SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Carotid Sinus

Device Trade Name: Barostim neo® Legacy System

Device Procode: DSR

Applicant's Name and Address: CVRx Inc.
9201 West Broadway Avenue
Suite 650
Minneapolis, MN 55445

Date of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H130007

Humanitarian Use Device (HUD) Designation Number: HUD #: 13-0307

Date of Humanitarian Use Device (HUD) Designation: July 2, 2013

Date of HUD Designation: October 1, 2014

Date of Notice of Approval to Applicant: December 12, 2014

II. INDICATIONS FOR USE

The Barostim neo® Legacy System is indicated for use in patients with resistant hypertension who have had bilateral implantation of the Rheos® Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R (which have been discontinued and are obsolete) and were determined responders in the Rheos® pivotal clinical study.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "use in patients with resistant hypertension who have had bilateral implantation of the Rheos® Carotid Sinus Leads Models 1010R, 1010L, 1014L, and 1014R which have been discontinued and are obsolete." It was modified for the HDE approval because evidence for probable benefit was provided only for those patients determined to be responders in the Rheos® pivotal trial.

III. CONTRAINDICATIONS

Use of the Carotid Sinus Lead Repair Kit is contraindicated in patients with infection at or near the implant pocket region.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Barostim neo® Legacy System labeling.

V. DEVICE DESCRIPTION

The Barostim neo® Legacy System consists of the following components:

- neo® Legacy Implantable Pulse Generator (IPG) Model 2100
- CVRx Programmer System Model 9010
- Rheos® Carotid Sinus Leads, Models 1010R, 1010L, 1014R, and 1014L (patient must have previously implanted; the leads are obsolete and there will be no new implants)
- Accessories including the Accessory Kit Model 5500, CSL Lead Repair Kit Model 5010 and Magnet Model 5000

The IPG contains a battery and circuitry in a hermetic enclosure. It provides control and delivery of the activation energy through the Carotid Sinus Lead to the baroreceptors. The left and right carotid sinus leads are attached to the pulse generator through the connector module.

The Programmer System allows noninvasive communication with the IPG for input of therapy parameters and retrieval of information regarding the status of the IPG. The Programmer Software is installed on a supplied computer. The Programmer Software will interrogate, adjust, and monitor the therapies being delivered by the IPG. The Programmer Interface provides the telemetry interface to the IPG. It is powered via the USB port on the computer.

The CVRx Accessory Kit contains a torque wrench and port plug. The torque wrench is used to tighten the set screws on the IPG. The port plug can be used to plug a lead port on the IPG.

The CVRx CSL Repair Kit contains tools and material to repair damage to the insulation and/or conductor coils of the therapy lead after chronic implantation.

The CVRx Magnet can be used to temporarily inhibit the IPG output by placing the solid part of the magnet over the IPG. The magnet must be kept over the IPG to continue inhibiting the output state. Once the magnet is removed, the output will continue.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are currently no commercially-available medical devices in the US indicated to treat drug resistant hypertension. The patients that are included in the proposed indications for use for this HDE have been treated with commercially available treatments for resistant hypertension and still have resistant hypertension. The only procedures that can be used in the treatment of resistant hypertension in patients who have been implanted with the Rheos® carotid sinus leads, are deemed responders to Rheos® system therapy, and are currently enrolled in the Rheos® Pivotal Trial under FDA IDE #G060182 is to have the generator replaced to continue that therapy for those responders.

VII. MARKETING HISTORY

The Barostim neo® Legacy System is marketed in the European Union and countries recognizing the CE marking for commercialization. It has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

It is anticipated that subjects will be exposed to operative and post-operative risks similar to related surgical procedures involving the neck and/or a pacemaker implant. These risks and potential risks of chronic device-based baroreflex activation may include, but are not limited to:

- Transient ischemic attack (TIA) – a neurological deficit lasting less than 24 hours without evidence of permanent cerebral infarction
- Systemic embolization – downstream obstruction of a blood vessel by migration of loosened intravascular plaque or clot
- Arterial damage – including carotid artery rupture or hemorrhage (sudden and significant blood loss at a site of blood vessel rupture that may require reoperation or transfusion)
- Pain – an unpleasant sensory experience
- Nerve Damage/Stimulation – including injury to or stimulation of Cranial, Marginal Mandibular, Glossopharyngeal, Recurrent Laryngeal, Vagus and Hypoglossal Nerves (numbness in head and neck, facial palsy/paralysis, altered speech, altered sense of taste, respiratory constriction, altered sensory and motor function of tongue, altered sensory function of pharynx and oropharynx, altered sensation in external auditory canal), stimulation of extravascular tissue (muscle twitching, pain, tingling, oral sensations)
- Atrial fibrillation – irregular rhythm in the upper heart chambers
- Hypertensive crisis – uncontrolled rise in blood pressure
- Exacerbation of heart failure
- Respiratory – including low oxygen saturation, respiratory distress, shortness of breath
- Injury to baroreceptors – an injury that results in baroreflex failure
- Fibrosis – replacement of normal tissue by the ingrowth of fibroblasts and the deposition of connective tissue
- Allergic Reaction
- General injury to user or patient – may be due to surgical procedure, device use, or interaction with other devices
- Secondary operative procedure – An increase in the complexity and risk of secondary operative procedures of the neck due to scar tissue and the presence of prosthetic material implanted for this device.
- Death

