June 3, 2021

CyMedica Orthopedics, Inc.
Kereshmeh Shahriari
Vice President, Regulatory, Clinical, & Quality
19120 N. Pima Rd.
Scottsdale, Arizona 85331

Re: K210604
Trade/Device Name: Intellihab System
Regulation Number: 21 CFR 890.5850
Regulation Name: Powered Muscle Stimulator
Regulatory Class: Class II
Product Code: IPF, KQX
Dated: May 7, 2021
Received: May 7, 2021

Dear Kereshmeh Shahriari:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for Jitendra Virani
Acting Assistant Director
DHT5B: Division of Neuromodulation
and Physical Medicine Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*

K210604

Device Name

Intellihab™ System

Indications for Use *(Describe)*

The Intellihab system is intended to strengthen the quadricep muscle using powered muscle stimulation to provide symptomatic temporary pain relief associated with knee osteoarthritis and improvement of the knee joint mobility when the recommended treatment regimens are followed.

In addition, the Intellihab System is indicated for the following:

- Retardation or prevention of disuse atrophy
- Evaluation of joint mobility by measuring and recording range of motion

The Intellihab System is indicated for adults of 22 years of age and older.

Type of Use *(Select one or both, as applicable)*

X Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary
Intellihab™ System
CyMedica Orthopedics, Inc.

1 Regulatory Information

1.1 Trade/Proprietary Name:

Intellihab™ System

1.2 Common Name:

Powered muscle stimulator

1.3 Regulation Names & Numbers:

Powered muscle stimulator, 21 CFR 890.5850
Goniometer, 21 CFR 888.1500

Product Codes:
Primary Code- Powered muscle stimulator**: IPF**
Secondary Code- Goniometer, AC-powered**: KQX**

1.4 Classification:

Powered muscle stimulator: II
Goniometer: I

1.5 Manufacturer Name:

CyMedica Orthopedics, Inc.
19120 N. Pima Rd. Suite 135
Scottsdale, AZ 85255
Telephone (480) 664-1282
FAX (866) 296-2772

These devices are reviewed by the Division of Neurological and Physical Medicine Devices.

2 Submission Information

Submission Number: K210604

Date: June 2, 2021

Contact:

Kereshmeh Shahriari
19120 N. Pima Rd. Suite 135
Scottsdale, AZ 85255
kereshmeh@cymedicaortho.com
Telephone (480) 664-1282
FAX (866) 296-2772

3 Indications for Use

The Intellihab system is intended to strengthen the quadricep muscle using powered muscle stimulation to provide symptomatic temporary pain relief associated with knee osteoarthritis and improvement of the knee joint mobility when the recommended treatment regimens are followed.

In addition, the Intellihab System is indicated for the following:

- Retardation or prevention of disuse atrophy
- Evaluation of joint mobility by measuring and recording range of motion

The Intellihab System is indicated for adults of 22 years of age and older.

4 Device Description

Intellihab System is a remote monitoring electrical muscle stimulator (or Neuromuscular Electrical Stimulation (NMES) therapy) with an integrated digital goniometer for osteoarthritis pain relief and joint mobility improvements. Intellihab device is used to apply an electrical current through a power regulated output closed-loop feedback NMES system to provide relief of knee pain associated with osteoarthritis. The stimulator is intended for medical purposes that continuously contracts muscle groups for an intended therapeutic application and allows for remote monitoring of therapeutic data by the healthcare Providers. The stimulator is provided with an integrated battery powered digital goniometer that allows for measurement of knee joint range of motion. The stimulator along with the digital goniometer is placed over or in proximity to affected joint. The Intellihab System includes a provider portal allowing for remote monitoring of collected patient data through Intellihab mobile app and API interface.

4.1 Electrical Muscle Stimulator (NMES therapy)

The device is used to apply a patented unique waveform by means of an electrical current through a power regulated output and closed- loop feedback system to provide relief of knee pain associated with osteoarthritis. The electrical muscle stimulator is intended for medical purposes that continuously contracts muscle groups for an intended therapeutic application and allows for remote monitoring of therapeutic data by the healthcare providers. Electrical stimulation waveform is generated using a Controller. Electrical stimulation is delivered non-invasively to the treatment site (quadriceps muscles of the knee joint) using three connected electrodes placed directly on the skin.

4.2 Mobile Application (App)

The electrical stimulation therapy is initiated and managed wirelessly by the patient using a mobile application (app) developed for use on smart phones or tablets that interact with the Intellihab Controller.

In addition, the app includes features that would allow to track patient's activity level and allow the patients to report their knee joint osteoarthritis related clinical outcomes including pain level using CyMedica Intellihab app based Visual Analog Scale (VAS) pain measuring instrument. VAS measures are stored in the app. Other knee-specific measuring instruments including KOOS questionnaire (Knee Injury and Osteoarthritis Outcome Score) and WOMAC questionnaire (Western Ontario and McMaster Universities Arthritis Index) are provided in the Intellihab app, allowing the patients to report their knee related outcomes. KOOS and WOMAC scores are calculated and stored in the app. The Intellihab app can improve therapy compliance through a multi-faceted approach of incentivizing patient engagement through a motivational Patient Dashboard, therapy reminders and a rewards system. The app serves as the primary user

interface and communication link between the Intellihab system and Provider portal as discussed below.

4.3 Digital Goniometer for Range of Motion Measurement

Intellihab includes an integrated digital goniometer for measurement of knee joint range of motion (ROM) to evaluate joint mobility. The device includes two accelerometers, some located in a conductive wrap and the other in the Intellihab Controller allowing for the measurement of knee joint extension and flexion degrees or range of motion measurement. The measured flexion, extension, and ROM angles are displayed and stored in the Intellihab app.

4.4 Conductive Garment or Wrap

The electrical muscle stimulator along with the cutaneous electrodes, wires, and ROM accelerometers are incorporated in a conductive wrap placed over or in proximity to the knee joint. The Intellihab system utilizes a conductive smart garment to actively communicate to the NMES Controller the patient's tibial sensor kinematics data, Controller docking status and garment identification data to the patient's mobile device. Additionally, the garment provides mild compression and warming benefits to the patient.

4.5 Web-based Provider Portal for Remote Patient Monitoring

A Medical Device Data System (MDDS), CyMedica web-based healthcare Provider portal is available to allow for the electronic transfer, storage, and display of data sent from the patients' mobile app.

CyMedica web-based portal allows the healthcare Providers to monitor patient's app-based therapy compliance and other collected health related data (ROM, PROs, activity) remotely. The portal is hosted on a secure cloud-based server that connects with an internal database using an API communication.

5 Wireless Communications

The Intellihab System incorporates a Bluetooth Low Energy, BLE 4.2 connection module to enable wireless communication that can be paired with a Bluetooth enabled mobile device running the Intellihab app, available from the App stores. The app implements a virtual control panel on the screen of the smart device where on-screen buttons are provided to the user.

The Controller is connected to the conductive garment via a multi-pin interface. The Controller contains the primary safety controls for operation of the device and a push button is available for switching the unit on or off. The power button remains active and can be used in the event of loss of Bluetooth connection to power on/off the device or start/stop stimulation while performing stimulation sessions. The Controller contains light emitting diodes (LED) which indicate status relating to battery charge, stimulation and Bluetooth™ activity. Power is derived from a 3.7V Li-Po rechargeable battery pack and the unit can be recharged by using the supplied USB cable.

6 Proposed software

The Intellihab system utilizes an embedded Controller/ROM software, mobile application software, and Web services software.

