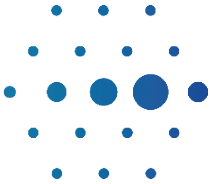

EXONEURAL NETWORK

Clinical Evaluation Report

EXOPULSE Devices

Content

Executive summary

The clinical evaluation is a methodologically sound ongoing procedure to collect, appraise and analyse clinical data pertaining to the EXOPULSE devices. This *Clinical Evaluation Report* summarises pre- and post-clinical data as well as clinical data from different sources.

The EXOPULSE devices is the collective name for the medical devices manufactured by EXONEURAL NETWORK (ENN). They are comprised of the EXOPULSE Mollii Suit (medical device components: EXOPULSE Mollii Control Unit and the EXOPULSE Body Garments) and EXOPULSE (medical device components: EXOPULSE Control Unit, EXOPULSE Garments, EXOPULSE HCP App, EXOPULSE App, and EXOPULSE Charging Station). The devices are personal assistive medical devices used for low energy transcutaneous electrical stimulation (20 Volt and 20 Hz), with up to a total of 58 embedded electrodes depending on the garment and in direct contact with the skin. The EXOPULSE devices can be used by children or adults – men, women, non-binary – and the suits come in sizes starting from 104 cm up to 5XL. They are used for neurological conditions such as cerebral palsy (CP), stroke, multiple sclerosis (MS), fibromyalgia and other neurologic disorders which may cause such type of symptoms. It is intended for home use or a clinical environment, 60 minutes every other day, unless otherwise specified by the HCP.

The medical device components of the EXOPULSE Mollii Suit and EXOPULSE respectively, are intended to be used together as described in the instructions for use (*IFU EXOPULSE Mollii* (DOC-52) and *IFU EXOPULSE* (DOC-691)). Therefore, as individual medical device components, they are not associated with any clinical performance, benefits or risks. The garments are intended to transmit electric pulses to key nerves and corresponding muscle groups in the body, the electric pulses are derived from the control unit, which (in the case of EXOPULSE) is programmed via the app. In the light of the above, this Clinical Evaluation pertains to the EXOPULSE Mollii Suit (the EXOPULSE Body Garments and EXOPULSE Mollii Control Unit) and the EXOPULSE (the EXOPULSE Garments, EXOPULSE Control Unit, and EXOPULSE App's) respectively, when operated together as units.

As part of this Clinical Evaluation, a comprehensive literature search has been performed to show the safety and performance of the medical devices. The literature generated an adequate number of relevant publications on the intended purpose which describes the clinical performance and benefits, and the information has been proven with evidence. The overall quality of the identified publications was assessed as sufficient. No safety-relevant complaints, potential risks or usability aspects have been identified, which have not yet been addressed within the risk management. Furthermore, the identified literature has been analysed with focus on alternative treatments and information on state of the art. The EXOPULSE devices show favorable clinical outcomes in the comparison with medical alternatives and complies with the state of the art.

The experience of the first marketed device the EXOPULSE Mollii Suit, provides valuable insights regarding clinical safety and performance. Between 2021 and 2022, 987 EXOPULSE Mollii Control Units and 3 506 EXOPULSE Body Garments were distributed. 107 complaints on the Control Units and 90 complaints on the Body Garments were received, out of which 2 in total were safety relevant. Moreover, a detailed search within the clinical experience databases of MHRA, BfArM, Swissmedic, TGA and MAUDE did not identify any risks or usability aspects that have not been already assessed within the risk management.

Moreover, the overall residual risks were assessed as acceptable, and the benefits associated with the use of the EXOPULSE devices outweigh the risks (*Risk Management Report EXOPULSE Mollii (*DOC-57) and *Risk Management Report EXOPULSE* (DOC-3159).

In summary, the clinical safety, performance and benefit of the EXOPULSE devices were demonstrated with this clinical evaluation. The analysis of the clinical data shows sufficient clinical evidence to confirm compliance with Regulation (EU) 2017/745, Article 61 and ANNEX XIV for safety and performance, when using the EXOPULSE devices according to the manufacturer's instructions for use (IFU). Furthermore, according to the regulatory requirements, the clinical evaluation together with the clinical assessment show that EXOPULSE is technically, biologically and clinically equivalent to EXOPULSE Mollii Suit. This *Clinical Evaluation Report* demonstrates that the EXOPULSE devices comply with the relevant general safety and performance requirements 1 and 8 of ANNEX I (Regulation (EU) 2017/745).

1 General Information

The *Clinical Evaluation Report* has been conducted in accordance with:

- Guideline on medical devices MEDDEV 2.7/1 rev. 4 (2016) 'Clinical Evaluation: A Guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC
- Medical Device Directive MDD 93/42/EEC
- Medical Device Regulation MDR (EU) 2017/745
- Medical Device Coordination Group MDCG 2020-5 Clinical Evaluation – Equivalence
- Medical Device Coordination Group MDCG 2020-6 Guidance on sufficient clinical evidence for legacy devices

The scope of the clinical evaluation is to perform a systematic review of available pre- and post-market clinical data (published literature and adverse event databases) relevant to the intended use of the EXOPULSE devices. Data on equivalent devices outside of the group of EXOPULSE devices is not applicable, although the EXOPULSE Mollii Suit has been compared to EXOPULSE in order to demonstrate equivalence.

The *Clinical Evaluation Report - EXOPULSE Devices* (DOC-84) is released following the release of the corresponding *Clinical Evaluation Plan – EXOPULSE Devices* (DOC-39).

2 Description of the devices and their applications

2.1 General

The EXOPULSE devices are comprised of the EXOPULSE Mollii Suit and EXOPULSE. A general description of the devices and their applications are presented in Table 1.

Table 1. Description of the EXOPULSE devices and their applications.

Device category	GMND code 46573 - Physical therapy TENS system	
Manufacturer	EXONEURAL NETWORK AB, Barks väg 7, 170 73 Solna, Sweden	
Trade names	EXOPULSE Mollii Suit	EXOPULSE
Code name during development	EXOPULSE Mollii Suit was previously called Elektrodress 100 or Mollii. EXOPULSE Body Garments were previously called Elektrodress 100 – Body Suit. EXOPULSE Mollii Control Unit was previously called Elektrodress 100 – CU	EXOPULSE was called EXOPULSE Active during development.
Classification	EXOPULSE Body Garments – Class I medical device EXOPULSE Mollii Control Unit - Class IIa medical device *Classification EXOPULSE Mollii Suit (EU)* (DOC-53)	EXOPULSE Garments – Class IIa accessory EXOPULSE Control Unit - Class IIa medical device EXOPULSE Charging Station, Class I accessory EXOPULSE HCP App, Class IIa accessory EXOPULSE App, Class IIa accessory *Classification (EU) EXOPULSE* (DOC-844) *Classification (EU) for EXOPULSE Apps* (DOC-3870)
Basic UDI-DI / UDI-DI / Article number / REF-number:	*UDI Master list EXOPULSE Mollii Suit* (DOC-20)	*EXOPULSE UDI Master List* (DOC-1778)
Innovation (Yes/No)		
Device is an established technology	Y	Y

Device results of incremental innovation of an existing technology	N	N
Device based on a new clinical application of an existing technology	N	N
Device based on a new technology	N	N
Predecessor	- EXOPULSE Body Garments - EXOPULSE MOLLII Control Unit – Previous versions of the Control Unit are 100-2, which corresponds to version 5.2-9.0. An exception is part number 100-3, which corresponds to version 9.1. Part number 100-4 corresponds to version 9.2. Part number 100-X corresponds to version 9.3.	
Technology	The EXOPULSE devices provide neuromodulation based on electrical stimulation at multiple locations across the body surface. They are personal assistive medical devices used for low energy stimulation at 20 Volt and 20 Hz, by up to 58 embedded electrodes, in direct contact with the skin.	
	The **EXOPULSE Mollii Suit** has a monophasic wave of varying pulse duration. It transfers electrical pulses to the patient which are lower than the values defined in the requirements for safety of nerve and muscle stimulators. <u>EXOPULSE Mollii Control Unit Technical Specifications:</u> • Power supply: 4 x AAA batteries (1.5V each, 6V total), alkaline • Maximum output: 20V, 40 mA • Pulse type: square, monophasic, 20 Hz • CU dimensions (with arms/without arms), L x W x H: 62 x 8 x 2,5 cm / 11 x 8 x 2,5 cm • Display: LCD with backlight, viewing area: 2 x 1 The EXOPULSE Mollii Control Unit generates pulses with the following parameters (applies at 1,000 Ω):	The **EXOPULSE** has a biphasic wave of varying pulse duration. The pulses generated by the Control Unit are distributed through a network of leads (passive components) onto dry rubber electrodes sewn into the suit. <u>EXOPULSE Control Unit Technical Specifications:</u> • Power supply: Li-ion battery • Maximum output: 20V, 50 mA • Pulse type: square, biphasic, 20 Hz • CU dimensions, Hexagon of 2,8 cm facet length The EXOPULSE Control Unit generates pulses with the following parameters (applies at 1,000 Ω):

	• Pulse width: variable between 30 and 175 µs • Length of period: 50 ms • Maximum amplitude: 20 V For more technology specifics see *Part A Description of the device* *EXOPULSE Mollii Control Unit* (DOC-170)	• Pulse width: variable between 20 µs and 400 µs • Length of period: 50 ms • Maximum amplitude: 20 V For more technology specifics see *Part A Description of the device* *EXOPULSE* (DOC-2047) *Part A - Description of the device - EXOPULSE Apps (DOC-3853)*

Overview of EXOPULSE Mollii Suit

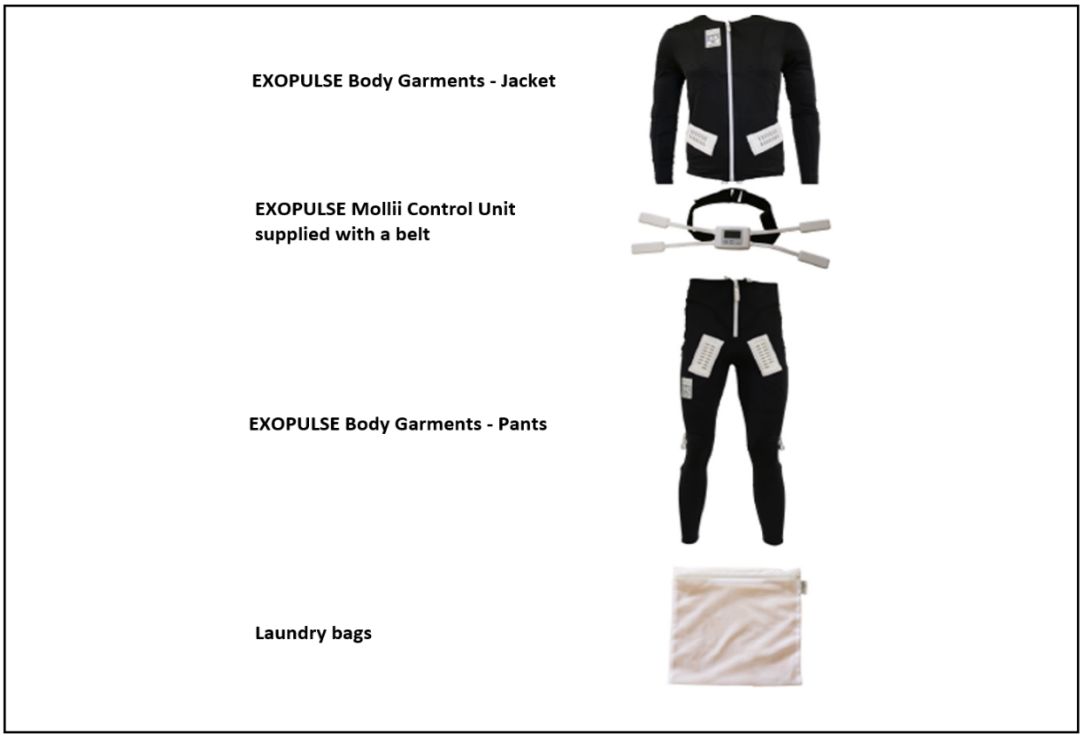

Figure 1. Overview of the EXOPULSE Mollii Suit. The EXOPULSE Mollii Suit consists of garments (jacket and pants) with embedded electrodes, a detachable EXOPULSE Mollii Control Unit and laundry bags. The figure is adapted from *IFU EXOPULSE Mollii Suit*.

Overview of EXOPULSE

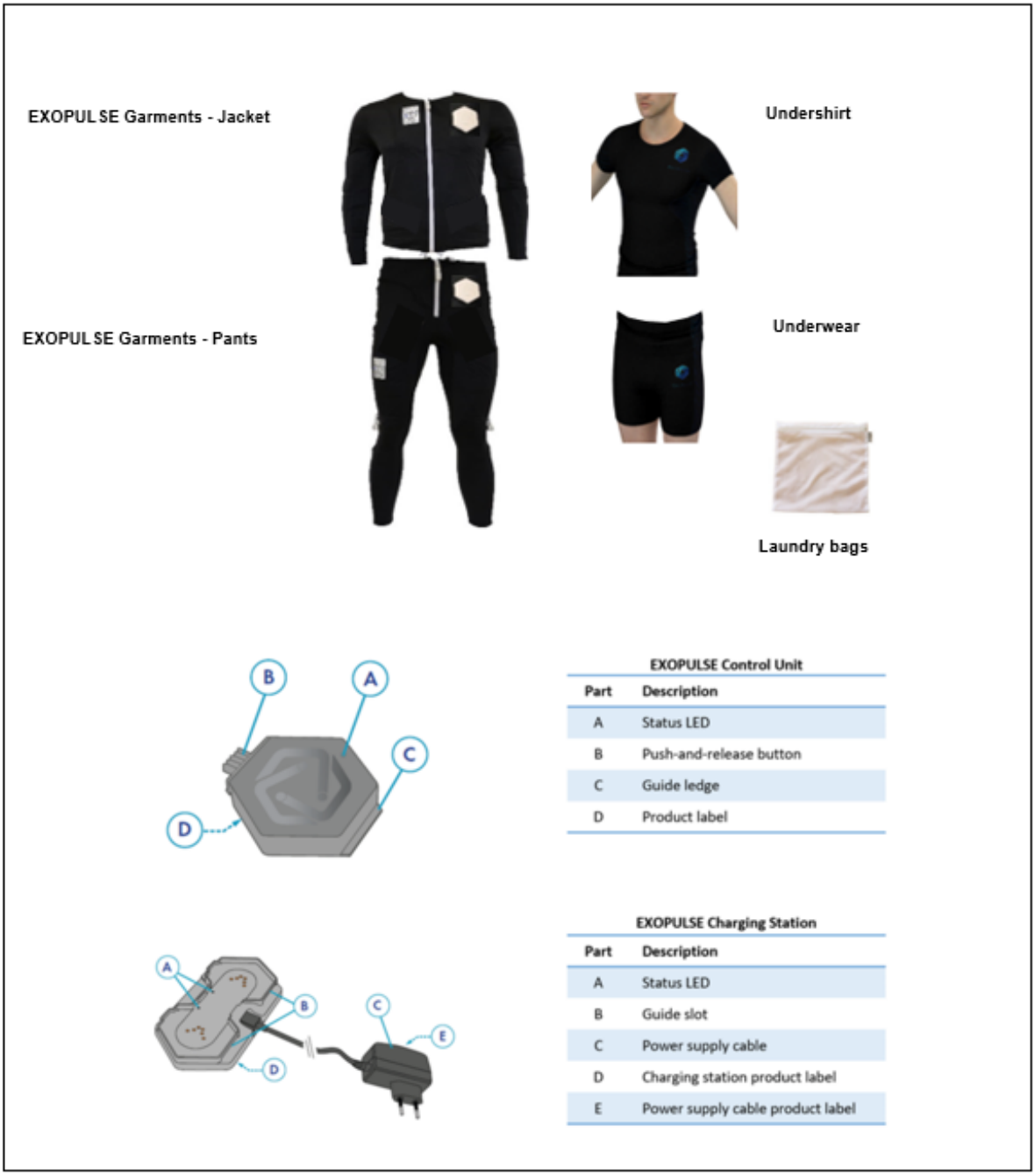

Figure 2. Overview of the EXOPULSE. The EXOPULSE consists of garments (jacket, pants, undershirt, underwear) with embedded electrodes, the EXOPULSE Control Unit and EXOPULSE Charging Station. EXOPULSE HCP App and EXOPULSE App are not included in the figure. The figure is adapted from *EXOPULSE IFU*.