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

CVRx has performed a series of bench tests on the individual devices and also on a system level. The results of bench testing follows in the immediate sections below beginning with the neo® Legacy IPG followed by the programmer and accessories.

neo® Legacy IPG Bench Tests

Successful testing of the IPG Hardware was completed and is summarized in the tables below, including acceptance criteria, sample size tested and results.

Table 1 IPG Electrical Test Summary

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Current Drain, DC/DC Converter, Therapy, Measurement System, Device Environmental (EN 45502-1 Section 20.2 Defib testing)	IPG Electrical Verification Test	• **Current Drain:** Max current drain shall be <8.5mA. • **DC/DC Converter:** Therapy supply accuracy shall be +10%/-5%. 3.3V supply shall be between 2.8V and 3.6V. Vcc supply accuracy shall be +/- 5%. • **Therapy:** Pulse width accuracy shall be +2/-15 µs. Pulse amplitude accuracy shall be -5%/+3%. • **Measurement System:** Battery voltage shall be within +/- 30mV of the actual battery voltage. Lead impedance measurements shall be within +/- 15% of the actual lead impedance. Compliance measurements shall be within 250mV of the actual pin or ring voltage. • **Device Environmental:** IPG shall pass functional test after exposure to defibrillation per EN 45502-1 Section 20.2.	3	Pass
Accelerated Operating Life Test	IPG Module Electrical Life Testing	• After completion of burn-in, electronic module shall pass all tests that passed prior to burn-in.	22	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Leakage Current, ESD, Time Variable Magnetic Field, Static Magnetic Field, Electronic Article Surveillance, Ultrasound	IPG Safety Testing	• **Leakage Current:** The direct leakage current in all connection pathways shall be less than 1µA when all therapies are programmed off. • **ESD:** After 2kV direct contact discharge, the IPG performance shall not be modified or shall be recoverable to normal operation through a device reset. For voltages between 2kV and 8kV, the device shall perform no worse than failure in a safe condition. • **Time Variable Magnetic Field:** Following exposure to a time variable magnetic field per EN 45502-2-1, Section 27.8, the IPG shall pass all functional tests that passed prior to exposure. • **Static Magnetic Field:** After exposure to a static magnetic field per EN 45502-2-1, Section 27.7, the IPG shall return to normal operation within 5 seconds. Also, the IPG shall pass all functional tests that passed prior to exposure. • **Electronic Article Surveillance:** The IPG output may be inhibited during exposure to a simulated electronic article surveillance electro-magnetic field per the GTRI E3 Test Protocol (840236-001), but shall resume normal operation after exposure. Also, the IPG shall pass all functional tests that passed prior to exposure. • **Ultrasound:** After exposure to ultrasound per EN 45502-1, Section 22.1, the IPG shall pass all functional tests that passed prior to exposure.	1	Pass
EMI, Diathermy, Cautery	IPG EMI and Diathermy Safety Verification Testing	• **EMI (spurious injection current):** Per EN 45502-2-1, Section 27.2, the spurious injection current shall be < 50µA for frequencies between 16.6Hz and 1KHz and shall be < (50µA * F / (1KHz)) for frequencies between 1KHz and 20KHz. • **EMI (IPG exposure):** After exposure to EMI as specified in EN 45502-2-1 sections 27.5.1 0- 27.5.4, the IPG shall continue to deliver a bilateral therapy output with pulse amplitude, width, and frequency as specified.	1	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Maximum temperature rise due to therapy output, Maximum temperature rise due to Single Fault	IPG Temperature Rise Verification Testing	• **EMI (IPG exposure):** The IPG shall not exceed 2°C above the stabilized temperature prior to application of a load equivalent to a worst case single fault short.	1	Pass
400 MHz Tx Frequency, Power, Sensitivity, Interference Rejection. Wake Up Receive Sensitivity	IPG RF Verification Tests	• **400MHz Tx Frequency:** The 400MHz Tx frequency accuracy shall be +/- 100ppm. • **400MHz Tx Power:** The 400MHz Tx power shall be between -30dBm (1uW) and -16dBm (25uW). • **400MHz Rx Sensitivity:** The 400MHz Rx sensitivity shall be at least -87dBm using 10% packet error rate as the sensitivity threshold. • **400MHz Interference Rejection:** The 400MHz Rx interference rejection shall be at least 60dB when measured at +/- 20MHz. • **2.4GHz Wakeup Rx Sensitivity:** The 2.4GHz Wakeup Rx Sensitivity shall be at least -40dBm.	3	Pass
47 CFR Part 95 Subpart I, Specific Absorption Rate	IPG RF Standards Testing	• **47 CFR Part 95 Subpart I:** The IPG shall comply with 47 CFR Part 95 Subpart I. • **Specific Absorption Rate:** The partial body SAR shall be <1.6W/kg. The whole body SAR shall be <0.08W/kg.	1	Pass