The treatment program embedded software is a fundamental component of the system that supports the selection, adjustment, and delivery of the treatment program. The embedded software runs on the Controller and is interfaced with the stimulation pulse generator and mobile app.

The mobile application (app) runs on a mobile platform operating system and communicates with the

Controller over a BLE 4.2 connection. The free mobile application is downloaded by the patients from the respective App Stores. The Intellihab system allows the patient to control the NMES therapy program in an easy and intuitive way. It allows the patient to select, administer, and adjust the NMES therapy intensities, perform a range of motion test, and manage their health and wellness conditions related to their therapy.

In addition, the app provides other tools to engage the patients with their NMES treatment and tracking of patient outcomes that may be valuable to their healthcare providers.

7 Controller and the Mobile App

The Controller's main function is the NMES therapy stimulation generator and communicating therapy and range of motion metrics to the mobile app. The Controller contains the primary safety controls for operation of the device. A push button is available for switching the unit on or off. The "Stop" control remains active at all times during stimulation and can be used in the event of loss of Bluetooth connection.

Once the mobile app is installed and a wireless connection is established between the Controller and the mobile device, the patient can interact with all of the device features. The mobile app downloaded on the patient's mobile device provides the graphical user interface and governs the interactions between the Controller and the patient. The screens and user interface are designed to be intuitive and interactive. Improved patient engagement and compliance through the mobile app are significant design features of the device.

Help and informational screens are provided throughout the app and on specific screens where a patient needs to be aware of a feature or condition. Upon downloading the mobile app, the patient is guided through chronological screens on the app to perform the following tasks:

- Reading and accepting the app Terms of Use and Conditions
- Creating a patient profile
- Pairing the mobile app on a smart device with the Intellihab conductive garment
- Starting the treatment
- Managing the treatment
- Completing Patient Reported Outcomes (PROs)
- Reviewing patient related data and information on the app

8 Joint Range of Motion Measure Function

The Intellihab system uses two 6-axis Accelerometer/Gyroscope (AG) to detect the knee range of motion. One accelerometer is located on the Controller board and the second accelerometer is located within a small plastic enclosure in the conductive garment knee opening area. The two accelerometers are connected using wires embedded in the garment. The data from the accelerometers is conveyed to the mobile device in real-time. The accelerometers detect the knee extension and flexion angles, and associated range of motion angle through the use of the Intellihab mobile app when initiated by the patient.

9 Remote Patient Monitoring

A cloud-based database and services are designed to allow for secure transfer, storage, and display

of the data reported by patient's mobile app through a Web Application Programming Interface (API) or Web API. Intellihab mobile app makes specific API calls to perform a desired task, save data to the central remote storage (cloud) or to retrieve data back. Intellihab Web Services provide a way for the mobile app to communicate with CyMedica cloud database and services.

In addition, a healthcare Provider facing portal is designed to allow for remote patient monitoring by the Providers. Through appropriate credentialing processes, healthcare providers are capable of viewing their patients reported data including the therapy compliance, knee range of motion, patient reported knee pain levels, and knee-specific outcomes surveys including KOOS JR. and WOMAC scores.

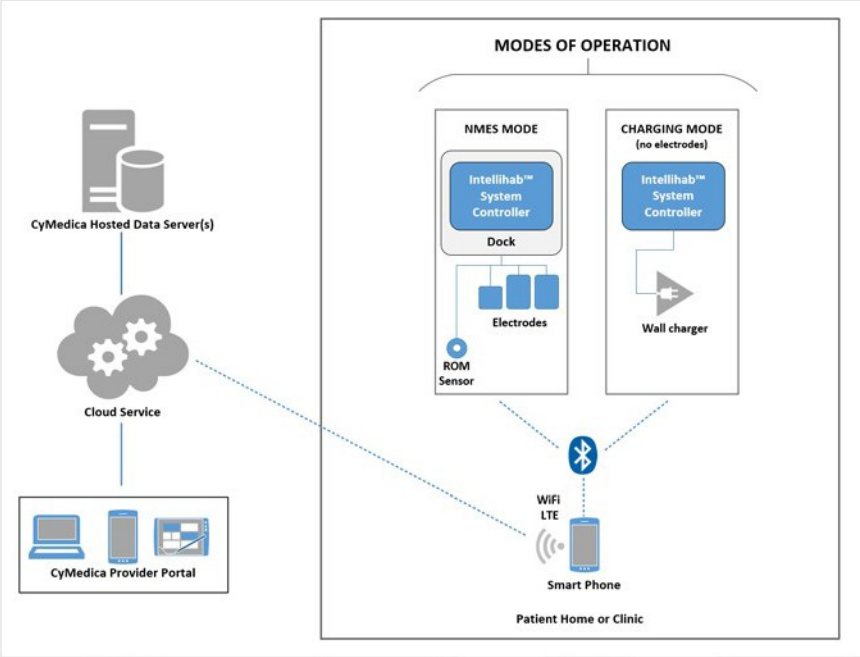

Figure 1- Intellihab system including electrical muscle stimulation therapy (NMES), conductive wrap, range of motion test function, mobile application, and a Provider web-portal for patient monitoring

10 General Electrical Muscle Stimulation Device Features and Output Characteristics

The following two Tables, Tables 1 and 2, represent the Intellihab electrical stimulation device features and the neuromuscular electrical stimulation (NMES) therapy output specifications.

Table 1- Intellihab NMES Therapy Program General Electrical Stimulation Device Features

No. of Output Modes	1
No. of Output Channels	2
Regulated Current, Voltage, or Power	Regulated Power
Software/Firmware/Microprocessor Control?	Yes
Automatic shut off?	Yes
Patient device control?	Yes
Indicator display- Low Battery?	Yes
Indicator display- Voltage/Current Level?	Yes
Timer range (minutes)	20 minutes

Table 2- Intellihab NMES Therapy Program Output Specifications

Waveform	Monophasic
Shape	Asymmetrical, Complex
Pulse width	5 ms
Frequency	50 pps
Maximum current density @ 500Ω	0.7 mA/cm^2 (rms)
Maximum power density (using smallest electrode conductive surface area) @ 500Ω	0.006 W/cm^2
Maximum phase charge @ 500Ω	359.8 µC
Maximum output voltage (V_{RMS}) (±10%) @ 500Ω	9.0 V
Maximum output current (I_{RMS}) (±10%) @ 500Ω	18 mA
Power source	Li-Polymer Battery 950mAh 3.7 VDC
Contraction time	1.0 s
Relaxation time	1.4 s
Treatment session	20 minutes

11 NMES Waveform

The NMES treatment program pulse parameters are defined below, Table 3:

Table 3- Intellihab NMES Waveform Pulse parameters	
Pulse shape	Asymmetrical, monophasic, and complex
Treatment duration	20 minutes
Frequency	50 pps
Pulse width	5 ms
Duty cycle	25%
Work cycle	12 s

Relaxation time	10 s	
Contraction time	5 cycles	1 s
Rest time		1.4 s

In the treatment program, the work cycle consists of the combination of five cycles of contraction and rest. Contraction time is the actual stimulation contraction period. Rest time is the period between contractions to wait to oscillate the stimulation between the two channels. Relaxation time is a period of no stimulation between the work cycles.

The following graphs show the individual pulses and pulse train. The waveform is a unique, asymmetrical, complex, and monophasic shaped pulse which is designed to provide optimized therapeutic benefits.

