JCAMD002 Core Submission Dossier

Evoke Spinal Cord Stimulation (SCS) System

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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
BMI	Body mass index
BPI	Brief Pain Inventory
CBT	Cognitive behavioural therapy
CDV	Evoke RECAP viewer
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Clinical interface
CLI	Critical limb ischaemia
CL-SCS	Closed-loop spinal cord stimulation
CLS	Closed-loop stimulator
CMM	Conventional medical management
CPA	Clarity Programming Application
CRPS	Complex regional pain syndrome
CST	Clinical System Transceiver
ECAP	Evoked compound action potential
eCLS	External closed-loop stimulator
EMDN	European Medical Device Nomenclature
EMI	Electromagnetic interference
EPC	Evoke patient controller
ERP	Effective radiated power
FBSS	Failed back surgery syndrome
FC	Feedback control
FDA	Food and Drug Administration
FSK	Frequency shift keying
FUA	Firmware upgrade application
GMDN	Global Medical Device Nomenclature
GPE	Global Perceived Effect
HRQoL	Health-related quality of life
HTD	Health technology developer
IASP	International Association for the Study of Pain
IDD	Intrathecal drug delivery
IDTE	Intradiscal Electrothermal Therapy
IMRDF	International Medical Device Regulators Forum
IPG	Implantable pulse generator
ITT	Intention-to-treat
MCS	Mental Component Summary
MDCE WG	Medical Device Clinical Evaluation Working Group
MDR	Medical Device Regulation
MICS	Medical Implant Communication System
MRI	Magnetic Resonance Imaging

NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
OL-SCS	Open-loop spinal cord stimulation
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PID	Proportional-integral-derivative
POMS	Profile of Mood States
PRO	Patient reported outcomes
PSPS	Persistent spinal pain syndrome
PSQI	Pittsburgh Sleep Quality Index
PT	Physical therapy
PVD	Peripheral vascular disease
RA	Refractory angina
RCT	Randomised controlled trial
RoB	Risk of bias
SCS	Spinal cord stimulation
TENS	Transcutaneous electrical nerve stimulation
TMD	Total Mood Disturbance
UDI-DI	Unique Device Identification-Device Identifier
USADE	Unanticipated serious adverse device effect
VAS	Visual Analogue Scale

1 Overview

1.1 Administrative Information

The medical device manufacturer is submitting the dossier (details below).

Legal Manufacturer Name:	Saluda Medical Pty. Ltd.
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SRN:	AU-MF-000010522

1.2 Executive Summary

1.2.1 Characteristics of the technology

The Evoke System is a spinal cord stimulation (SCS) device that enables the use of evoked compound action potentials (ECAPs) to i) guide programming of the stimulation parameters, and ii) provide closed-loop stimulation via a feedback mechanism that uses ECAP measurements to adjust the stimulation output level for every stimulation pulse to maintain the ECAP near the ECAP amplitude target. Therefore, ECAP-controlled closed-loop SCS (CL-SCS) modulates the energy delivered in real-time to maintain consistent spinal cord activation. This is in contrast with all other currently commercially available SCS devices which do not use feedback from the spinal cord to adjust stimulation.

1.2.2 Health condition to be treated

SCS is indicated for the treatment of chronic, intractable pain of the trunk and/or limbs. Chronic pain is different from acute pain as it persists well after the initial injury or illness that produced the initial pain has healed. SCS is mostly used for the treatment of chronic neuropathic, mixed neuropathic/nociceptive, or ischemic pain. Neuropathic pain is caused by nervous system damage or dysfunction, and is usually described as burning, shooting, or tingling. Neuropathic pain conditions include: persistent spinal pain syndrome type 2 (PSPS-T2; formerly failed back surgery syndrome [FBSS]), complex regional pain syndrome (CRPS) I and II, peripheral neuropathy, diabetic neuropathy, arachnoiditis, radiculopathy, traumatic and surgical nerve injury pain, intercostal neuralgia, phantom limb/post-amputation syndrome, spinal cord injury/lesion, and other pain indications of neuropathic origin.

1.2.3 Target patient population

The Evoke System is intended to be used in patients with chronic intractable pain of the trunk and/or limbs who are not contraindicated for the system.

1.2.4 Current clinical practice and comparators

There is consensus among national medical societies to recommend SCS as a treatment option in patients with chronic, intractable pain for which conservative treatment modalities have failed or are contraindicated. With the exception of Evoke, all currently commercially available SCS are open-loop SCS (OL-SCS) systems. The Evoke system operating in open-loop mode can be considered to represent a latest generation of OL-SCS because ECAP-guided programming provides an enhancement to other available OL-SCS systems. Conventional medical management (CMM) is no longer a relevant comparator for SCS in a population of PSPS. Placebo (sham) controlled trials to date are crossover randomised controlled trials (RCTs) with several methodological limitations and short follow-up periods.

1.2.5 Methods

A systematic review was conducted based on best practice guidance and informed by regulatory agencies' requirements. Electronic databases PubMed, EMBASE and Google Scholar were searched through June 2022. Database searches were complemented by screening of reference lists of eligible studies. Eight reports for two studies that evaluated Evoke closed-loop SCS were identified, the Evoke RCT and Avalon single-arm study. With the exception of the Evoke study, recent RCTs of SCS compared two versions of open-loop SCS and older RCTs compared open-loop SCS to conventional medical management. Placebo (sham) crossover RCTs were not considered eligible for inclusion in this dossier due to the short follow-up period in these trials. No indirect treatment comparisons were performed.

1.2.6 Results

1.2.6.1 PICO 1

The Evoke study was a prospective, multicentre, double-blind parallel arm RCT that compared CL-SCS to OL-SCS through 24-month follow-up. The Avalon study was a prospective, multicentre, single-arm study with 24-month follow-up. Both studies evaluated the Evoke system for a patient population with chronic, intractable pain of the trunk and/or limbs. In the Evoke RCT, superiority was observed for CL-SCS when compared to OL-SCS for reduction

in overall pain ≥50% (3-months: CL-SCS=82.3%, OL-SCS=60.3%, p=0.0052; 12-months: CL-SCS=83.1%, OL-SCS=61.0%, p=0.0060; 24-months: CL-SCS=79.1%, OL-SCS=53.7%, p=0.001) and ≥80% (3-months: CL-SCS=58.1%, OL-SCS=42.9%, p=0.0023; 12-months: CL-SCS=55.9%, OL-SCS=37.3%, p=0.039; 24-months: CL-SCS=46.3%, OL-SCS=29.9%, p=0.047). Statistically significant and clinically meaningful improvements with respect to baseline were observed in both treatment groups in all other patient-reported outcomes. In the Avalon study, overall pain responder rates (≥50% reduction) were 80.0%, 81.4%, and 89.5%, and high-responder rates (≥80% reduction) were 42.2%, 53.5%, and 68.4% at 3-, 12-, and 24-months, respectively, consistent with findings from the Evoke study.

The type, nature, and severity of adverse events were consistent with the published literature on other SCS systems.

1.2.6.2 PICO 2

PSPS is a recent definition that includes both Type 1 and Type 2. Both subtypes are included in the cohort of the Evoke and Avalon studies and refers to the same population as in PICO 1. Intervention, comparator and outcomes were the same as for PICO 1.

1.2.6.3 PICO 3

Population as for PICO 2, intervention and outcomes as for PICO 1. Regarding the comparator for PICO 3, CMM is no longer a relevant comparator for SCS in a population of PSPS. Once superiority of SCS was observed versus CMM and SCS approvals were obtained for an indication (e.g., PSPS-T2), the new standard of care became the SCS available at the time of approval. As chronic pain patients are considered for SCS if their pain is refractory to CMM, a comparison of SCS with CMM for this patient population refractory is not useful to inform decision-making. Placebo (sham) controlled trials to date are crossover RCTs with several methodological limitations and short follow-up periods.

1.2.7 Conclusions

The evidence provided in this dossier to support the safety, efficacy, and performance of the Evoke System includes clinical data from prospective clinical investigations of the Evoke System. The analyses through 24-months follow-up show statistically significant, clinically meaningful, ample, consistent, and strong evidence in support of the Evoke CL-SCS for the treatment of chronic intractable pain of the trunk and/or limbs. No new types of complications

were apparent. The Evoke SCS safety profile, including the type, rate, and severity of Evoke adverse events, is comparable to the literature.

2 Background

2.1 Characterisation of the Health Condition to be Treated or Diagnosed

2.1.1 Overview of the Health Condition to be Treated

Spinal cord stimulation (SCS) is indicated for the treatment of chronic, intractable pain of the trunk and/or limbs. Chronic pain is different from acute pain as it persists well after the initial injury or illness that produced the initial pain has healed. The International Association for the Study of Pain (IASP) has defined chronic pain as pain that lasts more than three to six months beyond the normal time of healing.

Chronic pain invariably is generated by physical, psychological, and environmental factors (bio-psycho-social concept of chronic pain). It is difficult to manage, and many afflicted patients will have a florid medical history with multiple comorbidities. Chronic pain is also difficult to generally define beyond its chronicity. Chronic pain is routinely characterised by multiple aspects including: the nature of the pain as perceived and reported (e.g., nociceptive, neuropathic, ischemic), the pathophysiology causing the pain (e.g., painful diabetic neuropathy), or the anatomical location that the pain is perceived (e.g., chronic low back pain), or a combination of these (e.g., discogenic low back pain). The published *Classification of Chronic Pain, Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms* from IASP lists around 100 separately identifiable chronic pain conditions (1). SCS is mostly used for the treatment of chronic neuropathic, mixed neuropathic/nociceptive, or ischemic pain.

Neuropathic pain is caused by nervous system damage or dysfunction, and is usually described as burning, shooting, or tingling. Neuropathic pain conditions include: failed back surgery syndrome (FBSS; most common presenting aetiology for SCS, now known as persistent spinal pain syndrome type 2 [PSPS-T2]), complex regional pain syndrome (CRPS) I and II, peripheral neuropathy, diabetic neuropathy, arachnoiditis, radiculopathy, traumatic and surgical nerve injury pain, intercostal neuralgia, phantom limb/post-amputation syndrome, spinal cord injury/lesion, and other pain indications of neuropathic origin.

Nociceptive pain is caused by damage to body tissue and is usually described as sharp, aching or throbbing. Examples of nociceptive pain include pain after trauma, pain after back surgery, arthritis pain, and other pain indications of nociceptive origin.

Ischemic pain is caused by a reduction in oxygen delivery to the tissues, usually due to reduction in blood flow because of constriction of a vessel (vasospasm) or its obstruction by atheroma or embolus. Ischemic pain conditions include peripheral vascular disease (PVD), critical limb ischaemia (CLI), refractory angina (RA), and other pain indications of ischemic origin.

Chronic pain affects approximately 20% of the European population and is more common in women, older people, and persons with relative deprivation (2). Chronic pain interferes with daily activities and impairs a patient's ability to perform physical activities, reduces their ability to perform their work and family responsibilities, and is the cause of mental health issues (3,4). In addition to the physical and emotional burden it brings, the financial cost to society is tremendous, currently estimated at more than €200 billion per annum in Europe (5).

2.1.2 Characterisation of the target population

The Evoke System is intended to be used in patients with chronic intractable pain of the trunk and/or limbs who are not contraindicated for the system (i.e., unable to operate the system, unsuitable surgical candidates, or unsuitable candidates for SCS; refer to section 2.2.1.15.1).

The Evoke System has not been tested for use in patients who are under 18 years old, or in patients who are pregnant or nursing.

2.1.2.1 Characterisation of the target population in PICO 1

The population specified in the EUnetHTA 21 PICO 1 of adult patients with chronic intractable pain of the trunk and/or limbs is as characterised in section 2.1.2.

2.1.2.2 Characterisation of the target population in PICOs 2 and 3

EUnetHTA 21 specified a subpopulation of adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome (PSPS), with insufficient effect from conventional pain management therapies for PICOs 2 and 3. PSPS is a recent definition that includes both Type 1 and Type 2. Both subtypes refer to the same population as in PICO 1 and characterised in section 2.1.2.

2.1.3 Clinical Management of the Health Condition

The multifaceted nature of chronic pain requires interdisciplinary assessment and multimodal treatment. First line treatment strategies are generally conservative treatments including: exercise programs, physical therapy (PT), occupational therapy, cognitive behavioural therapy (CBT), biofeedback, acupuncture, transcutaneous electrical nerve stimulation (TENS), and non-opioid pain medications. Second line treatments become more intensive and involve the use of systemic opioids and interventional techniques such as nerve blocks (local anaesthetic or steroids) and spinal injections. They can also include more powerful medications such as

systemic opioids. The last line of treatment involves more advanced therapies that require surgical interventions. Systems such as intrathecal drug delivery (IDD) or SCS may be implanted. Surgery to repair an anatomical issue responsible for the pain may be performed. Finally, surgical techniques that block pathways to the brain such as cordotomy, rhizotomy, and thalamotomy may be used rarely in extreme cases.

Recent guidelines and the literature on the treatment for chronic pain of the trunk and/or limbs demonstrate that each of the surgical interventions have the potential to be effective in managing pain, increasing patient activity, and to result in high patient satisfaction when conservative treatment modalities have failed. The risk profile for SCS therapy has advantages compared to surgical revision and neuroablation due to the fact it is reversible as the device can be surgically removed. Furthermore, it is common practice for patients to undergo a trial period with SCS, whereby implanted leads are connected to an external pulse generator prior to undergoing the permanent implant. During the trial stimulation period (typically 3 – 7 days, up to 30 days), tolerability (e.g., of the stimulation sensation or the device) and the degree of pain relief is assessed. If the trial stimulation is successful, lead(s) and a pulse generator are permanently implanted. The Neuromodulation Foundation recommends that an SCS trial precede major reconstructive procedures and ablative therapies (6). In addition, SCS therapy has the advantage of not having drug side effects, including respiratory distress, as compared to IDD systems. There is consensus among national medical societies to recommend SCS as a treatment option in patients with chronic, severe pain for which conservative treatment modalities have failed or are contraindicated (6–13). SCS may be delivered in parallel with other therapies and should be used as part of an overall multimodal treatment strategy.

Conventional (“low frequency”) SCS delivers a charge-balanced waveform (biphasic or monophasic) with programmable frequency (Hertz; 10-100 Hz), pulse duration (pulse width; 100-1000 µs), and strength (amplitude; 1-10 µA) (14). High frequency stimulation uses a frequency of 1-10 kHz with shorter pulse widths (e.g., 30-150 µs) and low amplitudes below the paraesthesia threshold (1-5 mA) (14). High density stimulation also uses low amplitudes below the paraesthesia threshold, but with higher frequencies and broader pulse widths within conventional stimulation parameters. Burst stimulation delivers groups of pulses at a constant pulse amplitude, pulse width and inter-pulse frequency (i.e., burst trains) separated by short pulse-free periods (i.e., inter-burst intervals) (e.g., 40 Hz burst mode with 5 pulses at 500 Hz per burst, fixed pulse width of 1000 µs, and subthreshold amplitude) (14,15).

Despite recent advances in this therapy, all approved SCS therapies other than the Evoke System (e.g., low frequency, high frequency, high density, and burst), regardless of whether stimulation induces paraesthesia, are open-loop in that they produce fixed-output stimuli; that

is, the energy delivered from the electrode array has a defined output irrespective of the neural activation of the spinal cord fibres (e.g., fixed frequency, fixed pulse width, fixed amplitude, and fixed pulse train) as seen in Figure 1 (16). These SCS systems do not take into account the broad range of electrical field strengths reaching the spinal cord due to changes in distance between the electrode and the spinal cord resulting from normal physiological activity (e.g., breathing and heartbeat) and movement (17–20). With decreased distance between the spinal cord and the electrode there is an increase in the strength of the electric field at the spinal cord and the volume of tissue stimulated. This may be perceived as uncomfortably strong stimulation, stimulation in unwanted areas, muscle activation, and/or cramping (19,21). Paraesthesia-based systems have the advantage that the uncomfortable stimuli are felt by the patients and can be managed via programming. In paraesthesia-free programming, stimulation of nerve root fibres that reduce pain relief may occur without uncomfortable side effects and therefore go on unacknowledged by the patient and clinician. Side effects resulting from this overstimulation, however, may be responsible for loss of efficacy over time (22). Conversely, increased separation between the leads and the spinal cord results in decreased electrical field strength at the spinal cord and may be perceived as insufficient stimulation with reduced therapeutic effect (17–19). Stimulation intensity changes that occur with movement may be non-therapeutic (i.e., outside the therapeutic usage range or window) and result in patients manually adjusting stimulation current to minimise over- and under-stimulation at the expense of optimised pain relief (19,21).

In contrast to these open-loop SCS (OL-SCS) systems that do not use feedback from the spinal cord to adjust stimulation, the Evoke System offers closed-loop stimulation via a feedback mechanism that uses evoked compound action potential (ECAP) measurements to adjust the stimulation output level for every stimulation pulse to maintain the ECAP near the ECAP amplitude target (Figure 1). Thus, ECAP-controlled closed-loop SCS (CL-SCS) modulates the energy delivered in real-time to maintain consistent spinal cord activation. Whereas modelling shows that changes in posture can result in activation ranging from periods of zero activation to more than five times the desired level with OL-SCS systems, ECAP-controlled CL-SCS reduces the variation with posture by more than ten times and eliminates the periods of no activation entirely (23).

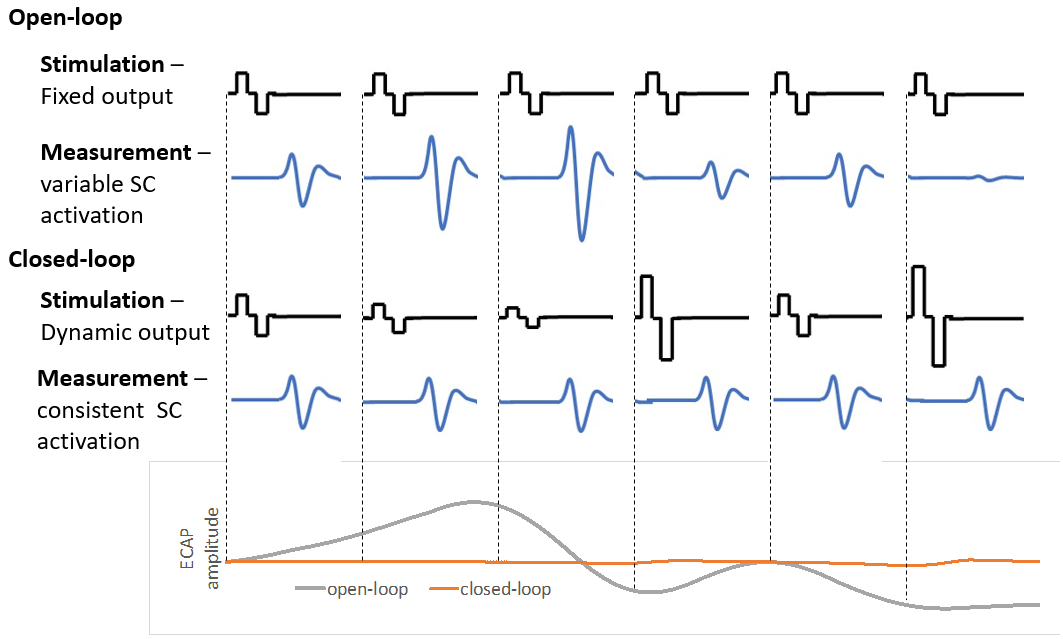

Figure 1. Illustration of Closed-Loop versus Open-Loop Stimulation and the Resulting Spinal Cord Activation

2.2 Characterisation of the Medical Device under Assessment

2.2.1 Characteristics of the Health Technology

Characteristics of the Evoke System are detailed in sections 2.2.1.1 through 2.2.1.20 below.