2.2 Changes due to redesign

The redesign changes made between EXOPULSE Mollii Suit and EXOPULSE and which may affect clinical safety and effectiveness are listed in the table below (Table 2). For further information regarding changes, refer to *Change record - technical upgrade of EXOPULSE products* (DOC-799).

Table 2. Description of changes made between EXOPULSE Mollii Suit to EXOPULSE.

Product name	**EXOPULSE**
Redesign changes	- The device generates biphasic pulses (instead of monophasic pulses as in the EXOPULSE Mollii Suit). - The electrodes are larger and fewer, in total 43 (instead of 58 as in the EXOPULSE Mollii Suit). - The electrodes stimulate more muscle groups – up to 43 depending on garment (instead of 40 as in the EXOPULSE Mollii Suit). - The device can target up to 122 muscles (whereas the EXOPULSE Mollii Suit target up to 88 muscles). - The fine-tuning frequency has been changed to 1 Hz (instead of 20 Hz as in the EXOPULE Mollii Suit). - The pulse width is broader – 20-400 µs (instead of 30-175 µs as in the EXOPULSE Mollii Suit).

2.3 Intended use

The intended use of the EXOPULSE devices is presented in Table 3 according to *Intended Use EXOPULSE Mollii CU (MDR)* (DOC-125), *Intended Use EXOPULSE Body Garments (MDR)* (DOC-293), *Intended Use* - EXOPULSE (DOC-606) *Intended Use for EXOPULSE Apps* (DOC-3867).

Table 3. Description of the intended use of the EXOPULSE devices.

Product Name	**EXOPULSE Mollii Suit**	**EXOPULSE**
Intended use	- Relaxation of tense and spastic muscles - Activation of muscles - Increasing local blood circulation - Symptomatic relief of chronic pain	- Relaxation of tense and spastic muscles - Activation of muscles - Increasing local blood circulation - Symptomatic relief of chronic pain
Intended purpose	The EXOPULSE Mollii Suit is intended to provide relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and pain relief in patients with CP, MS, stroke and other neurologic disorders which may cause such type of symptoms, together with pain relief in patients with fibromyalgia, and other neurologic disorders which may cause such type of symptoms.	The EXOPULSE is intended to provide relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and pain relief in patients with CP, MS, stroke, and other neurologic disorders which may cause such type of symptoms, together with pain relief in patients with fibromyalgia, and other neurologic disorders which may cause such type of symptoms.

Professional or home care	Home use and healthcare environment		Home use and healthcare environment	
Intended patient population	Any patient from 2 years and up, female, male, non-binary (for the Control Unit). From children, 100 cm and 13 kg up to women 200 cm and 100+ kg and men 205 cm and 115+ kg, including overweight users (for the Body Garments).		Any patient from 2 years and up, female, male, non-binary; height 100 cm to 205 cm	
Intended User(s)	Laypersons, caregivers and healthcare professionals		Laypersons, caregivers and healthcare professionals	
Contraindications	Absolute	*IFU EXOPULSE Mollii*	Absolute	*EXOPULSE IFU*
	Relative		Relative	

2.4 Equivalence within device/group system

In this Clinical Evaluation Report, a within device group equivalence evaluation for the EXOPULSE Mollii Suit and EXOPULSE is presented. The technical, biological, and clinical characteristics of the devices have been compared and are presented in Table 6.

2.5 Warnings and precautions in instructions for use

The IFUs for EXOPULSE Mollii Suit and EXOPULSE have been reviewed for warnings and precautions. For a complete list of warnings and precautions, refer to *IFU EXOPULSE Mollii* and *IFU EXOPULSE.*

2.6 Clinical Benefits

The clinical benefits of using the EXOPULSE devices, are that they relax tense and spastic muscles, activate muscles, increase local blood circulation and relieve chronic pain symptoms.

2.7 Device claims

The following device claims on clinical performance of the EXOPULSE devices, have been determined in the *Claims Matrix* (DOC-228):

- Relaxation of tense and spastic muscles,
- Activation of muscles,
- Increasing local blood circulation,
- Symptomatic relief of chronic pain,
- Analgesic and anti-fatigue effects, improvements in anxiety and depression in the context of Fibromyalgia.

2.8 Risk Management

Qualitative and quantitative aspects of clinical safety are described in the *Risk Management Report EXOPULSE Mollii* and *Risk Management Report EXOPULSE* of the medical device. All critical clinical risks and side-effects have been included in the analysis of clinical data. Furthermore, all additional identified hazards, risks and side-effects within the *Clinical Evaluation Report* have been evaluated in the risk management file.

2.9 Regulatory Requirements

This *Clinical Evaluation Report* confirms the conformity with the relevant general safety and performance requirements 1 and 8 (Annex I, Regulation (EU) 2017/745) under the normal conditions of the intended use of the medical device, and the evaluation of the undesirable side-effects and of the acceptability of the benefit-risk ratio. The *Clinical Evaluation Report* has been planned in accordance with Part A of Annex XIV (Regulation (EU) 2017/745).

3 Clinical Investigation and Study Data

3.1 Completed clinical investigations

The table below lists the published and unpublished clinical investigations on the EXOPULSE Mollii Suit.

Table 4. List on completed clinical studies on EXOPULSE Mollii Suit.

Author(s)	Title	Published or presented in	Relevance for clinical performance/safety	Type of study
Mattar, J. G., Chalah, M. A., Ouerchefani, N., Sorel, M., Le Guilloux, J., Lefaucheur, J. P., Abi Lahoud, G. N., & Ayache, S. S.	The effect of the EXOPULSE Mollii Suit on pain and fibromyalgia-related symptoms-A randomized sham-controlled crossover trial	European Journal of Pain, 00, 1–14. https://doi.org/10.1002/ejp.4729	**Performance**: Phase 1 - randomized sham-controlled double-blind trial with a 2-week intervention of daily stimulation with the EXOPULSE Mollii Suit (active or sham): The results demonstrated a significant decrease in VAS_{pain} after the active intervention period (pre-active VAS_{pain}:6.85±1.36; post-active VAS_{pain}:5.91±1.83, Dunn's p=0.029). In addition, a significant reduction in pain was also observed following the active intervention (pre- versus post-values) when assessed via the BPI, FIQ, and SF-36 ($BPI_{pain\ interference}$, FIQ_{pain} $SF\text{-}36_{bodily\ pain}$, respectively). Fatigue also decreased significantly following the active, but not the sham, intervention periods, as per $FIQ_{fatigue}$, FIQ_{rested}, and $SF\text{-}36_{vitality}$, but not $VAS_{fatigue}$. A statistically significant (or almost significant) difference after the active intervention	Investigator-initiated

Author(s)	Title	Published or presented in	Relevance for clinical performance/safety	Type of study
			period was found with regards to some anxiety-related endpoints (i.e., $FIQ_{anxiety}$, but not $HADS_{anxiety}$). The most important effect sizes were observed for $SF\text{-}36_{pain}$ scores (0.23) and FIQ_{total} (0.20). Phase 2 – open label 4-week period with daily stimulation sessions: Significant analgesic effects on all scales, significant anti-fatigue effects on all fatigue outcomes, significant improvement in anxiety endpoints (including HADS), improvement in depression endpoints, changes in almost all FIQ subscales and improvement in almost all quality-of-life dimensions. **Safety**: No serious adverse events were reported at any time.	
I. Bakaniene, G. Urbonaviciene, K. Janaviciute, A. Prasauskiene	Effects of the Inerventions method on gross motor function in children with spastic cerebral palsy	Neurol Neurochir Pol. 2018	**Performance**: Positive impact on a gross motor function, standing, walking, running and jumping dimensions by GMFM test. Improvement in mobility and TUG scores. **Safety**: Not reported	Investigator-initiated
H. Bourke-Taylor	Feasibility study and economic assessment of a transcutaneous electrical stimulation garment (Mollii Suit) to reduce pain, improve capabilities and quality of life in children with cerebral palsy	CPEC Board report 2019	**Performance**: Relaxing and easy to include in the weekly schedule. Improvements in attention, energy levels, concentration, improved standing posture, joint positioning, motor skills and reduced pain. **Safety**: Not reported	Investigator-Initiated
C. Flodström, S-A. Viklund Axelsson, B. Nordström	A pilot study of the impact of the electro-suit Mollii on body functions, activity, and participation in children with cerebral palsy	Assist Technol. 2022 Jul 4;34(4):411-417	**Performance**: A reduction in pain, small changes in activity and participation in self-selected activities. **Safety**: Not reported	Financially supported by ENN
A. Hahn, S. Moeller, A. Schlausch, M Ekmann, G. de Chelle, M. Westerlund, F. Braatz, W. Mayr *(interim data is presented in DOC-603)*	Effects of a full-body electrostimulation garment application in a cohort of subjects with cerebral palsy, multiple sclerosis, and stroke on upper motor neuron	Biomedical Engineering/ Biomedizinishe Technik. 2023 Sept	**Performance:** Improved Berg Balance Scale, Functional Gait Assessment, Timed up and Go, 10 m Walk Test, Wolf Motor Function Test and/or EQ-5D-5L in CP, MS and stroke. **Safety**: Not reported	Registry

Author(s)	Title	Published or presented in	Relevance for clinical performance/safety	Type of study
	syndrome symptoms			
H. Hedin, A. Sjödén, C. Wong	The Effects of using an Electrodress (Mollii) to reduce spasticity and enhance functioning in Children with Cerebral palsy. A Pilot Study	European Journal of Physiotherapy 14 Sep 2020	**Performance**: Improved passive range of motion, decreased spasticity. **Safety**: Not reported	Supported with study devices from ENN
L.L. Jonasson, A. Sörbo, P. Ertzgaard, L. Sandsjö	Patients' Experiences of Self-Administered Electrotherapy for Spasticity in Stroke and Cerebral Palsy: A Qualitative Study	J Rehabil Med. 2022 Feb 14	**Performance:** Increased mobility, reduced spasticity, reduced use of medication, and problems related to using the treatment concept. **Safety:** Not reported	Investigator-initiated study
B. Nordstrom and M. Prellwitz	A pilot study of children and parents' experiences of the use of a new assistive device, the electro suit Mollii	Assist Technol. 2021 Sep 3;33(5):238-245	**Performance**: Improved ability to perform activities, increased strength and ability to maintain body position, reduced pain, and improved sleep. **Safety**: Not reported	Investigator-initiated study
S. Palmcrantz, G.V. Pennati, H. Bergling, J. Borg	Feasibility and potential effects of using the electro-dress Mollii on spasticity and functioning in chronic stroke	J Neuroeng Rehabil. 2020 Aug 10;17(1):109	**Performance**: A decrease in muscle tone, improvement in gait pattern and voluntary movement. **Safety**: Not reported	Supported with study devices from ENN
G.V. Pennati, H. Bergling, L. Carment, J. Borg, PG. Lindberg, S. Palmcrantz	Effects of 60 Min Electrostimulation with the EXOPULSE Mollii Suit on Objective Signs of Spasticity	Front Neurol. 2021 Oct 15; 12:706610	**Performance**: 75% of participants reported an overall feeling of well-being, with 25% describing a muscle-relaxing effect on the affected hand and/or foot. No effect on the neural component (NC) and EMG amplitude. Modified Ashworth ratings of spasticity and range of motion did not change. **Safety**: Not reported	Supported with study devices from ENN
P.C. Raffalt, J. Becky, K. Mortensen, T.P. Torabi, C. Wong C, M.B. Speedtsberg	Electro-suit treatment of children with unilateral cerebral palsy alters nonlinear dynamics of walking.	Clin Biomech Bristol, Avon, 2022 Aug	**Performance:** 24 weeks treatment altered the nonlinear dynamics but not the variability of the trunk accelerations during walking. The temporal structure of the trunk acceleration in the anterior-posterior direction was altered towards that of healthy individuals. **Safety:** Not reported.	Investigator-initiated study
N. Riachi, M.A. Chalah, T. Ahdab, F. Arshad, S.S. Ayache	Effects of the TENS device, EXOPULSE Mollii Suit, on pain related to fibromyalgia: An open-label study	Neurophysiologie Clinique, 2023, March	**Performance:** 60 min session with the EXOPULSE Mollii Suit decreased VAS score right after the stimulation and 24 h after the stimulation. **Safety:** Not reported	Investigator-initiated study

Author(s)	Title	Published or presented in	Relevance for clinical performance/safety	Type of study
N. Riachi, G. Khazen, R. Ahdab, S. Jörgen	Pain reducing properties of the Mollii suit on adults with pain syndromes	J Neurolog Sci 2019; 405S, 116541	**Performance**: Pain reduction by the VAS. **Safety**: Not reported	Investigator-initiated study
A. Rubio-Zarapuz, M.D. Apolo-Arenas, V.J. Clemente-Suárez, A.R. Costa, D. Pardo-Caballero, J.A. Parraca.	Acute Effects of a Session with The EXOPULSE Mollii Suit in a Fibromyalgia Patient: A Case Report	Int J Environ Res Public Health. 2023 Jan 26;20(3):2209	**Performance:** A 60 min session with the suit had beneficial effects on pain perception, muscle oxygenation, parasympathetic modulation, and function. **Safety:** Not reported	Investigator-initiated study
T.P. Torabi, K. Mortensen, J. Michelsen, C. Wong	The Mollii-suit - A novel method using reciprocal inhibition on children with cerebral palsy, GFMCS IV-V - A 6-month prospective study	Nordic Neuropediatric congress, Copenhagen Denmark, 2018 (Poster)	**Performance**: Decreased spasticity, improvement in goals (GAS) achievement. **Safety**: Not reported.	Supported with study devices from ENN
Exoneural Network	Blood oxygenation internal registration (DOC-506)	Internal registry	**Performance:** Significant increase of oxygenated blood flow. **Safety:** Not reported	Registry

3.2 Ongoing and planned clinical investigations

The table below lists the planned and ongoing clinical investigations on the EXOPULSE Mollii Suit and EXOPULSE.

Table 5. List of ongoing and planned clinical investigations on EXOPULSE devices.