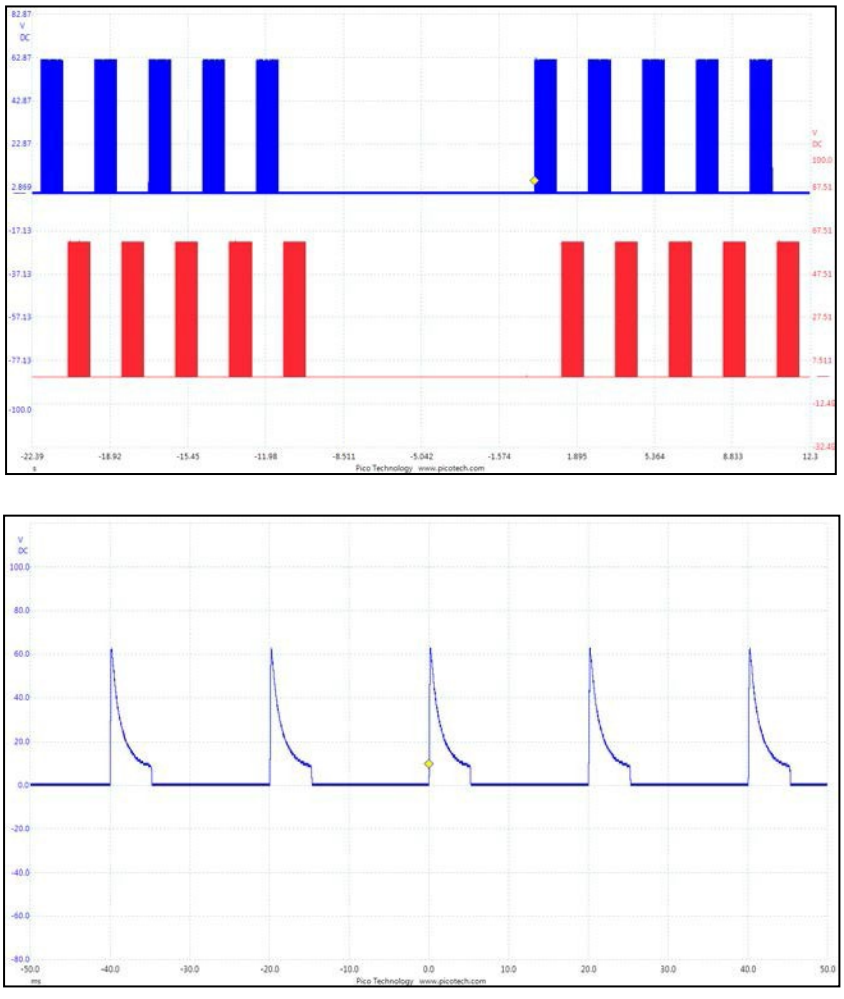

Figure 2- Intellihab NMES Pulse Plots- Pulse train and single pulse

12 Recommended Usage

Intellihab therapy is recommended to be used twice a day for a minimum of 5 days per week. Each session of NMES therapy is 20 minutes. The therapy is recommended to be applied as long as the

knee pain relief and joint functionality or mobility improvements are sustained.

13 Intellihab System NMES Therapy Mechanism of Action for Treatment of Knee Osteoarthritis Symptoms

Studies have suggested quadriceps weakness or atrophy plays a significant role in the knee osteoarthritis disease initiation and progression. Other publications suggest muscle atrophy as an underlying cause for early stage osteoarthritis. Regardless, the quadriceps muscle is critical to dynamic joint stability, and weakness of this muscle group is related to pain and poor functional outcomes in knee osteoarthritis patients[1-6]. The involvement of quadriceps weakness in the development or progression of the knee osteoarthritis may be linked to the role of quadriceps during gait, where an eccentric contraction of the quadriceps is responsible for providing the shock absorption at the knee. The inability to adequately attenuate large compressive forces at the knee can result in impulsive loading, which has been attributed to quadriceps weakness and inactivity and may be responsible for knee osteoarthritis changes. In addition, the decline in quadriceps strength has been attributed to the central nervous system lack of ability to fully volitionally activate the muscles (voluntary activation deficit). It is theorized that the voluntary activation deficit is caused by progressive joint degeneration that results in abnormal articular afferent information being sent to the motor neurons, thereby reducing their activation[1-6].

Therefore, therapies or modalities that improve quadriceps strength are important in managing knee osteoarthritis symptoms including pain relief and joint mobility improvements. Many recent clinical studies have shown that the addition of an at home NMES therapy system is a promising intervention to use in managing knee osteoarthritis symptoms[7-12]. NMES therapy may override activation deficit which would increase the quadriceps strength and ultimately reduce the compressive loads on the knee joint.

The results of isometric quadriceps strength test in the CyMedica NMES clinical study demonstrated an increase in quadricep strength by application of the NMES treatment over time at weeks 4, 8, and 12 post intervention. With the application of CyMedica NMES treatment the quadriceps strength gradually increased at week 4 by 30.5%, week 8 by 47.8%, and week 12 by 81.5% as compared to the baseline for the compliant patients.

14 Summary of Non-Clinical/ Bench Studies

To demonstrate the safety, the Intellihab system was tested for electrical safety, electromagnetic compatibility, usability, biocompatibility, and risk management requirements.

To demonstrate the safety, the Intellihab system was tested per the following standards:

- IEC 60601-1: 2005, 3rd Edition, Medical electrical equipment- General requirements for basic safety and essential performance + CORR. 1:2006 + CORR. 2:2007 + A1:2012
- IEC 60601-1-2: 2014-02, 4th Edition, Medical electrical equipment-Part 1-2: General requirements for basic safety and essential performance- Collateral standard: Electromagnetic compatibility requirements
- IEC 60601-2-10: 2012, 2nd Edition, Medical electrical equipment- Part 2-10: Particular

requirements for the basic safety and essential performance of nerve and muscle stimulator

- IEC 60601-1-11: 2015, 2nd Edition, Medical electrical equipment- Part 1-11: General requirements for basic safety and essential performance- Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

- IEC 60601-1-6: 2010+ A1:2013, 3rd Edition, Medical electrical equipment- Part 1-6: General requirements for basic safety and essential performance- Collateral standard: Usability including IEC 62366: Application of usability engineering to medical devices

- IEC 62366: 2007+ A1: 2014, 1st Edition, Medical devices -- Application of usability engineering to medical devices

- IEC 62304: 2006, 1ST Edition, Medical device software – Software life cycle processes

- ISO 10993-1: 2009, Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process

- ISO 10993-5: 2009, Biological evaluation of medical devices- Part 5: Tests for in vitro cytotoxicity

- ISO 10993-10: 2010, Biological evaluation of medical devices- Part 10: Tests for irritation and skin sensitization

In addition, the performance of Intellihab BLE module for wireless co-existence was tested in an environment with equipment operating in the ISM band i.e. Bluetooth and Wi-Fi devices, cellphones, cordless phones, etc. The device met all specified requirements.

BLE module testing was conducted in accordance with the following standards:

- FCC CFR47 Part 15, Subpart C**,** July 2019, Intentional Radiator, §15.247, Operation within the bands 902-928 MHz, 2400-2483.5 MHz, and 5725-5850 MHz
- FCC 47CFR PT 15 SPT B, August 2018 Title 47 CFR Part 15 Subpart B: Unintentional Radiators, FCC Part 15, Subpart B [FCC §15.107 & FCC §15.109]

Battery testing was conducted in accordance with IEC 62133:2012 Secondary cells and batteries containing alkaline or other non-acid electrolytes - Safety requirements for portable sealed secondary cells and for batteries made from them, for use in portable applications.

