rate of no more than 2.0 inappropriate shocks per 100 patient-months using a one-sided upper 97% confidence interval and >83% power at the interim analysis; and a 98% confidence interval and >98% power for the final analysis.

An inappropriate shock is defined as a shock delivered during a period where the study subject is not experiencing life threatening VT or VF. Only first inappropriate shocks will contribute the analysis of this endpoint. All inappropriate shocks will be reviewed and adjudicated by a Clinical Events Committee (CEC) and reported throughout the prescription period.

3.2.2 Primary Safety Endpoint

The primary safety endpoint is to observe a rate of subjects experiencing a clinically significant cutaneous Adverse Device Effects of <15%.

For the purpose of endpoint calculation, a cutaneous ADE will be considered clinically significant if it causes the subject to be permanently withdrawn from the trial by the Investigator.

All Adverse Device Effects and device-related Serious Adverse Events (SAE) will be tabulated and presented along with duration and severity. The proportion of subjects experiencing an ADE or SAE will also be presented. All device-related events will be reviewed by the Data Safety Monitoring Board (DSMB).

3.2.3 Secondary Endpoints

The first secondary endpoint is to observe successful conversion of at least one shockable rhythm with a salvo of up to five (5) shocks.

A shock is considered appropriate if the shock is delivered during a period where the subject is experiencing VF or a VT that is considered “life threatening” as defined in the CEC Charter and as adjudicated by the CEC. If multiple successful conversions occur in a single subject, conversions will be counted as separate events only if the rhythm returned to a non-shockable rhythm between conversions (i.e. the Jewel returns to Monitor Mode). All successful conversions will be included in the secondary endpoint analysis. All appropriate shocks and attempted conversions will be reviewed and adjudicated by the CEC and reported.

The second secondary endpoint is to observe a compliance rate of subjects wearing the Jewel of greater than 14.1 average hours per day during a prescription wear period.

3.2.4 Additional Exploratory Analyses

Jewel System Compliance

Subject compliance with using the Jewel system will be evaluated, including average weekly wear.

Detection of Ventricular Arrhythmias

An analysis of all events that trigger the alarm cycle after three (3) consecutive segments of shockable rhythm (~24 seconds in total) will be performed.

Quality of Life

A Quality of Life (QOL) measurement tool (EQ-5D-3L) will be used to quantify any impact that the Jewel has on a subjects QOL.

4. STUDY DESIGN

4.1 Overall Design

This study is a multi-center, prospective, single-arm evaluation of the Jewel P-WCD in adult subjects at risk for sudden cardiac arrest, who are not candidates for or who refuse an implanted cardioverter defibrillator. The study will include up to sixty (60) sites in the United States. This design incorporates one interim analysis at 179 analyzable subjects and one final analysis at 290 analyzable subjects.

There is another analysis point once 100 subjects have completed their prescription wear time, which will be performed to support application for CE mark.

4.2 Scientific Rationale for Study Design

As the patient population being evaluated in this study is at risk for SCA, it would not be ethical to withhold potentially lifesaving defibrillation. Further, the study is designed with a primary endpoint to demonstrate the absence of a rare event (inappropriate shock). For these reasons, a control or placebo arm is not employed in the Jewel IDE study, and all enrolled subjects will receive the study device.

4.3 End of Study Definition

A subject is considered to have completed the study when his or her physician-determined prescription period has ended. The Study Exit Visit will be performed at this time. After study completion, the subject will be asked to return all Jewels and study supplies to the Sponsor. Subject prescription periods may be altered during the course of the study at physician discretion. The end of the study is defined as when the last subject exits the study globally.

5. STUDY POPULATION

5.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Patients of any gender aged ≥ 18 years.
2. Patients with either:
    a. a measured LVEF less than or equal to 40% (as assessed by techniques such as, but not limited to, cardiac angiography, echocardiography, magnetic resonance imaging, or radionuclide angiography within the last 30 days prior to enrollment) AND identified as presenting with a diagnosis of an AMI, ischemic cardiomyopathy (includes congestive heart failure: NYHA Class I – III), non-ischemic cardiomyopathy, or myocarditis;

    OR

    b. who have a temporary or long-term contraindication to receiving an ICD, who have had an ICD removed, or who refuse an ICD

    OR

    c. whose ICD implantation is delayed due to COVID-19 infection or exposure-related risks

5.2 Exclusion Criteria

The opportunity to participate in the study will be offered to all qualifying populations at the Site. An individual who meets any of the following criteria will be excluded from participation in the study:

1. Member of a vulnerable patient population as defined in ISO 14155;
2. Life expectancy of less than one year, including end-stage heart failure, cancer, or other diagnosed condition;
3. Patients with an anticipated initial prescription period over 180 days (limitation only to allow timely closure of this clinical trial);
4. Patients with an advanced directive prohibiting resuscitation;
5. Existing ICD;
6. Existing unipolar pacemaker;
7. Existing FDA-cleared or FDA-approved active implantable or body worn medical device(s) that the Sponsor requires to be removed prior to the study but which cannot be removed;
8. Clinically significant valve disease, including aortic stenosis, mitral stenosis; mitral regurgitation, tricuspid regurgitation, insufficiency of the aortic or pulmonary valves, any of which is likely to require surgery in the next year;
9. A planned procedure, such as Coronary Artery Bypass Graft, within six (6) months;
10. End-stage renal disease, or chronic renal failure requiring hemodialysis;
11. Planned discharge to an institutional setting with an anticipated stay of greater than seven (7) days;
12. Having a mental, visual, physical, or auditory deficit, that could impair their ability to properly place, remove, or interact with the Jewel System;
13. Unable to understand English for the purposes of interacting with the device;
14. Unable to use a wearable defibrillator due to physical conditions (bandages preventing electrode contact, physical deformities preventing electrode contact, etc.);
15. Dextrocardia;
16. Body circumference of less than 27 inches or greater than 56 inches in the intended area of the Belt component of the Placement Accessory;
17. Participation in an investigational study of a drug, biologic, or device not currently approved for marketing;
18. Allergic to or have had a known adverse reaction to medical adhesives or hydrocolloids;
19. Active skin breakdown, erythema, or other signs of infection in the pectoral or torso regions where the Adhesive Electrode Patches are applied;
20. Females who are pregnant or breast-feeding, or planning to be pregnant in the next 12 months;
21. No US-based postal address that can be used to ship and receive study devices and supplies (a Post Office box is **not** an acceptable address for product shipments).
22. Patients who, in the opinion of the Investigator, are anticipated to be non-compliant with study instructions;

23. Unable to provide or have diminished capacity to provide informed consent;
24. Any condition that an Investigator believes would interfere with the intent of the study or make participation not in the best interest of the patient.