Table 2 IPG Mechanical Test Summary

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Dimensions, Volume, Mass, Device Sharpness / Roughness, Device Marking, Radiopaque Identifier (X-ray ID), header configuration	IPG Dimensional and Marking Verification Test	• **Dimensions:** The IPG height shall be <72mm. Width shall be <50mm. Thickness shall be <14mm. • **Volume:** The IPG volume shall be <40cc. • **Sharpness / Roughness:** No external radius shall be <1.5mm. The IPG case shall have a matte finish. • **Marking:** The company name (CVRx), model number, and serial number shall be marked on the IPG case, and all markings shall pass a wet rub test per EN 45502-1, section 13.1. • **Radiopaque Identifier:** The IPG shall have a unique radiopaque identifier for each IPG model allowing the use of x-ray to identify information about the device per EN 45502-1, section 13.3. • **Header configuration:** The IPG connector cavities shall be appropriately marked on the IPG with respect to left/right orientation. The connector cavities shall be oriented such that when the marked side is towards the viewer and the connector is at the top of the device, the leads shall exit to the right.	1 of each model	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Mech Shock, Mechanical Vibration, Temp Changes, Atmospheric Pressure Changes, Shelf Box Drop test, Shipping Carton ASTM D4169 test, Internal Moisture Content, Device Mass	IPG Mechanical Verification Tests	• **Mechanical Shock:** After exposure to mechanical shock per EN 60068-2-27, the IPG shall pass all functional tests that it passed prior to exposure. • **Mechanical Vibration:** After exposure to random vibration per EN 60068-2-47, the IPG shall pass all functional tests that it passed prior to exposure. • **Temperature Changes:** After exposure to thermal changes as specified in EN 45502-1, section 26.2, the IPG shall pass all functional tests that it passed prior to exposure. • **Atmospheric Pressure Changes:** After exposure to atmospheric pressure per EN 45502-1, section 25.1, the IPG shall pass all functional tests that it passed prior to exposure. • **Shelf Box Drop:** After exposure to a shelf box drop test per EN 45502-1, section 10.1**,** the IPG shall pass all functional tests that it passed prior to exposure. • **Shipping Carton:** After exposure to a shipping carton test per ASTM D4169, the IPG shall pass all functional tests that it passed prior to exposure. • **Internal Moisture Content:** The moisture content inside the IPG shall be less than 5000ppmv. • **Device Mass:** The IPG mass shall be <60 grams.	22	Pass
Connector Module Electrical Seal, Connector Module Interface Compatibility, Connector Module Set Screws	Header to Lead Seal and Integrity test	• **Connector Module Electrical Seal**: The connector system shall provide an electrical seal of >50KΩ between the pin and ring of each bore after a minimum 10 day soak in 0.9% saline at 37°C. • **Connector Module Interface Compatibility**: The connector cavity shall be similar to ISO 5841-3 except for the pin cavity diameter. The pin cavity diameter shall be 1.51 +/- 0.04mm. • **Connector Module Set Screws:** The connector module set screws shall be able to be tightened up to 14 oz/in and then be tightened/loosened 5 times onto a lead using the provided torque wrench and remain functional.	22	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Connector Module Side load strength test, Connector Module Front Load strength test	Header Side Load and Front Load Testing	• **Connector Module Side Load Strength:** The header to IPG case shall withstand a side load of 18 lbs with no damage to the header/IPG case joint as determined by visual inspection at 8x. • **Connector Module Front Load Strength:** The header to IPG case must withstand a front load of 5 lbs with no damage to the header/IPG case joint as determined by visual inspection at 8x.	22	Pass
2 year real time shelf life exposure followed by Shipping Carton ASTM D4169, Connector Module, Electrical Seal, Connector Module - Interface Compatibility, Sterile Tray Seal	Real time shelf life testing	**NOTE:** All tests were performed after 2 years of aging. • **Shipping Carton:** After exposure to a shipping carton test per ASTM D4169, the shipping box shall not have damage identified by visual inspection. • **Connector Module Electrical Seal**: The connector system shall provide an electrical seal of >50KΩ between the pin and ring of each bore after a minimum 10 day soak in 0.9% saline at 37°C. • **Connector Module Interface Compatibility**: The force required to insert a pin into the connector module shall be <9N. • **Sterile Tray Seal**: No obvious voids or breaches in the sterile barrier are allowed. Seals shall exhibit a minimum seal width of 75% of the corresponding tray flange width. No evidence of dye penetrant to the opposite side of the seal or to the interior of the seal via a defined channel. The inner and outer tray lids shall be sealed with a peel strength of >0.7lbs/in per ASTM F88.	22	Pass