2.2.1.1 Proprietary Name

Evoke® Spinal Cord Stimulation (SCS) System

2.2.1.2 Product Type

The European Medical Device Nomenclature (EMDN) and Global Medical Device Nomenclature (GMDN) (for UKCA) assigned to the devices of the Evoke System are listed below.

Device	EMDN	GMDN
Evoke Closed Loop Stimulator (CLS)	J020202 - Neurostimulators, Spine, Total Implantable	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke External Closed-Loop Stimulator (eCLS)	J020299 - Neurostimulators, Spine, Others	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable

Device	EMDN	GMDN
Evoke CAP12 Percutaneous Lead Kit (60 & 90cm)	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke CAP12 Trial Percutaneous Lead Kit (60 and 90cm)	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke CAP12X Lead Extension	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Spares Kit	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Tunneler	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Epidural Needle, 6.5”	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Lead Adapter Kit	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Active Anchor Kit	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Patient Controller (EPC)	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Charger (EU)/ Evoke Charger (AU)/ Evoke Charger (UK)	J020280 - Neurostimulators, Spine, Accessories	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Clinical System Transceiver (CST)	J020701 - programming units for neurostimulators	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke Clarity Programming Application (CPA)	J020782 - programming units for Neurostimulators - software	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable
Evoke RECAP Viewer	J020782 - programming units for Neurostimulators - software	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable

Device	EMDN	GMDN
Evoke Firmware Upgrade Application (FUA)	J020782 - programming units for Neurostimulators - software	64970 - Spinal cord/peripheral nerve implantable analgesic electrical stimulation system pulse generator, implantable

2.2.1.3 Medical Purpose

The Saluda Medical Evoke System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs.

2.2.1.4 Models, References, Software Versions, Basic Unique Device Identification-Device Identifier (UDI-DI)

Table 1. AIMDD and MDR Evoke System Component Names, Catalogue Numbers, Software Versions, Basic UDI-DI (MDR)

Device Name	Device Name (if different for MDR)	Catalogue Number	Catalogue Number (if different for MDR)	Basic UDI-DI (MDR)
Evoke Closed Loop Stimulator (CLS)	Evoke Closed-Loop Stimulator (CLS)	1002	1042	935230701042AY
Evoke External Closed Loop Stimulator (eCLS)	Evoke External Closed-Loop Stimulator (eCLS)	1020	Same	935230701020AN
Evoke 12C Percutaneous Lead Kit – 60cm	Evoke CAP12 Percutaneous Lead Kit – 60cm	1008 1016	Same	935230701008AY 935230701016AX
Evoke 12C Percutaneous Lead Kit – 90cm	Evoke CAP12 Percutaneous Lead Kit – 90cm	1009 1017	Same	935230701009B2 935230701017AZ
Evoke 12C Lead Extension Kit – 55cm	Evoke CAP12X Lead Extension Kit – 55cm	1011	Same	935230701011AM
Evoke Lead Adapter	Same	1028	Same	935230701028B6
N/A (active anchor packaged in Lead kits and Spares kit)	Evoke Active Anchor Kit	N/A	1043	935230701043B2
Evoke Tunnelling Tool	Evoke Tunneler	1012	Same	935230701012AP
Evoke Epidural Needle, 6.5”	Same	1014	Same	935230701014AT
Evoke Spares Kit	Same	1015	Same	935230701015AV
Evoke Pocket Console (EPC)	Evoke Patient Controller (EPC)	1003	1040	935230701040AU
Evoke Charger EU	Same	1006	Same	935230701006AU
Evoke Charger UK	Same	4006	Same	935230704006BH

Device Name	Device Name (if different for MDR)	Catalogue Number	Catalogue Number (if different for MDR)	Basic UDI-DI (MDR)
Evoke Charger AU	Same	5006	Same	935230705006BQ
Evoke Clinical Interface (CI) System: • Tablet (Microsoft Surface Pro; off-the-shelf; not a medical device) • Saluda Medical Software Applications: ○ Evoke Clinical Programming Application (CPA) ○ Evoke Clinical Data Viewer (CDV) ○ Evoke Firmware Upgrade Application (FUA)	CI System: • Tablet: Same • Software: ○ Evoke Clarity Programming Application (CPA) ○ Evoke RECAP Viewer ○ Same	CI System: 1024 • Tablet: N/A • Software: ○ 000870, version 1.50.9 ○ 002581, version 1.11.1 ○ 000897, version 2.4.0.0	CI System: Same • Tablet: N/A • Software: ○ 1044, version 2.1.0.0 ○ 1045, version 1.13.2.0 ○ 1046, version 2.4.1.0	CI System: 935230701024AW • Tablet: N/A • Software: ○ 935230701044B4 ○ 935230701045B6 ○ 935230701046B8
Evoke Clinical System Transceiver (CST)	Same	1004	Same	935230701004AQ

Table 2. Evoke System Device Components Evaluated in the Avalon Study

Device Name	Catalogue Number*†
Evoke Closed Loop Stimulator (CLS)	2002
Evoke External Closed-Loop Stimulator (eCLS)	2020
Evoke 12C Percutaneous Lead – 60cm	2008, 2016, 2026†
Evoke 12C Percutaneous Lead – 90cm	2009, 2017, 2027†
Evoke Lead Adapter	2028
Evoke Tunneling Tool	2012
Evoke Epidural Needle, 6.5”	2014
Evoke Spares Kit	2015
Evoke Pocket Console (EPC)	2003
Evoke Charger AU	2006
Evoke Clinical Interface (CI) System	2024
Evoke Clinical System Transceiver (CST)	2004

*The first digit of the catalogue number for each device component varies for each geographic region and commercial vs. clinical trial use.
†Note, 2008, 2026 and 2016 are the same 12C Percutaneous Lead – 60cm, and 2009, 2027 and 2017 are the same 12C Percutaneous Lead – 90cm, but have different catalogue numbers due to differences in device components packaged in the kits.

Table 3. Evoke System Device Components Evaluated in the Evoke Study

Device Name	Catalogue Number*
Evoke Closed Loop Stimulator (CLS)	0002
Evoke External Closed-Loop Stimulator (eCLS)	0020
Evoke 12C Percutaneous Lead – 60cm	0008, 0016, 0026†
Evoke 12C Percutaneous Lead – 90cm	0009, 0017, 0027†
Evoke Lead Adapter	0028
Evoke Tunneling Tool	0012
Evoke Epidural Needle, 6.5”	0014
Evoke Spares Kit	0015
Evoke Pocket Console (EPC)	0003
Evoke Charger US	0006
Evoke Clinical Interface (CI) System	0024
Evoke Clinical System Transceiver (CST)	0004

*The first digit of the catalogue number for each device component varies for each geographic region and commercial vs. clinical trial use.
†Note, 0008, 0026 and 0016 are the same 12C Percutaneous Lead – 60cm, and 0009, 0027 and 0017 are the same 12C Percutaneous Lead – 90cm, but have different catalogue numbers due to differences in device components packaged in the kits.

2.2.1.5 Medical Device Risk Class

Device Classification: Class III

Classification Rule (MDR): Rule 8

*Under Rule 8, all active implantable devices and their accessories are Class III. Thus, all models included in the system are considered Class III.

2.2.1.6 HTD Submitting the Dossier

The medical device manufacturer, Saluda Medical Pty. Ltd., is submitting the dossier.

2.2.1.7 Date the Medical Device was First Placed on the EU Market in the Course of Commercial Activity

CE marking was awarded on the June 17, 2019 under the requirements of Council Directive 90/385/EEC, Annex 2, excluding Section 4 (No. CE 653950) and in accordance with Council Directive 90/385/EEC, Annex 2 Section 4 (No. CE 653955).

The submission for EU Medical Device Regulation 2017/745 (MDR) is currently under review. BSI expects to complete the review of the MDR application by the end of the year (December 2023).

2.2.1.8 Product Description: Composition, Technologies Involved and Technical Characteristics

The Evoke System is a SCS system that has the ability to measure ECAPs, representative of spinal cord fibre activation that generates pain inhibition for an individual. The Evoke System may deliver 1) open-loop stimulation, equivalent to the mechanism used by other commercially available SCS systems but with the additional feature to measure ECAPs; or 2) ECAP-controlled closed-loop stimulation, where the stimulation amplitude is automatically adjusted in real-time to minimize the difference between the measured ECAP and the target ECAP to deliver consistent spinal cord activation at the target level. The Evoke System components that may be used during a stimulation trial or permanent implant are provided in sections 2.2.1.8.1 through 2.2.1.8.13 below.

2.2.1.8.1 Evoke Closed-Loop Stimulator (CLS)

The Evoke Closed-Loop Stimulator (CLS) is a totally implanted spinal cord stimulator that connects to the CAP12 Percutaneous Leads and is implanted under the skin for long-term therapy (Figure 2). The CLS delivers either closed-loop or open-loop stimulation through the leads and measures the neural response to stimulation. A port plug is provided with the CLS, for insertion into an unused CLS port when only one lead is implanted.

The CLS may be configured using the Clarity Programming Application (CPA) to provide the optimal therapy requirements of each patient. The CLS may have 1 to 4 programs loaded. Each of the 24 electrodes can be configured to be used for either stimulation or recording , and the case can be configured for recording. Stimulation is delivered by 4 constant current source outputs that can be programmed to deliver current through one electrode, or to different electrodes. Pulse shape is programmable to a rectangular symmetrical biphasic or triphasic pulse. The recording electrodes can be programmed with amplifier gain, measurement type, Feedback Control (FC) gain and FC target.

Each program may comprise up to 4 time-multiplexed stimulation pulses, with fixed current output ratios between them. In closed-loop mode, a single feedback variable controls the current of all stimulation pulse outputs.

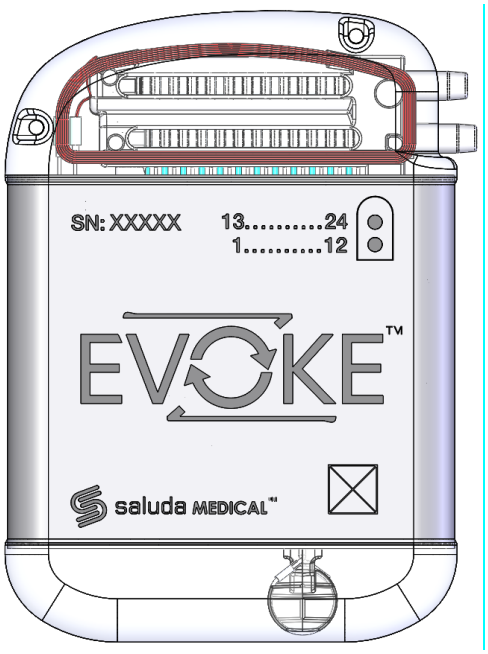

Figure 2. Evoke Closed Loop Stimulator (CLS)

Device	Component / Material	Characteristics
Evoke Closed Loop Stimulator (CLS)	**Components in direct contact with tissue, or may contact bodily fluids:** • Case: Titanium • Header: Epoxy • Seals: Liquid silicone rubber • Connector springs: Platinum Iridium (24 x connectors) • Set screw: Stainless steel	• Sterile • Single use • Implantable (long-term)
Evoke CLS Port Plug	**Components in direct contact with tissue:** • Stainless Steel	• Sterile • Single use • Implantable (long-term)

2.2.1.8.2 Evoke External Closed-Loop Stimulator (eCLS)

During the trial stimulation period, the CAP12 Percutaneous Leads are connected to the Evoke External Closed-Loop Stimulator (eCLS) (Figure 3). The eCLS is an external stimulator used for intraoperative testing and during the trial stimulation period. The eCLS delivers either closed-loop or open-loop stimulation through the leads and measures the neural response to stimulation.

Figure 3. Evoke External Closed-Loop Stimulator (eCLS)

Device	Component / Material	Characteristics
Evoke External Closed Loop Stimulator (eCLS)	Components are not in direct contact with the skin.	• Non-sterile • Reusable • Non-implantable

2.2.1.8.3 Evoke CAP12 Percutaneous Leads, 60cm and 90cm

The Evoke CAP12™ Percutaneous Leads are placed in the epidural space overlying the spinal cord and are connected to an eCLS for a trial stimulation period, or to a CLS for long-term therapy (Figure 4). One or two leads, each with 12 electrodes, are implanted. The lead kit is provided with one suture anchor to secure the lead, and surgical accessories (4.5" epidural needle and two stylets) for use during lead placement.

Figure 4. Evoke CAP12 Percutaneous Lead and Proximal End (right)

Device	Component / Material	Characteristics
Evoke CAP12 Percutaneous Lead	**Components in direct contact with tissue, or may contact bodily fluids:** • Lead body: Pellethane • Lead ends: Pellethane • Distal electrodes: Platinum Iridium • Proximal connectors: Platinum Iridium • Retention ring: MP35N (alloy of Nickel, Cobalt, Chromium and Molybdenum)	• Sterile • Single use • Implantable (long-term)
Evoke Suture Anchor	**Components in direct contact with tissue:** • Silicone Rubber	• Sterile • Single use • Implantable (long-term)
Evoke Stylet	Components are not in contact with tissue.	• Sterile • Single use • Non-implantable
Evoke Epidural Needle	**Components in temporary contact with tissue:** • Stylet and Cannula: Stainless Steel	• Sterile • Single use • Non-implantable

2.2.1.8.4 Evoke CAP12X Lead Extension, 55cm

The Evoke CAP12X™ Lead Extensions are used when trialing a permanently implanted lead, where the extension is externalized for connection to an eCLS (Figure **5**).

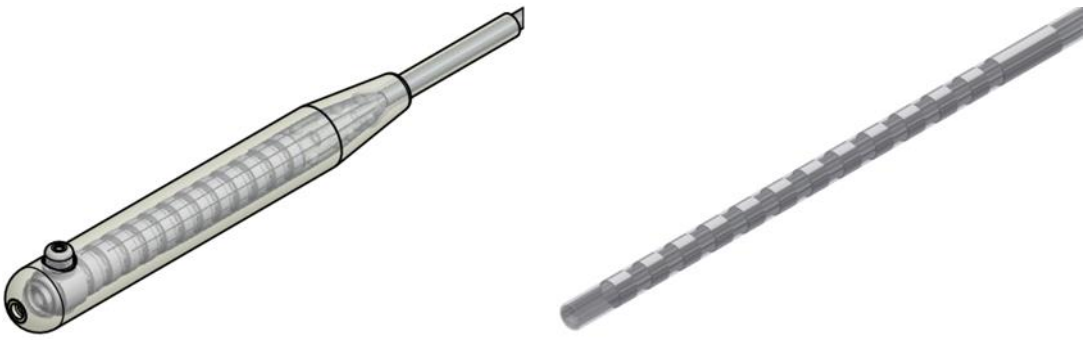

Figure 5. Evoke CAP12 Lead Extension Distal (left) and Proximal (right) Ends

Device	Component / Material	Characteristics
Evoke CAP12X Lead Extension	**Components in direct contact with tissue, or may contact bodily fluids:** • Lead extension body: Pellethane • Lead extension ends: Pellethane • Proximal connectors: Platinum Iridium	• Sterile • Single use • Implantable (short-term; up to 30 days)

Device	Component / Material	Characteristics
	• Retention ring: MP35N (alloy of Nickel, Cobalt, Chromium and Molybdenum) • Connector springs: Platinum Iridium • Set screw: Titanium • Header body: Silicone	

2.2.1.8.5 Evoke Lead Adapter, Lead Adapter Cable, and Lead Adapter Extension

The Evoke Lead Adapter, Lead Adapter Cable, and Lead Adapter Extension allows the surgeon to connect the eCLS to the implanted leads for intra-operative testing and trial stimulation (Figure 6).

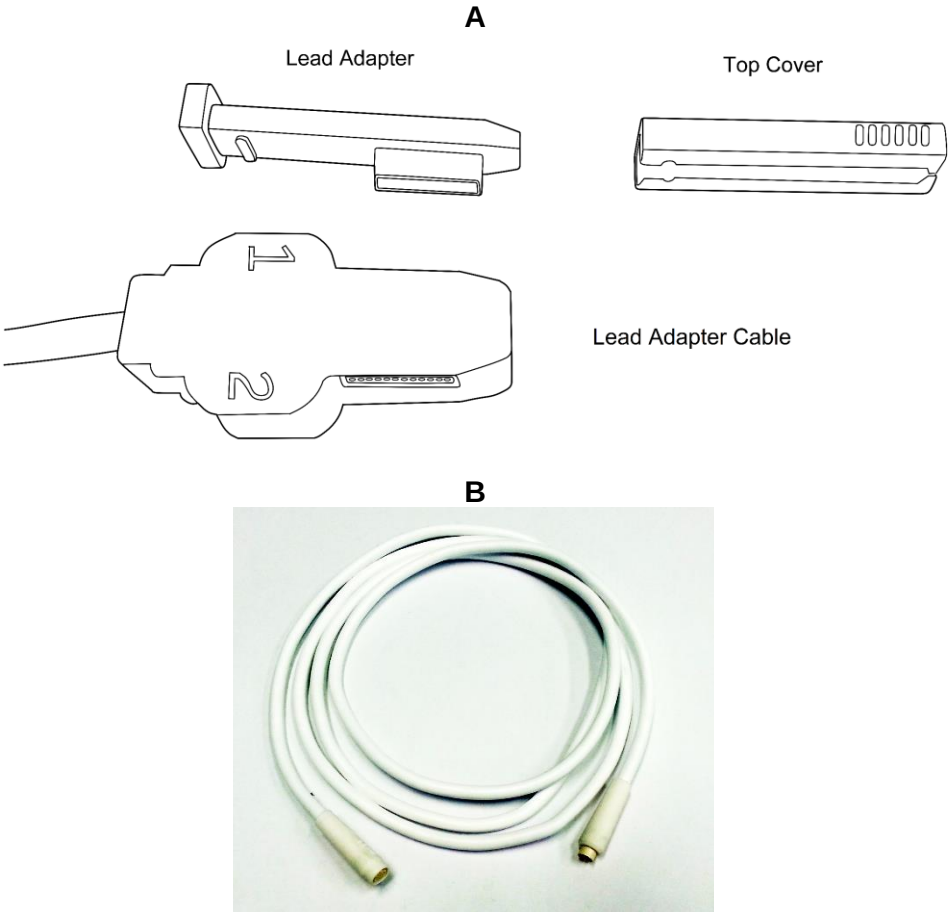

Figure 6. A) Evoke Lead Adaptor and Lead Adaptor Cable; B) Evoke Lead Adaptor Extension

Device	Component / Material	Characteristics
Evoke Lead Adapter, Lead Adaptor Cable, and Lead Adapter Extension	Components are not in direct contact with the skin.	• Sterile • Single use • Non-implantable

2.2.1.8.6 Evoke Active Anchor

The Evoke Active Anchor allows the surgeon to secure the lead after placement in the epidural space (Figure 7). The active anchor kit is provided with two active anchors and a torque wrench to tighten the anchor.