5.3 Lifestyle Considerations

During this study, subjects are asked to:

- Prepare their skin prior to each Jewel application. Preparation includes using the provided supplies for skin cleansing and any needed hair trimming.
- Use provided adhesive remover to remove the Jewel from the body and return the used study devices and supplies to the Sponsor using the provided pre-paid shipping materials.
- Wear the Jewel at all times and following instructions for interacting with the device, paying attention to and responding to audio, visual, and vibratory commands. The Jewel should be removed, the Patch Unit replaced, and the Jewel reapplied approximately once per week or as the device directs the subject.
- Try to keep the Jewel out of direct water spray when showering. Study subjects will be told not to submerge the Jewel (i.e., no baths, swimming, hot tubs, etc.).
- Avoid exposing Jewel patches to direct sunlight for more than 5 minutes.
- Avoid operating the Jewel System in hot environments (greater than 50°C /122°F) and cold environments (less than 10°C / 50°F).
- Avoid storing the Jewel System in hot environments (greater than 30°C /86°F) and cold environments (less than 15°C / 59°F).
- Minimize activities that include excessive stretching of the torso or profuse sweating, as such activities will reduce the ability of the device to remain on the skin and may result in the need to replace the Jewel early.
- Bring a back-up Patch Unit and the Placement Accessory when traveling for more than 24 hours.
- Keep cell phones at least 12 inches away from Jewel.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial, but who do not subsequently wear a Jewel (Jewel does not enter Monitor Mode). These subjects will not be included in any study analyses. A minimal set of screen failure information will be captured, including demographics, screen failure details, and eligibility criteria.

5.5 Strategies for Recruitment and Retention

Subjects will be recruited from inpatients who are nearing hospital discharge, or from patients discharged in the previous five (5) days, who meet the study inclusion criteria and have none of the exclusion criteria. Site staff will be responsible for identifying eligible patients within their respective clinical practices. Any subject who becomes a member of a vulnerable population during the clinical trial will be exited from the study.

6. STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Element Science, Inc. ("Element Science") has developed the Jewel for patients who are at risk for SCA. The Jewel monitors a patient's cardiac rhythm continuously, and if a patient experiences a life-threatening episode of VT or VF, the Jewel is able to deliver a therapeutic shock to convert a patient to normal sinus rhythm. By incorporating the functionality of an AED into a patch wearable adhesive system, the Jewel provides a patient-centric design that improves the comfort and convenience of wearing a WCD. Throughout the wear period, the Jewel does not need to be removed for any typical activity, which ensures that the patient is protected continuously during common daily activities, including cardiac rehabilitation, showering, and sleeping.

The Jewel P-WCD includes the following components: Upper Adhesive Electrode Patch, the Monitoring and Defibrillation Unit with Lower Adhesive Electrode Patch, and a Connection Cable. A schematic is shown below in Figure 1 and a brief description of each component is outlined in Table 1.

The Jewel is packaged with Accessories to aid in application and removal. Jewel Accessories include a Skin Prep Kit to aid in cleaning the torso and pectoral area prior to application of the Jewel. A custom-fitted Placement Accessory aids in placement of the Jewel on the subject's torso and pectoral area in an anterior-apical defibrillation vector. Removal Accessories are also provided to aid in removing the Jewel and cleaning the skin area.

Figure 1: Schematic of Jewel components.

Table 1. Jewel component descriptions

Jewel Component	Description
Upper Adhesive Electrode Patch	Conformable adhesive patch containing ECG electrodes and a defibrillation electrode.
Defibrillation Unit with Lower Adhesive Electrode Patch	Conformable adhesive patch containing ECG electrodes and a defibrillation electrode. All electronics are contained within the Defibrillation Unit, which is connected to the Lower Adhesive Electrode Patch and Battery Unit. Control Buttons are located on the Defibrillation Unit.
Connection Cable	Multi-conductor cable assembly connecting the Upper Adhesive Electrode Patch to the Defibrillation Unit with Lower Adhesive Electrode Patch.

The Upper Adhesive Electrode Patch is applied to the skin above the right pectoral muscle, and the Lower Adhesive Electrode Patch is applied such that the defibrillation pad area is located along the left mid-axillary line. The Jewel can be worn continuously, 24-hours per day for up to eight (8) days, until the Jewel is removed, disassembled, reassembled on a new Patch Unit, and reapplied. This process continues through the end of the prescription period. Figure 2 shows a depiction of the Jewel as applied to a patient.

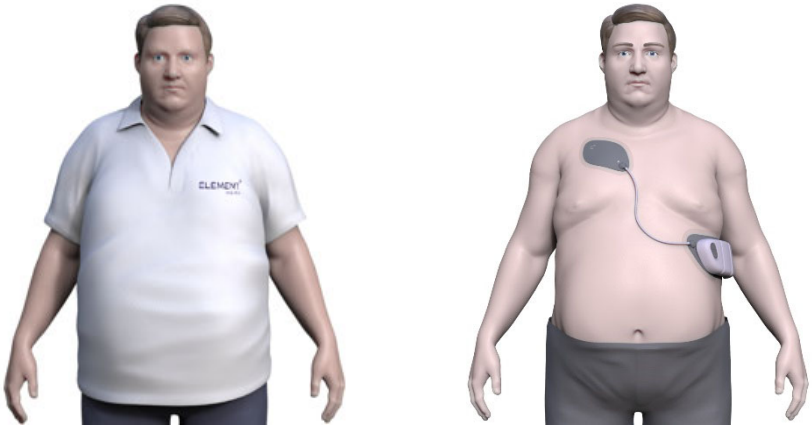

Figure 2: Jewel applied to a patient's torso.

Schematics of the Placement Accessory are shown in Figure 3. The Patch Unit Kit containing the Skin Prep Kit, Patch Unit Pouch, and Removal Kit are shown in Figure 4.