Investigation site	Intended use	Diagnosis	N	Aim	Design	Primary outcome	Status
EXOPULSE Mollii Suit							
Karolinska Institutet, Sweden	Chronic pain	Shoulder pain in stroke	15	To identify the method for optimal pain relief and the types of patients which responds to the type of treatment. (KI STROKE PAIN)	Company co-funded, randomized, blinded, X-over	Pain drawing	Ongoing
KK Children's Hospital, Singapore	Spasticity	CP	20	To examine the effectiveness and feasibility of the suit. (KKH MOLLII SUIT)	Company co-funded, interventional, non-randomized, non-blinded trial	3D gait analysis	Ongoing
Henri Mondor Hospital, France	Blood circulation	MS	34	To evaluate the short-term impact on muscular oxygenation in adult MS patients suffering from spasticity. (ENNOX 1)	Investigator-Initiated, randomized controlled, double blinded, X-over	Blood oxygenation by NIRS	Ongoing
Henri Mondor Hospital, France	Spasticity Muscle activation	MS	34	To evaluate the short-term impact on balance in adult MS patients suffering from spasticity. (EXOSEP 1)	Investigator-Initiated, randomized controlled, double blinded, X-over	BBS	Ongoing
Henri Mondor Hospital, France	Spasticity Muscle activation	Stroke	34	To evaluate the short-term impact on balance in adult patients with stroke and	Investigator-Initiated,	BBS	Ongoing

Investigation site	Intended use	Diagnosis	N	Aim	Design	Primary outcome	Status
				suffering from spasticity. (EXOSTROKE 1)	randomized controlled, double blinded, X-over		
Sheikh Shakhbout Medical City, UAE	Blood circulation	MS	34	To evaluate the short-term impact on muscular oxygenation in adult MS patients suffering from spasticity. (ENNOX 2)	Investigator-Initiated, randomized controlled, double blinded, X-over	Blood oxygenation by NIRS	Ongoing
Sheikh Shakhbout Medical City, UAE	Chronic pain	Fibromyalgia	34	To assess the pain reduction obtained following active stimulation compared to sham. (EXOFIB 2)	Investigator-Initiated, randomized controlled, double blinded, X-over	FIQ	Ongoing
Sheikh Shakhbout Medical City, UAE	Spasticity Muscle activation	MS	34	To evaluate the short-term impact on balance in adult MS patients suffering from spasticity. (EXOSEP 2)	Investigator-Initiated, randomized controlled, double blinded, X-over	BBS	Ongoing
Sheikh Shakhbout Medical City, UAE	Spasticity Muscle activation	Stroke	34	To evaluate the short-term impact on balance in adult patients with stroke and suffering from spasticity. (EXOSTROKE 2)	Investigator-Initiated, randomized controlled, double blinded, X-over	BBS	Ongoing
Centre de Santé Rossetti et.al.	Spasticity Muscle activation	CP	34	To evaluate the short-term impact on balance in pediatric patients with cerebral palsy suffering from spasticity. (EXOCEP 1)	Investigator-Initiated, randomized controlled, double blinded, X-over	PBS	Ongoing
MHH/J+B Pohlig, Germany	Spasticity Muscle activation	CP	34	To evaluate the short-term impact on balance in pediatric patients with cerebral palsy suffering from spasticity. (EXOCEP 2)	Company-sponsored randomized controlled, double blind, X-over	PBS	Ongoing
EXOPULSE							
TBD	TBD	TBD	TBD	To evaluate usability and/or market preference for EXOPULSE	Usability and/or market preference	TBD	In preparation

4 Equivalence assessment

The Equivalence assessment section presents a within device group comparison between the EXOPULSE Mollii Suit and EXOPULSE. Technical, biological, and clinical characteristics of the respective devices have been compared side-by-side and are presented in Table 6. The changes that could potentially affect the clinical safety and effectiveness of the devices have been evaluated in the accompanying document *Clinical Assessment Plan EXOPULSE* (DOC-1126) and *Clinical Assessment Report EXOPULSE* (DOC-2739). The demonstration of equivalence regarding clinical safety and performance, is based on the criteria stated by the *MDR, Annex XIV Part A* and *MEDDEV 2.7/1 rev 4, Appendix A*1 and the *Medical Device Coordination Group MDCG 2020-5 Clinical Evaluation – Equivalence*.

Table 6. Technical, biological and clinical characteristics for equivalence comparison between the EXOPULSE Mollii Suit and EXOPULSE.

	EQUIVALENCE		
1. Technical characteristics	**EXOPULSE Mollii Suit** Characteristics and reference documents	**EXOPULSE** Characteristics and reference documents	**Identified differences or conclusion that there are no differences**
	1.1 Device design		
1.1.1 Device design	The EXOPULSE Mollii Suit provides a wearable technology consisting of the detachable EXOPULSE Mollii Control Unit and EXOPULSE Body Garments (jacket and pants). *Part A Description of the device EXOPULSE Mollii Control Unit*	The EXOPULSE provides a wearable technology consisting of the detachable EXOPULSE Control Unit(s) and EXOPULSE Garments (EXOPULSE Jacket, EXOPULSE Pants, EXOPULSE Undershirt, EXOPULSE Underwear). *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have **similar design**, but the EXOPULSE consists of additional, shorter garments than the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.2 Mode of action	EXOPULSE Mollii Suit is intended to deliver transcutaneous electrical stimulation to provide a neuromodulary effect, indicated to treat skeletal muscle spasticity, activate weak muscles and relieve chronic pain. The effect is mediated by a physiological reflex mechanism referred to as reciprocal inhibition. By sending an electrical signal to the antagonistic muscle, the spastic muscle will subsequently relax. *Part A Description of the device EXOPULSE Mollii Control Unit*	EXOPULSE Suit is intended to deliver transcutaneous electrical stimulation to provide a neuromodulary effect, indicated to treat skeletal muscle spasticity, activate weak muscles and relieve chronic pain. The effect is mediated by a physiological reflex mechanism referred to as reciprocal inhibition. By sending an electrical signal to the antagonistic muscle, the spastic muscle will subsequently relax. *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have the **same mode of action.**
1.1.3 Number of electrodes	The EXOPULSE Body Garments have 58 embedded electrodes which are in direct contact with the skin and pre-positioned to stimulate up to 40 key muscle groups. *Part A Description of the device EXOPULSE Mollii Control Unit*	The EXOPULSE Garments have up to 43 embedded electrodes each which are in direct contact with the skin and pre-positioned to stimulate up to 43 key muscle groups. *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The EXOPULSE has **fewer electrodes** than the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.4 Electrode size	Electrode sizes in the garments: 3 x 3 cm or 4 x 4 cm	Electrode sizes in the garments: 6 x 12 cm and 4,5 x 8 cm, or 5 x 10 cm and 4 x 7 cm, or	The EXOPULSE has **larger electrodes** than

	Biological Evaluation Plan of EXOPULSE Mollii (DOC-60)	4 x 7 cm and 3 x 5 cm *EXOPULSE Garments Design Specification* (DOC-1840)	the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.5 Electrodes / area	2 electrode(s) per stimulated area *Clinical Assessment Report*	1 electrode(s) per stimulated area *Clinical Assessment Report*	The EXOPULSE has **one electrode** per stimulated area instead of two as in the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.6 Pulse shape	Monophasic pulse *Part A Description of the device EXOPULSE Mollii Control Unit*	Biphasic pulse *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The EXOPULSE has a **biphasic pulse** instead of monophasic as in the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.7 Pulse frequency for stimulation	Pulse frequency for stimulation: 20 Hz *Part A Description of the device EXOPULSE Mollii Control Unit*	Pulse frequency for stimulation: 20 Hz *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have the **same pulse frequency** for stimulation.
1.1.8 Pulse frequency for fine-tuning	Pulse frequency for fine tuning: 20 Hz *Part A Description of the device EXOPULSE Mollii Control Unit*	Pulse frequency for fine tuning: 1 Hz *Clinical Assessment Report*	The EXOPULSE has a lower **pulse frequency used for fine-tuning** than the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.1.9 Device sizes	The EXOPULSE Body Garments are available in 34 sizes, starting from size 104 cm up to 5XL men and women. *Part A Description of the device EXOPULSE Mollii Control Unit*	The EXOPULSE Garments are available in 34 sizes, starting from size 104 cm up to 5XL men and women. *Part A Description of the device EXOPULSE*	The devices are available in the **same suit sizes**.

	1.2 Conditions of use		
1.2.1 Use conditions	Home and clinical environment *Intended Use EXOPULSE Body Garments (MDR) (DOC-293)* *Intended Use EXOPULSE MOLLII Control Unit (MDR) (DOC-125)*	Home and clinical environment *Intended Use – EXOPULSE (DOC-606)* *Intended Use for EXOPULSE Apps (DOC-3867)*	The devices have the **same use conditions.**
1.2.2 Intended use environment	Indoors *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII Control Unit (MDR)*	Indoors *Intended Use – EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices are operated in the **same use environment.**
	1.3 Physical parameters		
1.3.1 Treatment parameters	Pulse width: 30-175 µs *Part A Description of the device EXOPULSE Mollii Control Unit*	Pulse width: 20-400 µs *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The EXOPULSE has a **wider pulse width range** than the EXOPULSE Mollii Suit. *Clinical Assessment Report*
1.3.2 Pulse length	Length of period: 50 ms *Part A Description of the device EXOPULSE Mollii Control Unit*	Length of period: 50 ms *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have the **same pulse length** period.
1.3.3 Pulse amplitude	Maximum amplitude: 20 V *Part A Description of the device EXOPULSE Mollii Control Unit*	Maximum amplitude: 20 V *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have the **same maximum pulse amplitude**.
1.3.4 Pulse transmission	The EXOPULSE Body Garments transmit electric pulses from the control unit to key nerves and corresponding muscle groups throughout the body. *Part A Description of the device EXOPULSE Mollii Control Unit*	The EXOPULSE Garments transmit electric pulses from the control unit to key nerves and corresponding muscle groups throughout the body. *Part A Description of the device EXOPULSE* *Part A - Description of the device - EXOPULSE Apps*	The devices have the **same pulse transmission**.
1.3.5 Software algorithm	Software algorithm: *EXOPULSE Suit 9.3 - Stimulation* (DOC-11)	Software algorithm: *EXOPULSE Active - Stimulation Algorithm* (DOC-1129)	The software algorithms generate the **same output stimulation.**
	1.4 Deployment method		

1.4.1 Deployment method	Neuromodulation through transcutaneous electrical nerve stimulation. *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII Control Unit (MDR)*	Neuromodulation through transcutaneous electrical nerve stimulation. *Intended Use – EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices have the **same deployment method**.
	1.5 Critical performance		
1.5.1 Critical performance requirements	N.A. *Risk Management Plan EXOPULSE Mollii* (DOC-56)	N.A. *Risk Management Plan EXOPULSE* (DOC-846)	N/A. The devices do not have functions related to essential performance.
	Scientific justification		**Clinically significant difference** Y / N
1.1.1	The EXOPULSE devices have similar, but not equal design. The shorter garments – i.e. the Undershirt and Underwear – have fewer electrodes than the longer Jacket and Pants. However, by activating a subset of electrodes in the longer garments, the same stimulation pattern as in the shorter garments can be obtained. Hence, there is no significant difference in terms of performance or safety between the devices.		
1.1.2	The mode of action is the same and hence, there is no significant difference between the devices.		
1.1.3	The EXOPULSE has fewer electrodes than the EXOPULSE Mollii Suit, however the device can stimulate the same target muscles plus additionally a few more. The introduction of electrodes in the pelvic floor region in the EXOPULSE, will not impose any additional risks or significantly change the clinical performance as this area is already targeted by the EXOPULSE Mollii Suit although with less accuracy (refer to section 3.2.1 below). Hence, there is no significant difference between the devices.		
1.1.4	The EXOPULSE has larger electrodes than the EXOPULSE Mollii Suit which results in improved recruitment of sensory nerves with higher accuracy. The performance obtained by the EXOPULSE will be the same or possibly slightly improved, but there will be no significant difference in terms of performance.		
1.1.5	The EXOPULSE has one instead of two electrodes per stimulated area which results in i improved recruitment of sensory nerves. The performance obtained by the device will be the same or possibly slightly improved, but there will be no significant difference in terms of performance.		
1.1.6	The EXOPULSE Mollii Suit has a monophasic pulse whereas EXOPULSE has a biphasic pulse shape. Decoupling of the electrical current as in the biphasic pulse, may reduce the risk of side effects, but there will no significant difference in terms of performance.		
1.1.7	The pulse frequency is the same and hence, there is no significant difference between the devices.		
1.1.8	The 1Hz pulse frequency used for fine-tuning in the EXOPULSE is lower than in the EXOPULSE Mollii Suit. The lowering of the pulse frequency will make it easier to reach a desired stimulation intensity without having to exceed the stimulation level needed to obtain a clinical effect. Hence, there is no significant difference in safety and performance.		
1.1.9	The recommended suit sizes for the intended users are the same and hence, there is no significant difference.		
1.2.1	The devices are operated under the same use conditions and hence, there is		

	no significant difference.	
1.2.2	The devices are operated in the same environment and hence, there is no significant difference.	
1.3.1	EXOPULSE has a wider pulse width range than the EXOPULSE Mollii Suit, which will improve the therapeutical options, but without significantly affecting safety.	
1.3.2	The pulse length is the same and hence, there is no significant difference between the devices.	
1.3.3	The pulse amplitude is the same and hence, there is no significant difference between the devices.	
1.3.4	The pulse transmission is the same and hence, there is no significant difference between the devices.	
1.3.5	The software algorithms generate the same output stimulation and hence there is no significant difference between the devices.	
1.4.1	The deployment methods are the same and hence, there is no significant difference between the devices.	
1.5.1	N.A. The devices do not feature an essential performance.	
Conclusion	The technical characteristics of the EXOPULSE Mollii Suit have been compared to the technical characteristics of EXOPULSE. The differences have been assessed with appropriate methods as described in the *Clinical Assessment Plan EXOPULSE* and *Clinical Assessment Report EXOPULSE.* Even though minor design changes have been introduced in the EXOPULSE, the majority of the technical characteristics remain unchanged. The changes should not entail any new risks and the clinical performance will be the same or possibly better. In summary, there is no technically significant difference between the devices.	There is **NO** technically significant difference.

2. Biological characteristics	**EXOPULSE Mollii Suit** Characteristics and reference documents	**EXOPULSE** Characteristics and reference documents	**Identified differences or conclusion that there are no differences**
	2.1 Materials and human tissue contact		
2.1.1 Materials	Textile: Polyamide 59%, 41% Elastane Electrodes: Carbon-enriched conductive silicone *BOM datasheets and certificates - EXOPULSE Body Garments ((DOC-3135)*	Textile: Polyamide 59%, 41% Elastane Electrodes: Carbon-enriched conductive silicone *EXOPULSE Garments Design Specification (DOC-1840)*	The devices have **the same materials** in contact with the skin.
2.1.2 Intended tissue type	Intact skin *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII Control Unit (MDR)*	Intact skin *Intended Use – EXOPULSE Intended Use for EXOPULSE Apps*	The devices have **the same intended tissue type** for application.
	2.2 Duration of contact with human tissue		
2.2.1 Duration of use	60 minutes every other day, unless otherwise specified by the HCP. *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII*	60 minutes every other day, unless otherwise specified by the HCP. *Intended Use – EXOPULSE Intended Use for EXOPULSE Apps*	The devices used for the **same duration.**

	Control Unit (MDR)		
2.2.2 Frequency of use	Every other day unless otherwise specified by the HCP. *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII Control Unit (MDR)*	Every other day unless otherwise specified by the HCP. *Intended Use – EXOPULSE Intended Use for EXOPULSE Apps*	The devices have the **same frequency of use**.
2.2.3 Conditions for reusability	EXOPULSE Mollii Suit is for use solely by the user for whom it is adapted. In the home environment: Single patient, multiple use instances In a clinical environment: Several patients, readaptation in between patients. *Intended Use EXOPULSE Body Garments (MDR)* *Intended Use EXOPULSE MOLLII Control Unit (MDR)*	EXOPULSE is for use solely by the user for whom it is adapted. In the home environment: Single patient, multiple use instances In a clinical environment: Several patients, reprocessing and reprogramming in between patients. *Intended Use – EXOPULSE Intended Use for EXOPULSE Apps*	The devices have the **same reusability conditions**.
	2.3 Release characteristics of substances		
2.3.1 Characteris-tics of substances	N.A.	N.A.	N.A. No substances are present

	Scientific justification	**Clinically significant difference** Y / N
2.1.1	The devices are composed of the same material and hence, there is no significant difference.	
2.1.2	The intended tissue type for application is the same and hence, there is no significant difference between the devices.	
2.2.1	The devices used for the same duration and hence there is no significant difference.	
2.2.2	The use frequencies are the same and hence, there is no significant difference between the devices.	
2.2.3	The reusability conditions are the same and hence, there is no significant difference between the devices.	
2.3.1	N.A. The devices don't release any substances.	
Conclusion	The biological characteristics of the EXOPULSE Mollii Suit have been compared to the biological characteristics of EXOPULSE. As all characteristics remain unchanged, there is no biologically significant difference between the devices.	There is **NO** biologically significant difference.