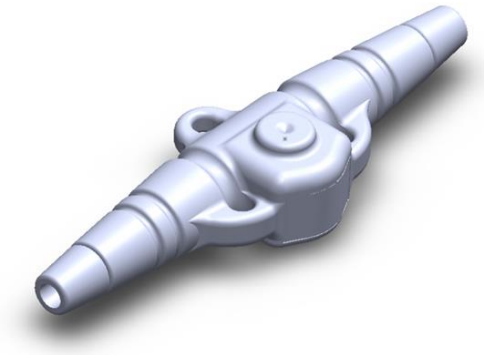

Figure 7. Evoke Active Anchor

Device	Component / Material	Characteristics
Evoke Active Anchor	**Components in direct contact with tissue:** • Body: Silicone rubber • Set screw: Titanium • Set Screw Block: Titanium	• Sterile • Single use • Implantable (long-term)
Evoke Torque Wrench	**Components in temporary contact with tissue:** • Handle: Polyetherimide plastic • Shaft: Stainless steel	• Sterile • Single use • Non-implantable

2.2.1.8.7 Evoke Tunneler

The Evoke Tunneler allows the subcutaneous threading of leads and/or lead extensions, either to an exit incision for the trial stimulation period, or to the CLS (leads only) (Figure 8).

Figure 8. Evoke Tunneler

Device	Component / Material	Characteristics
Evoke Tunneler	**Components in temporary contact with tissue:** • Body: Stainless steel • Straw: PTFE	• Sterile • Single use • Non-implantable

2.2.1.8.8 Epidural Needle, 6.5”

The 6.5” Epidural Needle Kit is an optional long needle for larger patients in whom the regular 4.5” needle supplied with the lead kits is too short to reach the epidural space (Figure 9).

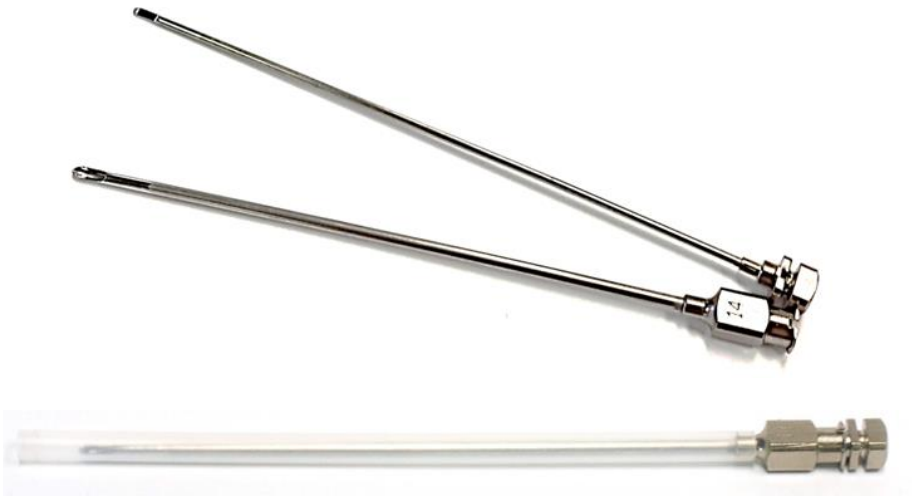

Figure 9. Epidural Needle and with Assembled Needle Tip Guard (bottom)

Device	Component / Material	Characteristics
Evoke Epidural Needle	**Components in temporary contact with tissue:** • Stylet and Cannula: Stainless Steel	• Sterile • Single use • Non-implantable

2.2.1.8.9 Evoke Spares Kit

The Evoke Spares Kit contains all items from the permanent lead kits except for the lead itself (suture anchor (Figure 10), stylet (Figure 11), epidural needle (Figure 9)), plus a CLS port plug (Figure 12) and torque wrench (Figure 13). The Evoke Spares Kit will save surgeons from opening a new lead kit should any of the small accessory items be dropped or damaged during the procedure.

Figure 10. Evoke Suture Anchor

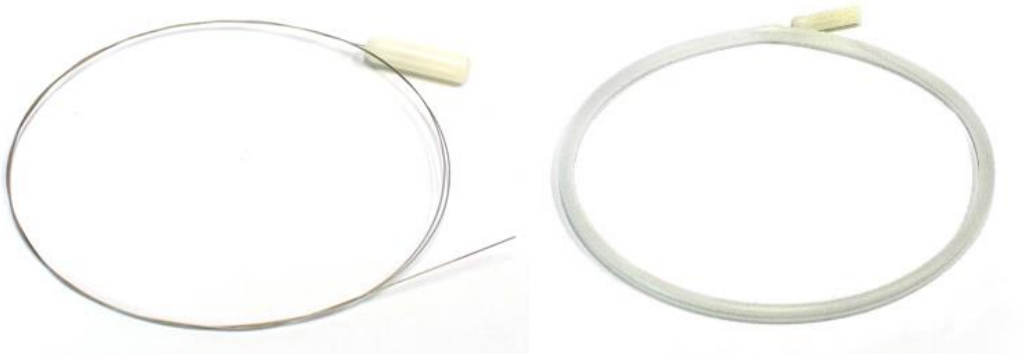

Figure 11. Evoke Stylet and with Hoop Cover (right)

Figure 12. Evoke Port Plug

Figure 13. Evoke Torque Wrench

Device	Component / Material	Characteristics
Evoke Suture Anchor	**Components in direct contact with tissue:** • Silicone Rubber	• Sterile • Single use • Implantable (long-term)
Evoke Stylet	Components are not in contact with tissue.	• Sterile • Single use • Non-implantable
Evoke Epidural Needle	**Components in temporary contact with tissue:** • Stylet and Cannula: Stainless Steel	• Sterile • Single use • Non-implantable
Evoke CLS Port Plug	**Components in direct contact with tissue:** • Stainless Steel	• Sterile • Single use • Implantable (long-term)
Evoke Torque Wrench	**Components in temporary contact with tissue:** • Handle: Polyetherimide plastic • Shaft: Stainless steel	• Sterile • Single use • Non-implantable

2.2.1.8.10 Evoke Patient Controller (EPC)

The Evoke Patient Controller (EPC) allows the patient to control their therapy and actively monitors the stimulator battery status and other elements of the system (Figure 14). The EPC and the stimulator communicate with each other wirelessly.

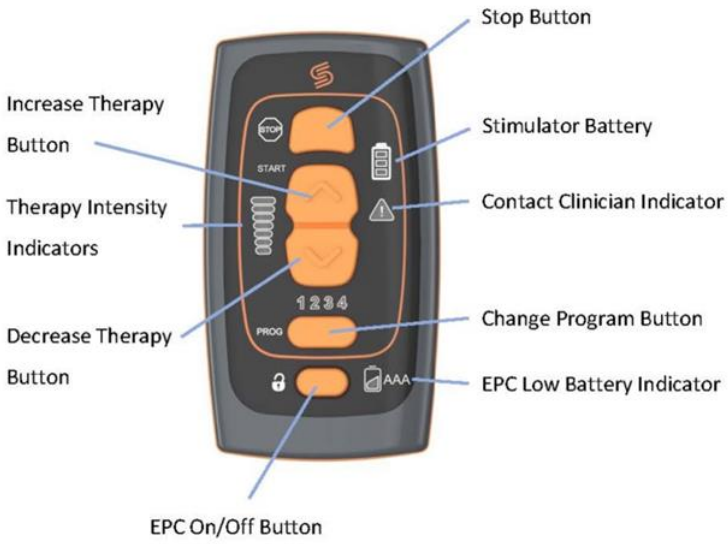

Figure 14. Evoke Patient Controller (EPC)

Device	Component / Material	Characteristics
Evoke Patient Controller (EPC) and Magnet	**Components in contact with the skin:** • Body and Battery Cover: ABS Plastic • Buttons and Seal: TPE • Lens: Polycarbonate	• Non-sterile • Reusable • Non-implantable

2.2.1.8.11 Evoke Charger

The Evoke Charger allows the patient to recharge the battery in a CLS (Figure 15). The Charger coil (attached to the Charger) is placed over the CLS, and charge is transferred to the CLS through thin clothing and the skin. The Charger kit also includes a power adapter for recharging the Charger.

Figure 15. Evoke Charger

Device	Component / Material	Characteristics
Evoke Charger	**Components in contact with the skin:** • Charger: ABS Plastic • Control Panel: PET • Charger Coil: Silicone	• Non-sterile • Reusable • Non-implantable

2.2.1.8.12 Evoke Clinical Interface System

The Evoke Clinical Interface System consists of an off-the-shelf tablet computer with preinstalled software applications developed by Saluda Medical (Figure 16). These include:

- **Evoke Clarity Programming Application (CPA):** the programming application used by the clinician to adjust the therapy settings of the Evoke CLS and eCLS.
- **Evoke RECAP Viewer (CDV):** used to read clinical data log files (which includes data retrieved from the CLS/eCLS or logged by the CPA) and display the data in summary form to the user with charts and tables.
- **Evoke Firmware Upgrade Application (FUA):** used to upgrade the firmware on the Therapy microcontroller and Telemetry microcontroller.

Figure 16. Evoke Clinical Interface

Device	Component / Material	Characteristics
Evoke Clinical Interface System	Components are not in direct contact with the patient's skin.	• Non-sterile • Reusable • Non-implantable

2.2.1.8.13 Evoke Clinical System Transceiver (CST)

The Evoke Clinical System Transceiver (CST) is a plug-in device (USB connection) that enables exchange of information wirelessly between the Clinical Interface and the stimulator (Figure 17).

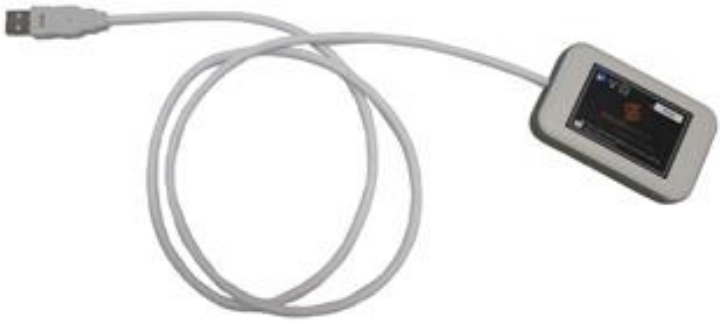

Figure 17. Evoke Clinical System Transceiver

Device	Component / Material	Characteristics
Evoke Clinical System Transceiver (CST)	Components are not in direct contact with the patient's skin.	• Non-sterile • Reusable

Device	Component / Material	Characteristics
		• Non-implantable

2.2.1.9 Stages of Development of Technology

The Saluda Medical Evoke System originally obtained CE mark June 17, 2019 in accordance with the requirements of AIMDD ("Original" device configuration). Modifications including design and manufacturing changes and software and firmware updates were made to the following device components of the Saluda Medical Evoke System for EU Medical Device Regulation 2017/745 (MDR) ("Modified" device configuration): CLS, eCLS, Clinical Interface System (i.e., to the CPA, CDV, and FUA SW applications), EPC, Percutaneous Leads, Stylets, Active Anchor, and Suture Anchor. In addition, name changes were made to the following products for marketing purposes: CPA, CDV, EPC, Percutaneous Leads, Lead Extensions, and Tunneler. For all changes, testing supported that there was no effect on the therapy delivered to the patient or on the safety and clinical performance of the device. Refer to Table 4 for details.

Table 4. Previous Generation and Variant Devices

Evoke System (Modified; MDR)	Evoke System (Original; AIMDD)	Differences
Evoke Closed Loop Stimulator (CLS) Catalogue # 1042	Same Catalogue # 1002	Changes were made to the header design and to upgrade the CLS firmware to improve available features and ensure compatibility with the programming application. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke External Closed Loop Stimulator (eCLS) Catalogue # 1020	Same	Changes were made to the firmware to improve available features and ensure compatibility with the programming application. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke CAP12 Percutaneous Lead Catalogue # 1008, 1009, 1016, 1017	Evoke 12C Percutaneous Lead Same	Changes were made to remove Saluda Medical as a manufacturing site and to increase the shelf life of the device to accommodate greater production capacity. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke Active Anchor Catalogue # 1043	Same	Changes were made to add a new manufacturing site to accommodate greater production capacity, to increase the eyelet thickness to provide additional robustness when securing, and to increase

Evoke System (Modified; MDR)	Evoke System (Original; AIMDD)	Differences
	Catalogue # N/A - packaged in Lead Kit and Spares Kit	engagement between the set screw and the bottom clamp component. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke Suture Anchor Catalogue # N/A - packaged in Lead Kit and Spares Kit	Same Same	Changes were made to add a new manufacturing site to accommodate greater production capacity and to increase the eyelet thickness to provide additional robustness when securing. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke Stylets Catalogue # N/A - packaged in Lead Kit and Spares Kit	Same Same	Changes were made to increase the shelf life of the device and to remove excess wire length extending from the proximal end. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke Patient Controller (EPC) Catalogue # 1040	Evoke Pocket Console (EPC) Catalogue # 1003	Design changes were made to improve the tactile user interface and replace obsolescent components, and firmware changes were made to enable communication with AIMDD and MDR configurations and add a Company ID. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.
Evoke Clinical Interface (CI) System: 1024 Evoke Clarify Programming Application (CPA): 1044 Evoke RECAP Viewer: 1045 Evoke Firmware Upgrade Application (FUA): 1046	Same Evoke Clinical Programming Application (CPA): 000870 Evoke Clinical Data Viewer: 002581 Evoke Firmware Upgrade Application (FUA): 000897	Changes were made to the software to improve the user interface, ensure compatibility with the programming application, cybersecurity, and MDR requirements. The changes have no effect on the therapy delivered to the patient or on the safety and clinical performance of the device.

2.2.1.10 Connected Technology

An overview of the interoperability of the devices of the Evoke System is detailed in Figure 18.

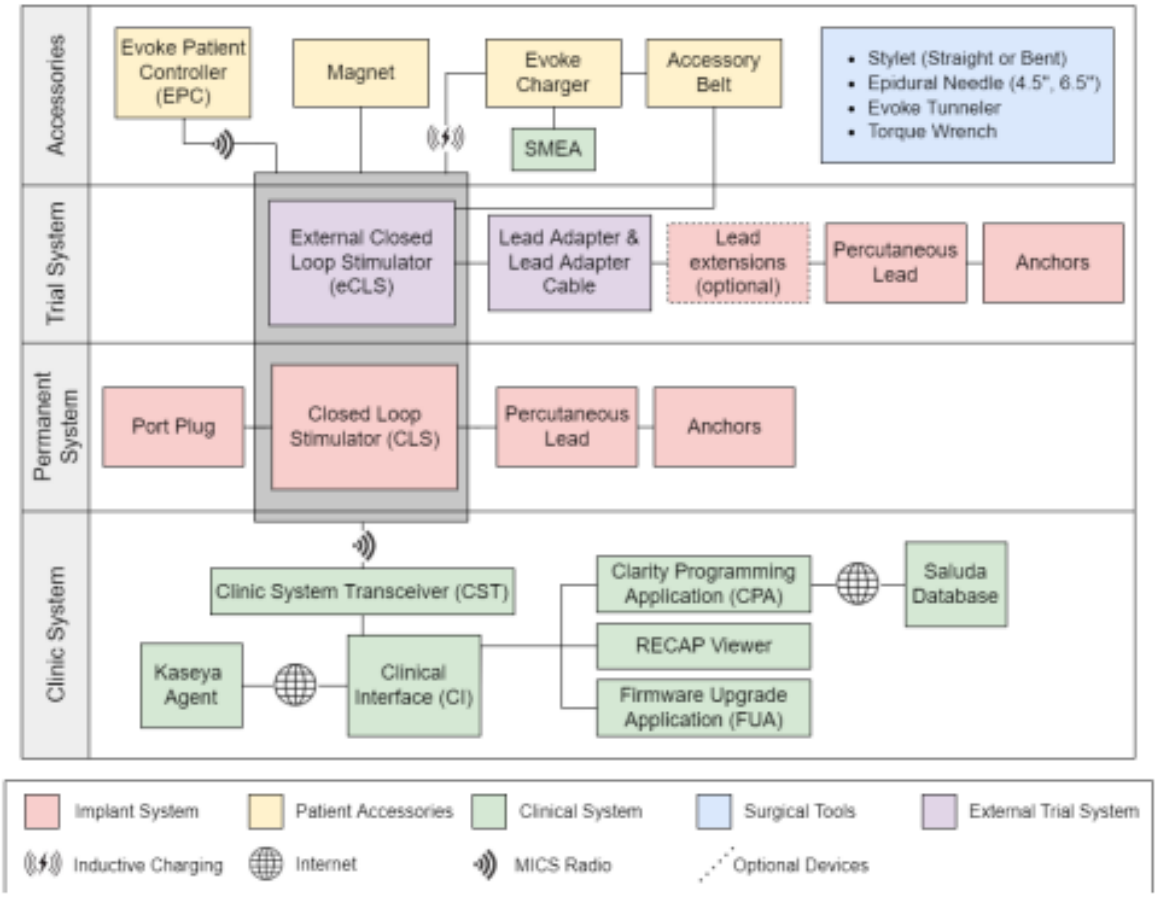

Figure 18. Interoperability of the devices of the Evoke System

Solid lines indicate mechanical interfaces between components. Remote interfaces are indicated with a type (radio or inductive). Sectioned background colour indicates the category of the component, as indicated by the in-figure legend. For Medical Implant Communication System (MICS) band communication (402 - 405 MHz):

- 8 channels* Centre frequency (MHz): 402.45, 402.75, 403.05, 403.35, 403.65, 403.95, 404.25, 404.55
- Transmit/Receive Channel Bandwidth: 300 kHz
- Modulation type: Frequency Shift Keying (FSK)
- Range:1.0 m (3.3 ft.)
- Effective Radiated Power (ERP): 25 µW (-16.02 dBm) maximum

When explicit informed consent is provided by patients, data can be uploaded from the CPA on the Clinical Interface (CI) to global Saluda data systems. This data may include:

- Pseudonymised patient identifier codes (e.g., slm-uk-abc-001) and device serial numbers
- Nerve recordings
- Stimulation settings
- Recharging data
- Device usage and error logs
- Demographics (age, gender, pain history, pain intensity, painful areas, diagnosis, BMI, treatment history, basic medication information)
- Treatment progress (changes in pain intensity and painful areas, changes in medication, stimulation sensation characteristics and satisfaction with treatment)

When explicit informed consent is not provided, data may be stored on the (e)CLS or CI but will not be uploaded to global Saluda data systems.

EU patient data is pseudonymised in Saluda data systems, with any links to identifying codes maintained externally. Any links to identifying codes held by Saluda will be deleted within 12 months of explantation of the system. Existing patient data then becomes anonymous and may be stored indefinitely.

Saluda data systems are accessible only to Saluda staff members who require access to assist in patient care or analysis.