15 Electrical Safety and Electromagnetic Compatibility (EMC)

Electrical safety and EMC testing were conducted on the Intellihab system and complies with the IEC 60601-1, IEC 60601-2-10, and 60601-11 standards for safety and the IEC 60601-1-2 standard for EMC.

16 Software Verification & Validation Testing

The device's software has been validated in accordance with the requirements set forth in the

FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005) and IEC 62304: 2006, 1ST Edition, Medical device software – Software life cycle processes. The software validation tests demonstrated that the software version meets its design requirements.

17 Cybersecurity Controls

Cybersecurity related activities included system assessment and mitigations for potential cybersecurity hazards and risks on the Intellihab System performance and data security. Information related to system design features, processes, testing, and controls to manage and mitigate the risks are included in this submission.

Cybersecurity information and supporting documents created and submitted according to the requirements of FDA guidance documents, *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices, October 2, 2014* and *Postmarket Management of Cybersecurity in Medical Devices, December 28, 2016*.

18 Human Factors and Usability

The human factors including usability study was conducted to validate the usability of the Intellihab system in the home environment. The results of the study support the instructions for successfully using the device as intended. The results of the human factors and usability study substantiates the acceptability of the risks identified during the risk assessment activities. The Intellihab system complies with the IEC 60601-1-6: 2010 for usability and IEC 62366: Application of usability engineering to medical devices.

19 Biocompatibility/ Material

The patient contacting materials used in the Intellihab system components include the conductive garment or wrap, electrodes, and electrode gel. The biocompatibility of the conductive garment, electrodes, and electrode gel were previously evaluated and cleared under 510(K) submission K163067. The biocompatibility testing had been conducted according to the requirements of ISO 10993: 2009 and tested as a surface contacting/skin contact/ >24 hour to 30 days prolonged exposure. From the evaluation and submitted information, the components of the Intellihab device were found to be biocompatible for its use.

20 Shelf life/ Sterility

The non-invasive nature of the device obviates the need for sterile components; however, patient-contacting surfaces should be capable of being cleaned as needed. The Intellihab system is provided for single person use and does not require any of the components to be sterilized by the end user. It is intended for external use only. The electrodes are disposable and can be replaced as needed. Cleaning instructions are provided in the User Manual for safe handling and proper care of the device.

21 Performance Testing- Bench Testing of Electrical Muscle Stimulation (NMES) Waveform

All features and output specifications of the device, including those identified in Tables 1 and 2, were verified by individual pulse output waveform tracings for loads of 500, 2k, and 10k ohms, to simulate conditions that the device could counter during use.

22 Comparison of Technological Characteristics with the Predicate Device

CyMedica Orthopedics, Inc. demonstrated that, for the purposes of FDA's regulation of medical devices, the Intellihab System is substantially equivalent in design principles to the predicate device, which has been determined by FDA to be substantially equivalent to CyMedica Orthopedics, Inc. CyMedica e-vive® System, K163067. The data included in this submission demonstrates design substantial equivalence to the predicate device, CyMedica e-vive.

The design, materials, and functional characteristics of the Intellihab System and the predicate device are substantially the same. The subject device and predicate device provide neuromuscular electrical stimulation therapy, are for prescription use, portable, hand-held, and for home healthcare environment use. Similar to the predicate device, Intellihab System provides NMES therapy for the purpose of muscle strengthening. Similar to the predicate device, Intellihab System includes an integrated battery powered goniometer for measurement of knee range of motion and intended to evaluate joint function.

However, the indications for use for the subject Intellihab system are different than the predicate device. Submitted clinical data shows that the proposed indications for use does not result into a new intended use and supports the basis for assessment of safety and effectiveness.

The following table demonstrates the similarities and differences between the subject Intellihab system and the predicate device, CyMedica e-vive system.

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
- **Intended Use**	The Intellihab system is intended for strengthening of the muscles by application of neuromuscular electrical stimulation (NMES) therapy.	The CyMedica e-vive System is intended for strengthening of the muscles by application of neuromuscular electrical stimulation (NMES) therapy.
- **Indications for use**	The Intellihab system is intended to strengthen the quadricep muscle using powered muscle stimulation to provide symptomatic temporary pain relief associated with knee osteoarthritis and improvement of the knee joint mobility when the recommended treatment regimens are followed. In addition, the Intellihab System is indicated for the following: • Retardation or prevention of disuse atrophy • Evaluation of joint mobility by measuring and recording range of motion The Intellihab System is indicated for adults of 22 years of age and older.	Indications for Use: • Relaxation of muscle spasms • Retardation or prevention of disuse atrophy • Increasing local blood circulation • Re-educating muscles • Immediate post-surgical stimulation of calf muscles to prevent venous thrombosis • Maintaining or increasing range of motion In addition, the e-vive device is intended to evaluate joint function by measuring and recording range of motion.
Regulation names and numbers	**Powered muscle stimulator**, 21 CFR 890.5850 **Goniometer**, 21 CFR 888.1500	**Powered muscle stimulator**, 21 CFR 890.5850 **Goniometer**, 21 CFR 888.1500 **TENS,** 21 CFR 882.5890
Product codes and classifications	**Powered muscle stimulator**, IPF, Class II **Goniometer, AC-powered**, KQX, Class I	**Powered muscle stimulator**, IPF, Class II **Goniometer, AC-powered**, KQX, Class I **TENS,** GZJ, Class II

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
Product identifications	**Powered muscle stimulator**, A powered muscle stimulator is an electrically powered device intended for medical purposes that repeatedly contracts muscles by passing electrical currents through electrodes contacting the affected body area. **Goniometer**, A goniometer is an AC-powered or battery powered device intended to evaluate joint function by measuring and recording ranges of motion, acceleration, or forces exerted by a joint.	**Powered muscle stimulator**, A powered muscle stimulator is an electrically powered device intended for medical purposes that repeatedly contracts muscles by passing electrical currents through electrodes contacting the affected body area. **Goniometer**, A goniometer is an AC-powered or battery powered device intended to evaluate joint function by measuring and recording ranges of motion, acceleration, or forces exerted by a joint. **TENS,** A transcutaneous electrical nerve stimulator for pain relief is a device used to apply an electrical current to electrodes on a patient's skin to treat pain.
Electrical stimulation modalities	NMES Strength	NMES Strength, NMES POST-OP, and TENS
System functions	• NMES therapy for knee osteoarthritis pain relief and treatment of disuse atrophy • Knee range of motion measurement	• NMES therapy for treatment of disuse atrophy, muscle spasms, increasing local blood, circulation, re-educating muscles, post-surgical prevention of venous thrombosis, and increase in ROM • Knee range of motion measurement • TENS
System components	Controller, mobile app, conductive garment, electrodes, and electrode gel	Same
TENS therapy	No TENS included	Includes TENS
Muscle stimulator (NMES therapy)		

