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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1. Introduction

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 heart ventricles 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 Wearable Cardioverter Defibrillator (WCD) has become a viable option to treat these temporary periods of elevated risk for SCA. Patients typically are 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.

The Jewel Patch Wearable Cardioverter Defibrillator (P-WCD) is a Wearable 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.

2. Study Design

This study is a multi-center, prospective, single-arm, non-randomized, unblinded 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 defibrillator. This trial has one interim analysis scheduled after 179 subjects have completed their prescription wear time.

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. 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.

[1] Sudden Cardiac Death (Sudden Cardiac Arrest) | Cleveland Clinic [Internet]. [cited 2018 Feb 19]. Available from: https://my.clevelandclinic.org/health/diseases/17522-sudden-cardiac-death-sudden-cardiac-arrest

3. Analysis Populations

3.1. Primary Analysis Population

All subjects with analyzable wear times following initial Jewel enrollment will be included in the analysis population for the primary effectiveness endpoint. Analyzable wear time is defined as beginning 12-hours after the date and time the first Jewel applied to the subject's body transitions to Monitor Mode to when the last Jewel worn by the subject transitioned to Off Body Mode. Periods of removal time as identified by timestamped transitions between modes, periods of removal time as attested to by a subject or health care provider and confirmed by electrocardiographic data, and periods of time in which there are missing data (e.g. due to unreturned or damaged devices) will be excluded.

3.2. Per Protocol Population

A per-protocol analysis population will be defined as those subjects that are part of the Primary Analysis Population, have worn the Jewel on average for at least 14.1 hours a day, and are without major protocol deviations which may affect the primary safety or effectiveness endpoint measurements. Analyses on the safety and effectiveness endpoints will be repeated on this population.

3.3. Safety Analysis Population

The safety analysis population will consist of all subjects who remain enrolled for longer than 12 hours after the date and time the first Jewel applied to the subject's body transitions to Monitor Mode, regardless of analyzable wear time. For example, if a subject wore the Jewel and subsequently does not return the device or the device was damaged, this subject is still part of the safety analysis population and will be assessed for clinically significant cutaneous Adverse Device Effects.

4. Study Objectives

4.1. Primary Effectiveness

The primary effectiveness endpoint is to demonstrate an observed inappropriate shock rate of no more than 2.0 inappropriate shocks per 100 patient-months using a one-sided upper 98% confidence interval at the final analysis.

4.2. Secondary Effectiveness

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

The second secondary effectiveness 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.

4.3. Primary Safety

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

5. Study Endpoints and Analysis

5.1. Primary Effectiveness Endpoints

All shocks during analyzable wear time will be recorded, centrally evaluated and adjudicated by the Clinical Events Committee (CEC), and reported.

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. Specifically, an intercept-only Poisson regression model will be fit to the data. All wear times through the first inappropriate shock or through death or withdrawal or wear times for subjects without inappropriate shock, death, or withdrawal at the time of analysis will contribute to the Poisson regression model. The one-sided upper 98% confidence limit inappropriate shock rate will be calculated by taking the one-sided upper 98% confidence limit of the intercept parameter in the regression model. The null hypothesis will be rejected if the upper confidence limit on the inappropriate shock rate is less than 2.0.

The formal hypotheses are:

H_0: Inappropriate shock rate ≥ 2.0 per 100 patient-months
H_a: Inappropriate shock rate < 2.0 per 100 patient-months

The analysis will be re-run on the per protocol analysis population if that population is different from the primary analysis population. Results of this analysis are strictly supportive.

Note that subjects experiencing an inappropriate shock will continue to be followed and accumulate wear time in order to collect data on the other endpoints of this trial.

5.2. Secondary Effectiveness Endpoints

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. 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 adjudicated by the CEC). Each shockable episode of life-threatening VT (as defined by the CEC) or VF encountered during the course of the trial will be described and the outcome of any conversion attempt documented. If multiple successful conversions occur in a single subject, all successful conversions will be included in the secondary endpoint analysis. The number and percentage of successful conversions will be given.

5.3. Primary Safety Endpoints

The statistical method used for testing 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 exact confidence bound will be constructed using the Clopper-Pearson method. The hypotheses tested will be as follows:

H_0: $\pi \geq 0.15$
H_a: $\pi < 0.15$

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

An ADE will be considered "clinically significant" if it results in the subject being permanently withdrawn from the clinical trial by the Investigator.

Additionally, 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 Oversight Committee. 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.