2.2.1.11 Embedded Decision-Making Based on Machine Learning Processes

The Evoke System does not have an embedded decision-making system based on machine learning processes.

2.2.1.12 Magnetic Resonance Imaging (MRI) Compatibility

The Evoke System is MR conditional; certain configurations of the Evoke System are compatible with Full Body and Head and knee scans under specific MRI settings and device implant locations.

Only the following device configurations can safely be used when performing an MRI scan. System components should be assessed for proper function prior to the scan.

- One CLS + one or two 60cm CAP12 Percutaneous leads
- One CLS + one or two 90cm CAP12 Percutaneous leads
- One CLS + one or two 60cm Evoke CAP12 Percutaneous leads connected to 55cm Lead Extensions

Where one lead configurations are used, the port plug is installed into the second lead port of the CLS.

The following devices and configurations are not compatible with an MRI scan.

- Any configuration with a CLS + a 90cm CAP12 Percutaneous lead attached to a 55cm Lead Extension is not acceptable for MRI scanning.
- Any configuration with a CLS connected to two leads/ extensions where each lead/ extension is a different length. For example, a 60cm lead and 90cm lead are connected in each port respectively.
- Any configuration with a CLS connected to leads/ extensions where the leads/ extensions are not placed in the same region of the spine. For example, combined prograde/ retrograde placement.
- External components of the Evoke System are not MRI compatible and should not be taken into the scanner suite.
- MRI scans should not be performed on patients currently undergoing a trial stimulation with externalized leads.

Full instructions and parameters for conducting an MRI scan with the Evoke SCS System may be found in the Evoke System MRI Guidelines (D102723). The warnings related to MRI are also listed in section 2.2.1.15.2.2 below.

2.2.1.13 Mode of Action

SCS consists of applying an electrical stimulus to the spinal cord via implanted electrodes in the epidural space which causes the activated fibers (e.g., Aβ-fibers) to generate action potentials. Aβ-fibers are the low-threshold sensory fibers in the dorsal column that contribute to inhibition of pain signals in the dorsal horn. The action potentials summed together form the electrically evoked compound action potential (ECAP). Therefore, ECAPs are a measure of spinal cord fiber activation that generates pain inhibition for an individual.

The Evoke System has the ability to record ECAPs following every stimulation pulse from two electrodes not involved in the stimulation. The recorded ECAP signal is sampled by the stimulator and processed to allow measurement of the ECAP amplitude. Thus, Evoke System ECAP measurement provides confirmation of activation of the intended neural targets.

Physiological functions such as breathing, heartbeat, and changing posture alters the distance between the spinal cord target fibers and epidural SCS electrodes. With fixed-output, open-loop stimulation, the number of nerve fibers activated continually changes resulting in inconsistent therapy delivery as the spinal cord moves in and out of the unchanged electric field.

In addition to open-loop stimulation, equivalent to the mechanism used by other commercially available SCS systems but with the additional feature to measure ECAPs, the Evoke System can use ECAP recordings in a feedback mechanism to deliver ECAP-controlled closed-loop stimulation. The Evoke System uses a proportional-integral-derivative (PID) controller to

minimize the difference between the measured ECAP amplitude and the ECAP amplitude target by automatically adjusting the therapeutic current amplitude in real time for every stimulus (Figure 19). Recording and adjustment occur at the same rate as the stimulation frequency. The Evoke System thereby maintains a consistent neural response at the target level, where the average error between the ECAP amplitude target and the measured ECAP amplitude is zero.

Either the closed- or open-loop stimulation modes may be used to provide optimal treatment for the patient. The stimulator may be programmed with up to four programs, which may be in closed- or open-loop stimulation mode (i.e., the patient may have both closed- and open-loop programs). The stimulation program(s), and thereby the stimulation mode, is determined by the treating clinician together with patient feedback. The patient can toggle between programs and can adjust the stimulation within a program (stimulation amplitude for open-loop programs and ECAP amplitude target for closed-loop programs). However, only the treating clinician may enable or disable the loop in a program.

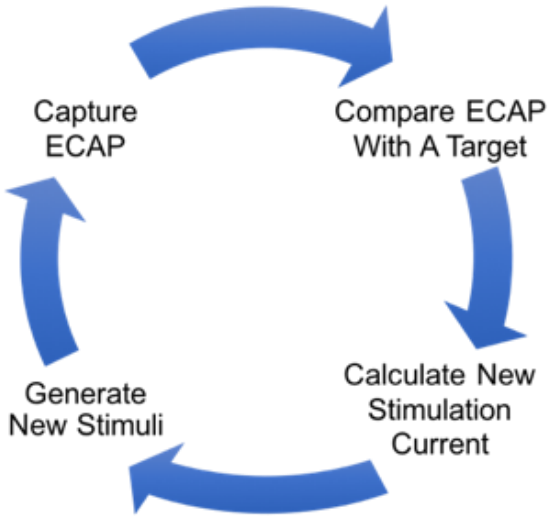

Figure 19. ECAP-Controlled Closed-Loop SCS

2.2.1.14 Intended Purpose

The Saluda Medical Evoke System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs.

2.2.1.15 Instructions for Use

The Evoke System Instructions for Use include the following:

- **Surgical Guide (D102707)** – provides the surgeon instructions on surgical implantation of the device
- **Clarity Clinical Manual (D102709)** – provides the clinician instructions on programming the device, including measurement of ECAPs and application of the feedback mechanism
- **User Manual (D102706)** – provides the patient instructions on how to operate the EPC and Charger
- **Quick Reference Guide (D102710)** – provides the patient abbreviated instructions on how to operate the EPC and Charger
- **MRI Guidelines (D102723)** – provides the patient and technician guidelines on safe use of the Evoke System in the MRI environment
- **RECAP Viewer User Manual (D102722)** – provides instructions for Saluda Medical representatives and clinicians on how to use the CDV to analyse data generated by the device

The contraindications, warnings, and precautions are detailed below in sections 2.2.1.15.1 through 2.2.1.15.3.

2.2.1.15.1 Contraindications

The Evoke SCS System should not be used in patients who:

- Are unable to operate the system.
- Are unsuitable surgical candidates.
- Are unsuitable candidates for SCS.

2.2.1.15.2 Warnings

2.2.1.15.2.1 General Evoke System Warnings

The Evoke System warnings include:

- **Diathermy**
  - Patients implanted with the Evoke System should not be subjected to shortwave, microwave and/or therapeutic ultrasound diathermy.
  - Diathermy generates energy that may cause heating at the lead site, resulting in damage to the CLS, tissue damage, severe injury, or death.

- **Magnetic Resonance Imaging (MRI)**
  The Evoke System is MR Conditional in certain system configurations, under specific scanning parameters. Full details can be found in the Evoke SCS System MRI Guidelines. These instructions should be followed exactly. MRI scanning of an unapproved system configuration could lead to vibration or torque on the device and heating of the implanted system, which may cause internal tissue damage, or permanent damage to the stimulator, which may cause loss of therapy.

- **CT Scans**

- Patients implanted with the Evoke System may experience a momentary increase in stimulation when receiving a CT scan. Some patients have described this as uncomfortable stimulation, jolting, or a shocking sensation.
- Prior to a patient undergoing a CT scan, turn the stimulator off.

- **Electrosurgery**
  - Patients implanted with the Evoke System should not be subjected to electrosurgical techniques, such as electrocautery, in close proximity to the Evoke System components.
    - Electrosurgical devices generate energy that may cause tissue damage at the lead site and result in severe injury.
    - Damage may also occur to the CLS.
  - If the patient is required to undergo electrosurgery, minimize the energy that may affect the Evoke System:
    - Turn off stimulation.
    - Disconnect the eCLS if this is in use.
    - Ensure all fields, electrodes, probes and/or ground plates are as far away as possible from the Evoke System.
    - Use the lowest energy setting needed for the therapy.
    - Check the functioning of the Evoke System after the procedure and contact Saluda Medical if any problems are apparent.
    - Use bipolar mode if available.

- **Interference with implanted cardiac devices**
  - The Evoke System may interfere with other implanted stimulators with sensing capabilities, such as demand type pacemakers or cardioverter defibrillators.
  - The effects of implanted stimulation devices on the Evoke System are unknown.

- **Stimulator damage**
  - If the CLS case is ruptured or pierced, then patient tissue may be exposed to battery chemicals, which could lead to burns or tissue damage.
  - Do not implant the CLS if the case is damaged.

- **Electromagnetic interference**
  - Strong electromagnetic fields may turn the stimulator off, cause uncomfortable or jolting stimulation or affect communication with the EPC.
  - Patients should be advised to avoid or turn stimulation off around:
    - Security screeners, such as those used at department stores, public buildings, and airports – patients should present their implantable device ID card and request to go around the screener. If they are required to go through the screener, they should turn stimulation off.
    - Power lines or power generators.
    - Electric steel furnaces and arc welders.
    - Large, magnetised stereo speakers.
    - Tag deactivators, such as those found in retail stores and libraries.
    - Radio communication transmitters or antennas, such as CB radio antennas.
  - Patients should be advised to seek medical advice before entering any environment that may adversely affect the operation of their stimulator, including

areas protected by a warning notice preventing entry by patients fitted with a pacemaker.

- **Heat due to charging**
  - During charging, the Charger, Charger coil, and/or CLS/eCLS may become hot.
  - Patients should not charge while sleeping, or with the Charger coil wrapped in blankets or clothing for prolonged periods, as this may result in heating leading to redness, skin irritation, or a burn.
  - Patients should ensure there are no metal objects between the Charger coil and the stimulator during charging, as the metal object may heat up and cause redness, skin irritation, or a burn. Additionally, the Charger may not operate correctly.
  - The Charger unit may become hot during use, with a surface temperature reaching 48 °C (118 °F). Patients should be advised not to hold the Charger unit for longer than 10 minutes during use to prevent risk of skin irritation, redness, or injury.
  - If patients experience pain or discomfort, they should cease charging and contact Saluda Medical.

- **Allergic reaction to system components**
  - If the patient may be allergic to system components, they should not be implanted.

- **The Evoke System has not been tested for use in patients who are pregnant or nursing.**

- **The Evoke System has not been tested for use in patients under 18 years old.**

2.2.1.15.2.2 Warnings Related to MRI

The warnings related to MRI are included in the MRI guidelines (D102723) and include:

- Only perform MRI scans on patients who have a system configuration as described in Section 3 ‘MR Conditional System Configurations’ in the MRI Guidelines.
    - Only perform MRI scans on patients who have a system configuration suitable for MR, implanted in the anatomical locations specified in Section 3.3 ‘MR Conditional Implant Locations’ in the MRI Guidelines.
    - Do not perform MRI scans on patients with broken or abandoned implanted components.
    - External components of the Evoke System are MR Unsafe and must not be taken into the scanner suite. The implanted stimulator must be prepared for the MRI scan prior to the patient entering the scanner suite. See Section 5.1.1 ‘Pre-scan preparation’ in the MRI Guidelines.
    - Do not perform MRI scans on patients currently undergoing a trial stimulation with externalised leads or lead extensions.
    - Only perform MRI scans when surgical wounds from the implantation of the system have healed.
    - Do not perform MRI scans on patients who have elevated body temperature or compromised thermoregulation at time of scan.
    - MRI scans can only be performed on patients with additional implanted devices if those devices are classified as MR Safe or MR Conditional
  - If the patient has other MR Conditional implants, all MR Conditional scan parameters for each implant must also be met.

- Only perform a maximum of one (1) examination session on a patient per day.
- Ensure patients are fully awake and continually monitored while in the MRI scanner in case the patient experiences any untoward events, such that the scan can be immediately terminated if necessary.
- Only perform MRI scans in accordance with the instructions detailed in Section 5.2 'MRI Parameters'.
- Head transmit coils must not be used if the percutaneous lead(s) is implanted with the tip(s) at or above the C7 vertebral body.
- Only perform MRI scans, as described in these instructions; no other magnet types have been tested with the Evoke System.
- Only perform MRI scans with a horizontal closed bore MRI system. Do not use MRI systems that are open-sided, vertical-field, or are operating at other static magnetic field strengths. The risks of using these other configurations with the Evoke System have not been determined.
- Imaging with atoms other than hydrogen has not been tested and could result in serious patient injury.
- Only circularly polarised RF transmit fields have been tested with the Evoke System. Do not use elliptically polarised transmit fields because these have not been tested and could result in serious patient injury.
- The presence of implanted material such as the Evoke System may cause some distortion of the images received so should be interpreted by radiology staff with this in mind.

2.2.1.15.2.3 Additional User Warnings

Additional User warnings include:

- **Before any other surgical procedures, notify your clinician or dentist that you have an implanted stimulator.**
  - Some surgical procedures use electrical current that could affect your implanted stimulator and leads. This may cause serious injury to you, and/or may damage your stimulator.
  - Before any procedure, tell your clinician that you have an implanted stimulator. They can then conduct the procedure without using electric current near your implanted stimulator or leads.

- **Cables and small parts**
  - The **cables** in this system pose a strangulation risk. To avoid strangulation, be careful when using **cables.** Keep out of the reach of children.
  - Small parts and accessories could be hazardous if swallowed or cause choking if ingested or inhaled. Keep small parts and accessories out of the reach of children.

2.2.1.15.3 Precautions

2.2.1.15.3.1 General Evoke System Precautions

The Evoke System precautions include:

- **Physician training**

1. Implanting physicians should be trained in SCS procedures.
2. Physicians should review this surgical manual before surgery.

- **Medical imaging**
  - MEG, PET, x-ray/fluoroscopy, and diagnostic ultrasound are unlikely to affect the Evoke System.

- **Medical therapies**

  When used in close proximity to the Evoke System, the following medical therapies may turn stimulation off or cause damage to the CLS:
  - Ultrasonic scanning
  - High-output ultrasound
  - Lithotripsy

  Implanted parts of a system should not be exposed to therapeutic levels of ultrasound energy as the implantable parts can inadvertently concentrate the ultrasound field and cause harm.
  - Electrocautery or electrosurgical diathermy
  - External defibrillation
  - Radiation therapy (any damage to the device by radiation may not be immediately detectable)
  - TENS
  - Psychotherapeutic procedures (e.g., electroconvulsive therapy, transcranial magnetic stimulation)
  - Laser procedures

  If the patient is required to undergo any of these therapies, minimize the energy that may affect the Evoke System:
  - Turn off stimulation.
  - Disconnect the eCLS if this is in use.
  - Ensure all fields, electrodes, probes and/or ground plates are as far away as possible from the Evoke System.
  - Use the lowest energy setting needed for the therapy.
  - Check the functioning of the Evoke System after the procedure and contact Saluda Medical if any problems are apparent.
  - Use bipolar mode if available.

- **Operating equipment**

  The Evoke System is an SCS system that measures the patient's Evoked Compound Action Potentials (ECAP) in response to stimulation and adjusts the amplitude of stimulation in order to maintain stable coverage of painful areas. This is known as ECAP-controlled closed-loop stimulation.
  - If the Evoke System has closed-loop stimulation enabled, patients may leave stimulation on while operating automobiles, other vehicles, or potentially dangerous equipment.
  - During charging closed-loop is disabled, so patients should turn stimulation off if charging while driving or operating equipment.
  - If the patient experiences sudden changes in stimulation with closed-loop enabled, they should turn stimulation off before driving or operating equipment. In this case,

the patient should contact the clinic to reprogram the closed-loop settings of the stimulator.

When operating with closed-loop stimulation disabled, the Evoke System may produce sudden changes in stimulation that may distract patients while driving or operating equipment.

- If the Evoke System has closed-loop disabled, patients should turn stimulation off before operating automobiles, other vehicles, or potentially dangerous equipment.

- **Post-operative patient instructions**

  After implantation of the Evoke System, patients should take care to allow adequate healing and ensure that the leads and CLS do not move.

  - For six to eight weeks after surgery, patients should avoid:
    - lifting more than 5 kg (11 lbs);
    - physical activities requiring stretching, bending or twisting;
    - raising their arms above their head repetitively.
  - Patients may experience temporary pain at the implant site as the incisions heal after the surgery.
  - Patients may experience redness or irritation at the implant site, in which case they should contact their physician to check the wound for infection or adverse reaction to the implanted materials.

- **Stimulator manipulation**
  - Patients should avoid manipulating the Evoke System through the skin. This may cause damage to the system, which could stop therapy, and may require surgery to rectify. Such manipulation of the device could also lead to painful tissue damage or skin erosion.
  - If the CLS is “flipped” over inside the skin pocket, it may no longer be able to be charged.

- **Scuba diving**
  - Patients should always obtain advice from their clinician prior to any diving activities.
  - Patients should not dive below 5 m (16 ft.) or use hyperbaric chambers above 1.5 atm (150 kPa).
  - The CLS may be damaged at greater depths or pressures.

- **Sterilisation, storage, and operation**
  - All surgical and implantable components of the Evoke System are supplied sterile.
  - The sterile components of the Evoke System are sterilised using ethylene oxide.
  - All sterilised components of the Evoke System are single use only, and should not be re-sterilised or reused, because of the risk of cross-contamination, infection, and device malfunction.
  - Please observe and use infection control procedures of the accredited site where procedure is being performed.
  - Please observe the storage conditions printed on the labels of each component – particularly storage and transport temperature and humidity, which varies between components – as inadequate storage could have a negative impact on operation, shelf-life, and sterility.

- Please observe the expiration dates printed on the labels and return any expired product to Saluda Medical because of the risk of infection.
- Do not use surgical or implantable components if the package appears to be damaged or has been previously opened. If the packaging appears to be damaged, please return it to Saluda Medical for replacement.
- Visually inspect the stainless-steel components of the device for evidence of rust prior to use. If any rust (corrosion) is visible, the devices should be discarded.
- All sterile products are packaged in an outer sealed tray or pouch and should be opened with care to maintain sterility of the contents. The sterile contents of the tray or pouch should only be handled inside the sterile surgical field.
- The CLS is packaged in an inner and outer tray. Only the outer tray is the validated sterile barrier and therefore the inner tray should not be placed back into storage once it is taken out of the outer tray.
- Handle system components carefully to protect them from striking hard surfaces or being dropped.
- Do not use system components if they appear damaged, broken or malfunctioning as this may result in electrocution or excess heat generation causing burns or tissue damage.
- Stop using the eCLS if it becomes warm during use.
- Do not get the eCLS wet.
- Patients should be advised to avoid storing or using the Evoke external accessories outside the labelled temperature ranges or in hot or steamy environments, such as bathrooms, and to keep them dry.
- Patients should be advised to refer to the Evoke SCS System User Manual for guidelines for safe use of batteries in the Evoke System.

- **Modifications to System**
  - The components of the Evoke System are not intended to be modified by users or surgeons in any way.
  - Do not modify or tamper with the EPC, the Charger or the eCLS. Modifying or tampering with system components could cause malfunctions, unpredictable device behaviour or failure, leading to harm to the patient.
  - Do not connect anything to the eCLS or Charger that is not supplied as part of the Evoke System. The eCLS should only be connected to the lead adapters and lead adapter cable by the clinician.
  - The Charger should only be connected to the supplied power adapter. Connecting these devices to other, unsupported items could damage them and lead to a loss of therapy.
  - Use of accessories, transducers, and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.
  - Connect only items that have been specified as part of the system or that have been specified as being compatible.