Lifecycle Testing was also performed to assess device longevity with various parameter settings. Packaging and sterilization was also tested to representative shipping conditions and according to ASTM D4169 and ASTM F1929-98. The IPG and package were DVT-qualified for a 1-year accelerated as well as 2 year real-time shelf life performance testing.

Programmer System Tests

Testing of the Programmer System Hardware was successfully completed and is summarized below.

Table 3 Programmer Testing Summary

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Supply current, USB, Power Supplies. 400MHz Antennas, Tx Frequency, Power, Sensitivity, Interference Rejection. RSSI. 2.4GHz Antenna, Frequency, Transmit Power.	Programmer Interface Electrical Verification Test	• **Supply Current:** The PI supply current shall be <500mA. • **USB:** The PI inrush charge shall not be >50µC. • **Power Supplies:** The PI shall meet all functional requirements with a power supply voltage of 4.75V and 5.25V. • **400MHz Antennas:** The PI shall have two 400MHz antennas that are selectable through a switch. • **400MHz Tx Frequency:** The 400MHz Tx frequency accuracy shall be +/- 100ppm. • **400MHz Rx Sensitivity:** The 400MHz Rx sensitivity shall be at least -85dBm. • **400MHz Interference Rejection:** The 400MHz Rx interference rejection shall be at least 60dB when measured at +/- 20MHz. • **Received Signal Strength Indicator (RSSI):** The RSSI circuit accuracy shall be at least 3dB and be capable of measuring at least -96dBm. • **2.4GHz Antenna:** The PI shall have one 2.4GHz antenna. • **2.4GHz Frequency:** The 2.4GHz frequency accuracy shall be +/- 100ppm. • **2.4GHz Tx Power:** The 2.4GHz Tx power shall be between 15.75 and 20dBm.	3	Pass
USB 2.0 Compatibility, Frequency Hopping Spread Spectrum, Manufacturing Test mode	Programmer Interface Electrical Verification testing	• **USB 2.0 Compatibility:** The Programmer Interface shall meet the requirements of USB 2.0 using the Full Speed mode. • **Frequency Hopping Spread Spectrum:** The wakeup telemetry on the PI shall use FHSS with a 15 channel hopping sequence and a channel dwell time <0.4 seconds. • **Manufacturing Test Verification:** The Programmer Interface manufacturing test shall verify 400MHz Tx, 400MHz Rx sensitivity, 400MHz antenna select, 400MHz Receive Signal Strength Indicator, 2.4GHz Tx, and digital clock output.	1	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Enclosure Tests, Enclosure Attachment Feature Tests, PI-PC Cable Tests, Cleaning Tests, Pressure, Temperature and Humidity, Mechanical Drop and Vibration, Transport and Table Configuration Tests	Programmer Interface Mechanical testing	• **Enclosure Tests:** The PI enclosure shall have a length <9 inches, width <4 inches, and height <9 inches. The PI must have an integrated stand which orients the device vertically and which orients the circuit board opposite the integrated stand. The PI weight shall be <2.0 lbs. The PI shall have a Type B USB connector in the lower quadrant of the unit. The PI shall have a green LED mounted near the USB connector. The PI enclosure shall by gray in color. • **Enclosure Attachment Feature Tests:** The PI shall have an integrated attachment feature which is impact resistant, non-metallic, and gray-scale or black in color. The attachment feature shall be able to withstand at least four times the weight of the PI without failure. • **PI-PC Cable Tests:** The PC end of the PI-PC cable shall be a Type A USB connector. The PI end shall be a Type B USB connector. The length shall be between 0.9 and 5.2m. The cable color shall be black or gray. The cable shall be shielded. • **Cleaning Tests**: After exposure to a 15 second hand rub with a soft cloth dampened with water, the PI shall pass all functional tests that it passed prior to exposure. • **Pressure, Temperature, and Humidity**: After exposure to a pressure of 10.2 psia or less, exposure to -20°C for one hour, exposure to 60°C for one hour, and exposure to 80-90% RH for one hour, the PI shall pass all functional tests that it passed prior to exposure. • **Mechanical Drop and Vibration**: After exposure to a drop to a hard wood surface from a height of 50mm, and exposure to vibration of 0.5G peak, 10 to 500Hz, sinusoidal with 0.5 octave/min sweep rate on each of three perpendicular axes for 30 minutes, the PI shall pass all functional tests that it passed prior to exposure. • **Transport and Table Configuration Tests**: The programmer case shall be capable of holding the PI, PC, power supply, cables, and documentation, and be transportable. The sum of the length, width, and height dimensions shall not exceed 41 inches and the longest dimension shall not exceed 22 inches. The weight of the case and all contents shall not exceed 20 lbs. The PC, PI, power supply, and associated cables shall fit in a 2 foot by 2 foot area without overlap of any component except cables.	3	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
UL 60601-1	Programmer Safety Standards testing	• **UL 60601-1:** The Programmer Interface shall comply with UL 60601-1. The test facility that provides this certification shall be certified by the appropriate certification body.	1	Pass
47 CFR Part 95 Subpart I, 47 CFR 15.249	Programmer RF and EMC Standards testing	• **47 CFR Part 95 Subpart I:** The Programmer Interface shall comply with 47 CFR Part 95 Subpart I. • **47 CFR 15.249:** The Programmer Interface shall comply with the 2400 – 2483.5MHz band requirements of 47 CFR 15.249.	1	Pass
Equivalence between 9011 and 9010, Production Test, Frequency Hopping Spread Spectrum, TX Modulation, Channel Monitoring, Tx Power During a Telemetry Session, TX power with and without the PI hook	Programmer Interface RF Equivalence testing	• **Equivalence between Models 9010 and 9011 PI Production Test Verification:** The test limits for the 400MHz TX power, 400MHz TX frequency, 2.4GHz TX power, 2.4GHz TX frequency, 400MHz RX sensitivity, 400MHz interference rejection, and 400MHz RSSI tests in the PI Final Functional test shall be identical for the Model 9010 and 9011 PIs. • **Frequency Hopping Spread Spectrum:** The wakeup telemetry on the PI shall use FHSS with a 15 channel hopping sequence and a channel dwell time <0.4 seconds. • **Tx Modulation:** The 400MHz transmitter 20dB bandwidth measured using the Model 9010 firmware shall be within +/-10% of the results measured using the Model 9011 firmware. • **Channel Monitoring:** The PI shall comply with the channel monitoring requirements in ETSI EN 301 389-1, section 10 using either the Model 9010 or 9011 PI firmware. • **Tx Power During a Telemetry Session:** The Tx power measured during a telemetry session shall be within +/-1dB from the Tx power measured using either the Model 9010 PI or 9011 PI firmware. • **Tx power with and without the PI hook:** The 400MHz and 2.4GHz Tx power measured with the hook shall be within +/- 1dB from the power measured without the hook.	1	Pass