5.4. Secondary Endpoint

The 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.

The prescription wear time will be 12-hours after the date and time the first Jewel which was applied to the subject's body transitions to Monitor Mode to the date and time that the last Jewel worn by the subject transitioned to Off Body. Periods of removal time as identified by timestamped transitions between modes, periods of removal time as attested to by a subject or health care provider and confirmed by electrocardiographic data, and periods of time in which there are missing data (e.g. due to unreturned or damaged devices) will be excluded. The prescription wear time will be calculated in hours and in days.

To calculate average hours per day, the gaps between individual device wears will be summed and the total will be subtracted from the total prescription wear time. That absolute device wear time will be divided by the total prescription wear time to obtain the average.

$$\frac{\text{(Total prescription wear period – Sum of gaps between individual wears)}}{\text{Total prescription wear time (expressed in days)}}$$

Duration of wear for individual device wears will be recorded in minutes, calculated based off the device memory logs, and will be defined as the duration of the date and time the Jewel applied to the subject's body transitions to Monitor Mode to the time that the Jewel worn detects Off Body with the exception of the first Jewel which starts 12-hours after the first Jewel transitions to Monitor Mode.

5.5. Interim Analyses

An interim analysis of the Primary Endpoints will be performed after 179 subjects or more have completed their prescription wear time. This analysis will be used to stop the trial early for both safety and effectiveness.

This interim analysis will be analyzed as described in Section 5.1 above, with the exception that a one-sided upper 97% confidence bound will be used. This effectively spends 0.03 alpha on the interim analysis, reserving 0.02 alpha for the final analysis. Splitting the overall alpha into two pieces that add up to the overall alpha is a recognized way of controlling the Type I error rate. This can be seen by calculating the probability of making a Type I error. First calculate the probability of not making a Type I error which is:

Prob(no Type I in interim analysis)*Prob(no Type I in final analysis)= 0.97*0.98=0.9506

The probability of making a Type I error is then one minus the probability of not making any Type I errors which is:

Prob(Type I error)= 1.0 – 0.9506 = 0.0494

This particular split in alpha also corresponds to using a cumulative error spending function of Jennison and Turnbull (2000) defined as:

$$E(t,\rho) = \begin{cases} 1 & if \quad t \geq 1 \\ t^{\rho} & if \ 0 < t < 1 \\ 0 & otherwise \end{cases}$$

where ρ is the power parameter (here ρ=1.059) and t is the information fraction at the time of the interim analysis (here t = 179/290). Given these values, the amount of alpha spent at the interim analysis is:

$\alpha * E(179/290, 1.059) = 0.05*(179/290)^{1.059} = 0.02999$

The safety endpoint will also be tested at this interim analysis only if the primary effectiveness endpoint is achieved. The trial will only be stopped if both the primary effectiveness and primary safety endpoints are achieved.

There is another planned analysis when 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 Type I error rate is necessary. Once discussions with the Notified Body are concluded, this document will be updated with details regarding the analysis.

6. Handling of Missing Data

It is expected that most subjects will wear the device between 40 and 90 days. Subjects with missing wear times will not have their data imputed for the purpose of the primary endpoint analysis.

There may be occasions when a treating physician recommends that a subject not wear the Jewel for a certain period of time for medical reasons. The duration of these periods when the subject is not wearing the Jewel at the treating physician direction will not be used in the analyses of primary, secondary, or additional endpoints. Reasons for not wearing the device may include, but are not limited to: undergoing a medical procedure (for example, MRI, CT), skin issues, resolution of adverse events that could impact device.

7. Study Subjects

7.1. Demographic, Baseline and Medical History

Baseline characteristics of the primary analysis population will be presented. These characteristics include demographics such as age, sex, race, and ethnicity as well as medical history and co-morbidities including COVID status.

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.

7.2. Subject Accountability

Subject accountability will be presented in tabular form. This table will summarize how many subjects were screened and enrolled into this trial. This table will also summarize the number of subjects withdrawing from the study and the reason for withdrawal.

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.

8. Sample Size Estimation

A Scientific Literature Review was performed to determine a clinically meaningful rate for inappropriate shocks and safety events. This is documented in the Report of Prior Investigations.