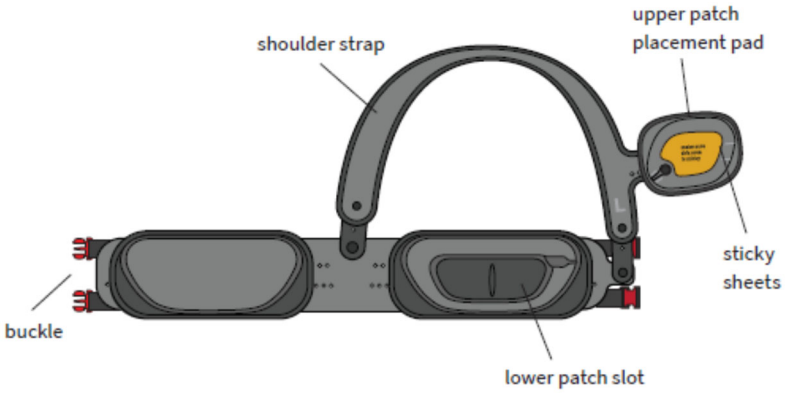

Figure 3: Placement Accessory

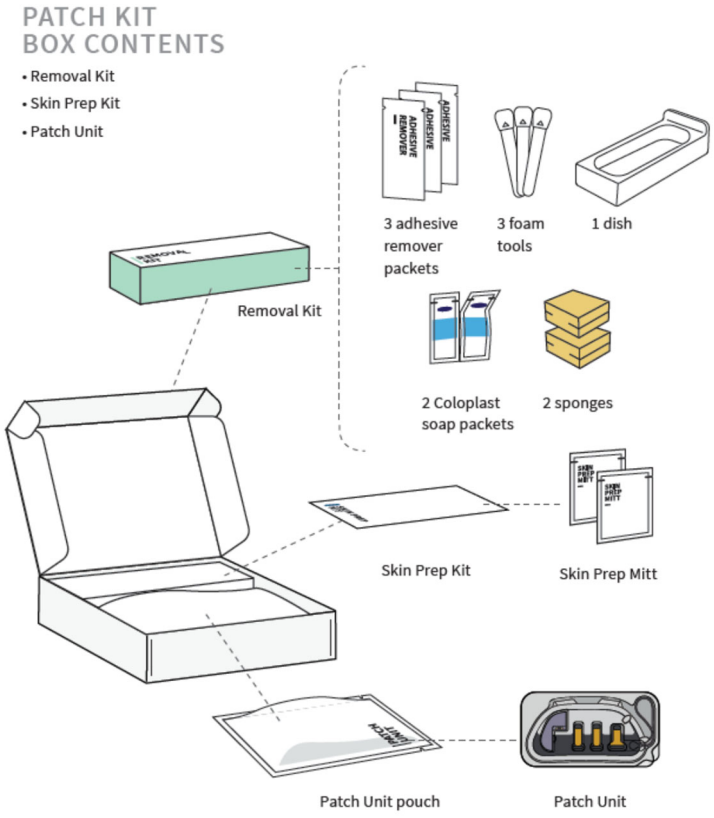

Figure 4: **Patch Kit**

The Jewel is a Class III medical device in the United States.

6.1.2 Therapy and Administration

The MADIT-RIT study results demonstrated a reduction in inappropriate therapy and all-cause mortality when ICDs were programmed to deliver therapy for tachyarrhythmias of 200 bpm and higher.(5) The Jewel algorithm was designed with the MADIT-RIT rate cut-off as a guide for determining if a rhythm is life-threatening, requiring therapy. The Jewel continuously monitors sensor data and classifies ECG segments as life-threatening or not life-threatening based on multiple features. It is designed to recognize life-threatening VT or VF and automatically deliver a therapeutic shock within 60 seconds of detection of these rhythms. As the Jewel uses multiple

inputs in addition to rate to classify ECG segments, it does not allow the physician to program heart rate detection thresholds.

During the prescription period, the Jewel monitors a patient's ECG through five (5) electrodes located on the Adhesive Electrode Patches. The Jewel employs a proprietary algorithm to detect and classify VT or VF that is deemed to be life-threatening ("shockable") versus cardiac rhythms that are non-life threatening ("non-shockable"). In the event of a shockable rhythm, the Jewel firmware initiates the charge cycle of the capacitors and in parallel, the Jewel initiates an alarm sequence to alert the patient that the device is preparing to deliver a shock. If the patient is conscious, the patient is instructed to press both Control Buttons simultaneously to stop the alarms and prevent shock delivery. If the patient does not respond and the shockable rhythm continues, the Jewel will continue to alarm and will give a verbal warning to bystanders that a shock will be delivered and to avoid touching the patient.

The Jewel delivers the initial therapeutic shock with a fixed energy of approximately 150 joules using a biphasic truncated exponential defibrillation waveform using a constant energy pulse that is adjusted based on the measured transthoracic impedance (TTI) of the patient at the time of therapy delivery. Using a cardioversion algorithm, the Jewel attempts to cardiovert the rhythm and synchronize the shock with the R-peak of the QRS complex. This automatic synchronization delivers a cardioversion shock to a patient if R-peaks are detected, suggesting that the rhythm is a life-threatening VT instead of VF. If the cardioversion algorithm is not able to identify a regular R-peak during the ventricular arrhythmia, the Jewel delivers an asynchronous defibrillation shock. If the Jewel continues to detect a shockable rhythm after the initial shock of approximately 150 joules, the Jewel re-initiates the alarm sequence and verbal warnings, and continues to deliver a salvo of up to four (4) additional shocks of approximately 162 joules, totaling five (5) consecutive shocks (150, 162, 162, 162, 162 joules). If the shockable rhythm is successfully converted to a non-shockable rhythm, the Jewel will 'reset' and continue monitoring for the occurrence of a new shockable rhythm episode. After delivery of all 5 shocks in a salvo or if the Jewel detects asystole, the Jewel will play an alarm directing bystanders to call 911 and start CPR.

6.2 Jewel Storage and Accountability

6.2.1 Acquisition and Accountability

Subjects will receive the initial Jewel System directly from the site staff or from the Sponsor's representative. The subject will have the initial Jewel applied during training and will return home with one (1) additional Patch Unit. Subjects are expected to replace the Patch Unit on a regular basis and as instructed. Used Patch Units shall be returned directly to the Sponsor using the pre-paid shipping label and provided packaging. Patch Units are returned individually as they are removed from the body. When the Sponsor is notified that a subject requires an additional Jewel or additional Patch Units, the Sponsor will send more product directly to the subject's home. At the end of the prescription period, the Jewel device and all supplies will be returned to the Sponsor.