Specification Feature	Test Method	Acceptance Criteria	Sample Size	Results
Computer hardware Configuration, Computer Power supply Configuration, Computer EMC and Safety	Programmer Computer Verification tests	• **Computer Hardware Configuration:** The PC shall have a color display, a display with at least a 12" viewable area, resolution of at least 1024x768 pixels, a keyboard, a mouse or other pointing device, an internal hard drive with at least 50GB, at least 2GB of RAM, at least two USB 2.0 compatible ports, and a processor with at least two cores running at a minimum clock speed of 2.0 GHz. • **Computer Power Supply Configuration:** The PC power supply shall operate with 100-240 VAC line voltage, and with 50 or 60Hz line frequency. • **Computer EMC and Safety:** the PC shall comply with FCC Part 15 Class B, EN 55022, EN 55024, and EN 60950-1.	1	Pass

Programmer packaging was also tested to representative shipping conditions and according to ASTM D4169.

IPG firmware and Programmer software were both developed under a controlled development life cycle model and thoroughly verified and validated for all applicable requirements. Testing was according to risk management process and included code analysis, performance analysis, unit testing, integration testing, and verification testing.

System testing was also performed with combined components based on anticipated clinical use scenarios to ensure proper operation as a system.

Accessory Bench Tests

Only the Lead Repair Kit (LRK) was deemed to require significant bench testing for the CVRx accessories. Testing of the Lead Repair Kit was successfully completed and is summarized in the table below. The External Interface Magnet (EIM) interface to the IPG was also verified during IPG verification testing.