The estimated power for the primary effectiveness endpoint analysis is based off Monte-Carlo simulations. In order to assess power, 10,000 studies were simulated using various study sizes. For each subject within a study, a random wear time was assigned using a normal distribution with an average of 2.5-months and a standard deviation of 0.5 month. Each subject was also assigned a time to inappropriate shock using an exponential distribution. If the time to inappropriate shock is greater than the wear time, then that subject did not experience an event during the course of the trial. If the time to inappropriate shock is less than the wear time, then that subject is considered to have had an event. For subjects experiencing an event, wear time beyond the time to inappropriate shock is not counted in the simulations. Since inappropriate shock is a rare event, some of the simulated studies had no subjects that experienced an inappropriate shock. When this happened, the study with zero total events was given a total of 0.5 events in order to allow for convergence of the models. Each study was then used to fit a Poisson regression model from which an estimated rate of inappropriate shock along with a one-sided 98% upper bound on that rate was generated. If

that upper bound was below the performance goal, then that study is considered successful, otherwise it is considered to have failed. Adding up the number of successful trials gives an estimate of power for a given sample size.

For the purposes of sample size calculation, the expected inappropriate shock rate was set to 0.37 shocks per 100 subject-months. This is the inappropriate shock rate observed in the NEJM published LifeVest "VEST" RCT[2] and it is assumed that the Jewel P-WCD will have a similar or better inappropriate shock rate. Assuming 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. For purposes of sample size calculation, the Type I error rate was set at 0.02 and it was assumed that the subjects had a 2.5-month average prescription wear time.

Sample sizes required to test the primary safety endpoint were lower than those needed for the effectiveness endpoint, so the sample size needed for effectiveness was chosen as the overall sample size.

A site enrollment cap of 20% will be employed in order to ensure no one site dominates enrollment in this trial.

The study is designed to provide data to support the secondary endpoint of demonstration of successful conversion of life-threatening VT or VF episodes. 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.

In order to adjust for a 20% early withdrawal and/or loss to follow-up subjects, a total enrollment of 290/0.80 = 363 subjects may be needed.

9. Poolability Assessment

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." Noting that each site had an enrollment cap of approximately 20%, an attempt will be made to test for poolability using a standard Pearson chi-square statistic, however, due to the low probability of receiving an inappropriate shock and the enrollment cap, the table may have many sampling zeros making the Person chi-square statistic invalid. If the standard asymptotic Pearson chi-square test is not valid, exact methods will be used for comparing the sites. A p-value less than 0.15 will indicate that the sites are not poolable and that adjustments for site must be made in the primary endpoint analysis.

10. Sub-group Analyses

The primary effectiveness endpoint of the rate of inappropriate shock will also be analyzed separately for males and females, COVID positive and COVID negative subjects, and for subjects whose BMI is >25 and those with BMI ≤25. Since these sub-groups are not powered, a formal analysis will not be done. Rather the rate of inappropriate shocks will be calculated and 95% two-tailed exact confidence intervals constructed about the rate will be given.

[2] Olgin JE. et al. Wearable Cardioverter-Defibrillator After Myocardial Infarction. NEJM 2018;379:1205-15

11. Additional Analyses

Jewel System Compliance

All additional analyses will be performed on the primary analysis population.

Subject compliance with using the Jewel will be evaluated using mean weekly wear, wear per device, and time between devices. Mean weekly wear will be measured every 7 days and time between devices will be measured in hours.

The number of hours a subject wears the Jewel during a particular week will be calculated for each subject over the duration of their prescription. The total time between devices will be subtracted from the total wear time, then be averaged for the number of weeks of wear within each subject to provide an average weekly wear time for that subject. The average weekly wear times will then be summarized across subjects using descriptive statistics.

Since each subject will use more than one device over their prescribed time, the time between a subject removing one Jewel and putting on another Jewel will be measured. The device syslog will timestamp transitions between Modes, enabling the calculation of removal time, application time and the time the device transitions the Monitor Mode. Upon availability of the mobile application in the study, the average number of hours for each subject during the transition from one Jewel to another will be calculated. Periods of removal time as attested to by a subject or health care provider and confirmed by electrocardiographic data will be included in the calculation of removal time. These transition times will be summarized across subjects using descriptive statistics.

These measures of compliance will be presented in table format.

Detection of Ventricular Arrhythmias

An analysis of all events that trigger the alarm cycle after three (3) segments of shockable rhythm (~24 seconds) during analyzable wear time will be performed. Each event will be categorized by the type of rhythm or event experienced. These categories of will be summarized in a frequency table showing the number and percentage of times each arrhythmia triggered the alarm cycle.

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.

12. Protocol Deviations

Protocol deviations will be summarized in tabular form using the frequency and proportion of each type of deviation observed.