- **Lead Extension**
  - The Lead Extension should only be used as part of a trial system, to connect the lead to the eCLS (via the lead adaptor). It should not be implanted for connection to an implanted CLS.

- Use of the Lead Extension for permanent implant carries a risk of disconnected electrodes, possibly leading to loss of stimulation therapy and requiring device revision.
- For permanent implant do not use a lead extension; select the permanent lead length (60 or 90 cm) appropriate for the patient and intended implant location.

- **Protection of external system components; eCLS, EPC and Charger**

  The electronics in external devices in the Evoke System such as the eCLS, Charger and, EPC, can be damaged by moisture, extreme heat, cold and humidity.
  - Avoid storing the eCLS at temperatures below -10°C (14 °F) or above 55 °C (131 °F).
  - Avoid storing the EPC and Charger at temperatures below -20 °C (-4 °F) or above 60 °C (140 °F).
  - Only use the eCLS and EPC at room temperatures of 5 °C (41 °F) to 40 °C (104 °F).
  - Only use the Charger at room temperatures of 5 °C (41 °F) to 30 °C (86 °F). Do not use the Charger if the room temperature is above 30 °C (86 °F).
  - External system components should be kept dry and never be immersed in water.
  - Handle external system components carefully to protect them from striking hard surfaces or being dropped.
  - The Charger should not be plugged into outlets that are in humid environments or near water.
  - The Serial connection  on the Charger is for Saluda Medical representative use only. This connection is protected by a silicone plug. Ensure the plug is fully inserted at all times.
  - Instruct patients not to leave devices in their car or outdoors for extended periods of time.
  - Instruct patients not to store devices in humid environments, such as the bathroom.
  - Instruct patients to allow devices to reach room temperature for 30 minutes before use if they have been stored in cold or warm conditions.
  - Instruct patients to ensure they can always access their EPC and to keep a spare set of AAA batteries at home for the EPC.
  - Instruct patients to plug in the power adapter for the Charger somewhere easy to access.
  - If any external system components require cleaning, refer to Section 15 ‘Maintenance of the Evoke eCLS, EPC, and Charger’.

- **Battery Care**

  The EPC is powered by two disposable AAA alkaline batteries. Observe the following guidelines for safe use of batteries with your EPC:
  - Insert batteries in the correct orientation by observing the plus (+) and minus (-) marks on the batteries and the EPC.
  - Do not mix batteries that differ by manufacturer, brand, type, age, or previous usage.
  - Replace both batteries at the same time.
  - Do not touch the battery contacts in the EPC.
  - Do not short-circuit batteries (e.g., do not let terminals of batteries contact each other, do not store batteries loosely).
  - Do not disassemble, deform, immerse in water, or dispose of batteries in fire.
  - Wipe batteries with a clean dry cloth if they become dirty.

- Store unused batteries in original packaging, in a clean and dry place.
- Do not use damaged or deformed batteries. If skin or eyes come into contact with battery fluid or liquid, wash out with water and seek medical attention immediately.
- Do not expose batteries to heat.
- Do not recharge batteries.
- Dispose of used batteries promptly and carefully, in accordance with local regulations. Keep away from children.

The Charger is powered by internal rechargeable lithium ion batteries that cannot be replaced:

- Only the power adapter supplied by Saluda Medical should be used to recharge the Charger.
- The power adapter socket on the Charger should not be touched.
- The Charger power adapter should be unplugged from the charger after recharging is complete.

- **Device malfunction or failure**

  Therapy should be discontinued immediately in the event of malfunction or failure of any component of the Evoke system.
  - Malfunction or failure may be indicated by excessive device heating, emission of smoke or strange smell, or abnormal device behaviour.
  - Continued use of system components after malfunction or failure may cause electrocution, burns, tissue damage or uncomfortable stimulation for the patient.
  - Please contact Saluda Medical in the event of any device malfunction or failure.

- **Disposal of Evoke System Components**
  - Do not dispose of the CLS, eCLS, EPC or Charger devices. These devices contain batteries that could explode if they are thrown into a fire.
  - All explanted, malfunctioning or failed Evoke devices should be returned to Saluda Medical.

2.2.1.15.3.2 Precautions Related to Evoke Clinical Interface (CI) and Clinical Systems Transceiver

The precautions related to the Evoke CI and CST include:

- **Unsupported software applications**
  - Do not load additional software applications onto the Evoke CI. The Evoke CI has all the necessary software required to interact with and program the Evoke SCS System from Saluda Medical. Other applications could interfere in unpredictable ways with the programming software installed and affect the delivery of therapy for patients. Any required software installations shall be supported directly by Saluda Medical representatives or via detailed instructions concerning specific installations as required.

- **Unsupported hardware**
  - Do not connect any device to the Evoke CI other than the supplied**:** keyboard, power adapter and Evoke CST. Do not connect the Evoke CST to any device other than a Saluda Medical supplied Evoke CI. Unsupported hardware

could interfere in unpredictable ways with the programming software installed and affect the delivery of therapy for patients. Do not modify, tamper, or use other equipment with the Evoke SCS System.

- For data file extraction, it is permissible to use an external USB memory stick that has passed a screening check by an up-to-date anti-virus software application, but no files should be transferred onto the CI unless otherwise instructed by Saluda Medical to do so.
- Use of accessories, transducers, and cables other than those specified or provided by the manufacturer of this equipment could result in increased electromagnetic emissions or decreased electromagnetic immunity of this equipment and result in improper operation.
- Connect only items that have been specified as part of the system or that have been specified as being compatible.

- **Shared IT networks**
  - Network connection (via Wi-Fi) is only permitted to secure networks. Connecting to unsecure networks could lead to the modification of the CI system or software that interfere in unpredictable ways with the programming software installed and affect the delivery of therapy for patients.

- **Modification of the programming software**
  - Do not attempt to modify the CPA software which comes preinstalled on the CI for the programming of Saluda Medical neurostimulators. Any deletion or modification of files associated with the CPA could adversely affect the system's ability to effectively adjust therapy for patients.
  - Required software upgrades will be supported directly by Saluda Medical representatives or via detailed instructions concerning specific upgrades as required. Additionally, any stimulator software upgrades will be fully supported by Saluda Medical representatives – do not attempt to modify the stimulator software without Saluda Medical's instruction.

- **Non-sterile components**
  - Do not sterilise the CI, CST, SMEA, eCLS, EPC or Charger; these items are not to be sterilised and doing so could irrevocably damage the devices.

- **Clinical staff training**
  - Clinical staff using the CI/CST to program the Evoke SCS System must be adequately trained in the programming of SCS systems generally. Additionally, clinical staff programming the Evoke SCS System should have been trained based on the instructions within this manual. A poor understanding of the programming of SCS systems generally, and the Evoke system specifically, could cause unpleasant or painful stimuli for patients.

- **Electromagnetic interference (EMI)**
  - As the CI communicates via the CST to the neurostimulator (eCLS or CLS) wirelessly, the quality of this connection can be adversely affected by some types of electrical equipment that generate EMI. Such equipment should be avoided where possible when programming and/or suspected if communication between stimulator and CI/CST is poor. Examples of such equipment found in clinical environments include but are not limited to: Mobile phones, electro-surgery tools,

electromagnets, radiofrequency identification devices and emergency vehicle/services radios. Avoid use of the CI and CST adjacent to or stacked with other equipment, because it could result in improper operation. If such use is necessary, observe the CI, CST, and the other equipment to verify that they are operating normally. Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should not be used closer than 30 cm to any part of the Evoke System, including cables specified by the manufacturer. Otherwise, degradation of the performance of this equipment could result.

- **General precautions for the CI and CST**
  - The CI is a critical piece of equipment to enable the delivery of therapy. Always handle it with care and regularly inspect the device for damage and/or impaired functioning. Never modify the CI in any way. If you have concerns about the integrity of the CI/CST, contact Saluda Medical representatives to arrange repair or replacement. The CI runs on a rechargeable battery and can be used wirelessly or while plugged in via the power adapter supplied. Care should be taken to keep the CI well charged so it can be used in clinical environments where plug sockets are not readily available. Always have a spare charged CI available in case of malfunction. Do not use the CST at the patient's home.

2.2.1.15.3.3 Additional User Precautions

Additional User precautions include:

- **If you suspect part of your system is not working properly.**
  - If you are having problems with your system, first consult Section 11 'Troubleshooting' in the User Manual D102706. If this does not help or you have more questions, please contact your clinician.

- **Storing your magnet when not in use.**
  - Store magnet with the keeper (small metal bar) in place.
  - Keep the magnet away from heat sources.
  - Keep the magnet away from strong magnetic fields (e.g., other magnets).
  - Handle the magnet carefully to protect it from striking hard surfaces or being dropped.

- **Avoid prolonged contact of the external parts on your skin**
  - External parts are the lead adapter, lead adapter cable, lead adapter extension, eCLS, EPC, and Charger with Charger coil.
  - Place clothing or dressings between your skin and these external parts.

2.2.1.16 Administration and/or Removal of a Medicinal Product

The Evoke System is not intended to administer and/or remove medicinal product.

2.2.1.17 Companion Diagnostic

The Evoke System is not intended to act as a companion diagnostic.

2.2.1.18 Emission of Hazardous, or Potentially Hazardous, Levels of Ionising and/or Nonionizing Radiation

The Evoke System is not intended to emit hazardous, or potentially hazardous, levels of ionising and/or non-ionising radiation.

2.2.1.19 Operation together with Other Devices or Products

The Evoke System is not intended to be operated together with other devices or products.

2.2.1.20 Surgical Procedures, Services and Organisational Aspects, Suggested Profile and Training for Users

The intended users of the Evoke System include implanting physicians/surgeons, clinicians, MRI clinicians, patients, and Saluda Medical Representatives. The implanting physicians/surgeons are primarily users of the closed loop stimulators and accessories, leads and accessories, and surgical tools for which the Evoke System Surgical Guide (D102707) provides instruction. The clinicians/clinical users (including Saluda Medical representatives) are primarily users of the programming system for which the Evoke System Clarity Clinical Manual (D102709) and RECAP Viewer User Manual (D102722) provide instruction. Patients are primarily users of the external accessories for which the Evoke System User Manual (D102706) and Evoke System Quick Reference Guide (D102710) provides instruction. The Evoke System MRI guidelines (D102723) provide the patient and MRI Clinician guidelines on safe use of the Evoke System in the MRI environment.

The implantation procedure for the Evoke System is the same as that for other SCS systems; as such, minimal additional training is required for experienced physicians. Implanting physicians should be trained in SCS procedures. Physicians should review the Evoke System Surgical Guide before surgery. Clinical staff using the CI/CST to program the Evoke System must be adequately trained in programming SCS systems generally and the Evoke System specifically. Additionally, clinical users programming the device should thoroughly review the Evoke System Clinical Manual prior to working with the system in patients. Patient operated devices are designed to be simple and intuitive; however, clinicians should spend time with patients to explain the functioning of their devices and go through the Evoke System User

Manual with them. Clinicians performing an MRI scan should be trained in MRI scanning procedures. Additionally, MRI clinicians should review the Evoke MRI Guidelines before performing an MRI scan. Saluda Medical will provide experienced, field-based experts to support implanting physicians/surgeons, clinicians/clinical users, and patients with the implementation of the therapy.

2.2.2 Requirements / Instructions for Use

There are no additional requirements or supplies required to use the Evoke System.

2.2.3 Regulatory Status of the Technology

Device Classification	**Classification:**	Class III
	Rule (MDR):	Rule 8 *Under Rule 8, all active implantable devices and their accessories are Class III. Thus, all models included in the system are considered Class III.
Notified Body	**Name:**	BSI Group The Netherlands B.V.
	Address:	Say Building John M. Keynesplein 9 1066 EP Amsterdam The Netherlands
	Single Identification Number:	NB 2797
CE Marking (AIMDD; the MDR submission is currently under review – BSI expects to complete the review of the MDR application by the end of the year (December 2023).)	**Date of CE Marking:**	June 17, 2019
	Expiry Date of Current Certificate:	May 26, 2024
	Date of Expert Panel Opinion:	N/A
	Indication:	The Saluda Medical Evoke System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs.
	Contraindications:	The Evoke SCS System should not be used in patients who: • Are unable to operate the system. • Are unsuitable surgical candidates. • Are unsuitable candidates for SCS.

2.3 Joint Scientific Consultation related to the Joint Clinical Assessment

There have been no European joint scientific consultations for the Evoke System.

3 Research Question and Assessment Scope

Table 5. EUnetHTA 21 consolidated PICOs requested

	PICO 1	PICO 2	PICO 3
Population*	According to the intended use: adult patients with chronic intractable pain of the trunk and/or limbs	Subpopulation: adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome, with insufficient effect from conventional pain management therapies	The same as for PICO 2
Intervention**	According to the intended use	The same as for PICO 1	The same as for PICO 1
Comparator	Latest generation of open-loop SCS systems (in addition to other pain management therapies)	The same as for PICO 1	Conventional non-surgical pain management therapies (including pharmacotherapy with or without physiotherapy and/or psychotherapy, etc.)***
Outcomes	**Time horizon for all outcomes:** preferably 24 months minimum with an annual evaluation Global pain measured preferably by Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) Responder rate measured by global pain relief ≥ 50% vs baseline at 6 months minimum Healthcare consumption including pain medication consumption, other non-surgical pain management therapies and number of outpatient visits Health-related quality of life (HrQoL): - Generic HrQoL preferably measured by SF-12 or 36 - Disease- or population specific HRQoL (e.g. neuropathic pain impact on QoL measured by NePIQoL) - Health status preferably measured by EQ-5D Functioning: - Functional disability measured by the Oswestry Disability Index (ODI) - Ability to perform activities of daily living - Exercise tolerance - Ability to return to work (or studies) - Sleep quality - Body function Patient satisfaction with treatment measured as Global Perceived Effect (GPE) Treatment discontinuation due to adverse events Sick leaves (number and duration) All-cause mortality Safety, including a description of each adverse event included in the following categories: - Any adverse events related to the procedure and to the medical device including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision, removal or replacement of the impanted components - Serious adverse events		
	*The type and anteriority of pain should be described in the "patient baseline characteristics" section of the submission dossier presenting the included studies. **Data on the conditions of use of the closed- and open-loop modes must be provided in the sections "Characterisation of the health technology" and "Results" of the submission dossier. ***Placebo (sham-controlled) studies shall be included under this PICO.		

Table 6. PICOs addressed in the HTD submission dossier

	EUnetHTA 21 consolidated PICOs	PICOs addressed in the HTD submission dossier	Rationale if different from the EUnetHTA 21 consolidated PICOs
Population	**PICO 1** According to the intended use: adult patients with chronic intractable pain of the trunk and/or limbs **PICO 2** Subpopulation: adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome, with insufficient effect from conventional pain management therapies **PICO 3** The same as for PICO 2	**PICO 1** According to the intended use: adult patients with chronic intractable pain of the trunk and/or limbs	**PICO 1** NA **PICO 2** The subpopulation specified by EUnetHTA 21 is the same population as in PICO 1 (i.e., includes PSPS). Further details in section 3.1.2. **PICO 3** The same as for PICO 2
Intervention	According to the intended use	Evoke closed-loop SCS	NA
Comparator	**PICO 1** Latest generation of open-loop SCS systems (in addition to other pain management therapies) **PICO 2** The same as for PICO 1 **PICO 3** Conventional non-surgical pain management therapies (including pharmacotherapy with or without physiotherapy and/or psychotherapy, etc.). Placebo (sham-controlled) studies shall be included under this PICO.	**PICO 1** Evoke open-loop SCS	**PICO 1** Evoke open-loop SCS was the comparator in the Evoke RCT. Even when operating as open-loop, the system provides an enhancement when compared to other commercially available open-loop systems because it uses ECAP measurements for programming of stimulation parameters. **PICO 2** The same as for PICO 1 **PICO 3** Placebo (sham-controlled) studies are not eligible for inclusion considering the

	EUnetHTA 21 consolidated PICOs	PICOs addressed in the HTD submission dossier	Rationale if different from the EUnetHTA 21 consolidated PICOs
			follow-up required for outcomes of interest. Further detail in section 3.1.3.
Outcomes	Time horizon for all outcomes: preferably 24 months minimum with an annual evaluation Global pain measured preferably by Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) Responder rate measured by global pain relief ≥50% vs baseline at 6 months minimum Healthcare consumption including pain medication consumption, other non-surgical pain management therapies and number of outpatient visits Health-related quality of life (HRQoL): - Generic HRQoL preferably measured by SF-12 or 36 - Disease- or population specific HRQoL (e.g. neuropathic pain impact on QoL measured by NePIQoL) - Health status preferably measured by EQ-5D Functioning: - Functional disability measured by the Oswestry Disability Index (ODI) - Ability to perform activities of daily living - Exercise tolerance - Ability to return to work (or studies) - Sleep quality - Body function Patient satisfaction with treatment measured as Global Perceived Effect (GPE) Treatment discontinuation due to adverse events	24 months minimum with an annual evaluation Global pain measured by VAS Responder rate measured by global pain relief ≥50% **and ≥80%** vs baseline at 6 months minimum Healthcare consumption – **opioid use** HRQoL: - Generic HRQoL measured by SF-12 - Health status measured by EQ-5D Functioning: - Functional disability measured by the ODI - Sleep quality (PSQI) **- Emotional function (POMS)** Patient satisfaction with treatment **Patient Global Impression of Change** Treatment discontinuation due to adverse events All-cause mortality Safety, including a description of each adverse event included in the following categories: - Any adverse events related to the procedure and to the medical device including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision, removal or	Outcomes not reported within this dossier were not collected in the studies available to date. Emotional function (POMS), Patient Global Impression of Change, and Neurophysiological data are also provided in addition to the outcomes requested by EUnetHTA 21.

	EUnetHTA 21 consolidated PICOs	PICOs addressed in the HTD submission dossier	Rationale if different from the EUnetHTA 21 consolidated PICOs
	Sick leaves (number and duration) All-cause mortality Safety, including a description of each adverse event included in the following categories: - Any adverse events related to the procedure and to the medical device including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision, removal or replacement of the implanted components - Serious adverse events	replacement of the implanted components - Serious adverse events **Neurophysiological data** **- Device utilisation** **- Mode ECAP** **- Percent time in therapeutic window** **- Neural accuracy** **- Conduction velocity**	

3.1 Research Question considerations

3.1.1 PICO 1

Direct evidence to address PICO 1 comes from the Evoke study (24,25). The Evoke study is to date, the only evaluation of SCS in a double-blind, parallel-arm randomised controlled trial (RCT). All other parallel-arm RCTs of SCS are open-label which introduces bias. An additional single-arm study (Avalon) that evaluated the safety and performance of Evoke CL-SCS has been included in this Submission Dossier (26,27). All outcomes collected in the Evoke and Avalon studies were reported including outcomes not stated in the consolidated PICO such as emotional function, patient global impression of change and neurophysiological data.