Table 4 Lead Repair Kit (LRK) Model 5010 Mechanical & Electrical Test Summary

Specification Feature	Requirement	Test Method	Sample Size	Results
Replacement Section				
Length	11.00 ± 0.25 in.	Dimensional inspection	22	Pass
Terminal Dimensions	• Pin Length: .200 ±.010 in. • Pin Diameter: .0555 ±.001 in. • Ring Length: .158 ±.008 in. • Ring Diameter: .105 ±.001 in. • Pin / Ring Offset Length: .360 +.010/-.020 in.	Dimensional inspection	22	Pass
Terminal Insertion/ Withdrawal	≤ 3.15 lb	Force gage	22	Pass
Set Screw Deformation	Insertion/withdrawal ≤ 3.15 lb following an applied torque of 11 +3/-2 oz/in from 2-56 set screw	Torque application and force gage	22	Pass
Lead Seal Integrity	Isolation Impedance >50 kOhm	EN 45502-2-1, section 23.3	22	Pass
Contact Assignment	Cathode electrode connected to terminal pin	DCR	22	Pass
Lead Bending Flexibility	Lead body must bend around 1.0 inch diameter rod with application of 45 grams load	Mechanical test	22	Pass
Terminal Pin to Lead Body Attachment Strength	≥ 3.15 lbs minimum axial force	Mechanical test	22	Pass

Specification Feature	Requirement	Test Method	Sample Size	Results
Terminal Ring to Lead Body Attachment Strength	≥ 3.15 lbs minimum axial force	Mechanical test	22	Pass
Comprehensive Axial Load	The lead must meet a minimum 1.1 lb axial or minimum 20% elongation; no permanent elongation >5%	Mechanical test	22	Pass
Terminal Durability	Withstand a minimum of 30 cycles of terminal insertion/withdrawal and maintain seal integrity	Mechanical test	22	Pass
Lead Body Flex Endurance	>94,000 flex cycles (± 90°) at 6 mm bend radius without conductor fracture or intermittency	Mechanical test	22	Pass
Terminal Connection Flex Endurance	> 164,000 flex cycles (± 45°) at 100g loading without conductor fracture or intermittency	Mechanical test	22	Pass
DC Resistance	5 ohms max	Electrical test	22	Pass
Insulation Integrity	Device insulation materials shall maintain electrical isolation integrity	Electrical test	22	Pass
System Requirements				
Lead Body Bending Flexibility	Repair section must bend around 1.0 inch diameter rod with application of 100 grams load	Mechanical test	22	Pass
Comprehensive Axial Load	Repair section must meet a minimum 1.1 lb axial or minimum 20% elongation; no permanent elongation >5%	Mechanical test	22	Pass
Flex Endurance	> 164,000 flex cycles (± 45°) at maximum 6.0 mm radius and 100g loading without conductor fracture or intermittency	Mechanical test	22	Pass
Contact Assignment	Cathode electrode connected to terminal pin; anode to terminal ring	Electrical test	22	Pass

Specification Feature	Requirement	Test Method	Sample Size	Results
Insulation Integrity	Device insulation materials shall maintain electrical isolation integrity	Electrical test	22	Pass

The LRK was fully DVT qualified for 2-year accelerated shelf life performance.

Biocompatibility Studies
All testing on the neo® Legacy system was performed in accordance to the ISO 10991 Standard. The IPG was tested for cytotoxicity, maximization sensitization, intracutaneous extract, systemic toxicity extract, and material mediated pyrogens and all tests passed meeting their acceptance criteria.

B. Animal Studies

CVRx performed an Ovine study with neo® demonstrating that the Baroreflex Activation Therapy with neo® has similar safety in animals as Baroreflex Activation Therapy with Rheos® (the first generation IPG). The neo® Legacy is the same as neo® with respect to the IPG physical properties; therefore, the Ovine study was included for the purpose of providing additional information regarding neo® Legacy IPG safety in animals, even though the study included a system with a lead for which the CVRx will seek approval at a later date. Pertaining to the 180 Day Survival Group animals, a total of 12 test articles were implanted within 3 ovine test-subjects with neo® Legacy applicable sections apply since the *neo legacy* IPG has the same physical properties as the neo® IPG. The 180 day study was completed with favorable conclusions for Baroreflex Activation Therapy (Barostim) with the neo® system regarding gross and histological tissue response and device integrity. These results were acceptable and similar to those for Barostim with the Rheos® system. No article related gross issues, histological issues, or adverse events were found in the 180 day study. No significant issues were determined when comparing the therapy on versus therapy off groups. The lack of adverse histological findings with and without electrical stimulation supports the safety of the neo® Legacy for use in humans.