All Jewel Defibrillation Units are controlled by serial number (SN) and lot number (LN). Patch Units are controlled by lot number (LN). The Sponsor and site will maintain device accountability logs indicating the location of each Jewel. The study site and the Sponsor will maintain logs of serial number for all Jewel Defibrillation Units used by each subject.

6.2.2 Product Storage

Jewel Defibrillation Units and Patch Units should be shipped and stored according to the Patient Guide (Instructions for Use (IFU)) and product labeling. The Jewel must be stored in ambient room temperatures. The expiration date is clearly marked on the packaging. Any Patch Unit that is nearing its expiration date (within 10 calendar days) should be returned to the Sponsor via the supplied packaging and a provided pre-paid shipping label.

6.3 Randomization and Blinding

This study is a single-arm study of a P-WCD. All subjects will receive devices for a prescription period determined by the site Principal Investigator (PI). As such, the study does not involve any randomization or blinding processes.

6.4 Study Intervention Compliance

Subject compliance with wearing the Jewel will be assessed using time-stamped data recorded directly by the Jewel. These data will be downloaded and reviewed after the Sponsor receives the used Jewel from the subject.

The site will maintain regular communication with the Sponsor and subjects to ensure subject compliance with wearing the Jewel and returning used Patch Units to the Sponsor.

6.5 Concomitant Therapy

It is anticipated that subjects will be prescribed medications for their medical condition(s). For this study, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported on the Case Report Forms (CRFs) include concomitant prescription medications and over the counter medications. In addition, medical procedures and other diagnoses occurring during the study will be reported. Sites will be responsible for collecting information about medications, procedures, and other diagnoses at the time of enrollment, and for updating this information as appropriate at each contact with the subject throughout the study duration.

7. STUDY DISCONTINUATION AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Subjects may remove the Jewel if required for situational circumstances as listed in the Patient Guide. Examples include but are not limited to: undergoing a medical procedure (for example, MRI, CT, or with the use of diathermy), or submerging of the body. Subjects will be counseled that Jewel removal for these reasons should be done as infrequently as possible, and only as absolutely required. These situational circumstances do not constitute discontinuation or withdrawal.

Subjects may discontinue use of the Jewel, either temporarily or permanently, if advised to do so by the Investigator. In cases where a subject discontinues use of the Jewel on their own (that is, without instruction from the Investigator), a protocol deviation should be filed. Discontinuation based on Investigator orders does not constitute a protocol deviation.

If the discontinuation is temporary and does not meet non-compliance criteria for study discontinuation, the subject may continue in the study through the duration of the prescription period, restarting use of the Jewel either independently or when advised by the Investigator. Any new clinically relevant finding that causes temporary Jewel discontinuation will be reported as an Adverse Event.

If the discontinuation is to be permanent, the subject will be withdrawn from the study. In the case of withdrawal, best efforts should be made to collect the Jewel and all used or unused Patch Units and to complete the Study Exit Visit CRF.

7.2 Subject Withdrawal from Study

Subjects are free to withdraw from study participation at any time upon request. An Investigator may withdraw a subject from the study at their discretion. Possible reasons for study withdrawal include, but are not limited to:

- Pregnancy
- Significant study non-compliance
- Significant wear non-compliance: discontinuation of device wear for longer than eight (8) days that is not related to Investigator direction or situational circumstances.
- Any AE or other medical condition or situation occurring such that continued participation in the study would not be in the best interest of the subject.
- Disease progression which requires discontinuation of the study device.
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Reasons for subject withdrawal from the study will be recorded on the appropriate CRF. Subjects who sign the informed consent form but are not enrolled may be replaced. Subjects who sign the informed consent form, are enrolled, but who subsequently are withdrawn from the study will not be replaced.

7.3 Lost to Follow-Up

A subject will be considered Lost To Follow-Up (LTFU) if he or she fails to return to the site for their final study visit or is unable to be contacted by the site staff. Every attempt will be made to secure return of the Jewel and any used/unused study supplies to the Sponsor or site staff.

The following actions must be taken if a subject fails to return to the site for a required study visit, or the subject cannot be reached:

- The site will attempt to contact the subject and reschedule the missed visit, will counsel the subject on the importance of maintaining the assigned visit schedule, and will ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed LTFU, the Investigator or designee will make every effort to regain contact with the subject and subject's emergency contact (where possible, three (3) telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of LTFU.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Procedures

8.1.1 Subject Identification and Consent

Subjects who are in-patients or who have been discharged in the previous 5 days, and who meet the inclusion/exclusion criteria, will be identified and approached by site personnel. Subjects who subsequently consent to study participation will be scheduled for a training session with the Site personnel and, most likely, the Sponsor personnel or their representative.

Baseline information including demographics, general medical history, cardiac-specific medical history, current medications, COVID-19 status, and contact information, including mailing address, for the subject and her/his emergency contact will be gathered. Note that contact information will be kept confidential by the site staff and will only be shared with the Sponsor for purposes of providing replacement study materials.

8.1.2 Subject Training

Subject training will occur at the study site as soon as possible, but no longer than seven (7) days after the subject provides informed consent.

As part of training, a model device will be on hand to familiarize the subject with the Jewel. Subjects will be shown the different alarms that may be heard and trained on how to respond to each one. The model device will mimic the initiation of the VT/VF alarm for the subject to practice therapy deferral. Other device interactions including Status Checks, the Press and Hold Alerts, battery replacement alerts, and Removal Mode initiation will also be demonstrated. The subject will practice responding to the different alarms and alerts.

The subject will be shown how to use the Placement Accessory to place a Jewel and will practice loading the model device into the Placement Accessory, putting the Placement Accessory on their body and correctly using the alignment markers.

The subject will also be shown how to disassemble the Defibrillation Unit from current Patch Unit and assemble it to a new Patch Unit.

During training, the site personnel, with assistance from the Sponsor representative, will assess the cognitive and physical capabilities of the subject. If the subject does not have the cognitive ability to understand the written and verbal instructions or has physical impairments that would limit the subject's ability to feel, see and hear the device notifications, defer a defibrillation shock, or apply the device to their body, the subject will be considered as having an Exclusion Criteria, and will not be enrolled in JEWEL.

8.1.3 Subject Enrollment

If the subject successfully completes device training, site personnel and/or a Sponsor representative will educate the subject on the Jewel to ensure safe and effective use throughout the prescribed duration. If present, caregivers will be invited to participate in all aspects of the training. This training will be performed in a clinical environment.