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
- **Stimulation pulse characteristics**	The patented waveform is a unique, asymmetrical, complex, and monophasic shaped pulse which is designed to provide optimized therapeutic benefits while maximizing comfort and compliance, Figure 2. The unique design features including a longer pulse width (5 ms), monophasic polarity, work cycles, and regulated power output provide a longer duration of muscle contraction within a 20 minutes treatment session. These unique waveform characteristics lead to the therapeutic benefits of Intellihab therapy reducing the knee pain and improving knee joint functionality. The Intellihab stimulation pulses have three distinct phases: - Phase 1: Pulse Spike (Rise Time, Peak, and Decay) - Phase 2: Pulse Mesa - Phase 3: Recharge (off period)	Same
- **Regulated power output**	Using a proprietary technology, the output of Intellihab stimulation circuit delivers energy to the patient at a constant power, independent of the load impedance, hence power regulation during the mesa portion of the pulse.	Same
- **Closed loop feedback system**	The Intellihab stimulation circuit employs a proprietary closed loop feedback technology to regulate energy transferred to the patient for stimulation sensation comfort.	Same
- **Waveform**	Asymmetrical, monophasic, complex	Same
- **Pulse width**	The Intellihab electrical muscle stimulation (NMES) pulse width (including spike and mesa) is 5ms, longer than other muscle stimulation devices which range 300 to 500 µs.	Same for NMES Strength program only
- **Pulse Train**	The Intellihab muscle electrical stimulation (NMES) pulse train consist of individual monophasic stimulation pulses of 50 pulses-per-second.	Same for NMES Strength program only
- **Integrated digital goniometer**	In addition to an electrical muscle stimulator, Intellihab system includes an integrated digital goniometer for measurement of knee joint range of motion (ROM) to evaluate joint mobility. The device includes two accelerometers located in a conductive wrap and Intellihab Controller allowing for the measurement of knee joint extension and flexion degrees or	Same

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
	range of motion measurement. The measured flexion, extension, and ROM angles are displayed and stored in the Intellihab patient app.	
- **Controller and PCBA**	Intellihab Controller consists of a printed-circuit board within a plastic enclosure that docks in a Garment docking receptacle via a 16-pin interface (4 unpopulated for future use). The Controller is the stimulation generator and the tactile control device for the Intellihab system. The user can establish a wireless connection between the Controller and their mobile device.	Same
- **Conductive Smart Garment**	The Intellihab system utilizes a Conductive Smart Garment to actively communicate to the NMES Controller the patient's tibial sensor kinematics data, Controller docking status and Garment identification data to the patient's mobile device.	Same
- **Embedded software**	The treatment program embedded software is a fundamental component of the system that supports the selection, adjustment, and delivery of the treatment program. The embedded software runs on the Controller and is interfaced with the stimulation pulse generator and mobile app. The Controller software drives the stimulation circuits to generate appropriate waveforms for the prescribed protocols and deliver them to the electrode interface. The power button, with integrated LED indicator, on the Controller is used for powering the Controller On/Off and Pause/Resume an active treatment; the button is always active and can be used in the event of loss of Bluetooth connection to the mobile device to pause or abort therapy. Additionally, the Controller collects sensor data to ascertain range of motion (ROM), therapy metrics, battery status, device details and system status. The Controller communicates collected data and commands in real-time to the Intellihab Mobile App wirelessly over Bluetooth communications.	Same

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
- **Mobile Application(App)**	The Intellihab patient mobile application (app) serves as the primary user interface and communication link between the Intellihab system and Provider portal. The Intellihab app improves therapy compliance through a multi-faceted approach of incentivizing patient engagement through a motivational Patient Dashboard, therapy reminders and a rewards system.	Same- The e-vive mobile app includes additional screens to provide the NMES POST-OP and TENS programs.
- **Wireless communications**	The Intellihab System incorporates a Bluetooth Low Energy, BLE 4.2 connection module to enable wireless communication that can be paired with a Bluetooth enabled mobile device running the Intellihab app, available from the App stores. The app implements a virtual control panel on the screen of the smart device where on-screen buttons are provided to the user. The Controller is connected to the conductive garment via a multi-pin interface. The Controller contains the primary safety controls for operation of the device and a push button is available for switching the unit on or off. The power button remains active and can be used in the event of loss of Bluetooth connection to power on/off the device or start/stop stimulation while performing stimulation sessions. The Controller contains light emitting diodes (LED) which indicate status relating to battery charge, stimulation and Bluetooth™ activity. Power is derived from a 3.7V Li-Po rechargeable battery pack and the unit can be recharged by using the supplied USB cable.	Same
- **Remote patient monitoring**	A Medical Device Data System (MDDS), CyMedica web-based healthcare Provider facing portal is available to allow for the electronic transfer, storage, and display of data sent from Intellihab Controller through the patients' mobile app. CyMedica web-based portal allows the healthcare providers to monitor patient's app-based therapy compliance and other collected health related data (ROM, PROs, activity) remotely. The portal is hosted on a secure cloud-based server that connects with an internal database using an encrypted API communication. The remote monitoring feature not only allows the healthcare provider to have access to the health data	This product feature was not included in the labeling of CyMedica e-vive 510(k), K163067.

Table 4- Product Features Comparison	CyMedica Intellihab™ System (K210604)	CyMedica e-vive® System (K163067)
	remotely, but also encourages patients for a better compliance with their home-based therapy.	
- **Summary**	CyMedica Intellihab system is a medical device that as a system utilizes an electrical muscle stimulator (NMES therapy), goniometer, and remote data monitoring technology (API) to manage the knee symptoms of knee osteoarthritis disease. Intellihab system is indicated to strengthen the quadricep muscle using powered muscle stimulation to provide symptomatic temporary pain relief associated with knee osteoarthritis and improvement of the knee joint mobility when the recommended treatment regimens are followed. In addition, the Intellihab System is indicated for the retardation or prevention of disuse atrophy and the evaluation of joint mobility by measuring and recording range of motion.	CyMedica e-vive system is a medical device that utilizes an electrical muscle stimulator (NMES therapy) and goniometer and is limited to use in rehabilitation. CyMedica e-vive is indicated for treatment of disuse atrophy and other indications stated above. CyMedica e-vive also includes a TENS therapy.

The following table summarizes the subject device, Intellihab system and the predicated device, CyMedica e-vive system technological characteristics:

Table 5- Technological characteristics of the subject device and predicate device

Parameter		Intellihab system	CyMedica e-vive System
510(k) Number		K210604	K163067
Device Name and Mode		Intellihab NMES	e-vive NMES Strength
Manufacturer		CyMedica Orthopedics	Same
Power Source(s)†		Single VD434053: 3.7V; 1000mAh; Lithium ion polymer battery	Same
- Method of Line Current Isolation		No line connection	Same
- Patient Leakage Current††		---	
- Normal Condition(μA)		4.88	Same
- Single Fault Condition (μA)		8.00	Same
Number of Output Modes †††		One (NMES)	three (2 NMES and 1 TENS)
Number of Output Channels ††††:	Synchronous or Alternating?	Alternating	Same
	Method of Channel Isolation	Transistor	Same
Regulated Current or Regulated Voltage?		Regulated Power	Same
Software/Firmware/Microprocessor Control?		Yes	Yes
Automatic Overload Trip?		No	No
Automatic No-Load Trip?		No	No
Automatic Shut Off?		Yes	Yes
User Override Control?		Yes Stop Buttons	Yes
Indicator Display:	On/Off Status?	Yes	Yes
	Low Battery?	Yes	Yes
	Voltage/Current Level?	No	No
Timer Range (minutes)		20-open	Same
Compliance with Voluntary Standards?		Yes. IEC 60601-2-10:2012 Part 2-10; IEC 60601-1-11:2015 Part 1-11; IEC 60601-1-6:2010; ISO 10993-1:2009 Part 1	Yes, Same standards
Compliance with 21 CFR 898?		Yes	Yes
Weight (lbs., oz.)		1.76 oz. (50g)	Same
Dimensions (in.) [W x H x D]		1.93” x 0.64” x 3.28”	Same
Housing Materials and Construction		Molded PC\ABS Plastic Bayblend FR3010	Same