3. Clinical characteris-tics	**EXOPULSE Mollii Suit** Characteristics and reference documents	**EXOPULSE** Characteristics and reference documents	**Identified differences or conclusion that there are no differences**

	3.1 Clinical condition/purpose		
3.1.1 Intended use	- Relaxation of tense and spastic muscles - Activation of muscles - Increasing local blood circulation - Symptomatic relief of chronic pain *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Garments (MDR)*	- Relaxation of tense and spastic muscles - Activation of muscles - Increasing local blood circulation - Symptomatic relief of chronic pain *Intended Use – EXOPULSE Intended Use for EXOPULSE Apps*	The devices have the **same intended use**.
3.2.1 Intended purpose	The EXOPULSE Mollii Suit is intended to provide: - relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and pain relief in patients with CP, MS, stroke and other neurologic disorders which may cause such type of symptoms, together with - pain relief in patients with fibromyalgia, and other neurologic disorders which may cause such type of symptoms. *Intended Use EXOPULSE MOLLII Control Unit (MDR) and Intended Use EXOPULSE Body Garments (MDR)*	The EXOPULSE is intended to provide: - relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and pain relief in patients with CP, MS, stroke, and other neurologic disorders which may cause such type of symptoms, together with - pain relief in patients with fibromyalgia, and other neurologic disorders which may cause such type of symptoms. *Intended Use - EXOPULSE Intended Use for EXOPULSE Apps*	The devices are used for the **same intended purpose**.
3.1.3 Indication of use	For relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and pain relief in patients with CP, MS, stroke and other neurologic disorders which may cause such type of symptoms. For pain relief in patients with fibromyalgia, and other neurologic disorders which may cause such type of symptoms. *Intended Use EXOPULSE MOLLII Control Unit (MDR)* (DOC-125) *Intended Use EXOPULSE Body Garments (MDR)* (DOC-293)	For relaxation of tense and spastic muscles and muscle activation, improved local blood circulation and/or pain relief in patients with CP, MS, stroke, fibromyalgia, and other neurologic disorders which may cause such type of symptoms. *Intended Use - EXOPULSE Intended Use for EXOPULSE Apps*	The devices have the **same indications of use.**
	3.2 Site on the body		
3.2.1 Place of application	Upper and lower extremities, torso and pelvic region *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body*	Upper and lower extremities, torso and pelvic region *Intended Use - EXOPULSE Intended Use for EXOPULSE Apps*	The devices have the **same place of application** on the body.

	Garments (MDR)		
	3.3 Target population		
3.3.1 Patient population	Any patient from 2 years and up, female, male, non-binary (Control Unit). From children, 100 cm and 13 kg up to women 200 cm and 100+ kg and men 205 cm and 115+ kg, including overweight users (Body Garments). *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Ga ments (MDR)*	The target population is any patient from 2 years and up, female, male, non-binary; height 100 cm to 205 cm *Intended Use - EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices are used in the **same patient population.**
3.3.2 Gender of patient	female/male/non-binary *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Garments (MDR)*	female/male/non-binary *Intended Use - EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices are used for the **same genders.**
3.3.3 Age of patient	From 2 years and up *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Garments (MDR)*	From 2 years and up *Intended Use - EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices are used for the **same patient ages**.
3.3.4 Nationality/et hnic group	All nationalities *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Garments (MDR)*	All nationalities *Intended Use - EXOPULSE* *Intended Use for EXOPULSE Apps*	The devices are used for the **same nationalities/eth nic groups.**
	3.4 Intended users and critical performance		
3.4.1 Intended users	Laypersons, caregivers, HCP *Intended Use EXOPULSE MOLLII Control Unit (MDR)* *Intended Use EXOPULSE Body Garments (MDR)*	Laypersons, caregivers, HCP *Intended Use - EXOPULSE*	The devices are used for the **same intended users.**
3.5.1 Critical performance in view of the expected clinical effect	N.A. *Risk Management Plan EXOPULSE Mollii* (DOC-56)	N.A. *Risk Management Plan EXOPULSE* (DOC-846)	N/A. The devices do not have functions related to essential performance.
	Scientific justification		**Clinically significant difference** Y / N
3.1.1	The intended use is the same and hence, there is no significant difference between the devices.		
3.1.2	The intended purpose is the same and hence, there is no significant difference		

	between the devices.	
3.1.3	The indications are the same and hence (minor change of wording only), there is no significant difference between the devices.	
3.2.1	The place of application on the body is the same and hence, there is no significant difference between the devices.	
3.3.1	The patient populations are the same and hence, there is no significant difference between the devices.	
3.3.2	The genders using the devices are the same and hence, there is no significant difference between the devices.	
3.3.3	The patients ages are the same and hence, there is no significant difference between the devices.	
3.3.4	The nationalities/ethnic groups using the devices are the same and hence, there is no significant difference between the devices.	
3.4.1	The intended users are the same and hence, there is no significant difference between the devices.	
3.5.1	N/A. The devices do not have functions related to essential performance.	
Conclusion	The clinical characteristics of the EXOPULSE Mollii Suit have been compared to the biological characteristics of EXOPULSE. As all characteristics remain the same, there is no clinically significant difference between the devices.	There is **NO** clinically significant difference.

5 Clinical background and state of the art

5.1 Data search method

The scientific databases were searched, and relevant state-of-the-art literature were collected, reviewed and analysed. As seen in Table 7, chronic pain is used as a common term, which includes different chronic conditions such as fibromyalgia etc.

Table 7. Overview of search terms used in scientific databases.

Search method	Search terms	Comments
Published literature	Neuromuscular electrical stimulation AND Spasticity, muscle tonus, muscle activation, blood circulation, chronic pain, AND multiple sclerosis, stroke, cerebral palsy Transcutaneous electrical muscle stimulation AND Spasticity, muscle tonus, muscle activation, blood circulation, chronic pain AND, multiple sclerosis, stroke, cerebral palsy	PubMed and Cochrane Library

5.2 Data search results for state-of-the-art literature

The total time period for the data search for state-of-the-art literature in all *Clinical Evaluation Reports* ranges from 2016-2023.

5.2.1. Data search on performance

The most recent literature search covers the time period 09.04.2016 – 01.01.2023, employing both the PubMed and the Cochrane Library in Table 8.

Table 8. Relevant literature search in PubMed and the Cochrane Library.

Literature search The literature search was conducted online in PubMed (search 1, 2, 3 and 4) and Cochrane Library (5, 6, 7 and 8). Filters used in search term 1-4 are: clinical study, clinical trial and the time period found in the table below.		
Search term(s)		**Hits**
1	“neuromuscular electrical stimulation” AND (“Spasticity” OR “muscle tonus” OR “muscle activation” OR “Blood circulation” OR “Chronic pain”) Time period: 04.11.2021-01.01.2023	4
2	“neuromuscular electrical stimulation” AND (“Multiple Sclerosis” OR “Stroke” OR “Cerebral Palsy”) Time period: 12.11.2021 – 01.01.2023	13
3	“transcutaneous electrical nerve stimulation” AND (“Spasticity” OR “muscle tonus” OR “muscle activation” OR “Blood circulation” OR “Chronic pain”) Time period: 01.11.2021 – 01.01.2023	5
4	“transcutaneous electrical nerve stimulation” AND (“Multiple Sclerosis” OR “Stroke” OR “Cerebral Palsy”) Time period: 01.01.2021 – 01.01.2023	2
5	“neuromuscular electrical stimulation” AND (“Spasticity” OR “muscle tonus” OR “muscle activation” OR “Blood circulation” OR “Chronic pain”) Time period: 01.11.2021-01.01.2023	0
6	“neuromuscular electrical stimulation” AND (“Multiple Sclerosis” OR “Stroke” OR “Cerebral Palsy”) Time period: 09.04.2016-01.01.2023	3
7	“transcutaneous electrical nerve stimulation” AND (“Spasticity” OR “muscle tonus” OR “muscle activation” OR “Blood circulation” OR “Chronic pain”) Time period: 01.11.2021 – 01.01.2023	0
8	“transcutaneous electrical nerve stimulation” AND (“Multiple Sclerosis” OR “Stroke” OR “Cerebral Palsy”) Time period: 09.04.2021 – 01.01.2023	0
Potentially relevant literature identified through the search		27
Literature excluded (reasons to find in Appendix A)	**Total**	**-23**
Elimination of duplicates		-1

	Not appropriate language					0
	Not in humans					0
	Another field of study (e.g., acupuncture, balneotherapy)					
	Inappropriate type of publication (i.e., preclinical study, socio-economic assessment/cost-effectiveness, non-peer-reviewed opinion, comments on an article, pilot study, systematic review, review meta-analysis).					-5
	Not passing suitability criteria					0
	Not appropriate medical condition and patient group					-7
	Not appropriate device/treatment					-10
	Not appropriate report data collation					-0
Additional relevant literature identified: (previous search)			**Total**			**59 (7+44+8)**
	References in literature from literature search					0
	Additional literature identified by the authors (e.g., used in former clinical evaluation)					59
Classification of literature						**63 (4 new + 59 from previous search)**
A Articles about device(s) under evaluation	B Studies about clinical background, alternative therapies, benchmark devices and state of the art	C Further documents such as overviews and expert opinions not requiring further evaluation for their inclusion		A	B	C
				0	7+8+ 44+4	0
A	Articles about device(s) under evaluation -> will be included in chapter 6.2.1					0
B	Literature for further selection based on data contribution (weighting) criteria In B excluded literature to find in Appendix A					
	Not passing data contribution (weighting) criteria					0
	Study or relevant content is part of a review already identified					0
Relevant literature for new clinical background and state of the art						**4 new** (59 from previous search)

A total of 27 publications were identified using search terms 1-8 (see Table 8). After removing duplicates and publications not meeting the requirements (as established in the *Clinical Evaluation Plan*), 4 publications remained. A schematic overview of the methodology of the literature search and selection criteria is presented in Table 9 below. Additionally, 59 articles were added from previous searches and are included in the summary in Section *Summary of previous literature searches*.

Table 9. Schematic overview of the result summary of the literature search and selection criteria.

Author(s)	Title	Published	Study type	Key results
Ohnishi H, Miyasaka H, Shindo N, Ito K, Tsuji S, Sonoda S.	Effectiveness of Repetitive Facilitative Exercise Combined with Electrical Stimulation Therapy to Improve Very Severe Paretic Upper Limbs in with Stroke Patients: A Randomized Controlled Trial	Occup. Ther. Int. 2022 Apr 27;2022:4847363	Randomized controlled trial	The study compared combined therapy with repetitive facilitative exercises (RFE) and NMES in 99 patients with severe upper limb paresis after stroke. Results suggest that the combination of voluntary movement and electrical stimulation may promote the activation and improve distal function of severely paralyzed upper limbs.
Yoon YS, Ko MH, Cho IY, Kim CS, Bajgai J, Jang HY, Kim KE, Lee KJ, Lee M.	Effects of Personal Low-Frequency Stimulation Device on Myalgia: A Randomized Controlled Trial	Int J Environ Res Public Health. 2022 Jan 10;19(2):735	Randomized controlled trial	A personal low frequency stimulation device (PLS) was compared with combined TENS and Ultrasound. VAS scores were significantly lower in both groups post treatment. The PLS group showed a tendency of muscle relaxation with a significant decrease in surface electromyography in the neck, shoulder and back region compared to the control group.
Martins-de-Sousa PH, Fidelis-de-Paula-Gomes CA, Pontes-Silva A, Henrique MFP, Araujo GGC, Kalatakis-Dos-Santos AE, Damasceno KLB, Dibai-Filho AV.	Additional effect of transcutaneous electrical nerve stimulation in a therapeutic exercise program for sedentary with chronic neck pain: A double-blind randomized controlled trial	Physiother Res Int. 2023 Jan;28(1):e1978	Randomized controlled trial	The addition of high or low frequency TENS to a specific therapeutic exercise program for the treatment of chronic neck pain was evaluated in this study. The results showed no statistical or clinical differences between high or low frequency TENS compared to placebo TENS in terms of pain intensity, disability, catastrophizing or kinesiophobia.
Chen P, Liu TW, Kwong PWH, Lai CKY, Chung RCK, Tsoh J, Ng SSM.	Bilateral Transcutaneous Electrical Nerve Stimulation Improves Upper Limb Motor Recovery in Stroke: A Randomized Controlled Trial	Stroke. 2022 Apr;53(4):1134-1140	Randomized controlled trial	Bilateral TENS and task-oriented training (TOT) were compared to unilateral TENS+TOT, Placebo TENS+TOT and no treatment. Patients who received bilateral TENS and TOT showed greater improvements in the Fugl-Meyer Assessment of Upper Extremity scores compared to the other groups. Results indicate that both uni- and bilateral TENS combined with TOT led to significant within-group improvements in the Fugl-Meyer Assessment.

The clinical studies described in Table 9 include a total of 318 participants and present evidence on patients with stroke and chronic pain. Overall, the results from these clinical studies show that the use of TENS and NMES can lead to improvements of muscle function, muscle activation and alleviation of pain. More specifically, the results from one of the articles suggests that that the combination of voluntary

movement and NMES may promote the activation and improve distal function of severely paralyzed upper limbs in stroke patients (Ohnishi et al., 2022). One study could not find any additional effects of TENS to a therapeutic exercise program for sedentary with chronic neck pain (Martins-de-Sousa et al., 2023). However, another randomized controlled trial that investigated the effect of a personal low frequency stimulation device (PLS) compared with combined TENS and ultrasound on myalgia, showed that the VAS scores were significantly lower in both groups after the treatment (Yoon et al., 2022).

Finally, a randomized controlled trial by Chen et al. (2022) suggested that bilateral TENS and task-oriented training improved upper limb motor recovery in stroke. In the same study, the results also indicated that both uni- and bilateral TENS in combination with task-oriented training led to significant within-group improvements in the Fugl-Meyer Assessment of Upper Extremity scores.

Summary of previous literature searches

The clinical studies from previous literature searches present evidence on participants with stroke, MS, and other neurological disorder such as spinal cord injuries and as well as in patients undergoing postoperative rehabilitation. Overall, the studies show decreased spasticity, increased walking capacity and increased muscle activity when using electrical stimulation.

Another review conducted on stroke survivors suggested that TENS improved walking capacity compared to a placebo group. However, a prospective randomized controlled study on 30 stroke patients did not find any difference between the three groups of task-oriented exercises, TENS for 30 min and task-oriented exercises or TENS for 60 min and task-oriented exercises.

A study conducted by Almuklass et al. (2020) showed clinically significant improvements in walking endurance, maximal walking speed and symptom relief after 6 weeks of NMES in an MS population. Other studies demonstrated that NMES did not only reduce shoulder pain and subluxation, but also improved shoulder abduction and arm function in patients with acute stroke. Schuhfried et al. (2012) also suggested that NMES can lead to improvements in voluntary motor control by strengthening muscles, reducing spasticity, decreasing pain, increasing range of motion, and reorganizing damaged corticocerebral circuits after stroke. A study that assessed the effect of NMES and TENS on hemiplegic shoulder pain showed that both treatments effectively improved the symptoms of the disease and that the effect of the NMES intervention was superior to that of TENS in maintaining long-term analgesia (Zhou et al., 2018).

An article by Yang et al. (2018) showed that NMES can lead to improvements in muscle strength of the ankle dorsiflexors as well as reduced foot drop and decreased plantar muscle spasticity in a stroke population. Furthermore, the results showed an increase in the gait symmetry, gait speed and walking distance. Another article by Takeda et al. (2020) indicated that applying low intensity NMES of the gluteus medius to gait significantly increased the rate of force development of the hip abductor muscles.

This had an important clinical implication on the effective use of a limited amount of training time, as gait training is one of the most used exercises for patients with hip abductor muscle weakness.

Moreover, articles from previous literature searches showed evidence of decreased spasticity and muscle activation when using TENS, as well as a moderate level of evidence for chronic pain, and improved blood circulation.

In conclusion, the research articles identified herein, support the use of TENS and/or NMES for relaxation of spastic and tense muscles, muscle activation, improved blood circulation and symptomatic chronic pain relief.

5.2.2 Data search on risk

The period for the data search on risk in the previous versions of the Clinical Evaluation Reports (*Clinical Evaluation Reports EXOPULSE Mollii 1.00 – 3.00*) was 12.05.2016 – 01.11.2021. In Table 10 the period of data search on risk, an overview of the methodology, search terms and selection criteria are presented for the current version of the report.

Table 10. The latest performed data search on risk in the *Clinical Evaluation Report*.