As part of the training curriculum, the Patient Guide and the Quick Guide, which the subject will take home with him/her, will be utilized to walk a subject through different aspects of the device interaction and care. The Placement Accessory will be custom fit to the subject to aid in applying the device in the correct location. Once the Placement Accessory is fit to the subject, the dimensions are maintained with mechanical rivets and Velcro fasteners which are not intended to be modified by the subject. In the event a subject gains/loses weight, they can contact the study

site who will arrange with Sponsor personnel to refit or replace the Placement Accessory. After the first Jewel is successfully applied to the subject, and the Jewel enters Monitor Mode, the subject will be considered enrolled in the trial.

If the subject has an iPhone 6 or greater and chooses to use the Jewel Mobile Application ("App"), the App will be downloaded to their phone and paired with the Jewel at the time of Enrollment.

The subject will be instructed on whom to call should any device questions arise. The subject will also be instructed to return all used Jewel device supplies back to the Sponsor, using the supplied packaging and pre-paid shipping labels. Site personnel or Sponsor representatives may help facilitate shipping when appropriate.

8.1.4 Wear-Time During Prescription Period

For the first four (4) Patch Unit replacements ("Exchanges"), subjects will be asked to electronically complete a questionnaire regarding their wear experience, and if possible, to take a photograph of the Jewel after the home application. If photographs are taken, they will be provided by the subject to the site electronically.

During the wear-time portion of the study, any delivered shocks should be immediately reported to the site staff by the subject or their family/caregiver. Any aborted shocks (i.e. shocks that were deferred by the subject pressing the Control Buttons on the Defibrillation Unit) should also be immediately reported to site staff. If the subject has an iPhone with the Jewel Mobile App running, the App will tell the study site when the subject replaces a Patch Unit. If the subject has access to the internet, the subject will report the Exchange using a secure, dedicated weblink. The subject will enter changes to her/his health status, any adverse events, any shocks (deferred or received), compliance, needs for assistance, training, or supplies from Element Science, and changes to cardiac, medical, or medication history. If the subject does not have access to the internet, when the subject replaces the Patch Unit, the subject will call the site to report the Patch Unit replacement within 72 hours. During these calls, the site staff will assess the subject's health status, any adverse events, any shocks (deferred or received), compliance, needs for assistance, training, or supplies from Element Science, and changes to cardiac, medical, or medication history.

If the subject does not replace a Patch Unit (if the subject has the App), does not report an Exchange, or does not contact site staff for a period of ten (10) days or longer since the last date of contact, the site staff will contact the subject by phone or during in-person follow-up visits to assess compliance with wearing the Jewel, the need for additional Patch Units or supplies, and to assess any adverse events, any shocks (deferred or received), compliance, needs for assistance, training, or supplies from Element Science, and changes to cardiac, medical, or medication history.

<u>Data for Any Shock(s)</u>

If a subject receives a shock or a salvo of shocks and has the Mobile App, the shock data will be sent to the ES Cloud where a Therapy Report will be generated and sent to the Site. If the subject does not have the Mobile App, a Sponsor representative will go to the subject and download the data from the device to generate the Therapy Report.

<u>Study Exit Visit</u>

Within 14 days of the end of the prescription period, site staff will contact the subject to complete the Study Exit Visit. At this interview, site staff will inquire about any adverse events, any shocks (deferred or received), compliance, and changes to cardiac, medical, or medication history. Subjects will be instructed to return all used and unused Jewel study supplies to the Sponsor.

8.2 Adverse Events and Serious Adverse Events

8.2.1 Definitions

Adverse Event (AE)

An Adverse Event is any unfavorable and unintended sign, symptom, or disease, temporally associated with the use of the Jewel, whether or not it is related to the Jewel.

No causal relationship with the clinical trial product is implied by the use of the term "Adverse Event". Exacerbations of a pre-existing condition/illness that are defined as a "more frequent occurrence" or as "an increase in the severity of the pre-existing conditions" are considered AEs.

Serious Adverse Event (SAE)

An adverse event is considered "serious" if, in the view of either the Investigator, Sponsor, or DSMB, it:

- Results in death;
- Is considered life-threatening (meaning that its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or disability; or
- Results in a congenital anomaly/birth defect.

Adverse Device Effect (ADE)

An adverse device effect is any AE that is related to the Jewel. All ADEs are further categorized as anticipated or unanticipated by the Sponsor.

Unanticipated Adverse Device Effect (UADE)

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

Device Deficiency

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as a malfunction, misuse or use error, and inadequate labeling.

8.2.2 Classification of an Adverse Event

Severity of Event

All AEs will be assessed for severity by the site Investigator using the following grading system:

- **Mild –** The AE does not interfere in a significant manner with the subject's normal functioning level and requires minimal or no treatment.
- **Moderate –** The AE produces some impairment of function, but is not hazardous to health.
- **Severe** – The AE produces significant impairment of function or incapacities and/or is a hazard to the subject. These events may require systemic therapy or other treatment.

Relationship to Study Device

All AEs will be assessed for relationship to the Jewel by the Investigator who examines and evaluates the participant, based on temporal relationship and his/her clinical judgment. 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 use of the study device and cannot be explained by concurrent disease or other drugs or chemicals.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after use of the study device, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Potentially Related** – There is some evidence to suggest a causal relationship, however, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to use of the study device makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after use of the study device) and in which other drugs or chemicals or underlying disease provides plausible explanations.
- **Not Related** – The AE is completely independent of use of the study device, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Expectedness

The DSMB will be responsible for determining whether a given AE is expected or unexpected. An AE 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 in the product risk management documentation, device labeling, protocol, and/or informed consent document.

In addition to the Potential Risks in Section 2.2.1, the following are anticipated with use of the Jewel:

- Failure to sense and detect a treatable arrhythmia
- Unsuccessful cardioversion or defibrillation
- Inappropriate shock
- Improper, ineffective, or non-operation of the device
- Device failure
- Ineffective cardioversion or defibrillation by another external defibrillator
- Non-operation due to patient or bystander disabling therapy
- Fire hazard in the presence of a high-oxygen concentration
- Bystander shock
- Pacemaker interaction

8.2.3 Time Period and Frequency for Event Assessment and Follow-Up

AEs and/or SAEs may come to the attention of study personnel during study follow-up phone calls, when the subject presents for office visits/medical care, or upon review of source documents by a study monitor.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to the Jewel, and resolution/stabilization of the event. All AEs occurring during the study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution or will be marked as ongoing at the time of study exit.