The comparator in the Evoke study can be considered to already represent latest generation of open-loop SCS systems. ECAP-guided programming provides an enhancement to other available open-loop SCS systems. As detailed in section 2.1.3, all other approved SCS therapies other than the Evoke System (e.g., low frequency, high frequency, high density, and burst), regardless of whether stimulation induces paraesthesia, are open-loop in that they produce fixed-output stimuli. This also makes indirect comparisons challenging because recent RCT evidence in SCS has compared new stimulation paradigms (e.g., high-frequency, burst) with low-frequency stimulation but all these stimulation types are fixed-output, open-loop SCS.

Long-term evaluations should be performed when assessing the effects of treatment options for chronic pain. In this submission dossier, we present results of the Evoke and Avalon studies through 24-month follow-up. Results from RCTs of OL-SCS through this time point are presented in Appendix A.

3.1.2 PICO 2

Persistent spinal pain syndrome (PSPS) is a recent definition that includes both Type 1 and Type 2 (28,29). Both subtypes are included in the cohort of the Evoke and Avalon studies and refers to the same population as in PICO 1.

3.1.3 PICO 3

Historical RCTs of SCS have compared SCS to conventional medical management (CMM; first- and second-line treatments detailed in section 2.1.3), which was the standard of care at the time of the studies. Chronic pain patients are considered for SCS if their pain is refractory

to CMM. Once superiority of SCS was observed versus CMM and SCS approvals were obtained for an indication (e.g., PSPS-T2, previously referred to as failed back surgery syndrome [FBSS]), the new standard of care became the SCS available at the time of approval. Trials of new stimulation paradigms have therefore used open-loop / fixed-output, low-frequency SCS as the comparator arm. As such, a comparison of SCS with CMM for this patient population is not useful to inform decision-making.

To date, only crossover RCTs have compared SCS to placebo (sham) in a population with PSPS. These studies have very limited value to inform decision making as all the studies to date have major methodological limitations (30). Furthermore, for ethical reasons, the overall study duration for most of these studies is limited to 3-months. The only exception is the study by Hara et al. which had a study duration of 12-months but crossover phases with active or sham stimulation were limited to two phases of 3-months each (31). Therefore, a maximum of six-months follow-up with active or sham stimulation were reported. Several methodological limitations have also been observed in the recent study by Hara et al. and detailed in several editorials and letters (32–35). Considering the time horizon for all outcomes in the consolidated PICO was specified as “preferably 24 months minimum with an annual evaluation”, no comparisons of SCS with placebo (sham) would be eligible for inclusion in this dossier.

4 Methods Used in the Development of the Dossier Content

4.1 Criteria for Identifying Studies for Joint Clinical Assessment

The systematic review used replicable methodology based on best practice guidance and informed by regulatory agencies' requirements. The key strategy of the literature review is to provide information that is:

1. Comprehensive; that is, representing all available publications.
2. Precise; that is, accurately reflecting the knowledge base without extraneous details.
3. Based on transparent, reproducible, standardised methods.
4. Living, flexible, and replicable; that is, the aggregate coded reference list forms a data repository that can be readily updated with new titles over time, allowing for resubmissions or re-analyses with consistency over time, at minimal rework.

Literature searches were conducted using the following databases:

1. PubMed, an extensive online database that comprises more than 34 million citations for biomedical literature from MEDLINE, life science journals, and online books.
2. EMBASE, a database specific to biomedical research which includes 2,900 more journals than MEDLINE, in addition to conference coverage. More than half of the journals included in EMBASE are published in Europe.
3. Google Scholar, a freely accessible web search engine that uses the ubiquitous Google algorithms to search across scholarly literature by keywords.

Combining the results of multiple database searches[1] ensures confidence in a comprehensive reflection of all available literature. Duplicate titles were stripped.

Databases were searched according to the query strings and filters as described below in Table 7 and Table 8. Query 'hits' were combined into a single spreadsheet and duplicates were stripped. The queried dates of publication were from January 1, 2017, through June 2022 and updated on March 2, 2023. The searches were supplemented by screening of reference lists of eligible studies.

Table 7. Database Queries

PubMed	(evoked compound action potential OR ECAP) AND spinal • Filter 1: English language • Filter 2: 2017 and later

[1] In preparing this work, we considered using the Cochrane Central Register of Controlled Trials (CENTRAL). However, we ultimately decided against using it because empirical assessment showed that it resulted in titles that duplicated the output of the other databases, without adding unique information. Furthermore, because a large proportion of the SCS literature does not use controlled designs, this is likely to be of limited utility.

EMBASE	(evoked compound action potential OR ECAP) AND spinal • Filter 1: English language • Filter 2: 2017 and later
Google Scholar	(evoked compound action potential OR ECAP) AND spinal • Filter 1: uncheck 'include patents' and 'include citations" • Filter 2: select 'Since 2017' For practicability, the first three pages 'sorted by relevance' and the first three pages 'sorted by date' were included.

Table 8. Clinical trial databases queries

Resource	Search string
https://clinicaltrials.gov	(evoked compound action potential OR ECAP) AND spinal
https://www.isrctn.com/	(evoked compound action potential OR ECAP) AND spinal
http://www.anzctr.org.au/TrialSearch.aspx	(evoked compound action potential OR ECAP) AND spinal
https://apps.who.int/trialsearch/ https://trialsearch.who.int/Default.aspx ICTRP search portal (who.int)	(evoked compound action potential OR ECAP) AND spinal

4.2 Selection of Relevant Studies and Information Retrieval

The identified titles were categorised based on inclusion/exclusion criteria (Table 9). Titles were sequentially considered by database meta-data (the most superficial appraisal), titles, abstracts, and finally full text (the most in-depth appraisal). If multiple reports exist on the same cohort of patients, this was noted, and the sample size was counted only once for summary purposes. The inclusion/exclusion criteria are intentionally broad to 'cast a wide net' in the searches.

The primary contributor to this literature review, a PhD-level medical writing consultant independent to the sponsor reviewed articles and full-text articles against the eligibility criteria. Clinical/Regulatory staff members employed by the Sponsor reviewed and confirmed search methods and acted as a second reviewer for study selection process. Any disagreements were resolved by consensus.

Table 9. Inclusion and Exclusion Criteria

Inclusion criteria	• Adult subjects. • Indication is chronic pain of the trunk or limbs. • Treatment is SCS (of any waveform), dorsal column or dorsal root ganglion stimulation, or similar intervention. • Device used is the Evoke SCS system. • Device is implanted at the C2 spinal level or lower.

Exclusion criteria	• Non-English. • Non-clinical (animal, computer, etc.). • Review. • Conference proceeding.

The following information, if available, was abstracted from the included articles:

- Study design
- Follow-up time points
- Objectives
- Eligibility criteria
- Sample size (defined, unless otherwise specified, as the number of subjects with permanent SCS implants. This is to give consistency of reporting across studies, as authors may define sample size in numerous ways [e.g., number enrolled, number trialled, number randomised, number at last follow-up.])
- Subject demographics
- Device (specific model, etc.) and stimulation
- Location of pain being treated (e.g., legs, arms, back)
- Mean pain relief
- Proportion of responders (≥50% pain reduction relative to baseline)
- Patient reported outcomes (PROs); e.g., questionnaires for satisfaction, quality of life, or function (especially those that the sponsor uses consistently, such as EQ-5D, Oswestry Disability Index [ODI], and others)
- Medication usage
- Rate of adverse events (AEs)
- Technical information summaries

Favourable and unfavourable data alike were included. Data extraction was performed by the independent consultant and verified by one reviewer for accuracy, using consensus for disagreements.

4.3 Appraisal of Selected Studies

Each article that met all inclusion criteria and no exclusion criteria was appraised as described below. Articles were eligible for inclusion in the literature review regardless of appraisal level.

1. Appraisal according to the Oxford Centre for Evidence-Based Medicine (36):
   - Level I: Systematic review.
   - Level II: Randomised trial.
   - Level III: Cohort study or poor-quality RCT.
   - Level IV: Case series or poor-quality cohort study.
   - Level V: Mechanism-based reasoning.

2. Appraisal according to Appendix F of International Medical Device Regulators Forum (IMDRF) Medical Device Clinical Evaluation Working Group (MDCE

WG)/N56FINAL:2019 Clinical Evaluation guidance document (37), reproduced in Table 10 and Table 11 below.

According to this rating system, articles with good suitability (and hence, strong impact on the interpretation of the results) are rated '1', moderate suitability are rated '2', and limited suitability are rated '3' (see Table 10). Similarly, articles that make good data contributions to the results are rated '1' and those that make limited contributions are rated '2' (see Table 11).

Risk of bias (RoB) of included RCTs was assessed by using the revised Cochrane RoB tool (RoB 2.0) (38).

Table 10. IMDRF MDCE WG/N56FINAL:2019 Appraisal Criteria for Suitability

Suitability Criteria	Description	Code	Score	Definition
Appropriate device	Were the data generated from the device in question?	D	1	Actual device
			2	Equivalent / similar device
			3	Other device
Appropriate device application	Was the device used for the same intended use (e.g., methods of deployment, application, etc.)?	A	1	Same use
			2	Minor deviation
			3	Major deviation
Appropriate patient selection	Were the data generated from a patient group that is representative of the intended treatment population (e.g., age, sex, etc.) and clinical condition (i.e., disease, including state and severity)?	P	1	Applicable
			2	Limited
			3	Different population
Acceptable report / data collation	Do the reports or collations of data contain sufficient information to be able to undertake a rational and objective assessment?	R	1	High quality
			2	Minor deficiencies
			3	Insufficient information

Table 11. IMDRF MDCE WG/N56FINAL:2019 Appraisal Criteria for Data Contribution

Data Contribution Criteria	Description	Code	Score	Definition
Data source type	Was the design of the study appropriate?	T	1	Yes
			2	No
Outcome measures	Do the outcome measures reported reflect the intended performance of the device?	O	1	Yes
			2	No
Follow up	Is the duration of follow-up long enough to assess whether duration of treatment effects and identify complications?	F	1	Yes
			2	No

Data Contribution Criteria	Description	Code	Score	Definition
Statistical significance	Has a statistical analysis of the data been provided and is it appropriate?	S	1	Yes
			2	No
Clinical significance	Was the magnitude of the treatment effect observed clinically significant?	C	1	Yes
			2	No

4.4 Data Analysis and Synthesis

In the following sections, we present text and tabular evidence in each of the following categories:

- Summary and characteristics of included articles (e.g., design, patient characteristics, sample size, intervention, pain location, outcome measures used).
- Summary of pain relief and percentage of responders.
- Summary of patient-reported outcomes (e.g., disability, quality of life).
- Summary of complications and AEs, including the rates (range) of each AE type.

Unless otherwise noted, data are presented as means, standard deviations, percentages, or percentage change. Totals may not sum to 100% due to rounding.

5 Results

5.1 Results from the Information Retrieval Process

The searches resulted in 15,220 records identified. After removal of duplicate titles, 11,364 records were screened. Using titles and/or abstracts, 11,139 were excluded based on the inclusion/exclusion criteria. Full text versions of the remaining 225 articles were reviewed. Of these, 217 were excluded based on the inclusion/exclusion criteria.

A total of 8 articles were included in this systematic review, representing 2 studies and 175 subjects with permanent implants (Figure 20) (39,40).

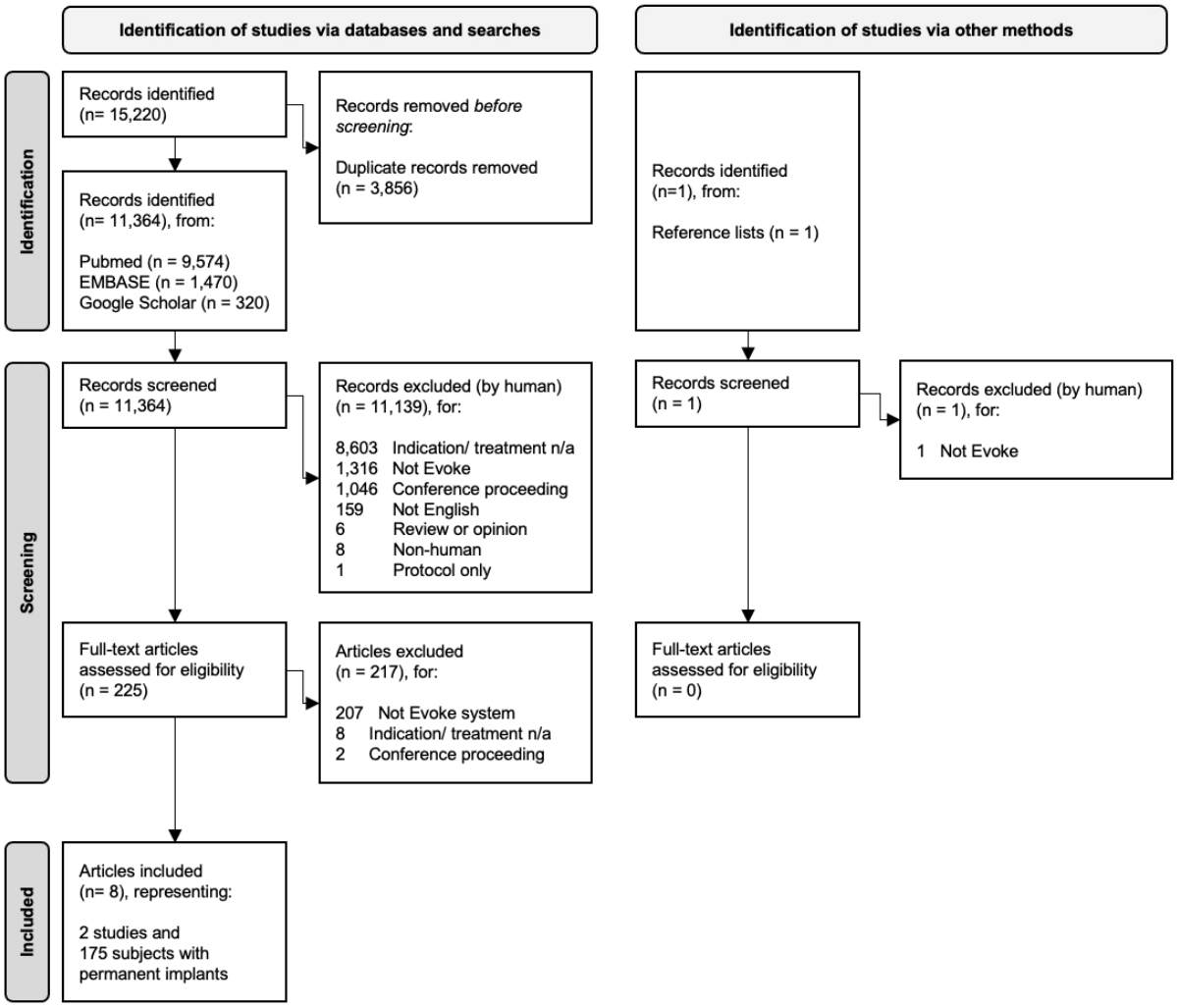

Figure 20. Article Selection Flowchart

5.2 Characteristics of the Studies Included

The 8 articles represented 2 studies. Because the studies had multiple articles due to repeated follow-ups over time or sub-set analyses, data abstraction and summary was approached on a per-study basis instead of a per-article basis to provide the most-detailed information and to count each subject only once.

The 2 studies included:

- One RCT using the Evoke System (Evoke study sponsored by Saluda Medical). This study had long-duration follow-up (24 months) and 125 subjects. There were 5 articles regarding this study.
- One prospective cohort study using the Evoke System (Avalon study sponsored by Saluda Medical). This study had long-duration follow-up (24 months) and 50 subjects. There were 3 articles regarding this study.

All studies enrolled subjects with pain in the back and/or legs. All studies used ECAP-guided closed-loop SCS; the RCT also used open-loop SCS as a control.

The RCT and prospective cohort studies reported pain, patient-reported outcomes, and adverse event outcomes (Table 12.).

Table 12. Study characteristics

Study	First author and year	Study acronym/ identifier	Abstracted for			Design	N	Stimulation type
			Pain	PROs	Safety			
•	Mekhail 2020 (24) Mekhail 2022 (25) Duarte 2021 (41) Taylor 2022 (42) Costandi 2022 (43)	Evoke (Evoke System)	X	X	X	RCT	125*	Closed-loop, open-loop LF
•	Russo 2018 (22) Russo 2020 (26) Brooker 2021 (27)	AVALON (Evoke System)	X	X	X	Cohort	50*	Closed-loop
2 studies	**8 articles**	**-**	**2 studies N=175**	**2 studies N=175**	**2 studies N=175**	**1 RCT 1 cohort study**	**N= 175**	**2 Closed-loop 1 LF (control)**

* Subjects had permanently implanted devices

The Evoke study was a prospective, multicentre, participant, investigator, and outcome assessor-blind parallel arm RCT conducted at 13 investigation sites throughout the United States under an Investigational Device Exemption to gain US Food and Drug Administration (FDA) approval (NCT02924129). The RCT compared CL-SCS to OL-SCS for the treatment of patients with chronic, intractable pain of the trunk and/or limbs. This study design was

developed to be generalisable, preserve objectivity and minimise bias. The study design and sample size calculation for the Evoke study was reviewed and approved by FDA to test non-inferiority and superiority of Evoke closed-loop SCS compared to open-loop SCS, equivalent to the mechanism used by other commercially available SCS systems but with the additional feature to measure ECAPs and inform programming of stimulation parameters based on ECAP measurement. Additionally, objective neurophysiological data was collected in both treatment groups providing a basis for interpretation of the treatment effect.

The Avalon study was a prospective, multicentre, single-arm study conducted in 5 centres in Australia (ACTRN12615000713594) designed to evaluate the safety and performance of Evoke closed-loop SCS for the treatment of chronic, intractable pain of the trunk and/or limbs.

Data through 24-month follow-up is available for both Evoke and Avalon studies.

5.3 Appraisal of Selected Studies

Each included article was assessed according to the Oxford Centre for Evidence-Based Medicine (36). The RCT contributed Level II evidence and the prospective cohort study contributed Level III evidence (Table 13). Because of the broad inclusion/exclusion criteria, no articles were excluded from the literature review on the basis of this appraisal.

Table 13. Levels of Evidence

	Level I: Systematic review	Level II: Randomised trial	Level III: Cohort study or poor-quality RCT	Level IV: Case series or poor-quality cohort study	Level V: Mechanism-based reasoning
RCT	0	1	0	0	0
Cohort study	0	0	1	0	0
All	**0**	**1**	**1**	**0**	**0**

Study appraisal according to Appendix F of the IMDRF MDCE WG/N56FINAL:2019 Clinical Evaluation guidance document (37) revealed that the RCT and the prospective cohort study used the actual device (Evoke SCS System), and both studies were rated ‘1’ on all appraisal domains (Table 14). Because of the broad inclusion/exclusion criteria, no articles were excluded from the literature review based on this appraisal.