Literature search Search was conducted online in PubMed and Cochrane Library. Period of search for respectively search terms are described in the table below.		
Search term(s)		**Hits**
1	"Transcutaneous Electrical Nerve Stimulation" AND ("risk" OR "complication" OR "adverse events" OR "use error" OR "Equipment Failure" OR "skin irritation" OR "skin blister" OR "Skin burn") Filters in PubMed: Clinical Study, Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial, Humans, English Period of search: 01.11.2021 – 01.01.2023	5
2	"Transcutaneous Electrical Nerve Stimulation" AND ("risk" OR "complication" OR "adverse events" OR "use error" OR "Equipment Failure" OR "skin irritation" OR "skin blister" OR "Skin burn") Filters in Cochrane: 01.11.2021 – 01.01.2023 Period of search: 01.11.2021 – 01.01.2023	0
3	"Neuromuscular Electrical Stimulation AND" ("risk"[Mesh] OR "adverse events" OR "complication" OR "use error" OR "Equipment Failure"[Mesh] OR "skin irritation" OR "skin blister" OR "Skin burn") Filters in PubMed: Clinical Study, Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial, Humans, English. Period of search: 01.11.2021 – 01.01.2023	3

4	"Neuromuscular Electrical Stimulation AND" ("risk" [Mesh] OR "adverse events" OR "complication" OR "use error" OR "Equipment Failure" [Mesh] OR "skin irritation" OR "skin blister" OR "Skin burn") Filters in Cochrane: 01.11.2021 – 01.01.2023 Period of search: 01.11.2021 – 01.01.2023	0
Potentially relevant literature identified through the search		8
Literature excluded:	**Total**	**-5**
	Elimination of duplicates	0
	Not appropriate language	0
	Not in humans	0
	Another field of study (e.g., tooth implants, cardiovascular surgery)	-1
	Inappropriate type of publication (i.e., preclinical study, socio-economic assessment/cost-effectiveness, non-peer-reviewed opinion, comments on an article).	0
	Not passing suitability criteria	-4
	Not appropriate medical condition and patient group	-1
	Not appropriate device/treatment	-3
	Not appropriate report/data collation	0
Additional relevant literature identified:	**Total**	**12 (4+4+4) from previous search)**
	References in literature from literature search	0
	Additional literature identified by the authors (e.g. used in former clinical evaluation)	12
Classification of literature		**15 (3 new, 12 (4+4+4) from previous search)**

A	B	C	A	B	C
Articles about device(s) under evaluation	Studies about clinical background, alternative therapies, benchmark devices and state of the art	Further documents such as overviews and expert opinions not requiring further evaluation for their inclusion	0	15	0

A	Articles about device(s) under evaluation -> will be included in chapter 5.2.1	0
B	Literature for further selection based on data contribution (weighting) criteria In B excluded literature to find in Appendix A	
	Not passing data contribution (weighting) criteria	0

	Study or relevant content is part of a review already identified	0
Relevant new literature for clinical background and state of the art		**3**

The search for state-of-the-art literature on risk identified 8 articles. After removing duplicates and publications not meeting requirements (as established in the *Clinical Evaluation Plan*), 3 new articles were considered for further classification, which are presented in Table 11. Articles from previous searches are found in APPENDIX G and are included in the overall evaluation of data search on risk for the product under evaluation.

Table 11. Overview on new articles considered for further classification.

Author(s)	Title	Published	Study type	Key results
Namsawang J, Muanjai P.	Combined Use of Transcutaneous Electrical Nerve Stimulation and Short Foot Exercise Improves Navicular Height, Muscle Size, Function Mobility, and Risk of Falls in Healthy Older Adults.	Int J Environ Res Public Health. 2022 Jun 11;19(12):7196.	Clinical study	No reported adverse events.
Reichenbach S, Jüni P, Hincapié CA, Schneider C, Meli DN, Schürch R, Streit S, Lucas C, Mebes C, Rutjes AWS, da Costa BR.	Effect of transcutaneous electrical nerve stimulation (TENS) on knee pain and physical function in patients with symptomatic knee osteoarthritis: the ETRELKA randomized clinical trial.	Osteoarthritis Cartilage. 2022 Mar;30(3):426-435.	Randomized clinical trial	The occurrence of adverse events was similar across groups, with 10.4% and 10.6% of patients reporting events in the TENS and placebo TENS groups, respectively (P 1⁄4 0.95). No relevant differences were observed in secondary outcomes.
Jamison RN, Curran S, Wan L, Ross EL, Gilligan CJ, Edwards RR.	Higher Pain Sensitivity Predicts Efficacy of a Wearable Transcutaneous Electrical Nerve Stimulation Device for Persons With Fibromyalgia: A Randomized Double-Blind Sham-Controlled Trial.	Neuromodulation. 2022 Dec;25(8):1410-1420.	A Randomized Double-Blind Sham-Controlled Trial	No reported adverse events.

In two of the articles in Table 11, no adverse events were reported when using TENS or NMES (Namsawang and Muanjai 2022 and Jamison et al., 2022). In the third article where TENS was compared with placebo, the occurrence of adverse events was similar across the two groups, with 10.4% and 10.6% of patients reporting events in the TENS and placebo TENS groups, respectively (Reichenbach et al., 2022). In a previous search an article presented that 8 out of 83 patients reported

minor and acceptable side effects such as dizziness, discomfort, headache, muscle spasms and itchy skin, caused by NMES.

In summary, based on the large number of publications on TENS and NMES found in PubMed and Cochrane, the relatively few adverse events reported and the relatively mild severity, the method is considered to be safe for its intended use as described in the present report.

5.2.3 Data search on alternative treatments

A schematic overview of the methodology of the literature search and selection criteria is presented. Search terms were selected according to standard of care, known by the authors, for the intended use of the device under evaluation. In total 387 articles were found in PubMed and 23 in Cochrane. Duplicates and other fields of study were excluded. Special techniques of injection, surgery techniques or Phase 3 or earlier drug studies, as well as studies comparing treatments which were not part of the search to other treatments, were excluded as 'other field of study'. 37 articles were assessed for the literature weighting while 10 publications passed the weighting and were included in the clinical evaluation. Some references from a previous version of the clinical evaluation were used to explain the basic mechanism of action or general information about baclofen, chronic pain or botulinum toxins. The main findings from the articles are summarized in the sub-sections below.

There are multiple treatments available for spasticity and chronic pain, with different advantageous and side effects, however we have decided to focus on baclofen, botulinum toxin and analgesics. Baclofen and botulinum toxin are two alternative treatments for spasticity which are both well-known and common treatments. Data on baclofen and botulinum toxin is being presented in the first section below and, in the second section, data on analgesics as an alternative treatment for chronic pain is presented.

5.2.4.1 Baclofen for spasticity

Baclofen is the main drug treatment considered for muscle spasticity. It works as a GABA-agonist selectively binding to presynaptic GABA-B receptors, resulting in hyperpolarization of motor horn cells (Meythaler et al., 2001) and a subsequent reduction in the hyperactivity of muscle stretch reflexes, clonus, and cutaneous reflexes that elicit muscle spasms (Campbell et al., 1995). Although widely used, baclofen is mainly water soluble and thus does not readily cross the blood-brain barrier (Misra et al., 2003). As a result, patients may require a high dose to treat their spasticity effectively, which can cause intolerable side-effects (Jose et al., 2013). An alternative way to deliver baclofen is directly into the cerebrospinal fluid (CSF) in the intrathecal space, bypassing the blood-brain barrier entirely. To directly infuse baclofen into the cerebrospinal fluid, through a catheter, a much higher CSF concentration can be achieved at a lower plasma concentration, than would be possible to be achieved with an oral baclofen medication. As a result, the central nervous system side-effects of oral baclofen (e.g. headache, sedation and drowsiness) may be reduced (Meythaler et al., 2001).

Intrathecal baclofen may be a useful medication for patients with severe chronic spasticity caused by CP or stroke as it can lead to an increased quality of life, achievement of individual goals and reduction in pain and spasticity (Bonouvrié et al., 2019 and Creamer et al., 2018). Bonouvrié et al., investigated the effect of intrathecal baclofen in patients with dyskinetic CP (between 4 and 25 years old, Gross Motor Functioning Classification System (GMFCS) level of IV and V) in a multicenter, double-blind, placebo-controlled clinical trial. The treatment group received an increasing over time dose of intrathecal baclofen (ITB) and the placebo group received sodium chloride via an implanted microinfusion pump. For the ITB group the individual goals (primary outcome) are completely achieved significantly more often than for the placebo group, as 29% of the patients of the ITB group achieved three goals, 12% two goals, 18% one goal and 41% zero goals compared to 13% of the patients in the placebo group achieving one goal and 87% achieving zero goals. For the number of goals partially achieved there was also a significant difference in favor of the ITB group. For dystonia assessed by Dyskinesia Impairment Scale (DIS) a significant difference was investigated for the total DIS and DIS at rest but not for DIS at activity. There were no significant differences between the two groups regarding the number of adverse events reported. For the secondary outcomes regarding body functions and structures (spasticity, pain and comfort), choreoathetosis or in the domain of activities and participation no significant differences could be found. In contrast Creamer et al. (2018) found a significant improvement of the actual pain and least pain in favor of ITB after 6 months of treatment (no significant difference was found for worst pain). The study was conducted as a multicenter randomized controlled trial with 48 patients (24 patients received ITB and 24 patients received conventional medical management (CMM)) which were assessed during the baseline measurement and after three and six months. In addition to pain a significant difference between the changes from baseline to the six months measurement in the ITB and the CMM group for the EuroQol-5-dimensional 3 level utility scores and the satisfaction with the reduction of spasticity was observed.

5.2.4.2 Botulinum toxin for spasticity

Botulinum toxin, commonly referred to as Botox (Jankovic and Brin, 1991) is currently the most widely used treatment for focal spasticity (Brashear and Lambeth, 2009) and avoids the generalized weakness and sedation accompanying oral medications (Khedar and Nair, 2012). Botulinum works by inhibiting the release of vesicular acetylcholine from presynaptic nerve terminals at the neuromuscular junction (Burchiel and Hsu, 2001).

For an effective treatment of spasticity, botulinum toxin injections have to be repeated regularly (every 3-4 months) as the time of effectiveness after injection is limited (Chen et al., 2022). Chen et al., investigated the time course of biomechanical, electrophysiological and neuro-motor effects after botulinum toxin injections in 12 stroke patients with spastic upper limb hemiplegia. Assessment of the investigated parameters like Modified Ashworth Scale (MAS) and muscle strength took place pre-injection, after 3-4 weeks and 3 months. While a significant reduced MAS score and therefore improved

spasticity was observed during the first follow up visit, the MAS score has again significantly increased between the first follow up and the 3-month assessment whereas the MAS score did not fully return to the value measured pre-injection. For the maximum voluntary contraction an opposite behaviour was observed, as the value at the first follow up was significantly lower than for the pre-injection and the 3-month measurement. The study results suggest that the reduced spasticity, which is accompanied by a decreased muscle strength at 3-4 weeks after the injection, turn towards the baseline level after 3 months.
Other studies by Tan et al. (2021) and Marque et al. (2019) dealing with upper limb spasticity and botulinum toxin type A injections, also found significant reduced MAS score values after 3-4 weeks. Regarding pain significant results were obtained, proving that the effectiveness of botulinum toxin as pain has decreased significantly whereas quality of life has increased. No major adverse effects related to botulinum toxins were found in both studies which include in total 348 patients who had received botulinum injections in the course of their respectively study.

Concerning lower limb spasticity botulinum toxins, like onabutolinumtoxinA, are also a common treatment and are used for many different kinds of spasticity (Esquenazi et al., 2021). The authors investigated in an international, multicentre (54 clinical sites) prospective observational study with 320 patients with lower limb spasticity, the real-world indications for a onabutolinumtoxinA treatment. The results showed that the Equinovarus foot was treated most often (80.9% of patients), followed by flexed knee (26.0%), stiff extended knee (22.5%), and flexed toes (22.3%). Regarding safety and tolerability, in total 643 adverse events were reported by 197 patients throughout the whole study which lasts for 108 weeks. 21 of these adverse events (reported by 18 patients) were related to the treatment (only 3 were rated as serious (1x dysphagia, 1x muscular weakness, 1x slow speech). The effectiveness of botulinum injections for the treatment of lower limb spasticity caused by stroke, multiple sclerosis or spinal cord injury in 25 patients were investigated by De Icco et al. (2019). A significant reduced MAS score attained by a reduced rating of pain 30 days after injection could be observed.

5.2.4.3 Opioids for chronic pain

For patients suffering from chronic pain, which is defined as pain that lasts longer than three months (Merskey, 1994), an adequate treatment is important in order to reduce the pain intensity and therefore improve several aspects of daily living like work performance and quality of life (Hwang et al., 2018) as pain leads to reduced mobility and physical activity as well as increased frailty and frequency of falls in combination with a poor sleeping quality (Aurilio, 2019). Long term opioid therapy is a standard treatment for severe chronic pain although it contains risks for serious harms (Krebs et al., 2018) and adverse events like constipation, nausea and vomiting (Hwang et al., 2018).

In order to reduce constipation, which is the most common and bothersome adverse effect of opioid treatment, the combination of the opioid with naloxone, which is a peripherally acting opioid antagonist,

may be a proper solution. Hwang et al. (2018) investigated the analgesic efficacy and safety of a combined treatment of Ocycodone and Naloxon in patients with chronic pain from spinal disorders.

In total 209 patients with moderate to severe spinal disorder related pain (not satisfactorily controlled with weak opioids) received prolonged oral oxycodone/naloxone combination for 8 weeks during a multicenter single-arm study. While the overall mean numerical rating scale (NRS) pain score decreased significantly (from 6.5 ± 1.4 at baseline to 4.8 ± 2.0 at week 8), quality of life was significantly improved (EQ-5D score improved by 37.5%). In total 95 drug related adverse events were reported in 61 patients whereas the most common adverse events were nausea, constipation and dizziness. The vast majority of the adverse events were rated as mild and had resolved at the end of the study period and no serious adverse reactions caused by the drug were reported. An improved tolerability compared with standard opioids could also be the treatment with tapentadol prolonged release, a centrally acting analgesic with a dual mechanism of action, combining μ-opioid receptor agonism and noradrenaline reuptake inhibition (Aurilio 2019).

The investigation of the efficacy and tolerability of tapentadol in 20 geriatric patients (70-79 years) with chronic non-oncologic pain who received an increasing amount of tapentadol over the study time of 90 days, was the aim of a study conducted by Aurilio in 2019. A 26% decrease of pain intensity during loading was observed at T1 (after 3-5 days), 38% decrease at T2 (after 14-21 days), 50% decrease at T3 (after 30-40 days) and 63% significant decrease at T4 (after at least 90 days). For pain intensity at rest a similar decrease was found. In addition, the quality of sleep improved significantly. As only one minor side effect was reported by one patient the tolerability and safety are stated as very good and the study results suggest that tapentadol is a safe and effective treatment for pain control in elderly people.

Besides the common adverse events related to treatment with opioids the death rate of opioid overdose is rising (Krebs et al., 2018). Therefore, Krebs and co-workers investigated the effect of opioid vs nonopioid medications over a period of 12 months. In total the results of 234 patients (119 received opioids, 119 received non-opioid medication) with severe chronic back pain or hip or knee osteoarthritis were available. The pain intensity was significantly better in the non-opioid group and no significant difference was observed regarding pain related function. In addition, there were significantly more adverse symptoms related to medication in the opioid group but there was no significant difference regarding potential misuse between the two treatment groups. Overall, the results showed that treatment with opioid was not superior in this study and the results do not support the initiation of opioid therapy for the study population.

5.2.4 Comparison of the EXOPULSE Molli Suit to other treatment options

The efficacy of the EXOPULSE Mollii Suit can be directly compared to other treatment options, like for instance botulinum toxin injections. The suit is advantageous in being non-invasive and non-

pharmacological and with a long-lasting effect when used 60 minutes every other day. In a comparative study using a Neuroflexor device to measure spasticity in stroke patients, a significant decrease was observed at 4 weeks, while the drop in the neuronal component from 25.7 to 18.3 Newton, 4 weeks after the botulinum toxin injection was comparable to the magnitude of the effect obtained with the EXOPULSE Mollii Suit (Gäverth et al., 2014; Palmcrantz et al., 2020). However, the spasticity returned to almost baseline 12 weeks after the botulinum toxin injection, whereas the effect of the EXOPULSE Mollii Suit is known to last for at least 6 months or possibly more (Hedin et al., 2020; Torabi et al., 2021). Moreover, the EXOPULSE Mollii Suit has none of the negative side effects, like immune resistance to the drug, denervation, muscle atrophy, headache, paralysis, dizziness, nausea, which botulinum toxin injections have.

The effects of the EXOPULSE Mollii Suit can also be directly compared with intensive physiotherapy. The device has been shown to have similar effects on gross motor function and mobility as intensive physiotherapy (Bakaniene et al., 2018). The results of the GMFM test showed significant improvement from 79.7 to 82.4 in the EXOPULSE Mollii Suit group and from 84.6 to 86.9 in the physiotherapy group. The TUG mean decreased significantly from 17.2 to 15.0 seconds in the case of the EXOPULSE Mollii Suit, whereas the corresponding decrease in the physiotherapy group was 15.5 to 13.6. This shows that the EXOPULSE Mollii Suit can be used to obtain the same effects as with intensive physiotherapy (3 sessions per week), but without the need for involvement of a health care professional or a rehabilitation clinic, i.e. lower costs and higher degree of autonomy for the patient.