Any medical condition present at the time the subject is screened will be considered as baseline and not reported as an AE. However, if the subject's condition deteriorates at any time during the study, that condition's deterioration will be recorded as an AE.

Changes in severity of an AE will be documented to allow for an assessment of the duration of the event at each level of severity. All AEs will be characterized for severity when reported and, if ongoing, updates to the severity of any ongoing AEs will be assessed at subsequent visits.

8.2.4 Adverse Event Reporting

AEs must be documented on a CRFs by site staff. It is the responsibility of the Investigator to ensure that all information is correct. When reporting any AEs or SAEs, the following information should be included:

- Description of event (including diagnosis)
- Onset date
- Severity
- Relationship to study device
- Action taken
- Outcome
- Duration / Resolution date

8.2.5 Serious Adverse Event Reporting

All SAEs must be reported to the Sponsor within 24 hours of learning about the event, regardless of the time that may have elapsed from the time the event occurred. The Sponsor must also receive a completed AE form within three (3) working days of the site being notified of the event. Investigators shall comply with all local reporting requirements. The Sponsor will inform regulatory authorities of SAEs per local and federal requirements.

8.2.6 Unanticipated Adverse Device Effect Reporting

The Investigator shall complete an AE Form and submit it to the Sponsor and to the reviewing IRB immediately, but no later than ten (10) working days after the Investigator first learns of the effect, as required by 21 CFR §812.150. The Sponsor is responsible for conducting an evaluation of a suspected UADE, and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all other participating IRBs and Investigators within ten (10) working days after the Sponsor first receives notice from the Investigator. Thereafter, the Sponsor shall submit such additional reports concerning the effect as the FDA requests.

8.2.7 Device Deficiencies

All device deficiencies must be documented and reported to the Sponsor within three (3) days. The DSMB is also responsible for assessing whether a device deficiency poses an unreasonable risk to patients if the study is continued.

8.2.8 Reporting of Other Events

Other Reported Events are any other clinical events that are submitted by the Investigator which are not caused by or associated with the study device and/or system component(s) and/or defined as an AE.

8.2.9 Reporting of Clinical Events

All clinical events resulting in outpatient (< 24 hours) or inpatient (≥ 24 hours) hospitalizations, observational care visits, emergency room visits, urgent care center visits, or physician's office visits must be reported to the Sponsor. Detailed source documentation surrounding the clinical event should also be provided to the Sponsor. These detailed source documents may include, but are not limited to:

- Emergency department notes
- Physician consultation notes
- Medication records and logs
- Admission notes
- Laboratory results and summary details
- Discharge summary
- Operative notes
- Clinician progress notes
- X-ray and other radiological reports
- Diagnostic test reports

The applicable eCRFs should be completed for each episode of a clinical event. Supporting documentation should be submitted to the Sponsor along with the applicable eCRF.

8.2.10 Reporting Events to Participants

The DSMB will periodically review study data and will determine if any new, previously undisclosed risks should be added to the informed consent document. Should any informed consent updates be required, after approval by the relevant IRB, subjects may be asked to reconsent to the study, per local regulations.

Furthermore, any new or previously undisclosed risks will be appropriately communicated to participating Investigators.

8.2.11 Reporting of Pregnancy

If a subject becomes pregnant during participation in the study, study participation will be discontinued and documented.

9. STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) provides details of the statistical analyses separately.

9.1 Statistical Hypotheses

Primary Effectiveness Endpoint:

The primary effectiveness endpoint is the rate of inappropriate shock. A one-sided upper 98% confidence limit will be calculated for the inappropriate shock rate per 100 patient-months at the final analysis.

Only first inappropriate shocks will contribute the analysis of this endpoint. All wear times through the first inappropriate shock or through death or withdrawal will contribute to the Poisson regression model. All follow-up beyond the first inappropriate shock will not be used.

The formal hypotheses are:

H0: Inappropriate shock rate ≥ 2.0 per 100 patient-months

Ha: Inappropriate shock rate < 2.0 per 100 patient-months.

Primary Safety Endpoint:

The primary safety endpoint is the rate of subjects experiencing a clinically significant ADE. The primary safety endpoint will use a one-sided, exact 95% upper confidence bound which will be compared to the performance goal of 15%. The hypotheses tested will be as follows:

H0: $\pi \geq 0.15$

Ha: $\pi < 0.15$

where π is the observed proportion of subjects experiencing a clinically significant cutaneous adverse device event.

Secondary Endpoint:

The secondary endpoint of successful conversion of at least one shockable rhythm with a salvo of up to five (5) shocks will not be formally tested.

The secondary endpoints of compliance rate of subjects wearing the Jewel, and the QOL analysis will not be formally tested.

9.2 Samples Size Determination

The estimated power for the Primary Endpoint analysis is based off Monte-Carlo simulations. Assuming an average of 2.5 subject-months of wear time per subject and an expected inappropriate shock rate of 0.37 per 100 subject-month, a total of 290 subjects are required to provide approximately 98% power to demonstrate that the inappropriate shock rate is below 2.0% per 100 subject months, assuming the Type I error rate at the final analysis is 0.02. A total of up to 370 subjects may be enrolled in the study to account for 20% subject withdrawals, LTFUs, and devices that may be lost or damaged when being returned to Element Science.

Although the secondary endpoint of successful termination of life-threatening VT or VF episodes is not being formally tested, this study is designed to provide data to support this secondary endpoint. The number of shockable episodes will be monitored over the course of the trial with the goal to observe at least one (1) successful conversion of life-threatening VT or VF with a salvo of up to five (5) shocks. It is anticipated that three (3) such events will occur during this trial.

9.3 Populations for Analyses

All subjects enrolled will be evaluated on the primary and secondary endpoints. All actual wearable device times following a subject's initial Jewel placement will be included in the primary analysis. The actual wear times will be used. Data will not be imputed for endpoint calculations. A subject is considered analyzable in this population if they contribute any length of wear time with the Jewel.

A per-protocol analysis population will be defined as those subjects without major protocol deviations. Analyses on the safety and effectiveness endpoints will be repeated on this population. A subject is considered analyzable in this population if they have worn the Jewel on average for at least 14.1 hours a day.

9.4 Statistical Analyses

9.4.1 General Approach

Descriptive statistics for continuous variables will include the mean, standard deviation, N, median, and range in the form of a minimum and maximum. Categorical data will be summarized using percentages and the count (numerator) and N (denominator) used to calculate the percentage. All formal testing will be done at the 0.05 level of significance unless otherwise stated.