X. SUMMARY OF CLINICAL INFORMATION

The patient population consists of 207 resistant hypertension patients with a neo® Legacy or Rheos® implantable pulse generator (models 2100 or 2000, respectively) and Rheos® carotid sinus leads (now obsolete). These patients were implanted during the conduct of US FDA IDE #G040166 and #G060182, and have been subsequently followed long-term under the Rheos® Pivotal Trial under US FDA IDE G060182. Due to lack of adequate evidence of effectiveness in the full study population (338 implanted subjects), each implanted subject was assessed after a minimum of 6 months of the Barostim therapy to determine if they were responding to therapy in a clinically meaningful manner and should continue to receive IPG replacements. Only those determined to be responders continued to receive IPG replacements at the discretion of the investigator and subject, and therefore, remain enrolled and are included in the proposed indications for use for this HDE application.

A responder to Baroreflex Activation Therapy was defined as a subject that had achieved at least one of the following in a sustained manner:

- Goal office Systolic Blood Pressure (SBP) defined as ≤ 140 mmHg (≤ 130 mmHg for subjects with diabetes or renal disease)
- Office SBP reduction of at least 20 mmHg from device activation (Month 0 for subjects originally in the ON arm, and Month 6 for subjects originally in the OFF arm)

A sustained manner was defined as two (2) of the most recent three (3) automated office cuff blood pressure (BP) assessments meeting this criterion and the average of the three (3) assessments also meeting the criterion.

If the subject was not deemed a responder per the above definition, then they could be assessed by turning the device off in a blinded manner after automated office cuff BP assessment and followed for up to 30 days for the occurrence of clinically meaningful events.

The table below identifies the responder status for all active patients.

Table 5 Subject Responder Status, Active Patients Only

Subject Status	N	%
Responder per Protocol Definition	**188**	**91**
Reduced SBP by 20 mmHg or reached goal SBP	149	72
Device OFF – Increase in SBP	32	15
Device OFF – HTN crisis	7	3
Compassionate use approval	**19**	**9**
Other clinical benefit	11	5
Total	**207**	

"Other clinical benefit" referred to the more detailed clinical status and history considered on a case-by-case basis for continued treatment under IDE G060182. The 11 patients in the "Other clinical benefit" HDE cohort had SBP reduction of 27.5 mmHg. The total implant duration for these subjects ranges between 48 and 105 months as shown below in the table below.

There is a total of 12,167 months of implant experience across all subjects, with an average implanted duration of 59 months.

Table 6 Implant Duration (Months)

Statistic	Result
N	207
Mean ± SD	58 ± 10.2
Range	48.4 – 104.5
Total	12.167

In this subject cohort of remaining active patients in the clinical study, there were 205 subjects that had 623 device replacements. Two (2) subjects have not had a replacement yet and are still active with the original Rheos® device. In the 205 subjects that received a

replacement, the median number of pulse generator replacements is three (3). The majority (74%) of the replacements were Rheos® devices being replaced with the same Rheos® device. The neo® Legacy device was not made available for replacements until Rheos® Pivotal Trial protocol revision F (dated October 24, 2011). All future replacements will use the neo® Legacy device.

The study was able to predict responders over a 5 year period with 95% sensitivity 196/207 patients. The probability of the active patients experiencing a sustained defined benefit once they are identified as responders is 43%. The study did not look at sub-populations and did not look at different populations. The study design used BpTru to accurately measure and remove site bias from BP measurement which makes the effectiveness data robust and provide assurance to the sustained therapeutic effect.

It is important to note that all patients but two (2) have required generator replacement and thus the health risk has the generator included in its total assessment since it's anticipated all subjects will have multiple generator replacement.

Among the full n=338 subjects implanted in the Rheos® Pivotal and Feasibility studies, there have been 174 device replacements with neo® Legacy and 97 other device procedures (e.g., study withdrawal explants, lead repairs) for a total of 271 procedures over a period of 1,414 implant years. Procedure-related serious adverse events that were related to the initial implant are not included here. Observed rates of occurrence of these adverse effects based on clinical experience in this cohort are also listed in the table below.

Table 7 Observed Adverse Effects

Potential Risks	# observed events	Rate per Year of Implant	Rate per Procedures
• Stroke – a neurological deficit lasting more than 24 hours or less than 24 hours with a brain imaging study showing infarction	1	0.0007 (1/1414)	0.0037 (1/271)
• Surgical or anesthetic complications	5	0.0035 (5/1414)	0.0185 (5/271)
• Infection – the need for antibiotics or possible removal of the IPG	8	0.0057 (8/1414)	0.0295 (8/271)
• Wound Complication – including hematoma (i.e. bruising and/or swelling)	2	0.0014 (2/1414)	0.0074 (2/271)
• Hypotension – a decrease in systolic and diastolic blood pressure below normal levels that may result in dizziness, fainting, and/or falls	1	0.0007 (1/1414)	0.0037 (1/271)
• Bradycardia – abnormally low heart rate	1	0.0007 (1/1414)	0.0037 (1/271)
• Tissue erosion/IPG migration – movement of device resulting in need	2	0.0014 (2/1414)	0.0074 (2/271)