5.3 Clinical Background and state of the art literature

5.3.1 Electrostimulation

Electrostimulation (ES) is a non-invasive strategy for modulating the nervous system and the use of the therapy started already in the 1970's (Baker et al., 1979; Pape et al., 1993; Pape et al., 1994). There are several modalities depending on the length and intensity of the stimulation (Kerr et al., 2006; van der Linden et al., 2008). The method is based on application of electrical pulses to the muscles and/or tendons that cause muscle contraction or afferent fibers that reactivate the spinal cord circuits and its neurons. It is used as a tool for treatment of motor impairment pathologies, acute and chronic pain conditions and improving blood circulation.

The specific magnitude of the parameters of stimulation may vary and clinical studies commonly report the use of different parameters within the same modality of stimulation, to attain a desired effect and at the same time avoid discomfort, pain, and skin irritations. This is because the parameters can vary from one individual to another. Stimulation parameters are commonly set to 20-50 Hz, 30-500 µs and ≤100 mA. The waveform of electrical current pulses is defined by the amplitude (mA), pulse width (µs or ms)

and frequency (Hz). The frequency and pulse width are usually set at constant level, whereas the amplitude may vary.

5.3.2 Neuromodulation

Neuromodulation is part of the spectrum of functional electrical stimulation and is alternatively also addressed with pharmacological modalities. It is characterized by focused influence on neural excitability:

- in peripheral or central neurons, by modifying resting potentials in the cell membranes, or
- in spinal or brain interneuron processing by artificial neural inputs, namely via afferent neurons, for inducing inhibitory or excitatory functional changes.

This physiological process can be addressed by direct current stimulation or depolarizing or hyperpolarizing pre-pulses to stimuli, to lower or elevate the threshold for electrical discharge in electrically excited cellular membranes. The process is based on eliciting action-potentials in afferent sensory neurons to provide additional input to central interneuron networks and there are two ways to realize this – intensity, which can be modulated via stimulus pulse amplitude or pulse width which is the decisive parameter for recruitment of nerve fibers.

With growing intensity, first proprioceptive afferent neurons (Group I afferents) are recruited from just few fibers to a growing group. Group I have the largest diameter and, as excitability to external electrical fields is proportional to fiber size, they can be recruited with selectivity. With further increase of intensity, the next, smaller neurons (cutaneous afferents, Group II and then Group III) get growingly co-recruited. Each single stimulus triggers a single action-potential in all recruited nerve fibers at the same time and in the same location. Action-potentials travel in both directions along the fiber and as travel speed is influenced by size, it leads to variation in arrival time at the next synaptic input junction. All orthodromically arriving action-potentials act as additional afferent input to the spinal interneuron networks. In addition to modulating the amount of afferent input in interneuron networks, the frequency modulation of arriving action-potentials is the second modality of influence. Both modalities can cause excitatory and inhibitory effects in spinal reflex processing, from monosynaptic and polysynaptic responses to involvement of multiple interneurons and increasingly complex control algorithms.

5.3.3 Cerebral palsy

Cerebral palsy (CP) encompasses a spectrum of non-progressive syndromes characterized by posture and motor impairments, typically manifesting before or within two years after birth (Dabney et al., 1997; Flett, 2003). These impairments result from diverse forms of damage to different regions within the developing nervous system, leading to a wide variability in clinical presentations (Koman, 2004). While historical associations have been made with delivery complications, emerging research indicates a complex interplay of genetic predispositions and hereditary polymorphisms as potential contributors to

CP (Wu et al., 2011). Motor impairments, such as spasticity, dyskinesia, and ataxia, are hallmark features, often accompanied by disturbances in posture, balance, and coordination. The condition's heterogeneity extends beyond motor dysfunction, with a significant proportion of individuals exhibiting cognitive, sensory, and behavioral deficits. Structural abnormalities, including periventricular leukomalacia and cortical malformations, are frequently observed, highlighting the intricate relationship between genetic susceptibility and environmental insults during critical developmental periods. Environmental factors, such as maternal infections, prematurity, neonatal hypoxic-ischemic events, and socio-economic disparities, also play significant roles in modulating CP risk and severity.

5.3.4 Stroke

Stroke is a medical condition in which poor blood supply to the brain causes cell death. There are two main types of the disease, ischemic and haemorrhagic stroke. Ischemic stroke is the most common type (87%) caused by formation of blood clots which block arteries and cut off the blood flow. An ischemic stroke can occur in two ways: embolic and thrombotic strokes. (i) In an embolic stroke, a blood clot forms somewhere in the body (usually in the heart) and travels through the bloodstream to the brain. The clot eventually reaches small blood vessels in the brain blocking the passage and causing a stroke (embolus). (ii) In the second type of blood-clot stroke, blood flow is impaired because of a blockage of one or more of the arteries that supplying the blood to the brain. The process leading to this blockage is known as thrombosis. Blood-clot strokes can also happen as the result of unhealthy blood vessels clogged with a build-up of fatty deposits and cholesterol.

A hemorrhagic stroke caused by the breakage of blood vessels in the brain. Hemorrhages can be caused by several disorders, including long-standing high blood pressure and cerebral aneurysms. An aneurysm is a weak or thin spot on a blood vessel wall. Deep wounds and infections can also lead to aneurysms, or one can also be born with weakness in one of artery wall. Clinical studies have been shown that electrical stimulation can improve motor function and reduced spasticity in post-stroke patients (Lin et al., 2018; Kwong et al., 2017; Marcolino et al., 2018; Sharififar et al., 2018).

5.3.5 Multiple sclerosis

MS is a potentially disabling neurodegenerative disease of the brain and spinal cord caused by the immune system attacking the protective myelin sheet that cover the nerve fibers and causes impaired communication between the brain, spinal cord and the rest of the body. The myelin enables electrical signals to pass quickly and smoothly between the brain and the peripheral nervous system. When the myelin is degenerated, nerve signals are sent more slowly and less efficiently. Patches of scar tissue, called plaques, form over the affected areas, further disrupting the communication. The symptoms of MS occur when the brain and spinal cord no longer communicate properly with other parts of the body. It causes a wide variety of symptoms and can affect vision, balance, strength, sensation, coordination, and other body functions.

5.3.6 Spasticity

Spasticity is commonly seen in patients with CP, MS and/or stroke. The muscles of the arms, legs, and trunk are resistant to movement, difficult to control, aching and prone to spasms or involuntary movements. Spasticity may be used to help with transfers and walking or may help keep the muscles from decreasing in size. However, spasticity is also accompanied by several difficulties. Long-term spasticity can lead to decreased range of motion, prevent safe positioning, limit mobility, and impede hygiene. It can also lead to increased discomfort and pain. Spasticity is often a result of a combination of causes. It is not just defined as resistance to movement when an arm or leg is moved quickly. Some patients also have spasms and clonus (repeated movement of a body part when positioned with the muscle stretched).

5.3.7 Muscle activation

Transcutaneous sub-threshold electrical stimulation can be used to activate and prepare muscles for contraction. It can also be used to re-educate muscles and facilitate the return of normal movements. Re-education will reinforce nerve signals to the muscles and improve functional movements. It may be applied to patients with different forms of neurological conditions, such as stroke or traumatic brain injurires. When the nerve signals are re-educated and the muscle movement is repeated, the movement will again become automatic. By these means, the nerve signal-strength required by the user to generate muscle contraction is reduced. Muscle fibers respond to frequencies of 20 Hz which is low enough to not cause fatigue but effective enough to have a lasting effect during the length of its active involvement. Voluntary contraction is more fatiguing than low level electrical stimulation at both the cardiovascular and nervous levels (neurotransmitter fatigue). Electrical stimulation at 20 Hz has been shown produce an enhancement of beta synchronization in the basal ganglia, which also exacerbates antikinetic symptoms. Work by Brown and coworkers has shown that subthalamic nucleus stimulation at 20 Hz increases Globus Pallidus (GPi) synchrony (Cooke and Brown, 1994).

5.3.8 Reciprocal inhibition

Reciprocal inhibition is a natural inhibitory response which plays a major role in the control of voluntary movements (Burridge and McLellan, 2000; Perez et al., 2003). Joints are controlled by two opposing sets of muscles, extensors and flexors, which work in synchrony for smooth movements. When a muscle spindle is stretched and the stretch reflex is activated, the opposing muscle group must be inhibited to prevent it from working against the resulting contraction of the homonymous muscle. Afferent signals of the muscle spindles bifurcate in the spinal cord. One branch innervates the alpha motor neuron that causes the homonymous muscle to contract, producing the reflex. The other branch innervates the inhibitory interneuron, which in turn innervates the alpha motor neuron that synapses with the opposing muscle. Since the interneuron is inhibitory, it prevents the opposing alpha motor neuron from firing,

thereby reducing the contraction of the opposing muscle. Without this reciprocal inhibition, both groups of muscles might contract simultaneously and work against each other. Thus, causing difficulties in voluntary motor activity as well as passive motor control (Burridge and McLellan, 2000; Perez et al., 2003; Tinazzi et al., 2005).

5.3.9 Blood circulation

Electrical stimulation has been shown to improve blood circulation (Doran et al., 1970; Velmahos et al., 2005; Thakral et al., 2013). It may influence the circulation by triggering the release of vasodilatory substances such as nitric oxide and substance P which causes vasodilatation, which in turn will lead to increased blood flow to the stimulated area. Electrical stimulation has also been associated with increased production of nitric oxide (NO), which is a potent vasodilator which helps relax the smooth muscle cells in blood vessel walls, promoting vasodilation and enhanced blood flow and tissue saturation. (Refer to Ikawa and Karita (2015) for the relationship between blood circulation and blood oxygenation).

Reduced or poor blood circulation in a tissue may result in a number of different symptoms, particularly affecting the extremities. It includes cold or numb feet or hands, hair loss on feet or legs, dry or cracked skin, erectile dysfunction and/or prolonged healing of wounds or sores. In a study using a low-frequency TENS, the cutaneous blood flow was significantly increased when measured by laser Doppler flowmetry (Cramp et al., 2000). Tanaka et al., 2016, showed that a single session of NMES enhanced vascular endothelial function and improved peripheral blood circulation in patients with acute myocardial infection. In addition to improve the venous flow, electrical stimulation is known to have an effect on tissue perfusion. Increased perfusion may be mediated by release of endothelial growth factor (VEGF) which is thought to be angiogenic (Kanno et al., 1999).

5.3.10 Chronic pain

Chronic pain is defined as ongoing pain either persists beyond the point that healing would be expected to be complete, or that occurs in disease processes in which healing does not take place. Chronic pain is a significant health problem with a global incidence of 20–25%. It causes a significant reduction in life quality and presents a high economic burden (Gold and Gebhart, 2010; McCarberg and Billington 2006). While both, central and peripheral nervous systems (CNS and PNS) can underlie pain processes, PNS changes are necessary and sufficient to initiate and maintain CNS changes in chronic pain states. This makes it more effective to focus on controlling the pathophysiological changes in the PNS, since they are more accessible, and likely to have greater therapeutic impact (Ma et al., 2019).

It is well established that electrical stimulation constitutes a non-pharmacologic and non-invasive treatment method for pain relief, and it has been widely used for several decades (Samuel and Maiya,

2015; Song and Marvizon, 2003). The underlying mechanism may include both neurophysiological blockage of nerve impulses on a spinal level, called the 'gate control' theory and effects on transmitter substances in the CNS that are sensitive to different stimulation characteristics (frequency, impulse duration/intensity) (Doucet et al., 2012; Schuhfried et al., 2012). According to the gate control theory, pain signals are not free to reach the brain when they are generated at the injured tissues or sites. They need to encounter certain 'neurological gates' at the spinal cord level and these gates determine whether the pain signals reach the brain or not. Hence, pain is perceived when the gate gives way to the pain signals, and it is less intense or not at all perceived when the gate closes for the signals to pass through. When the pain signals are more intense compared to the non-pain signals, the inhibitory neurons are inactivated, and the gate is opened. The cells transmit the pain signals to the part of the spinal cord that carries those signals to the brain. As a result, the neurological gate is influenced by the relative amount of activity in the large and the small nerve fibres.

It has been shown that different frequencies of stimulation activate different opioid receptors to produce analgesia and provide analgesic effect specifically when applied at a strong, nonpainful intensity. It has been demonstrated that treatment with low-frequency TENS increases the concentration of serotonin during and after the treatment. And they also showed that the stimulation sites are not crucial to get this effect while the number of electrodes applied are important for increasing the level of spinal serotonin as well as opioid receptor activity. Increase in beta endorphin and met-enkephalin has also been reported with low-frequency electrical stimulation (Samuel and Maiya, 2015; Sternini et al., 2000; Song and Marvizon, 2003).

5.3.11 Fibromyalgia

Fibromyalgia is a chronic pain condition that is characterized by widespread musculoskeletal pain, fatigue, and sleep disturbances, and is associated with a range of comorbidities, including depression and anxiety (Arnold et al., 2016). It is a common chronic widespread disorder that can affect children and adolescents but is more frequent in adult women and it is one of the conditions contributing to the pervasiveness and expense of chronic pain as a whole (Lawrence et al., 2008; Knight et al., 2013). Unlike nociceptive and neuropathic pain, which are associated with identifiable tissue or nerve damage, the pain of fibromyalgia is less clear but may result from neurochemical imbalances in the central nervous system that lead to an augmentation of pain perception, typified by allodynia (pain due to a stimulus that does not usually provoke pain) and hyperalgesia (increased pain from a stimulus that usually provokes pain) (Clauw et al., 2011).

6 Results of relevant data search for device under evaluation

6.1 Data search method

Relevant data was gathered in four stages as presented in Table 12. First, the scientific databases were searched for published literature on EXOPULSE Mollii Suit. Second, study databases were searched. Third, adverse event report databases were searched. Finally, the data generated through experience with the own device was reviewed and summarized.

Table 12. Gathered search in databases for EXOPULSE Mollii Suit.

Search method	Search terms	Comments
Published literature see 6.2.1	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress" Performance and Benefits, Claim, Safety	PubMed, Cochrane Library
Study databases see 6.2.2	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress"	ClinicalTrials.gov https://drks.de/search/en
Adverse Events see 6.2.3	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress" "Transcutaneous Electrical Nerve Stimulation" Specific MAUDE product codes: QAJ, KPI, GZI, IPF, QSQ	MHRA (Medicines and Healthcare products Regulatory Agency), Swissmedic, BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte), TGA System for Australian Recall Actions and TGA Database of Adverse Event Notifications and MAUDE (Manufacturer and User Facility Device Experience).
Internal or unpublished data see 6.2.4	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress"	Complaints, field tests, design verification, design validation, expert opinion, in-house presentations, registries, PMCF data, etc.

The current version of the *Clinical Evaluation Report* does not include any searches related to EXOPULSE as the device is not yet on the market. However, this will be included in coming versions of the report when relevant data becomes available.

6.2 Data search results

6.2.1 Results of search for published literature

Search strategy applied for retrieval of clinical data, including selection criteria applied and quality control measures are described in the *Clinical Evaluation Plan*. The search interval was from 01.11.2021 – 01.01.2023. A schematic overview of the methodology of the literature search and appraisal is presented table below.

Table 13. Schematic overview of the methodology of the literature search and appraisal.