The details of the statistical analysis can be found in the JEWEL SAP.

9.4.2 Additional Analyses

All Adverse Device Effects and device-related SAEs will be tabulated and presented. A summary of all AEs and SAEs, including the proportion of subjects experiencing an AE or SAE, along with duration, severity, and relatedness to the Jewel will also be presented to ensure that device safety performance is adequately summarized.

As a measure of compliance, daily wear time will be calculated for all subjects enrolled in JEWEL.

Details regarding the analysis of Jewel System Compliance calculations, the Detection of Ventricular Arrhythmias, and QOL will be outlined in the SAP.

9.4.3 Baseline Descriptive Statistics

Baseline characteristics of the enrolled population will be presented. These characteristics include demographics such as gender, age, sex, medical history, and co-morbidities including COVID status. These characteristics will be summarized as outlined in Section 9.4.1.

9.4.4 Planned Interim Analyses

A single interim analysis will be performed after 179 or more subjects have completed their prescription wear time. This analysis will be used to stop the trial early for both safety and effectiveness. The Type I error rate for this analysis will be set to 0.03.

There is another planned analysis once 100 subjects have completed their prescription wear time, which will be performed to support application for CE mark. The data will be summarized descriptively and no formal hypothesis testing will be done at this point, so no adjustment for the Type I error rate is necessary. The results of the 100 subject interim analysis will not be used to terminate the IDE trial prior to completion of enrollment and subject follow up.

9.4.5 Sub-Group Analyses

Since sub-groups are not powered, a formal comparison to the rate of 2.0% per 100 patient months will not be done. The rate of inappropriate shock will be analyzed separately for males and females, COVID positive versus COVID negative, as well as for individuals with a Body Mass Index of ≤25 and >25. Details of the sub-group analysis can be found in the SAP.

9.4.6 Tabulation of Individual Subject Data

Individual subject data will be listed by measure and time point. We will describe subject wear-time and any notable events, specifically inappropriate shocks and/or successful conversions.

9.4.7 Study Site Poolability

Site poolability will be assessed using an Rx2 table where each site is a row in the table and the two columns are “number of subjects experiencing an inappropriate shock” and “number of subjects free from inappropriate shocks.” Details of the analysis will be outlined in the SAP.

9.4.8 Handling Missing Data

It is expected that most subjects will wear the device between 40 and 90 days. Wear time and handling of missing data will be described in detail the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Subjects

Consent forms describing in detail the Jewel, study visits/calls, and risks are given to the patient. Written documentation of informed consent is required prior to enrollment in the study.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the patient will be asked to read and review the document. The Investigator will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study, and of their rights as research subjects. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient must sign the informed consent document prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the fully executed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the subject's medical record (including the date and time), and the informed consent form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects 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 the study.

10.1.2 Study Discontinuation and Closure

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Suspension/termination may occur at the site-level or at the study-level. Written notification documenting the reasons for study suspension or termination will be provided by the suspending or terminating party to study Investigators, the Sponsor, and regulatory authorities, as appropriate. If the study is prematurely terminated or suspended, the PI at each site will promptly inform the IRB, and will provide the reason(s) for the termination or suspension. Subjects will be contacted, as applicable, and be informed of any changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of effectiveness that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Following suspension, study activities may resume once concerns regarding safety, protocol compliance, and/or data quality are addressed and satisfy the sponsor and/or Food and Drug Administration (FDA), as appropriate.

10.1.3 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating Investigators, their site staff, and the Sponsor. Confidentiality is extended to cover all clinical, demographic, and contact information relating to patients. The study protocol, documentation, data, and all other information generated 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.

All research activities, including subject training, will be conducted in as private a setting as possible.

The study monitor, other authorized Sponsor representatives, representatives of the IRB and/or regulatory agencies, may inspect all documents and records required to be maintained by the PI, including but not limited to medical records (office, clinic, or hospital), and pharmacy records for subjects. The site will permit access to such records.

The subject's contact information will be securely stored in Sponsor's database(s) and at each clinical site for internal use throughout the study. At the completion of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

For purposes of study conduct, specifically including shipping and receiving of investigational product directly to subjects, Sponsor representatives may find themselves in possession of subject contact information. This contact information will be held in the strictest confidence and will only be used to fulfill requests from the subjects for training and assistance and for provision and receipt of Jewel study supplies.

Subject device data will be transmitted to and stored by the Sponsor. These data will not include the subject's contact or identifying information. Individual subjects and their device data will be identified by a unique study identification number. Device data stored directly on the Jewel will be retrieved from Jewel by trained Sponsor personnel. These data will be identified by device serial number which will be used to link the data to a specific subject. Study data entry and study management systems used by sites and by the Sponsor and their research staff and designees will be secured and password protected. At the completion of the study, all study databases will be de-identified and archived by the Sponsor or their representative.

10.1.4 Future Use of Stored Data

Data collected for this study will be analyzed and stored by Element Science. Permission to transmit data to Element Science will be included in the informed consent.

10.1.5 Key Roles and Study Governance

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10.1.6 Safety Oversight

All delivered shocks, both appropriate and inappropriate, will be reviewed and adjudicated by a CEC. The CEC will meet regularly, and may meet on-demand, as needed.

Safety oversight will be provided under the direction of a DSMB composed of individuals with appropriate expertise, including interventional cardiology and/or electrophysiology. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The DSMB will meet regularly to assess safety and study conduct. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At that time, each data element that the DSMB will assess will be clearly defined. The DSMB will provide its input to the Sponsor.

10.1.7 Clinical Monitoring, Quality Assurance and Quality Control

Monitoring for this study will be performed by the Sponsor or their representative and will consist of a combination of on-site monitoring visits and centralized reviews of data on an ongoing basis. Before acceptance of the clinical data, the Sponsor will review the data entered on electronic case report forms (eCRFs) for completeness and adherence to the protocol based upon source documentation verification (SDV). Procedures to be followed and the data to be fully monitored to SDV will be described in detail in the Clinical Monitoring Plan (CMP). For example, all safety data and primary and secondary endpoint measures as defined by the protocol will be 100% monitored against the source data.

The Sponsor will qualify investigative sites through review of the adequacy of the subject population, facilities, equipment and resource needs of the study, and will familiarize the Investigator with the study protocol.