The following table summarizes the subject device, Intellihab system and the predicated device, CyMedica e-vive system NMES therapy waveform characteristics:

Table 6- Intellihab NMES Waveform & e-vive NMES Strength Waveform Parameters			
NMES Waveform Parameters	**Subject device, Intellihab NMES program, K210604**	**Predicate device, e-vive, NMES Strength program, K163067**	**Discussion of similarities and differences**
Waveform (e.g., pulsed monophasic, biphasic)	Pulsed Monophasic	Pulsed Monophasic	Same between the subject device and predicate device
Shape (e.g., rectangular, spike, rectified sinusoidal)	Complex	Complex	Same between the subject device and predicate device
Maximum Output Voltage (volts, rms) (+/-____%)	9.0 @500Ω	8.0 @500Ω	Similar output voltages, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
	16.2 @ 2 k Ω	14.7 @ 2 k Ω	Similar output voltages, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
	21.1 @10 k Ω	19.3 @10 k Ω	Similar output voltages, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
	18.0 @500Ω	15.9 @500Ω	Similar output currents, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device

Maximum Output Current (mA, rms) (+/- _%)		8.1 @ 2 k Ω	7.3 @ 2 k Ω	Similar output currents, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
		2.1 @10 k Ω	1.9 @10 k Ω	Similar output currents, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
Duration of primary (depolarizing) phase (μsec)		5000	5000	Same between the subject device and predicate device
Pulse Duration (μsec)		5000	5000	Same between the subject device and predicate device
Frequency (Hz) [or Rate (pps)]		50	50	Same between the subject device and predicate device
For interferential modes only: Beat Frequency (Hz)		N/A	N/A	N/A
For multiphasic waveforms only:	Symmetrical phases?	N/A	N/A	N/A
	Phase duration	N/A	N/A	N/A
Net Charge (microcoulombs (μC) per pulse) (If zero, state method of achieving zero net charge.)		359.8 @500Ω	318.5 @500Ω	Similar net charges, a slightly higher net charge in Intellihab is potentially due to variations in electrodes manufacturing from lot to lot. Small differences do not adversely affect the safety and effectiveness of the subject device compared to the predicate device.
Maximum Phase Charge, (μC)		359.8 @500Ω	318.5 @500Ω	Similar maximum charges, a slightly higher net charge in Intellihab is potentially due to variations in electrodes manufacturing from lot to lot. Small differences do not adversely affect the safety and effectiveness of the subject device compared to the predicate device.
Maximum Current Density (mA/cm², r.m.s.)		0.7 @500Ω	0.6 @500Ω	Similar max. current density, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device

Maximum Average Current (average absolute value), mA		18.0 @500Ω	16.0 @500Ω	Similar max. avg. current, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
Maximum Average Power Density, (W/cm²), (using smallest electrode conductive surface area)		0.006 @500Ω	0.005 @500Ω	Similar max. avg. power density, small differences are due to the variations in the loads and manufacturing of the components and do not adversely affect the safety and effectiveness of the subject device compared to the predicate device
Burst Mode	(a) Pulses per burst	50	50	Same between the subject device and predicate device
	(b) Bursts per second	0.23	0.23	Same between the subject device and predicate device
	(c) Burst duration (seconds)	1	1	Same between the subject device and predicate device
	(d) Duty Cycle: Line (b) x Line (c)	0.23	0.23	Same between the subject device and predicate device
ON Time (seconds)		276	276	Same between the subject device and predicate device
OFF Time (seconds)		924	924	Same between the subject device and predicate device
Additional Features (specify, if applicable)		N/A	N/A	N/A

23 Summary of Clinical Study

Pivotal USA Trial

The aim of this study was to evaluate the safety and effectiveness of the CyMedica neuromuscular electrical stimulation (NMES) therapy, a home-based electrotherapy device as a non-surgical therapy for knee pain relief and joint functional recovery in patients with knee osteoarthritis.

23.1 Study Design

This was a randomized, sham controlled, double-blind, multi-center study performed at 7 sites in the USA. The study involved subjects who had been diagnosed with knee osteoarthritis, Kellgren-Lawrence grades II, III, and IV and a symptomatic knee pain of the target knee (visual analog pain, VAS score of at least 4 cm on a 10 cm scale).

A total of 177 potential subjects were screened per the pre-determined inclusion and exclusion criteria. A total of 159 subjects were enrolled and 156 subjects were randomized into two groups: Treatment NMES and Sham Low Voltage NMES. Randomization assignment was in a 2: 1 ratio of NMES treatment therapy to sham treatment. One hundred and six (106) subjects were randomized in the Treatment NMES group and 50 subjects were randomized in the sham low voltage NMES group.

The subjects' knee pain and knee joint functionality were assessed at baseline visit. At the baseline visit, the Treatment group received a CyMedica NMES therapy device and the sham group received the modified version of the NMES therapy device with a low voltage output. All subjects were instructed to use the device two sessions a day (each session was 20 minutes), 5 days of the week for a total duration of 12 weeks. The subjects were asked not to take or receive any concomitant medications or therapies during the course of study. The subjects returned to the sites at weeks 4, 8, and 12 for their assessments of knee pain and knee joint mobility or function.

23.2 Objectives

23.3 Primary objective

The primary objective of this study was to provide evidence of pain relief with CyMedica NMES therapy when used on a daily basis by subjects. The pain assessments included Pain Visual Analog Score (VAS) for a subject's nominated activity, general knee pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, Knee Injury and Osteoarthritis Outcome Score (KOOS) JR pain subscale, VAS knee pain during walk, and VAS knee pain at rest.

23.4 Secondary objectives

Secondary objectives were to gain knowledge and evidence of knee functional outcome improvement in subjects using the CyMedica NMES therapy as compared to those assigned sham treatment. The knee joint functionality assessment tools included WOMAC function subscale, KOOS JR function subscale, isometric quadriceps strength, Timed Up and Go (TUG) test, repeated chair rise test, and three-minute walk test.

23.5 Criteria for Evaluation

23.5.1 Effectiveness

Effectiveness assessments included evidence of knee pain relief associated with knee osteoarthritis and improvements in knee joint mobility or function.

23.5.2 Safety

Safety assessment included any adverse event (AE) including serious adverse events (SAE) and unanticipated adverse events (UADE). All adverse events were required reported, whether or not their occurrence had a causal relationship with the administration of the study material.

23.5.3 Primary endpoint

The primary endpoint was change in the Pain Visual Analog Score ($VAS_{Nominated\ activity}$) at week 12 from baseline. A nominated activity was defined as a physical activity that caused the worst knee pain for the subject (e.g. climbing the stairs).

23.5.4 Secondary endpoints

Similar to the primary endpoint analysis, the secondary endpoints were change in the $VAS_{General}$, $WOMAC_{pain}$ subscale, KOOS JR pain subscale, VAS_{Walk}, VAS_{Rest}, WOMAC function subscale, WOMAC stiffness subscale, KOOS JR and its subscales, PGIC, and other functional tests at week 12 from baseline.

23.6 Analysis of Data

- Descriptive statistics was conducted for the primary and secondary endpoints at baseline and weeks 4 through 12.
- Chi-Square test was utilized to compare the number and proportion of subjects who achieved 30% or greater improvement from baseline in knee pain (treatment responders) as measured by VAS Nominated Activity with an associated 95% confidence interval.
- Analysis of change over time (week 4 through 12) for the primary and secondary endpoints (percentage change from baseline or PCFB) and the statistical comparison against the sham low voltage NMES was conducted using Shapiro-Wilk test or Mann- Whitney U test.