Literature search Searches were conducted online in PubMed and Cochrane Library. Period of search: from 01.11.2021 until 01.01.2023			
	Search term(s)		**Hits**
1	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress" PubMed filters: 01.11.2021 – 01.01.2023		2
2	"EXOPULSE Mollii Suit" OR "Mollii" OR "Elektrodress" Cochrane filters: 01.11.2021 – 01.01.2023		0
Potentially relevant literature identified through the search			**2**
Identified by the search for basic literature (see chapter 5.2)		**Total**	**0**
Literature excluded:		**Total**	**0**
	Elimination of duplicates		0
	Not appropriate language		0
	Not in humans		0
	Another field of study (e.g., tooth implants, cardiovascular surgery)		0
	Inappropriate type of publication (i.e., preclinical study, socio-economic assessment/cost-effectiveness, non-peer-reviewed opinion, comments on an article).		0
Additional relevant literature identified:		**Total**	**9**
	References in literature from literature search		0
	Additional literature identified by the authors (e.g. used in former clinical evaluation)		9 + 1
Literature for detailed evaluation			**11 (2 new, 9 from previous search)**
Excluded literature (reasons to find in Appendix E)			
	Not passing suitability criteria		0
	Not passing data contribution (weighting) criteria		0
	Study irrelevant content is part of a review already identified		0
Pivotal studies			**2 + 1**

In total 2 articles were found in PubMed and 0 in Cochrane. Additional relevant literature found in previous searches was 10 and added to the list in Section 3.1 Completed clinical investigations. In the table below, Table 14, the pivotal studies are summarized.

6.2.2 Published studies

Table 14. List on published studies that were found based on the criteria in Table 12.

Author(s)	Title	Published	Study type	Conclusion
Flodström C, Viklund Axelsson SA, Nordström B.	A pilot study of the impact of the electro-suit Mollii on body functions, activity, and participation in children with cerebral palsy.	Assist Technol. 2022 Jul 4;34(4):411-417.	Pilot study	All participants improved in the total score for Canadian Occupational Performance Measure (COPM), three of them showed significant clinical improvements. Pain was reduced for children who estimated pain when the study started. The suit had a positive impact on activity and participation in self-selected activities.
Jonasson LL, Sörbo A, Ertzgaard P, Sandsjö L.	Patients' Experiences of Self-Administered Electrotherapy for Spasticity in Stroke and Cerebral Palsy: A Qualitative Study.	J Rehabil Med. 2022 Feb 14	Qualtitative study	The qualitative approach used in this study elicited complementary information that was not evident from the previous randomized controlled trial. This included statements regarding increased mobility, reduced spasticity, reduced use of medication, and problems related to using the treatment concept.
Mattar, J. G., Chalah, M. A., Ouerchefani, N., Sorel, M., Le Guilloux, J., Lefaucheur, J. P., Abi Lahoud, G. N., & Ayache, S. S.	The effect of the EXOPULSE Mollii Suit on pain and fibromyalgia-related symptoms: A randomized sham-controlled crossover trial	European Journal of Pain, 00, 1–14. https://doi.org/10.1002/ejp.4729	Randomized sham-controlled double-blind trial	Phase 1 - randomized sham-controlled double-blind trial with a 2-week intervention of daily stimulation with the EXOPULSE Mollii Suit (active and sham): The results demonstrated significant analgesic effects, significant improvement in some anxiety endpoints, changes in several aspects the disease impact. Phase 2 – open label 4-week period with daily stimulation sessions: Significant analgesic effects on all scales, significant anti-fatigue effects on all fatigue outcomes, significant improvement in anxiety endpoints (including HADS), improvement in depression endpoints, changes in almost all FIQ subscales and improvement in almost all quality-of-life dimensions.

A summary of the results from the search for published data on the device under evaluation is presented in Section 'Data search method'.

6.2.3 Study databases

The results from study databases are presented below in Table 15.

Table 15. Results from search in study databases.

Search conducted online on: 13.02.2023		
Database	**Search term(s)**	**Hit(s)**
https://clinicaltrials.gov	EXOPULSE Mollii Suit	3

	Mollii	8
	Elektrodress	1
https://drks.de/search/en	EXOPULSE Mollii Suit	81
	Mollii	0
	Elektrodress	0
Potentially relevant literature identified through the search		**93**
Excluded studies:	**Total:**	**-10**
Elimination of duplicates		-10
Other intended use		81
Therapy / Treatment not comparable		0
Relevant studies		**8**

There were 8 relevant studies identified through the search as documented in Table 15 and presented in Table 16.

Table 16. Relevant studies found from search in study databases.

Official Title	Mollii - Personalized Suit for Treatment of Spasticity, GFMCS 3-5
Sponsor	Hvidovre University Hospital
Collaborator	Eurostars
Actual Enrollment	31 participants
Actual Study Start Date	June 1, 2017
Actual Study Completion Date	July 1, 2019

Official Title	Development of an Electronic Suit to Reduce Hemiplegic Shoulder Pain
Sponsor	Danderyd Hospital
Collaborator	Vinnova
Actual Enrollment	15 participants
Actual Study Start Date	August 9, 2020
Estimated Study Completion Date	December 30, 2022

Official Title	Can Transcutaneous Electrical Stimulation Garment Improve Gait in Children with Cerebral Palsy?
Sponsor	KK Women's and Children's Hospital
Collaborator	Inerventions AB
Actual Enrolment	20 participants
Actual Study Start Date	December 8, 2020
Estimated Study Completion Date	December 31, 2021

Official Title	Evaluation of Multifocal Transcutaneous Electrical Stimulation for Self-treatment Among Children With Cerebral Palsy
Sponsor	Sormland County Council, Sweden
Collaborator	Sormland County Council, Sweden
Actual Enrolment	10 participants
Actual Study Start Date	May 1, 2019
Actual Study Completion Date	September 1, 2021

Official Title	Efficacy and Cost-effectiveness of Spasticity Treatment with Multifocal TENS
Sponsor	Linköping University, University of Borås, University Hospital, Linköping, Sodra Alvsborgs Hospital
Collaborator	Linköping University, University of Borås, University Hospital, Linköping, Sodra Alvsborgs Hospital
Actual Study Start Date	September, 2013
Actual Study Completion Date	February, 2015

Official Title	Effects of Using the Electrodress Mollii on Spasticity
Sponsor	Danderyd Hospital
Collaborator	Danderyd Hospital
Actual Study Start Date	August 15, 2017
Actual Study Completion Date	February 1, 2019

Official Title	EXOPULSE Mollii Suit, Spasticity & Tissue Oxygenation (ENNOX)
Sponsor	Institut De La Colonne Vertebrale Et Des Neurosciences
Collaborator	Henri Mondor Hospital, France
Actual Study Start Date	March 1, 2022
Estimated Study Completion Date	April, 2023

Official Title	EXOPULSE Mollii Suit and Fibromyalgia (EXOFIB)
Sponsor	Institut De La Colonne Vertebrale Et Des Neurosciences
Collaborator	Henri Mondor Hospital, France
Actual Study Start Date	March 1, 2022
Estimated Study Completion Date	March, 2023

6.2.4 Results of search in external adverse event databases

Adverse event databases were interrogated with brand names and/or keywords, accordingly (Table 17). The remaining data was then taken for more detailed review.

Table 17. Results from search in databases with relevant search terms connected to the device.

Source: **MHRA** (Medicines and Healthcare products Regulatory Agency) (https://www.gov.uk/drug-device-alerts?keywords=&alert_type[]=devices&issued_date[from]=&issued_date[to]=)		
Search Term	**Hits**	**Comments**

EXOPULSE Mollii Suit OR Mollii OR Elektrodress Time period: 01.11.2021 – 01.01.2023 Filter: Field safety notice, national patient safety, device safety, physiotherapy and occupational therapy	0	No hits were found.
Transcutaneous Electrical Nerve Stimulation Time period: 01.11.2021 – 01.01.2023 Filter: field safety notice, national patient safety, device safety information, physiotherapy and occupational therapy	0	No hits were found.
Neuromuscular Electrical Stimulation Time period: 01.11.2021- 01.01.2023 Filter: field safety notice, national patient safety, device safety, physiotherapy and occupational therapy	0	No hits were found.
Source: **Swissmedic** (https://fsca.swissmedic.ch/mep/#/)		
Search Term	**Hits**	**Comments**
EXOPULSE Mollii Suit OR Mollii OR Elektrodress Time period: 01.11.2021 – 01.01.2023	0	No hits were found.
Transcutaneous Electrical Nerve Stimulation Time period: 01.11.2021 - 01.01.2023	0	No hits were found.
Neuromuscular Electrical Stimulation Time period: 01.11.2021 – 01.01.2023	0	No hits were found.
Source: **BfArM** (Bundesinstitut für Arzneimittel und Medizinprodukte) (https://www.bfarm.de/SiteGlobals/Forms/Suche/EN/Servicesuche_Formular.html?nn=468478&resourceId=469726&input_=468478&pageLocale=en&templateQueryString=ottobock&submit.x=0&submit.y=0)		
Search Term	**Hits**	**Comments**
EXOPULSE Mollii Suit OR Mollii OR Elektrodress Time period: all alerts during 2022 Filter: Medical devices, customer information, medical electronics/electromedical devices, electrotherapy	0	Not applicable for the device under evaluation, published articles applies to e.g., invasive and monitoring devices.
Transcutaneous Electrical Nerve Stimulation Time period: all alerts during 2022 Filter: Medical devices, customer information, medical electronics/electromedical devices, electrotherapy	4	Not applicable for the device under evaluation
Neuromuscular Electrical Stimulation Time period: All years before 2022 Filter: Medical devices, customer information, medical electronics/electromedical devices, electrotherapy	1	Not applicable for the device under evaluation, published article applies to e.g., invasive electrodes for other population than indicated for the device under evaluation.
Source: **TGA System for Australian Recall Actions** (https://apps.tga.gov.au/PROD/SARA/arn-entry.aspx)		
Search Term	**Hits**	**Comments**
EXOPULSE Mollii Suit OR Mollii OR Elektrodress Time period: 01.11.2021– 01.01.2023 Filter: None	0	No hits were found.
Transcutaneous Electrical Nerve Stimulation Time period: 01.11.2021– 01.01.2023	0	No hits were found.

Filter: None		
Neuromuscular Electrical Stimulation Time period: 01.11.2021– 01.01.2023 Filter: None	1	Not applicable for the device under evaluation, published report applies to an implantable/invasive device.
Source: **TGA Database of Adverse Event Notifications** (https://apps.tga.gov.au/prod/DEVICES/daen-entry.aspx)		
Search Term	**Hits**	**Comments**
EXOPULSE Mollii Suit OR Mollii OR Elektrodress Time period: 01.11.2021 – 02.11.2022 Filter: None	0	No hits were found.
Transcutaneous Electrical Nerve Stimulation Time period: 01.11.2021 – 02.11.2022 Filter: None	0	No hits were found.
Neuromuscular Electrical Stimulation **Time period:** 01.11.2021 – 02.11.2022 Filter: None	25	Not applicable for the device under evaluation, published report applies to implantable/invasive devices.
Source: **MAUDE** (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm)		
Search Term	**Hits**	**Comments**
Product code: QAJ (Cutaneous Electrode Stimulator For Urinary Incontinence) Time period: 01.04.2012 – 23.04.2023 Filter: None	7	6/7 results applicable (discarded: 1 duplicate)
Product code: KPI (Stimulator, Electrical, Non-Implantable, For Incontinence) Time period: 01.04.2012 – 23.04.2023 Filter: None	15	2/15 results applicable (discarded: 1 duplicate, 12 not appropriate device/treatment)
Product code: GZI (Stimulator, Neuromuscular, External Functional) Time period: 01.04.2012 – 23.04.2023 Filter: None	17	8/17 applicable (discarded: 6 not appropriate device/treatment, 3 “other”-device malfunction without adverse event)
Product code: IPF (Stimulator, Muscle, Powered) Time period: 01.04.2012 – 23.04.2023 Filter: None	82	24/82 applicable (discarded: 2 duplicates, 37 not appropriate device/treatment, 18 “other” - device malfunctions without adverse events, missing information, or no information; 1 product code QPL wrongly classified within IPF)
Product code: QSQ (Transcutaneous Electrical Nerve Stimulator To Treat Fibromyalgia Symptoms) Time period: 01.04.2012 – 23.04.2023	0	No records found

National and international adverse event databases were searched (MHRA (Medicines and Healthcare products Regulatory Agency)), Swissmedic, BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte), TGA System for Australian Recall Actions, TGA Database of Adverse Event Notifications) and MAUDE. No relevant hits could be identified except from the search in MAUDE. Please see the result from the MAUDE search below.

From all MAUDE product codes searched (QAJ, KPI, GZI, IPF, QSQ), a total of 121 reports were found and after discarding non-applicable reports, only 40 reports remained, selected due to the technology being similar/equivalent (i.e., electrical stimulation under motor threshold using electrodes that can be placed anywhere and not limited to specific sites), mostly (24/40) classified as IPF 'stimulator, muscle, powered'.

From those 40 reports, 23 were classified as injury (MAUDE ‘event type’), 14 as malfunction, 1 as other, and 2 as ‘N/A’. The risks (in MAUDE identified as ‘patient problem’) identified for the 23 injury reports include:

- Burns (up to 3rd degree); scarring, erythema and swelling
- Burning sensation
- Electric shock
- Pain
- Syncope (loss of consciousness)

Note that 12 out of 23 reports from devices with similar technology are from devices who need to be connected to an electrical outlet directly, where a risk of burns or strong electric shock is possible; EXOPULSE is battery-operated and therefore the voltage/current delivered to the user are limited and less likely to cause serious burns (*Intended Use EXOPULSE MOLLII Control Unit (MDR)*).
Moreover, 11 out of 23 reports do not have enough information to assess whether the device was at fault or not (MAUDE 'device problem' indicated as AE without identified device or use problem, or insufficient information). The complaints identified therefore do not include new risks/adverse events than already considered in *Risk Analysis Worksheet EXOPULSE Mollii* and *Risk analysis worksheet EXOPULSE* (e.g., skin irritation, pain and discomfort). Regarding syncope, which has not been included in the risk analysis, it has been reported once in association to EXOPULSE Mollii Suit, but the investigation showed that no causal relationship could be found with the device.

6.2.5 Results of internal data

Clinical data from experience with the EXOPULSE Mollii Suit have reviewed and summarized, refer to *Blood oxygenation internal registration* (DOC-506) and *EXOPULSE Mollii Suit Registry results 2021* (DOC-603).

6.2.5.1 Complaints

The internal database was searched for complaints for the period 01.01.2016 – 31.12.2022 (last 6 years) and evaluated from a safety perspective. For further information regarding complaints see *PSUR EXOPULSE Mollii 2021-2022* (DOC-924). The table below, Table 18, presents the result of the search of complaints.

Table 18. Results of complaints from the internal database from the period 01.01.2016 – 31.12.2022.

Device	Sold/ distributed	Complaints		Safety critical		Injury	
		Total	In % sold	Total	In % sold	Total	In % sold
EXOPULSE Mollii Suit (Mollii Control Unit + Body Garments) 2016-2020	3010	611	24%	9	0,35%	7	0,27%
EXOPULSE Mollii Control Unit 2021-2022	987	107	10.8%	0	0	2	0.2%
EXOPULSE Body Garments 2021-2022	3506	90	2.6%	0	0	2 (same injuries as above)	0.06%

The 9 safety critical incidents related to injuries are summarized as the following events in Table 19:

- Skin irritation/burn under the site of the electrodes (7 incidents)
- Epilepsy during use of the suit (2 incidents)

Table 19. Overview on a detailed investigation and description of incidents.

Type of incident	Internal ID number	Description of incident	Reference document
Epilepsy	NC79	Epileptic seizures during use. The device was not identified as the triggering factor and considered safe to use. (Not reported)	Bilaga 4. Investigation of epileptic seizures
Epilepsy	NC70	Epilepsy during use. It was concluded that the incident was not caused by the device. (Not reported)	CAPA EP Schweiz

Type of incident	Internal ID number	Description of incident	Reference document
Skin irritation/burn	2019-0005 / CRM 11403	Lesions at the site of active and inactive electrodes. Covered by Risk Management Report and IFU. (Not reported)	Complaint 2019-0005
Skin irritation/burn	2019-0007 / CRM 11405	Skin irritations/blisters. The user experienced a small shock when the control unit was turned on. Device failure due to mechanical wear and tear (Not reported)	Complaint 2019-0007
Skin irritation/burn	2019-0008 / CRM 11355	Skin irritation. Covered by Risk Management Report and IFU (Not reported)	Complaint 2019-0008
Skin irritation/burn	2019-0009 / CRM 11358	Skin irritation. Covered by Risk Management Report and IFU (Not reported)	Complaint 2019-0009
Skin irritation/burn	2020-0003 / 11547	Skin irritated after stimulation over bra buckle (misuse). (Reported)	Complaint 2020-0003
Skin irritation/burn	2021-0001 / 11569	Skin irritation/burn degree one (Not reported)	Complaint 2021-0001
Skin irritation/burn	11653	Skin irritation/rash/blisters from stimulation (Not reported)	Complaint 2021-0002

Table 20. Overview of number of complaints during 2021-2022.