At the time of enrollment, the Sponsor will meet with the Investigator to ensure that subjects will be properly selected, consented, and enrolled, that the study protocol is thoroughly understood,

the method(s) surrounding clinical data collection and capture are understood, and to confirm the Investigators acceptance of her/his regulatory obligations.

Assigned Clinical Monitors of the Sponsor may visit the site(s) periodically during the study to perform SDV. Visits may also be performed remotely. The Investigator and Institution must guarantee direct access to all relevant medical records by designated monitors and regulatory authorities.

The study may be subject to a quality assurance audit by either the Sponsor or by regulatory authorities. It is important that the Investigator and the assigned authorized study personnel are available during monitoring visits and possible audits, and that sufficient time is dedicated to the process. The site will provide direct access to all trial related sites, source data/ documents, and reports, for monitoring and auditing by the Sponsor, and for inspection by local and regulatory authorities. In the event of a local or regulatory authority audit, the site is expected to immediately notify the Sponsor of the audit.

The Sponsor will be responsible for coordinating and conducting the handling of clinical study data. Procedures will be described in detail in the Data Management Plan and the Statistical Analysis Plan. Data quality control checks will be run on the database on a regular basis. Any missing data, anomalies, or questionable fields will be communicated to the site for clarification/resolution.

10.1.8 Data Handling and Record Keeping

Data Collection and Management Responsibilities

Case Report Form Data

All source documents should meet the ALCOA criteria (accurate, legible, contemporaneous / complete, original, and attributable) to ensure correct interpretation of data. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

The Investigator is responsible for ensuring the quality and accuracy of the data reported. All data generated at the site deemed related to the clinical trial will be entered into an eCRF via an electronic data capture (EDC) system. eCRF data is the responsibility of the clinical trial staff at the site, at the discretion of the PI. Data related to Investigational Product accountability and data from Jewel that is entered in the EDC will be done via API (Application Programming Interface). The EDC will be 21 CFR Part 11-compliant, provided by the Sponsor. The EDC system will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into the EDC from the source documents, and within seven (7) days of data collection if possible.

Jewel Device Data

All Jewel devices will be collected by the Sponsor following the end of the prescription period or device use, and the electronic records will be extracted and archived as source data. Primary and secondary endpoint data will be collected from analysis and relevant CEC review of the source data. For each wear duration, the Jewel records the electrocardiogram, trans-thoracic impedance, defibrillation data, algorithm results for every time the shockable rhythm classification algorithm is run, all button presses and all alarms. Each of these data points are time stamped.

If a subject receives a delivered shock (either appropriate or inappropriate) a report of the 60 seconds preceding and 30 seconds following the shock will be provided to the Investigator.

It is anticipated that the Site and Sponsor may become aware of events of interest, but Jewel data are not available for the events due to mishandling, non-compliance with returning the device, inappropriate disposal, data overwriting, or data corruption. These events may include, for example, inappropriate shock delivery or appropriate shocks that may or may not have resulted in conversion of life-threatening VT or VF. Should any of these events of interest be reported by the subject or study site without the concurrent Jewel data available, the site shall provide the Sponsor and CEC with as much information regarding the event as possible. The CEC will review and adjudicate these situations on a case-by-case basis for inclusion in the endpoint analysis. Any such events will also be described.

As the Jewel collects some limited information on electrograms during wear-time, it is possible that cardiac events of interest may be captured by the Jewel. Data on incidental findings (i.e., arrhythmias not associated with a delivered or deferred shock) will not be provided to the investigation site team. However, if an event is adjudicated by the CEC and a cardiac rhythm of interest is observed, the CEC will inform the Investigator and provide the relevant supporting data.

Study Records Retention

Study documents should be retained for a minimum of two (2) years after the last approval of a marketing application or until at least two (2) years have elapsed since the formal discontinuation of clinical development of the Jewel. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the site when these documents no longer need to be retained.

10.1.9 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. The deviation may be either on the part of the subject, the Investigator, or the site staff. As a result of repeated deviations, corrective actions are to be developed and implemented promptly.

Major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, major protocol deviations include enrolling subjects in violation of key eligibility criteria, failing to properly obtain informed consent, or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

It is the responsibility of the Investigator to use continuous vigilance to identify and report all protocol deviations within seven (7) working days of identification of the deviation. All deviations must be addressed in study source documents and reported to the Sponsor. Protocol deviations must be sent to the reviewing IRB per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 Publication and Data Sharing Policy

Study outcomes will be reported in a peer reviewed journal, as appropriate. Authorship and publication shall be according to the Sponsor’s policies. The study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

10.1.11 Conflict of Interest Policy

All Investigators shall provide the Sponsor with a Financial Disclosure Form prior to initiating any study activities at their sites, at the conclusion of the study, and one year after the study ends.

Further, during the course of the study, Investigators should make best efforts to disclose any new conflicts (both actual and perceived) to the Sponsor in a timely manner. Any actual or perceived conflicts of interest shall be reviewed by the Sponsor and shall be disclosed and managed as appropriate.

10.2 Abbreviations

AE	Adverse Event
AED	Automated External Defibrillator
CABG	Coronary Artery Bypass Grafting
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EP	Electrophysiology
FDA	Food and Drug Administration
ICD	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
LN	Lot Number
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
P-WCD	Patch – Wearable Cardioverter Defibrillator
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCA	Sudden Cardiac Arrest
SCD	Sudden Cardiac Death
SN	Serial Number
TTI	Transthoracic Impedance
US	United States
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
WCD	Wearable Cardioverter Defibrillator

10.3 Protocol Amendment History

Revision	Date	Comment
A	28 Mar 2018	Initial Release
B	12 Jun 2018	Updates per FDA feedback. -Primary Safety and Effectiveness Endpoint revision -Additions to Exclusion Criteria -General Clarifications
C	03 Aug 2018	Section 9.4.5 was inadvertently not updated in Rev B. Rev C updated this section to remove reference to a performance goal and freedom from inappropriate shock.
D	16 Apr 2021	Updates to revise device used in study; adjust study processes to reflect Durable Medical Equipment nature of the ES-2; include allowances for the COVID-19/SARS-CoV-2 pandemic; update Section 9.2 to match the Statistical Analysis Plan, include Subject requests for Sponsor contact.
E	22 October 2021	Revised Primary Effectiveness endpoint and incorporated an interim analysis at 179 analyzable subjects to allow for early stopping for safety and effectiveness.

11. REFERENCES

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