23.7 Effectiveness Results

Effectiveness related endpoints were analyzed for both Intent-to-Treat (ITT) and Per Protocol Therapy Compliant (PPTC) population.

- **ITT population** included all the randomized subjects regardless of their compliance with the NMES therapy usage at home.
- **PPTC population** included all randomized subjects with at least one session of study therapy applied, without major protocol deviations.
  PPTC population included subjects who had adhered to the protocol NMES therapy usage at home. Any subject in the Treatment NMES group who had applied a minimum of 800 minutes of NMES therapy per visit at weeks 4, 8, or 12 was defined as a “Therapy Compliant” subject. A total of 69 subjects (61.3% of the ITT Treatment NMES group) resulted in the PP Treatment NMES Therapy Compliant population.

From this subset, all 69 of these subjects were compliant at week 4, 61 of these subjects were compliant at week 8, and 45 of these subjects were compliant at week 12. The sham group in the PP population analysis remained the same as the ITT sham population, since the duration of therapy was not relevant in the sham group. In general, subjects in the sham group were compliant with the therapy usage with a mean treatment usage of 803.2 minutes at week 12. Demographic analysis of the Therapy Compliant subjects against the sham group at baseline did not demonstrate a difference in the subjects' age, gender, ethnicity, race, or knee OA grade distribution.

23.7.1 ITT Analysis

In the ITT analysis, effectiveness of NMES therapy for knee pain, stiffness, and function at week 12 is supported based on the totality of the following results:

1. A PCFB of 38.5% clinically meaningful reduction of knee pain for $VAS_{Nominated\ Activity}$ endpoint in the Treatment NMES group and a PCFB of 38.1% reduction for the sham low voltage NMES group. In the ITT population, the changes were not statistically different between the two groups.
2. The $VAS_{General}$, WOMAC pain subscale, KOOS JR pain subscale VAS_{Walk}, and VAS_{Rest} all demonstrated a clinically meaningful reduction of knee pain that exceeded an MCID of 30% at week 12 (PCFBs of 37.2, 31.5, 34.1, 39.3, 33.3 respectively). In the ITT population, the changes were not statistically different between the two groups.
3. Knee related function and stiffness subscales including the WOMAC stiffness, KOOS JR stiffness, WOMAC function, and KOOS JR function all demonstrated clinically meaningful changes compared to the baseline that exceeded an MCID of 30% at week 12 (PCFBs of 32.3, 30.5, 32.7, and 33.8 respectively). In the ITT population, the Treatment NMES group experienced a clinically meaningful mean PCFB of -32.3% at week 12 for WOMAC stiffness subscale compared to a PCFB of -17.3% for the sham group. In addition, the mean difference of PCFB at week 12 was statistically significant (**p= 0.03**). In the ITT population, the changes were not statistically different between the two groups for the KOOS JR stiffness, WOMAC function, or KOOS JR function.

In the ITT population, the treatment NMES group demonstrated a clinically meaningful PCFB of 38.5% reduction of $VAS_{Nominated\ Activity}$ compared to the baseline at week 12, which satisfies one part of the primary endpoint. While the ITT population did not demonstrate a statistically significant difference in pain reduction compared to the sham low voltage NMES group (the other part of the primary endpoint), it did demonstrate a clinically meaningful reduction of pain consistently and with multiple patient-reported pain outcome measures. It appears that smaller effect size in between groups in the ITT population resulted from a mix of different NMES therapy compliance levels in the Treatment group. In addition, a potential unknown level of therapeutic benefits in the sham group, from the usage of a low voltage NMES treatment over time, was substantiated by the observed improvements in the quadriceps strength and functional test results.

In a study of this type, where a home-based treatment is applied by the patients through the course of study and time, it is not expected to observe a fully applied treatment or a full compliance by all the subjects in the ITT population. This is a disadvantage when compared to other treatments, such as injectable steroids or hyaluronic acid preparations which are

administered by clinicians, or in-clinic-delivered stimulation or physical therapy methods. In home-based self-treatment studies, the full therapy compliance is dependent on the subjects' daily compliance level at home in the ITT population. More specifically, full compliance is achieved usually by only a subset of the subjects. If a subject who actually received less or minimal treatment is included in the same analysis group as a subject who received a full treatment, then the magnitude of effect determined by the analysis is attenuated. Consequently, in this and other home-based, self-treatment administration studies, the ITT population unlikely reveals the full potential effectiveness of the treatment. In an ITT analysis, estimate of treatment effect is generally conservative because of the dilution effect of non-compliance or less-compliance. Therefore, the effectiveness of the treatment is more reliably assessed when the outcomes of fully compliant subjects are compared against the outcomes of the control group. This observation was validated by analyzing the outcomes of the PPTC treatment NMES group against the sham subjects. For these compliant subjects, a statistically significant difference against the sham group was observed and treatment's effectiveness was demonstrated.

23.7.2 PPTC Analysis

In the PPTC treatment NMES group, clinically meaningful improvements in knee pain, stiffness, and function and statistically significant difference against the sham group's results were demonstrated at week 12, consistently and across multiple endpoints, see Tables A and B below.

The study effectiveness-related results demonstrated that the CyMedica NMES therapy dose of 2 sessions per day (20 minutes each) and 5 days of the week, when used for 12 weeks, provides clinical benefits to the knee osteoarthritis patients including knee pain relief, reduction of knee stiffness, and improvements in knee joint mobility. The reduction in knee pain (PCFB of -43.3% for $VAS_{General}$), knee stiffness (PCFB of -44.7% for WOMAC stiffness), and improvements in knee mobility (PCFB of -40.1% for WOMAC function) were clinically meaningful and statistically different from the sham results for PPTC treatment NMES group. Even in the overall (ITT) population, the treatment NMES group including less-compliant patients demonstrated a clinically meaningful PCFB of 38.5% reduction of $VAS_{Nominated\ Activity}$ at week 12 compared to baseline. In addition, these patients demonstrated a consistent and compelling pattern of improvements for all the pain, stiffness, and knee functionality outcomes. Per OMERACT-OARSI Set of Responder Criteria[13], these improvements fall between the moderate to high improvement categories for knee pain and function. The improvements from baseline were observed starting at the week 4 post-intervention visit and continued at weeks 8 and 12 with the largest change from baseline observed at week 12. Between group differences also started at week 4 and continued to week 12. The largest differences between the Treatment and Sham groups were observed at week 12.

In addition to the endpoints that reached statistical significance, those that did not reach significance still trended in favor of the treatment arm.

Most of the pain measures consistently improved at each of the visits over time (better at week 4 vs baseline, even better at week 8 vs baseline, and best at week 12 vs baseline). The pain reductions were consistent from month to month and repeatable among different scales or surveys ($VAS_{Nominated\ Activity}$, $VAS_{General}$, VAS_{Walk}, and VAS_{Rest}, WOMAC pain subscale, and KOOS JR pain subscale).

When looking at the totality of the data for knee pain endpoints [a total of 36 endpoints when considering a) three timepoints versus baseline and, b) ITT and PP Therapy Compliant groups], it is very compelling that, in addition to the four statistically significant measures discussed above, the trend of improvement in pain supports across the vast majority of endpoints supports the likelihood of effectiveness in the Treatment NMES group over the Sham Low Voltage NMES group.