Table 14. IMDRF MDCE WG/N56FINAL:2019 Appraisal

Suitability and Data Contribution Criteria	Code	Appraisal Rating		
		1	2	3
Appropriate device	D	2 (100%) Actual device	0 (0%) Similar device	0 (0%) Other device
Appropriate device application	A	2 (100%) Same use	0 (0%) Minor deviation	0 (0%) Major deviation
Appropriate patient selection	P	2 (100%) Applicable	0 (0%) Limited	0 (0%) Different population
Acceptable report / data collation	R	2 (100%) High quality	0 (0%) Minor deficiencies	0 (0%) Insufficient information
Study design	T	2 (100%) Yes	0 (0%) No	-
Outcome measures	O	2 (100%) Yes	0 (0%) No	-
Follow-up	F	2 (100%) Yes	0 (0%) No	-
Statistical analysis	S	2 (100%) Yes	0 (0%) No	-
Clinically significant treatment effect	C	2 (100%) Yes	0 (0%) No	-

The summary of the RoB assessment is presented in Table 15. The bias was judged as low for all domains in the included RCT. Patients were randomly assigned in a 1:1 ratio to receive ECAP-controlled CL-SCS or OL-SCS and there were no between-group differences in diagnoses, previous treatment or other baseline demographics or characteristics. Masking was maintained for the full study duration and no patients or investigators were made aware of the treatment assignments in either group. The primary analysis was conducted following the intention to treat principle. A published study protocol was available,(44) and analysis followed a prespecified statistical analysis plan. The overall bias was therefore considered to be low.

Table 15. Risk of bias assessment

Author (year)	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Mekhail 2020 (24)	Low	Low	Low	Low	Low	Low

5.4 Study Results on Relative Effectiveness and Relative Safety

5.4.1 Results for the Patient Population (PICO 1)

5.4.1.1 Patient Characteristics

5.4.1.1.1 Evoke Study

The Evoke study randomised 134 subjects across 13 investigation sites in the United States between 27 January 2017 to 16 January 2018. No one site enrolled more than 18% of study subjects (the Statistical Analysis Plan permitted any one site to enrol up to 20% of the study population) and no interaction was found in post hoc testing between study sites and treatments in the assessment of the primary study endpoint (p=0.673). Additionally, the randomisation effectively generated directly comparable treatment groups. There were no statistically significant between-group differences in the diagnoses, prior treatments, or other baseline demographics or characteristics (Table 16). Therefore, both the multicentre and randomisation requirements of this trial were effectively fulfilled which enhances both the internal and external validity of the statistical conclusions drawn from this study. The most frequent pain aetiologies in both groups were radiculopathy (91·0% CL-SCS; 88·1% OL-SCS), PSPS-T2 (56·7% CL-SCS; 61·2% OL-SCS) and degenerative disc disease (49·3% CL-SCS; 62·7% OL-SCS). Approximately 60% of patients in both treatment groups had prior back surgery. Mean (± standard deviation) baseline overall back and leg, back, and leg pain scores (mm) were 81·9±10·6, 81·4±10·2, and 82·2±10·8, respectively, for closed-loop patients, and 82·3±8·8, 80·4±11·2, and 80·0±9·9, respectively for open-loop patients.

Table 16. Baseline Demographics and Characteristics for all Randomised Patients

	CL-SCS (N=67)	OL-SCS (N=67)
Age (years)	54.6 (9.7)	55.9 (11.6)
Sex		
Male	34 (50.7%)	35 (52.2%)
Female	33 (49.3%)	32 (47.8%)
BMI (kg/m^2)	31·3 (5.7)	32·4 (6.8)
Duration of Pain (years)	13·6 (9.6)	11·2 (9.9)
Pain Aetiology (not mutually exclusive)		
Arachnoiditis	0 (0.0%)	2 (3.0%)
Complex Regional Pain Syndrome (CRPS) I	0 (0.0%)	1 (1.5%)
Degenerative Disc Disease	33 (49.3%)	42 (62.7%)
Failed back surgery syndrome (FBSS)	38 (56.7%)	41 (61.2%)
Internal Disc Disruption or Tear / Discogenic Pain	7 (10.4%)	10 (14.9%)
Lumbar Facet-Mediated Pain	8 (11.9%)	8 (11.9%)
Mild-Moderate Spinal Stenosis	26 (38.8%)	27 (40.3%)

	CL-SCS (N=67)	OL-SCS (N=67)
Radiculopathy	61 (91.0%)	59 (88.1%)
Sacroiliac Joint-Mediated Pain	9 (13.4%)	5 (7.5%)
Spondylolisthesis	6 (9.0%)	5 (7.5%)
Spondylosis with Myelopathy	2 (3.0%)	3 (4.5%)
Spondylosis without Myelopathy	26 (38.8%)	24 (35.8%)
Other Chronic Pain	6 (9.0%)	3 (4.5%)
Baseline Pain Medication Usage	63 (94.0%)	59 (88.1%)
Opioids	41 (61.2%)	40 (59.7%)
Non-opioids[1]	51 (76.1%)	52 (77.6%)
Previous Non-Invasive Therapies[2]	65 (97.0%)	64 (95.5%)
Previous Interventional Procedure[3]	63 (94.0%)	62 (92.5%)
Previous Back Surgery[4]	39 (58.2%)	41 (61.2%)

Data are mean (SD) or n (%).

[1]Non-opioid pain medication classes include: anticonvulsant, antidepressant, local anaesthetic, muscle relaxant, NSAIDs, and other pain medications.

[2]Non-invasive therapies include: acupuncture, aquatherapy, assistive device, biofeedback, chiropractic care, exercise therapy, massage therapy, psychotherapy, physical therapy, transcutaneous electrical nerve stimulator (TENS).

[3]Interventional procedures include: ankle surgery, benign cyst removal, block/injection – other, epidural steroid injection, facet joint injection, intradiscal bilateral lumbar biacuplasty, intradiscal procedure (e.g., Intradiscal Electrothermal Therapy (IDET)), lumbar rhizotomy, lumbar surgical ablation, lumbar sympathetic block, medial branch block, radiofrequency denervation, sacroiliac joint injection, trigger point injection.

[4]Back surgeries include: artificial disc replacement, discectomy or microdiscectomy, foraminotomy, kyphoplasty or vertebroplasty, laminectomy, nucleoplasty (e.g., disc decompression, laser surgery), spinal fusion, back surgery – not otherwise specified, back surgery – other.

5.4.1.1.2 Avalon Study

The Avalon study recruited 70 patients between August 2015 to April 2017. Fifty patients proceeded to permanent implant following a screening trial procedure. Demographics and baseline characteristics for the cohort of implanted patients are presented in Table 17. Persistent or recurrent pain following spinal surgery was the main diagnosis across the cohort (56.0%), and the lower back was the most commonly reported primary pain area (78.0%). Three patients had previous experience with SCS.

Table 17. Baseline demographics and characteristics for permanently implanted patients

	Implanted patients (N=50)
Age (years)	56.7 (12.2)
Sex	
Male	23 (46.0%)
Female	27 (54.0%)
Duration of pain (years)	15.0 (11.0)
Primary diagnosis	
Failed back surgery syndrome (FBSS)	28 (56.0%)
Radiculopathy	9 (18.0%)
Other Chronic Pain[1]	13 (26.0%)
Primary region of pain	

	Implanted patients (N=50)
Lower back	39 (78.0%)
Leg	8 (16.0%)
Foot	3 (6.0%)
Previous Back Surgery	35 (70.0%)
Prior history of SCS	3 (6.0%)
[1] *Other diagnoses: discogenic back (or lower back) pain/internal disc disruption (n=5), lumbar spondylosis (n=4), lumbar degenerative disease (n=1), neuropathic pain/neuropathic low back pain post trauma (n=1), peripheral neuropathy (n=1), and sciatica and gluteal tendinopathy (n=1).*	

5.4.1.2 Outcomes (PICO 1)

5.4.1.2.1 Evoke Study

The results of the primary composite endpoint, which evaluated pain relief in combination with no increase in baseline pain medication, successfully demonstrated both non-inferiority ($p<0.001$) and superiority (3 months: $p=0.005$; 12 months: p-value=0.006) of ECAP-controlled CL-SCS to OL-SCS. In total, greater than 82% (3 months: 82.3%; 12 months: 83.1%) of CL-SCS patients met the primary endpoint individual success criteria compared to approximately 60% (3 months: 60.3%, 12 months: 61.0%) of OL-SCS patients. Additionally, the analysis of the primary endpoint was performed in the subset of subjects in the intention-to-treat (ITT) population with a permanent implant, and demonstrated both non-inferiority ($p<0.001$) and superiority (3 months: $p=0.031$; 12 months: $p=0.039$) of CL-SCS (3 months: 87.9%; 12 months: 89.1%) to OL-SCS (3 months: 71.7%; 12 months: 73.5%), confirming the robustness of the study conclusions. Thus, regardless of the methodology used to analyse the primary endpoint, the results consistently demonstrated superiority in clinical outcomes associated with CL-SCS compared to OL-SCS.

Non-inferiority was demonstrated across all the hierarchical secondary endpoints ($p\leq0.002$). In addition, numerically better improvement was consistently observed, with statistical superiority of CL-SCS to OL-SCS in the percentage change in VAS average back pain (3 months: 72.1% CL-SCS vs. 57.5% OL-SCS, $p=0.015$; 12 months: 69.4% CL-SCS vs. 54.0% OL-SCS, $p=0.020$) and incidence of ≥50% reduction in VAS average back pain (3 months: 80.6% CL-SCS vs. 57.1% OL-SCS, $p=0.003$; 12 months: 79.7% CL-SCS vs. 57.6% OL-SCS, $p=0.008$) at 3 and 12 months. Statistical superiority of CL-SCS to OL-SCS was also observed in the incidence of ≥80% reduction in VAS average overall trunk and limb pain at 12 months (12 months: 55.9% CL-SCS vs. 37.3% OL-SCS, $p=0.039$). Results at 24-months confirmed the durable effects of Evoke CL-SCS and OL-SCS. The ITT analysis at 24-month follow-up, showed that a significantly greater proportion of CL-SCS patients obtained ≥50% reduction

(CL-SCS=79.1%, OL-SCS=53.7%, p=0.001) and ≥80% reduction (CL-SCS=46.3%, OL-SCS=29.9%, p=0.047) in overall back and leg pain.

Statistically significant and clinically meaningful improvements with respect to baseline were observed in both treatment groups in all other patient-reported outcomes including physical function (ODI), emotional function (Profile of Mood States [POMS]), sleep quality (Pittsburgh Sleep Quality Index [PSQI]), and quality of life (EQ-5D); Short-Form Health Survey [SF-12]). Additionally, there were high rates of subject satisfaction with the therapy and the majority of subjects perceived their overall status to be very much or much improved. In general, the improvement was greater in the CL-SCS group compared to the OL-SCS group.

In parallel with the improvements in these clinical outcomes, voluntary opioid reduction or elimination was observed in 66.7% of CL-SCS patients and 60.9% of OL-SCS patients, with 66.7% and 56.5% of patients, respectively, having clinically meaningful reductions (≥20%) at 24 months.

Device utilisation was >80% for both groups through 24 months. Additionally, conduction velocity, the speed at which an action potential propagates along the neural pathway indicative of the type of nerve fibres being activated, was between 50 and 65 m/s for both groups, within the range of Aβ fibres responsible for pain inhibition. Measurement of spinal cord activation revealed that the most frequent (mode) ECAP amplitude, time within the patients' therapeutic window, and neural accuracy was statistically greater for CL-SCS compared to OL-SCS throughout follow-up. Outcomes at 3-, 12-, and 24-months follow-up are presented in Table 18.

Table 18. Evoke study results

	3 Month		12 Month		24 Month	
	Closed-Loop	**Open-Loop**	**Closed-Loop**	**Open-Loop**	**Closed-Loop**	**Open-Loop**
Visual Analog Scale (VAS) Overall Pain						
Percent Change from Baseline	73.8 (28.0) *	59.4 (35.8)	72.3 (29.0) *	56.2 (38.5)	68.5 (30.2) *	53.7 (35.3)
≥50% Reduction	51/62 (82.3%)*	38/63 (60.3%)	49/59 (83.1%)*	36/59 (61.0%)	53/67 (79.1%) *	36/67 (53.7%)
≥80% Reduction	36/62 (58.1%)	27/63 (42.9%)	33/59 (55.9%)*	22/59 (37.3%)	31/67 (46.3%) *	20/67 (29.9%)
Oswestry Disability Index (ODI)						
Change from Baseline	30.3 (16.4)	26.5 (15.5)	28.0 (16.3)	26.1 (14.5)	26.0 (13.6)	23.2 (14.5)
Clinically Important Change (≥10)[1]	47/58 (81.0%)	42/53 (79.2%)	43/55 (78.2%)	37/48 (77.1%)	41/50 (82.0%)	30/42 (71.4%)
Profile of Mood states (POMS) Total Mood Disturbance (TMD)						
Change from Baseline	20.2 (21.2) *	10.1 (14.1)	21.7 (19.8) *	8.9 (14.6)	18.6 (19.4) *	9.4 (15.1)
Clinically Important Change (≥10)[2]	40/58 (69.0%) *	22/53 (41.5%)	39/55 (70.9%) *	22/48 (45.8%)	34/50 (68.0%) *	18/42 (42.9%)
Short Form Health Survey (SF-12) Physical Component Summary (PCS)						
Change from Baseline	13.9 (9.8)	11.5 (9.4)	11.7 (10.6)	11.6 (9.6)	10.1 (11.0)	11.0 (10.0)
Clinically Important Change (≥6)[3]	47/58 (81.0%)	35/53 (66.0%)	40/55 (72.7%)	35/48 (72.9%)	33/50 (66.0%)	26/50 (63.4%)
Short Form Health Survey (SF-12) Mental Component Summary (MCS)						
Change from Baseline	8.9 (10.4) *	1.9 (10.2)	7.4 (12.2) *	-0.8 (10.0)	6.7 (11.6) *	-1.4 (10.0)
Clinically Important Change (≥7)[3]	32/58 (55.2%) *	15/53 (28.3%)	28/55 (50.9%) *	10/48 (20.8%)	23/50 (46.0%) *	9/42 (22.0%)
EQ-5D-5L Index Score						
Change from Baseline	0.269 (0.172)	0.256 (0.162)	0.245 (0.194)	0.226 (0.170)	0.254 (0.157)	0.208 (0.163)
Clinically Important Change (≥0.074) [4]	52/58 (89.7%)	46/53 (86.8%)	47/55 (85.5%)	38/48 (79.2%)	43/50 (86.0%)	35/42 (83.3%)
EQ-VAS						
Change from Baseline	28.3 (22.7)	22.0 (23.1)	27.1 (23.4)	20.3 (20.7)	26.9 (19.9)	19.5 (21.7)
Pittsburgh Sleep Quality Index (PSQI)						
Change from Baseline	5.7 (4.6)	4.5 (4.0)	5.7 (4.2)	4.5 (4.7)	4.1 (4.3)	4.1 (4.7)
Clinically Important Change (≥3)[5]	44/58 (75.9%)	35/53 (66.0%)	42/55 (76.4%)	30/48 (62.5%)	31/50 (63.3%)	26/42 (61.9%)
Patient Global Impression of Change (PGIC)						
Percent Much Improved or Very Much Improved	52/58 (89.7%)	43/53 (81.1%)	45/55 (81.8%)	36/48 (75.0%)	42/50 (84.0%)	34/42 (81.0%)

	3 Month		12 Month		24 Month	
	Closed-Loop	**Open-Loop**	**Closed-Loop**	**Open-Loop**	**Closed-Loop**	**Open-Loop**
Satisfaction with Therapy						
Percent Satisfied or Very Satisfied	55/58 (94.8%)	46/53 (86.8%)	50/55 (90.9%)	41/48 (85.4%)	46/50 (92.0%)	37/42 (88.1%)
Opioid Usage						
Percent Change from Baseline	6.1 (24.2)	2.3 (18.4)	28.4 (43.2)	20.1 (39.3)	42.3 (39.3)	24.5 (81.4)
≥20% Reduction	2/33 (6.1%)	1/32 (3.1%)	17/31 (54.8%)	11/30 (36.7%)	18/27 (66.7%)	13/23 (56.5%)
Percent Reduced or Eliminated	2/33 (6.1%)	1/32 (3.1%)	17/31 (54.8%)	11/30 (36.7%)	18/27 (66.7%)	14/23 (60.9%)
Device Utilisation						
Total Percent Usage (out of total time)	87.7	91.7	81.3	87.4	88.0	95.0
ECAP Amplitude Histogram Statistics						
Mode ECAP Amplitude (µV)	33.0*	4.3	27.0*	4.5	22.5*	7.5
Therapeutic Window						
Percent Time in Therapeutic Window	91.1*	59.5	95.2*	47.9	93.9*	46.1
Neural Accuracy (Deviation in Elicited Neural Response from Target Neural Response) (median)						
RMSE (µV)	3.1*	12.8	4.4*	28.0	3.2*	26.7
Conduction Velocity						
Conduction Velocity (m/s)	57.3	58.9	60.2	58.9	62.4	64.4

Data are mean (SD), median, or n/N (%).

Positive change indicates improvement. All, except for SF-12 MCS for OL, were statistically significant within-group improvements from baseline at all time points (p<0.001).

**Statistically significant between-group difference (p<0.05).*

[1] *Roland M, Fairbank J. The Roland–Morris Disability Questionnaire and the Oswestry Disability Questionnaire: Spine. 2000 Dec;25(24):3115–24.*

[2] *Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008 Feb;9(2):105–21.*

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[4] *Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2005 Aug;14(6):1523–32.*

[5] *Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch Intern Med. 2011 May 23;171(10):887–95.*

There were no differences in the safety profiles between treatment groups and the type, frequency, and severity of adverse events (AEs) were similar to those reported in other SCS studies (Table 19 and Table 20). There were 42 study-related AEs in 28 patients (20.9%) (CL-SCS: 28 AEs, 23.9% patients; OL-SCS: 14 AEs, 17.9% patients; risk difference [95% CI]: 6.0 [-7.8 to 19.7]). The most frequently reported study-related AEs in both groups were implantable pulse generator (IPG) pocket pain (10 AEs, 6.7% patients) and lead migration (10 AEs, 6.7% patients). Importantly, there were no differences between groups in stimulation therapy-related AEs with 10 stimulation therapy-related AEs in 8 patients (CL-SCS: 7 AEs, 7.5% patients; OL-SCS: 3 AEs, 4.5% patients; risk difference [95% CI]: 3.0 [-5.0 to 11.0]). Four serious AEs in four patients (3.0%) (CL-SCS: 2 AEs, 3.0% patients; OL-SCS: 2 AEs, 3.0% patients; risk difference [95% CI]: 0.0 [-5.8 to 5.8]) were study-related, but not stimulation related, including wound infection (2 [1.5%]), epidural abscess (1 [0.7%]), and lead breakage/fracture (1 [0.7%]). There were two explants due to loss of efficacy (CL-SCS: 0 [0.0%], OL-SCS: 2 [3.0%]) and three explants due to procedure-related infections (CL-SCS: 2 [3.0%], OL-SCS: 1 [1.5%]). There has been one death due to cardiac arrest secondary to uncontrolled hypertension and unrelated to the study.

Table 19. Summary of study-related adverse events for all randomised patients

Adverse events (AEs)	Total (N=134)		Difference between groups
	Events n	Patients n (%)	Risk difference (%) and 95% CI
Study-related AEs [1]	42	28 (20.9%)	6.0 (-7.8 to 19.7)
Procedure-related AEs	28	21 (15.7%)	4.5 (-7.8 to 16.8)
Device-related AEs	18	17 (12.7%)	4.5 (-6.8 to 15.7)
Stimulation therapy-related AEs	10	8 (6.0%)	3.0 (-5.0 to 11.0)

[1] Adverse events adjudicated as definitely or possibly related to the device, procedure, or stimulation therapy were considered study-related.