Potential Risks	# observed events	Rate per Year of Implant	Rate per Procedures
for reoperation			
• Need for reoperation – operation to explant/replace IPG or CSLs due to tissue damage, infection, and/or device failure	3	0.0021 (3/1414)	0.0111 (3/271)

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 35 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. RISK PROBABLE BENEFIT ANALYSIS

In this HDE cohort, the safety profile is acceptable as there was only 1 (0.6%) serious adverse event related to the 161 lead replacements that implanted the neo® Legacy device. SAEs related to additional system procedures were also low in this subject population, in which only two (2) subjects in 31 procedures (6%) had an SAE. System related SAEs had a rate of 0.01 per patient year and all recovered with no residual effect. There were no unanticipated adverse events.

Probable Benefit

The table below is a summary of systolic blood pressure (SBP), diastolic blood pressure (DBP), and number of medications at pre-implant, the last visit and the change between these time points. SBP dropped a statistically significant 34 mmHg ($p<0.001$) over an average of 59 months post-implant and DBP dropped 17 mmHg ($p<0.001$). The number of anti-hypertension medications has increased by less than one medication.

Table 8 BP, HR, and Number of Meds

Measure	N	Pre-Implant	Last Visit	Change
SBP (mmHg)	207	176.8±21.6	143.2±27.3	-33.6±30.0
DBP (mmHg)	207	100.6±14.8	83.1±15.0	-17.5±16.9
Number of Meds	207	5.0±1.6	5.8±2.3	0.7±2.0

Performance by Responder Qualification:

The table below shows the percent of subjects at goal (SBP≤140 or ≤130 if diabetes or CKD) at their last visit. Forty-three percent (43%) of the subjects were at goal in the population who were determined to be responders based on the protocol definition. Thirty-two percent (32%) were at goal out of the population that was determined to be responders through the compassionate use approach.

Table 9 Change in SBP at Most Recent Visit by Subject Status

Subject Status	N	Pre-Implant	Last Visit	Change	At Goal Last Visit
Responder per Protocol Definition	188	176.8 ± 21.3	142.8 ± 26.4	-34.0 ± 29.9	42.6%
Reduced SBP by 20 mmHg or reached goal SBP	149	176.7 ± 21.0	140.2 ± 25.2	-36.5 ± 29.4	46.3%
Device OFF – Increase in SBP	32	175.3 ± 21.6	149.4 ± 24.0	-25.9 ± 29.9	31.3%
Device OFF – HTN crisis	7	187.1 ± 26.2	169.3 ± 42.3	-17.9 ± 33.2	14.3%
Compassionate use approval	19	176.7 ± 25.1	146.6 ± 35.5	-30.1 ± 31.3	31.6%
Responder - drop of 20 or goal	8	179.5 ± 24.9	146.0 ± 24.1	-33.5 ± 27.1	25.0%
Other clinical benefit	11	174.6 ± 26.3	147.1 ± 43.1	-27.5 ± 35.1	36.4%

As can be seen in this table, all responders have a significant lowering in blood pressure in the cohort study which defines how this device will be used under the HDE.

The expected rate of a harmful event is 6.6% based on the total of SAEs from the replacement of the device and the procedure related complications, and the incidence of a harmful event is <1% for any event.

The patients would be willing to risk this low rate of safety events for the long term benefit of reduced BP in this group of patients that have failed medical therapy, because uncontrollable hypertension that has failed a four (4) drug therapy will lead to renal failure and death. Every 20 point increase in systolic blood pressure doubles the risk of cardiovascular death and is thought to be a significant contributor to stoke. In support that this is an acceptable risk to the patients is that the patients (n=25) have agreed in the past for compassionate use requests and agreed to the risks before the surgery.

This is specifically for an orphaned group of patients that are approaching the end of the IDE study which will be closed out and for whom there are no acceptable alternative therapies.

The probable benefits outweigh the risk as these patients have no alternative therapies to control their hypertension. The applicant has provided prospective data collected over 5 years that demonstrates a sustained decrease in blood pressure of an average of 20 mmHg over 5 years in responder patients, which will decrease their long term morbidity and mortality of cardiovascular disease. There was also low morbidity related to the surgical procedure of replacing the IPG, with a 6.6% rate of serious adverse effects. The reported SAEs directly caused by the device for replacement procedures are not life-threatening.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Cardiovascular Devices Panel because the marketing of the device does not expose new patients to the device that were not already approved for investigational treatment with the investigational device.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, that the Barostim neo® Legacy System does not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on December 12, 2014.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.