Table A- Summary of Treatment NMES Group against the Sham Low Voltage NMES Group, Comparison of Treatment Responder Rates at Week 12

	Treatment NMES (N= 106, ITT, N=45 PPTC) Treatment Responder Rate	**Sham Low Voltage NMES (N= 50, ITT & PP) Treatment Responder Rate**	***P*-value (Chi-square test)**
VAS $_{\text{Nominated Act}}$- ITT			
	51%	54%	0.888
VAS $_{\text{Nominated Act}}$- PPTC			
	71%	62%	0.348
VAS $_{\text{General}}$- ITT			
	48%	42%	0.339
VAS $_{\text{General}}$- PPTC			
	67%	46%	**0.043**
WOMAC Pain Subscale- ITT			
	44%	38%	0.377
WOMAC Pain Subscale- PPTC			
	64%	42%	**0.029**
KOOS JR Pain Subscale- ITT			
	48%	46%	0.681
KOOS JR Pain Subscale- PPTC			
	64%	48%	0.107
WOMAC Stiffness Subscale- ITT			
	45%	34%	0.099
WOMAC Stiffness Subscale- PPTC			
	62%	36%	**0.011**
WOMAC Function Subscale- ITT			
	45%	44%	0.728
WOMAC Function Subscale- PPTC			
	60%	46%	0.172

Table B- Summary of Treatment NMES Group against the Sham Low Voltage NMES Group, Comparison of PCFBs at Week 12

	Treatment NMES (N= 106, ITT, N= 45, PPTC) PCFB	**Sham Low Voltage NMES (N= 50, ITT & PP) PCFB**	***P*-value (t-test)**
VAS Nominated Act- ITT			
	-38.5% (33.7)	-38.1% (35.0)	0.946
VAS Nominated Act- PPTC			
	-42.8% (37.8)	-38.6% (33.9)	0.562
VAS General- ITT			
	-37.2% (37.0)	-33.2% (39.8)	0.558
VAS General- PPTC			
	-43.4% (40.0)	-32.7% (38.5)	0.175
WOMAC Pain subscale- ITT			
	-31.5% (44.8)	-26.9% (34.0)	0.282
WOMAC Pain subscale- PPTC			
	-36.8% (54.5)	-26.6% (32.7)	**0.038**
KOOS JR Pain subscale- ITT			
	-34.1% (36.7)	-28.1% (31.2)	0.248
KOOS JR Pain subscale- PPTC			
	-43.2% (40.1)	-27.7% (30.0)	**0.010**
WOMAC Stiffness Subscale- ITT			
	-32.3% (42.3)	-17.3% (43.0)	**0.030**
WOMAC Stiffness Subscale- PPTC			
	-44.7% (35.5)	-17.4% (41.3)	**0.002**
KOOS JR Stiffness Subscale- ITT			
	-30.5% (41.8)	-17.2% (48.0)	0.190
KOOS JR Stiffness Subscale- PPTC			
	-39.8% (40.0)	-14.5% (49.0)	**0.010**
WOMAC Function Subscale- ITT			
	-32.7% (33.0)	-24.9% (35.4)	0.198
WOMAC Function Subscale- PPTC			
	-40.1% (34.3)	-24.5% (34.2)	**0.029**
KOOS JR Function Subscale- ITT			
	-33.8% (35.3)	-24.6% (44.4)	0.394
KOOS JR Function Subscale- PPTC			
	-39.3% (38.0)	-19.7% (47.4)	**0.029**

23.8 Safety Results

Safety related endpoints were analyzed using the safety population. The Safety population included all subjects randomized and received at least one session of study therapy (Treatment N= 106, Sham N= 49). There were 9 (8.5%) subject reported adverse events (AEs) in the Treatment group and 3 (6.1%) in the sham group.

There were only two subjects (1.9%) with three reported device-related adverse events in the treatment NMES arm and none in the sham arm. The three device-related adverse events were reported from a total of 17,847 treatment sessions (0.016%) in the Treatment NMES group and they were not serious. Both subjects continued the device use (treatment application) and completed the study, thus, these events did not result in study discontinuation. These adverse events included calf muscle spasms, pain consistent with an electric shock, and skin marks consistent with burn in location of device electrodes. These adverse events are consistent with the predicate device, CyMedica e-vive adverse events and did not introduce a new risk.

23.9 Uncertainties from the Clinical Study

Some uncertainty is acceptable in clinical trials and is weighed against potential benefits and potential risks. The following list includes a list of potential uncertainties resulted from the Intellihab NMES treatment clinical study.

1- 1) Conclusions about the effectiveness are based on an analysis of a subgroup of patients identified after completion of the study who were fully compliant with the recommended treatment regimen, 2) the primary endpoint was not achieved in this subgroup, and 3) clinically meaningful differences between the treatment and sham groups were not seen in the overall study population.

2- The clinical effectiveness of NMES treatment for knee OA pain relief and joint functionality improvements was concluded based on the secondary endpoints including WOMAC pain subscale, KOOS JR pain subscale, and VAS $_{General}$. The VAS $_{Nominated\ Anticity}$ as the primary endpoint did demonstrate a clinically meaningful pain reduction. However, it did not demonstrate a statistically significant difference against the sham low voltage NMES group. Statistically significant differences against the sham group were observed for a small portion of the secondary endpoints in a subgroup of compliant patients. Other secondary endpoints including VAS $_{General}$, VAS $_{Walk}$, and VAS $_{Rest}$ in the treatment NMES group did not demonstrate statistically significant difference against the sham group.

3- The study Statistical Analysis Plan (SAP), including the analysis for missing data was finalized and released prior to study unblinding, but after study enrollment initiation. Additionally, analysis of the results for a subgroup of compliant patients in the treatment NMES group was conducted later in the study after SAP release. These practices may have caused a potential for an unintentional bias in the study.

4- The study utilized a 2:1 randomization ratio to allocate more subjects to the intervention and assist with subjects' recruitment and retention. However, with an unbalanced randomization ratio, there is a potential for an unintentional bias in the study.

5- The sham device provided low voltage NMES stimulation at a maximum intensity level of 5 (V_{RMS} range of 1.66 to 2.96 V at 500Ω to 2kΩ). Level 5 was determined to be the minimum intensity level necessary for subjects to feel a treatment in the form of paresthesia. It is likely that at this level, the sham device elicited an effect on pain relief which adds uncertainty into the trial results. In addition, a potential unknown level of therapeutic benefit is likely in this group from the usage of a low voltage NMES treatment over time. This could alter the trial results and account for the minimal difference observed between the treatment and sham groups for certain endpoints.

6- In this clinical study multiple pain related endpoints including VAS Nominated activity as the primary endpoint, and VAS General, VAS Walk, VAS Rest, WOMAC pain subscale, and KOOS JR pain subscale as the secondary endpoints were collected and analyzed. The high number of endpoints could cause an effect of *multiplicity* on the results and increasing the rate of type I error (the multiplicity effect could increase the likelihood of having a statistically significant result that is not truly meaningful).

24 Conclusion

Based on the submitted clinical data, device performance testing, and the supporting documentation, it can be concluded that the Intellihab system is safe, effective, and substantially equivalent to the predicate device. The Intellihab NMES therapy output pulse parameters provide a safe and effective treatment for strengthening the quadricep muscle to provide symptomatic temporary pain relief associated with knee osteoarthritis and improvement of the knee joint

mobility when the recommended treatment regimens are followed.

Based on the clinical data and acceptable bench test results and Intellihab system compliance with the applicable standards, the Intellihab System is considered as safe and effective as the predicate device for its intended use.

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