Table 20. Rates of study-related adverse events for all randomised patients

Adverse event	Total (N=134)	
	Events n	Patients n (%)
Wound infection	3	3 (2.2%)
Dural puncture or tear	2	2 (1.5%)
IPG malfunction due to electrocautery	2	2 (1.5%)
Unwanted stimulation location	2	2 (1.5%)
Back pain and bilateral radiation into legs	1	1 (0.7%)
Dysesthesia – lower extremity	1	1 (0.7%)
Epidural abscess	1	1 (0.7%)
Inadequate lead placement	1	1 (0.7%)

Adverse event	Total (N=134)	
	Events n	Patients n (%)
Lead breakage/fracture	1	1 (0.7%)
Low back pain	1	1 (0.7%)
Nausea and/or vomiting	1	1 (0.7%)
Pain – implant/incision site	1	1 (0.7%)
Skin irritation or redness	1	1 (0.7%)
Wound dehiscence	1	1 (0.7%)

5.4.1.2.2 Avalon Study

The primary performance outcome was met, with all subjects (100%) successfully programmed in feedback-controlled (closed-loop) stimulation mode at all time points, including the 1-month primary time point.

Statistically significant and clinically meaningful improvements with respect to baseline were observed in pain (VAS, BPI), physical function (ODI), sleep quality (PSQI), and quality of life (EQ-5D). Overall pain responder rates (≥50% reduction) were 80.0%, 81.4%, and 89.5%, and high-responder rates (≥80% reduction) were 42.2%, 53.5%, and 68.4% at 3-, 12-, and 24-months, respectively, consistent with the Evoke study. Additionally, there were high rates (>88%) of subject satisfaction with the therapy and the majority of subjects (>94%) perceived their overall status to be very much or much improved. In parallel with the improvements in these clinical outcomes, voluntary opioid reduction or elimination was observed in 83% of patients at 24 months. Device utilisation was >50% throughout the duration of the study. Measurement of spinal cord activation indicated that the most frequent (mode) ECAP amplitude was ~25µV and that activation was within the patients' therapeutic window >90% of the time. Conduction velocity, the speed at which an action potential propagates along the neural pathway indicative of the type of nerve fibres being activated, was between 50 and 60 m/s, within the range of Aβ fibres responsible for pain inhibition. Outcomes at baseline, 3-, 12-, and 24-months follow-up are presented in Table 21.

Table 21. Avalon study results

	3 Month	12 Month	24 Month
Visual Analog Scale (VAS) – Overall Pain			
Percent Change from Baseline	71.2 (27.0)	73.6 (28.0)	81.2 (24.0)
Responders (≥50% Reduction)	36/45 (80.0%)	35/43 (81.4%)	34/38 (89.5%)
High Responders (≥80% Reduction)	19/45 (42.2%)	23/43 (53.5%)	26/38 (68.4%)
Brief Pain Inventory (BPI) Severity			
Change from Baseline	3.5 (1.7)	3.6 (1.9)	3.9 (2.9)

	3 Month	12 Month	24 Month
Clinically Important Change (≥1.0)[1]	40/45 (88.9%)	39/43 (90.7%)	33/38 (86.8%)
Brief Pain Inventory (BPI) Interference			
Change from Baseline	3.5 (2.6)	3.8 (2.8)	4.2 (3.0)
Clinically Important Change (≥1.0)[1]	34/45 (75.6%)	36/43 (83.7%)	31/38 (81.6%)
Oswestry Disability Index (ODI)			
Change from Baseline	17.1 (11.9)	20.3 (13.9)	18.4 (20.3)
Clinically Important Change (≥10)[2]	31/44 (70.5%)	33/43 (76.7%)	27/38 (71.1%)
EQ-5D-5L Index Score			
Change from Baseline	0.233 (0.245)	0.214 (0.213)	0.221 (0.288)
Clinically Important Change (≥0.074)[3]	36/45 (80.0%)	38/43 (88.4%)	31/38 (81.6%)
EQ-VAS			
Change from Baseline	18.4 (25.1)	17.4 (26.8)	22.2 (31.4)
Pittsburgh Sleep Quality Index (PSQI)			
Change from Baseline	3.5 (4.6)	3.1 (4.5)	3.8 (5.0)
Clinically Important Change (≥3)[4]	29/45 (64.4%)	22/42 (52.4%)	22/38 (57.9%)
Patient Global Impression of Change (PGIC)			
Percent Better	43/45 (95.6%)	42/43 (97.7%)	36/38 (94.7%)
Satisfaction with Device			
Percent Satisfied or Very Satisfied	42/45 (93.3%)	38/43 (88.4%)	36/38 (94.7%)
Opioid Usage			
Percent Reduced or Eliminated	20/33 (60.6%)	22/32 (68.8%)	24/29 (82.8%)
Device Utilisation			
Total Percent Usage (out of total time)	85.5	58.4	57.3
Therapeutic Window			
Percent Time in Therapeutic Window	96.7	84.9	90.2
ECAP Amplitude Histogram Statistics			
Mode ECAP Amplitude (µV)	22.5	28.5	25.5
Conduction Velocity			
Conduction Velocity (m/s)	56.1	53.2	57.9

Data are mean (SD), median, or n/N (%).

Positive change indicates improvement. All were statistically significant within-group improvements from baseline (p<0.001).

[1] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008 Feb;9(2):105–21.

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[4] Buysse DJ, Germain A, Moul DE, Franzen PL, Brar LK, Fletcher ME, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch Intern Med. 2011 May 23;171(10):887–95.

There were no unanticipated serious adverse device effects (USADEs). There were no AEs related to feedback-controlled (closed-loop) stimulation. There were 3 serious adverse events that were determined to be possibly, probably, or definitely related to the procedure and/or device – an allergic reaction to the device components (titanium) post-implant, wound dehiscence post-implant, and low back pain post-trial – all of which resolved with treatment.

The type, nature, and severity of adverse events were consistent with the published literature on other SCS systems.

5.5 Overview of completed and ongoing studies of the Evoke SCS system

Study name and identifier	Primary Objective	Study Design	Date Initiated (First Consent)	Follow-up	Status
Avalon Study Australia New Zealand Clinical Trials Registry (ACTRN12615000713594)	To evaluate the safety and performance of the Evoke SCS system in the treatment of patients with chronic pain of the trunk and/or limbs.	Prospective, multicentre, single-arm, pivotal study (pre-market, AU)	August 2015	24 months (extended from 12 to 24 months mid study; 3 subjects elected not to participate beyond 12 months)	Complete
Evoke Study Clinicaltrials.gov (NCT02924129)	To evaluate the safety and efficacy of the Saluda Medical Evoke SCS System with feedback (Investigational, Closed-Loop) and without feedback (Control, Open-Loop) to treat chronic pain of the trunk and/or limbs	Pivotal, multicentre, double-blind, randomised, controlled trial (pre-market, US)	January 2017	Up to 36 months	Enrolment complete; Follow up ongoing through 36 months
Brighton Study Australia New Zealand Clinical Trials Registry (ACTRN12618001808235)	To examine evoked compound action potentials (ECAPs) and other neurophysiological measurements in relation to lead placement, programming parameters, and closed-loop refinement in nerves targeted for upper limb and/or neck pain.	Prospective, multicenter, single-arm feasibility study (pre-market, AU)	March 2019	24 months	Enrolment complete; Follow up ongoing through 24 months
ECAP Study Clinicaltrials.gov (NCT04319887)	To evaluate neurophysiological measures and clinical outcomes of the Evoke System to treat trunk and/or limb pain in a real-world population.	Prospective, multicenter, single-arm feasibility study (pre-market, US)	October 2020	24 months	Enrolment and follow-up ongoing
Freshwater Study Clinicaltrials.gov (NCT04662905)	To evaluate device performance and/or usability, and safety of new device features, as they become available, to improve closed-loop therapy delivery.	Prospective, multicenter, single-arm feasibility study (pre-market, AU)	February 2021	24 months	Enrolment ongoing
PMCF Study Clinicaltrials.gov (NCT04627974)	To evaluate the long-term effectiveness, safety, and performance of the Saluda Medical's Evoke Closed-Loop Spinal Cord Stimulation System to treat patients with chronic pain of the trunk and/or limbs.	Prospective, multicounty, multicentre, single-arm study (post-market, EU and UK)	October 2020	60 months	Enrolment and follow-up ongoing
Post-Market Data Collection Clinicaltrials.gov Germany (NCT05272137) ISRCTN	To collect neurophysiological and device data under normal conditions of use.	Prospective, multicounty, multicentre, data collection/ survey (post-	August 2019	24 months	Enrolment and follow-up ongoing

Study name and identifier	Primary Objective	Study Design	Date Initiated (First Consent)	Follow-up	Status
UK (ISRCTN27710516) Netherlands Trial register via ICTRP Netherlands (NL7889)		market, EU and UK)			
Spinal versus local anaesthesia for CL-SCS implantation and its influence on the ECAP Netherlands Trial register via ICTRP (NL9392)	To evaluate patient pain and comfort level under spinal or local anaesthesia during SCS trial lead implantation.	Prospective randomised, double-arm, open label pilot study	April 2021	Study exit after permanent or trial implant	Enrolment ongoing
A prospective single-centre study to assess the effectiveness of Closed-Loop Spinal Cord Stimulation (CL-SCS) in the treatment of chronic pain associated with primary and secondary Raynaud's Phenomenon German Clinical Trials Register (DRKS00030179)	Evaluate the effect of CL-SCS on the severity and frequency of Raynaud's attacks.	Prospective, single-centre, single-arm, open-label study	June 2021	6 months	Enrolment and follow-up ongoing
EVOKE ECAP-Controlled Lead Placement and Programming in Chronic Pain Patients Clinicaltrials.gov (NCT05704751)	Evaluate the feasibility of using intra-operative ECAP and LR recordings for confirmation of activation of the neural target of the dorsal column in a single-stage SCS lead placement procedure. Evaluate average pain relief using the Visual Analogue Scale (VAS).	Prospective, single centre, single arm, open-label feasibility study	Not yet recruiting	12 months	Not yet recruiting

6 Conclusions

Evidence on Evoke CL-SCS has generated promising study results which are comparable or better than the ranges reported in the literature. The analyses through to 24-months follow-up show statistically significant, clinically meaningful, ample, consistent, and strong evidence in support of the Evoke CL-SCS for the treatment of chronic intractable pain of the trunk and/or limbs. No new types of complications were apparent, the Evoke SCS safety profile is comparable to the literature, and the type, rate, and severity of Evoke adverse events are comparable to adverse events reported in the literature.

The evidence provided in this dossier to support the safety and performance of the Evoke System includes clinical data from prospective clinical investigations of the Evoke System. The results of the clinical evaluation support the reasonable assurance of the safety and performance of the Evoke System when used as intended. Based on the current clinical data for the Evoke System, the anticipated benefits outweigh the risks of the device. There is sufficient clinical evidence provided in this dossier to support the contention that the device demonstrates conformity with the relevant European General Safety and Performance Requirements.

The treatment effects identified in the Evoke pivotal study represent robust estimates of the substantial clinical improvements expected with Evoke CL-SCS over OL-SCS. In fact, on November 1, 2022, the US Centers for Medicare & Medicaid Services (CMS) approved a Transitional Pass-Through (TPT) code (C1826) for the Evoke CL-SCS System. This TPT creates a new device category for CL-SCS, increasing patient access to this innovative technology. Excerpts from the CY2023 OPPS/ASC Final Rule include:

- “The Evoke® SCS System represents a substantial clinical improvement over existing technologies based on the data received from commenters.”
- “Because the Evoke® SCS System measures and uses the evoked compound action potentials to instantaneously adjust subsequent stimulation output on every stimulation pulse, we believe it is uniquely a true closed-loop system.”
- “We believe this RCT comparison served to demonstrate the substantial clinical improvement provided by the closed-loop system, differentiating it from open-loop systems typically described by existing device categories, thus supporting the creation of a new device category.”

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8 Appendix

Appendix A. 24-month follow-results of RCTs of open-loop SCS

	Evoke RCT CL-SCS (25)	**PROCESS RCT OL-SCS** (45)	**Senza RCT OL-SCS (HF)** (46)	**Senza RCT OL-SCS (LF)** (46)	**PROMISE RCT OL-SCS** (47)
Pain (primary outcome)	**Overall back and leg, VAS**	**Leg, VAS**	**Back, VAS**	**Back, VAS**	**Back, NRS**
Percent Change from Baseline (mean)	72.6%	43.5%[1]	66.9%	41.1%	29.3%[1]
Responders (≥50% Reduction)	84.0%	40.5%	76.5%	49.3%	20.6%
High Responders (≥80% Reduction)	50.0%	14.3%	43.5%[1]	19.7%[1]	NR
Oswestry Disability Index (ODI)					
Change from Baseline (mean)	26.0	15[1]	NR[2]	NR[3]	9.4
Percent Change from Baseline (mean)	47.8%	20.3%[1]	NR[4]	NR[5]	NR
Percent minimal to moderate	78.0%	NR	64.7%	49.3%	NR
EQ-5D Index Score					
Change from Baseline (mean)	0.254	0.27[1]	NC	NC	0.18
SF-12 PCS					
Change from Baseline (mean)	10.1	NR in Kumar 2008; 5[1,6] in Eldabe 2009	NR[7]	NR[8]	6.5[6]
SF-12 MCS					
Change from Baseline (mean)	6.7	NR in Kumar 2008; 5[1,6] in Eldabe 2009	NR[9]	NR[10]	NR
Profile of Mood States (POMS)					
Change from Baseline (mean)	18.6	NC	NC	NC	NC
Pittsburgh Sleep Quality Index (PSQI)					
Change from Baseline (mean)	4.1	NC	NR[11]	NR[12]	NR
Patient Global Impression of Change (PGIC)					
Percent very much or much improved	84.0%	NC	63.5%[13]	36.6%	NR
Opioid Usage					

Percent Decrease MME (mean)	42.3%	-2.2% / -6.1%[1] (increases in MME for low use and high use patients)	NR	NR	NR
Percent Reduced or Eliminated	66.7%	NR	NR[14]	NR[15]	NR
Device Utilisation					
Percent device utilisation outside the clinic (median)	88%	NC	NC	NC	NC
Device Performance					
Deviation in Elicited Neural Response from Target Neural Response Inside the Clinic (RMSE, median)	3.2 µV	NC	NC	NC	NC
Neural activation					
Most Frequent Neural Response Outside the Clinic (median)	22.5 µV	NC	NC	NC	NC
Therapeutic Window					
Percent time within therapeutic window outside the clinic (median)	93.9%	NC	NC	NC	NC

[1]Estimated from data provided in the publication.
[2]Senza RCT Open-Loop SCS Test: 16.5 mean change from baseline in ODI at 12 months [Kapural 2015]
[3]Senza RCT Open-Loop SCS Control: 13.0 mean change from baseline in ODI at 12 months [Kapural 2015]
[4]Senza RCT Open-Loop SCS Test: 29.2% mean percent change from baseline in ODI at 12 months [SSED P130022]
[5]Senza RCT Open-Loop SCS Control: 21.6% mean percent change from baseline in ODI at 12 months [SSED P130022]
[6]SF-36
[7]Senza RCT Open-Loop SCS Test: 8.1 mean change from baseline in SF-12 PCS at 12 months [SSED P130022]
[8]Senza RCT Open-Loop SCS Control: 6.0 mean change from baseline in SF-12 PCS at 12 months [SSED P130022]
[9]Senza RCT Open-Loop SCS Test: 2.7 mean change from baseline in SF-12 MCS at 12 months [SSED P130022]
[10]Senza RCT Open-Loop SCS Control: 1.2 mean change from baseline in SF-12 MCS at 12 months [SSED P130022]
[11]Senza RCT Open-Loop SCS Test: 2.6 mean change from baseline in PSQI at 12 months [SSED P130022]
[12]Senza RCT Open-Loop SCS Control: 1.8 mean change from baseline in PSQI at 12 months [SSED P130022]
[13]Percent a great deal better or better
[14]Senza RCT Open-Loop SCS Test: 35.5% patients reduced or eliminated opioids at 12 months [SSED P130022]
[15]Senza RCT Open-Loop SCS Control: 26.4% patients reduced or eliminated opioids at 12 months [SSED P130022]

Appendix B. Underlying Documentation for Medicinal Products

Not applicable, as the Evoke System is a medical device. Refer to Appendix C.

Appendix C. Underlying Documentation for Medical Devices

C1. Full Text of References

See attachments.

C2. Documentation of Information Retrieval

This documentation is above in section 4.

C3. Programming Code for Programs used for Analysis

Not applicable; analyses and associated calculations are performed using standard methods, as described in the publications.

C4. Study Reports

See attachments. Request to keep confidential (request not to publish).

Evoke Study

Protocol / Statistical Analysis Plan (separate from protocol)

Clinical Study Report (12-month primary endpoint report; 24-month report not completed as there was not a pre-defined endpoint at 24-months; final 36-month report not yet completed as the study is still in the process of being closed)

Avalon Study

Protocol / Statistical Analysis Plan (included in protocol)

Clinical Study Report (final, 24-month report)

C5. For Medical Devices: Clinical Evaluation Documentation

Clinical Evaluation Assessment Report

Not applicable; the submission for EU Medical Device Regulation 2017/745 (MDR) is currently under review by the Notified Body. Initial CE marking was awarded on the June 17, 2019 under the requirements of Council Directive 90/385/EEC, Annex 2, excluding Section 4 (No. CE 653950) and in accordance with Council Directive 90/385/EEC, Annex 2 Section 4 (No. CE 653955).

Clinical Evaluation Report

See attached for the CER submitted for EU MDR, currently under review by the Notified Body. Request to keep confidential (request not to publish).

Clinical Evaluation Consultation Procedure – Expert Panel Scientific Opinion

Not applicable; the EU MDR submission is currently under review by the Notified Body.

EU Declaration of Conformity of the Medical Device

See attached for AIMDD CE marking (EU MDR submission currently under review by the Notified Body).

CE Marking Certificate(s) relating to the Medical Device

See attached for AIMDD CE marking (EU MDR submission currently under review by the Notified Body).

Instructions for Use

See attachments.

Surgical Guide (D102707)

Clarity Clinical Manual (D102709)

User Manual (D102706)

Quick Reference Guide (D102710)

MRI Guidelines (D102723)

RECAP Viewer User Manual (D102722)

Summary of Safety and Clinical Performance

See attachment for the initial SSCP included in the EU MDR submission (not yet finalised and validated by the Notified Body).

C6. For In Vitro Diagnostic Medical Devices: Performance Evaluation Documentation

Not applicable; the Evoke System is a medical device, not an in vitro diagnostic.

C7. HTA Reports of the Health Technology Subject to the Joint Clinical assessment

Not applicable; there have not been any other joint clinical assessments in any jurisdiction.

C8. Information on Studies based on Registries

Not applicable; none of the studies of the Evoke System are from patient registries.

C9. Information on Joint Scientific Consultations

Not applicable; the Evoke System has not been subject to a joint scientific consultation.