EXOPULSE Control Unit: 07340106500035W			
IMDRF Problem Code	**2022**	**2021**	**Total**
E1705 (Burning Sensation) / E1714 (Rash)	0	2	2
E2403 (No Clinical Signs, Symptoms or Conditions)	54	50	104
E2401 (Insufficient Information)	1	0	1
	N/A	N/A	**107**
EXOPULSE Body Garments (Jacket & Pants): 7340106500005Q			
E1705 (Burning Sensation) / E1714 (Rash)	0	2	2
E2403 (No Clinical Signs, Symptoms or Conditions)	63	24	87
E2401 (Insufficient Information)	1	0	1
	N/A	N/A	**90**

6.2.6 Unpublished data

The sources identified are described in the following Table 21:

Table 21. Identified sources of unpublished data.

Unpublished Data		
Source	**Description**	**DOC-ID**
Clinical Development Plan and all data generated according to it	*Clinical Evaluation Plan EXOPULSE Devices*	DOC-39
All PMCF activities (studies, Registries, PMCF Plan, etc)	*PMCF Plan - EXOPULSE Devices*	DOC-103
Clinical investigations	*PMCF Plan - EXOPULSE Devices*	DOC-103
Field test experiences	N/A	
Design verification testing	N/A	
Design validation testing	*Human Factors Usability Engineering report:* *IRV-001 HFEUE Report* *Usability Evaluation Summary Report*	DOC-75 DOC-1555
Expert opinion	N/A	
Clinical evaluations	N/A	
Inhouse presentations	N/A	

6.2.7 Risk analysis

The following risk analysis have been reviewed: *Risk Management Report EXOPULSE Mollii and Risk Management Report EXOPULSE* and no unacceptable risks were identified. The risk policy is defined in *QM100 Quality Manual* (DOC-339).

7 Data analysis

The EXOPULSE Mollii Suit has been marketed since 2012 and has been assessed regarding performance and safety in 2016-2022 through the Clinical Evaluation.

7.1 Performance data on EXOPULSE Mollii Suit

7.1.1 Published and unpublished data

The below clinical studies and clinical case reports on the EXOPULSE Mollii Suit provide clinical data on the performance of the device. The trials which have been published in peer-reviewed scientific journals included:

- 70 children with cerebral palsy (Bakaniene et al., 2018; Flodström et al., 2022; Hedin et al., 2020; Nordström and Prellwitz 2021; Jonasson et al., 2022; Raffalt et al., 2022),

- 60 adults with stroke spasticity and hemiplegia (Palmcrantz et al., 2020; Pennati et al., 2021)

- 84 adult patient with fibromyalgia (Rubio-Zarapuz et al., 2023; Riachi et al., 2023; Mattar et al., 2024).

Two of the trials used in the evaluation have been published as congress abstracts or reports, and included:

- 41 children and teenagers with cerebral palsy (Bourke-Taylor, 2019; Torabi et al., 2018), and

- 200 adults with chronic pain from fibromyalgia and other neurological disorders such as stroke, MS and Parkinson's disease (Riachi et al., 2019).

In addition to the trials, clinical data on performance has also been obtained from internal patient data registries held by the manufacturer, which included:

- 45 patients (CP n=17, MS n=17 and stroke n=11) and 5 healthy individuals.

The total number of patients is deemed sufficient as they are in line with the power calculations performed for the planned clinical trials on the EXOPULSE Mollii Suit (*Clinical Evaluation Report Plan – EXOPULSE Devices*). Moreover, strong effect sizes were observed in the registry data with a patient number of n=17.

The patients in the clinical trials and the registry include children and teenagers from the age of 2-18 years (Bakaniene et al., 2018; Torabi et al., 2018; Bourke-Taylor, 2019; Flodström et al., 2022; Hedin et al., 2020 and Nordström and Prellwitz 2021) as well as adults (Riachi et al., 2019; Palmcrantz et al., 2020 and Mattar et al., 2024).

7.1.2 Relaxation of tense and spastic muscles

Decreased muscle tone has been reported in 9 of 20 adults with stroke spasticity and hemiplegia reported by Palmcrantz et al. (2020). On a group level, the neuronal component of spasticity measured by the Neuroflexor decreased significantly in the wrist flexors of the affected hand (p=0.023).

A statistical significantly decreased change in spasticity has also been reported in m. biceps femoris and m. semitendinosus (p= 0.015 and 0.014) and in m. quadriceps femoris (p= 0.046) by Torabi et al., 2018. Moreover, the same group reported an increase in Tardieu for m. biceps femoris and m. semitendinosus (p=0.002) and in m. flexor carpi radialis, m. palmaris longus and m. flexor carpi ulnaris (p=0.041).

In a study by Pennati et al. (2021) twenty patients in the chronic phase after stroke were enrolled in a cross-over, double-blind controlled study. The study showed no consistent reduction on spasticity in the upper and lower extremities in the chronic phase after stroke, after 60 min of electrical stimulation with EXOPULSE Mollii Suit.

The spasticity level has also been found to be reduced using the modified Ashworth scale (MAS) as reported by Hedin et al. (2020). The authors reported a significant drop at one (p=0.007) and six months (p=0.011), and almost significant after three months (p=0.076). Modified Tardieu was also found to decrease significantly after one month (p=0.030), however not after three (p=0.392) or six months (p=0.426).

7.1.3 Muscle activation

In a study by Flodström et al. (2022) on six children with cerebral palsy, all participants improved in the total score for Canadian Occupational Performance Measure (COPM), three of them showed significant clinical improvements. There were also small changes in positive impact on activity and participation in self-selected activities among the children in this study.

Moreover, improved gait pattern in 7 of 20, as well as improved voluntary movement in the upper extremity in 6 of 20 adults with stroke spasticity has been reported (Palmcrantz et al., 2020). The same research group also reported significant improvements according to Fugl Meyer - Upper Extremity ($p = 0.000$) and Fugl Meyer - Lower Extremity ($p = 0.003$) after EXOPULSE Mollii Suit intervention for six weeks (Palmcrantz et al., 2020).

The EXOPULSE Mollii Suit has also a positive impact on a gross motor function in all 16 children with CP children, as reported by Bakaniene et al. (2018). Positive changes were also reported in standing, walking, running and jumping dimensions, registered by the Gross Motor Function Measure (GMFM) test. The mean change in GMFM in the group using the EXOPULSE Mollii Suit was 3.38% ($F = 16.715$; $p = 0.005$). All patients (n=16) also experienced improvement in mobility after three weeks of regular use (Bakaniene et al., 2018).

Torabi et al. (2018) reported improved improvements of individualized goals (GAS) related to function and mobility throughout the intervention period of 6 months ($p = 0,004$) (Torabi et al., 2018).

In a qualitative study on children with cerebral palsy, all 6 children (Nordstrom and Prellvitz, 2021) showed positive impact such as improved ability to perform activities, increased strength, or ability to maintain body position. And in another qualitative report on 10 children and 1 teenager, perceived improvements in standing posture, joint positioning, motor skills were reported (Bourke-Taylor, 2019).

A study by Raffalt et al. (2022) suggests that 24 weeks of EXOPULSE Mollii suit treatment increases the stability during walking. It was shown that the treatment alters the nonlinear dynamics but not the variability of the trunk accelerations during walking in children with unilateral CP. The temporal structure of the trunk acceleration in the anterior-posterior direction was altered towards that of healthy individuals, i.e., walking ability of the patients increased.

In an internal study, EXOPULSE Mollii Suit Registry 2021, the outcome measures Berg balance scale (BBS), Timed Up and Go (TUG), Functional Gait Assessment (FGA), 10 Metre Walking Test (10MWT),

Wolf Motor Function Test (WMFT) were used as outcome measures. The results showed significant changes after four weeks for all tests and diagnoses. Balance improved as shown by an increase in the total score of the BBS – 8.25 for cerebral palsy ($p<0.001$), 4.44 for MS ($p<0.001$) and 7.93 for stroke ($p=0.002$), indicating a reduced risk of falls. After intervention with the EXOPUSE Suit for 4 weeks, the scores improved to 46.4, 43.8 and 42.8 respectively, indicating a reduced risk of falls. The total time for patients to complete the TUG test, decreased significantly by 4.19 sec. for CP ($p=0.009$), 8.38 sec. for MS ($p<0.001$) and 2.65 sec. for stroke ($p=0.033$), indicating improved mobility and reduced risk of falling. Furthermore, the total score of the FGA increased and all three aetiologies reached a score of 18 or more after the intervention, confirming the reduced risk of falls – CP ($p<0.001$), MS ($p=0.007$) and stroke ($p=0.135$, probably due to the small sample set, n=7). The 10mMT test showed increased velocity (m/s) in both CP and MS patients and the utility value of the EQ-5D-5L increased in all three aetiologies.

7.1.4 Blood circulation

The performance of EXOPULSE Mollii Suit on local circulation is based on an internal report and a published case study. The study by Rubio-Zarapuz et al. (2023) included a female patient with fibromyalgia and the main findings showed drastic change in muscle oxygenation, with a 10.4% increase in SmO2, and the changes in HHb and O2Hb distribution, with both values being more equal than before the intervention.

The findings, documented in an internal report *Blood oxygenation internal registration* (DOC-506) where data on five subjects had been collected, showed a significant ($p<0.03$) increase in blood oxygenation suggesting that the suit may increase local blood oxygenation thus improving peripheral blood circulation.

7.1.5 Chronic pain

In a large-scale uncontrolled study (Riachi et al., 2019) on 200 patients with different pain conditions, such as fibromyalgia and Parkinson's disease, MS, stroke etc. the authors reported a significant drop on the Visual Analogue Scale (VAS) after one hour of use (VAS-1) of the EXOPULSE Mollii Suit (3.46±1.4). The reduction was found to be significantly lower also after 24 hours (VAS-24) (4.72±1.68), paired test p-values <0.001.

Reduced pain has also been reported in a small quantitative study on six children with cerebral palsy (Flodström et al., 2022) and in a report by Bourke-Taylor (2019) on 11 children and/or teenagers.

In a case study by Rubio-Zarapuz et al. (2023), it was shown that a 60 min session with the EXOPULSE Mollii Suit had beneficial effects on pain perception, parasympathetic modulation, and function in a female fibromyalgia patient.

A randomized clinical trial on 50 subjects diagnosed with fibromyalgia was conducted by Riachi et al. (2023), where the patients received one session of active stimulation (one hour). Pain intensity was

evaluated by means of the visual analogue scale (VAS), before (T0) and after the session (T1), and 24 h later (T24). Compared to baseline scores, a significant decrease in VAS was observed after the session ($p<0.001$), and 24 h later ($p<0.001$). T1 scores were significantly lower than T24 scores ($p<0.001$).

Another study (Mattar et al., 2024) with fibromyalgia patients was conducted as a randomized sham-controlled double-blind trial with a 2-week intervention in phase 1 and as an open label trial over a 4-week period in phase 2. Both phases included daily stimulation sessions with the EXOPULSE Mollii Suit. Thirty-three patients completed the study (n=31 females, age: 51.33 ± 8.99 years, disease duration: 8.94 ± 10.74 years, Widespread Pain Index: 14.15 ± 3.36, Symptom Severity Scale: 8.00 ± 2.38). All the stimulation sessions were well tolerated, and no serious adverse events were reported at any time. Results from ***phase 1*** revealed, compared to baseline (pre-active VAS_{pain}: 6.85 ±1.36), a significant decrease in VAS_{pain} scores following the active condition (post-active VAS_{pain}: 5.91 ±1.83, Dunn's $p=0.029$). Neither significant differences within the sham condition (pre-sham VAS_{pain}: 6.80 ±1.44, post-sham VAS_{pain}: 6.63 ±1.45, Dunn's $p=1.000$) nor significant baseline differences between active and sham conditions (Dunn's $p=1.000$) were observed. In addition, a significant pain reduction was also observed following the active intervention when assessed using BPI ($BPI_{pain\ interference}$ Friedman's $X2=12.79$ and $p=0.005$), FIQ_{pain} (Friedman's $X2=9.16$ and $p=0.027$) and $SF\text{-}36_{pain}$ (Friedman's $X2=22.34$ and $p<0.001$), but not PCS_{total} (Friedman's $X2=4.66$ and $p=0.199$) or its subscales which assess cognitions related to pain. Results of ***phase 2***, after one month intervention, Wilcoxon's test yielded significant ($p<0.05$) analgesic effects on all scales (VAS, BPI, PCS, FIQ_{pain}, and $SF\text{-}36_{pain}$).

7.1.6 Anti-fatigue effects, improvements in anxiety and depression in the context of Fibromyalgia

Ayache (2024) reported on further outcomes. Results of ***phase 1:*** Fatigue significantly decreased following the active intervention as per $FIQ_{fatigue}$ (Friedman's $X2=8.04$ and $p=0.045$), FIQ_{rested} (Friedman's $X2=16.61$and $p<0.001$), and SF-36 *energy/vitality* (Friedman's $X2= 13.38$ and $p=0.004$), but not $VAS_{fatigue}$ (Friedman $X2=5.84$ and $p=0.120$). A significant or a trend toward a significant difference was found with regards to anxiety: $FIQ_{anxiety}$ (Friedman's $X2=14.88$ and $p=0.002$) and $HADS_{anxiety}$ (Friedman's $X2=7.14$ and $p=0.068$). In addition, following the active intervention, a significant improvement was observed in terms of the disease impact (FIQ_{total}: Friedman's $X2=20.09$ and $p<0.001$, $FIQ_{physical\ impairment}$ Friedman's $X2=14.13$ and $p=0.003$, and $FIQ_{stiffness}$ with Friedman's $X2=10.11$ and $p=0.018$). Neither intervention had significant effects on depression according to $HADS_{depression}$ (Friedman's $X2=3.25$ and $p=0.355$) or $FIQ_{depression}$ (Friedman's $X2=4.19$ and $p=0.241$). Lastly, no significant effects were observed on the remaining quality of life domains (SF-36 subscales for physical functioning, role limitation due to physical functioning, role limitation due to emotional functioning, emotional well-being, social functioning, general health and health change). Following one month of active intervention in ***phase 2***, Wilcoxon's test yielded significant effects for most of the study outcomes ($p<0.05$): $VAS_{fatigue}$, BPI_{total} and both subscales (severity of interference), PCS_{total} and all subscales

(rumination and magnification and helplessness), $HADS_{anxiety}$, $HADS_{depression}$, FIQ_{total} and most of subscales (physical impairment, feel good, pain, fatigue, rested, stiffness, and anxiety), and most of SF-36 domains (physical functioning, role limitation due to physical health and emotional problems, energy/fatigue, emotional well-being, social functioning, pain and health change). Conversely, SF-36 general health did not change following intervention (p=0.128) while $FIQ_{depression}$ showed a trend toward a decrease (p=0.091). In summary, results are detailed in the followingtable.

Study Outcome		**Phase 1**	**Phase 2**
		p-value	**p-value**
VAS	VAS_{pain}	**0.014**	**<0.001**
	$VAS_{fatigue}$	0.144	**<0.001**
BPI	BPI_{total}	0.157	**0.003**
	$BPI_{pain\ severity}$	0.417	**0.007**
	$BPI_{pain\ interference}$	**0.005**	**0.002**
FIQ	FIQ_{total}	**<0.001**	**<0.001**
	$FIQ_{physical\ impairment}$	**0.003**	**0.017**
	$FIQ_{feel\ good}$	0.100	**0.006**
	FIQ_{pain}	**0.027**	**<0.001**
	$FIQ_{fatigue}$	**0.045**	**<0.001**
	FIQ_{rested}	**<0.001**	**0.002**
	$FIQ_{stiffness}$	**0.018**	**0.002**
	$FIQ_{depression}$	0.241	0.091
	$FIQ_{anxiety}$	**0.002**	**0.012**
VAS= Visual Analog Scale; **BPI**= Brief Pain Inventory; **FIQ**= Fibromyalgia Impact Questionnaire; **HDAS**= Hospital Anxiety and Depression Scale; **SF-36**= Short Form 36 Health Survey.			

Study Outcome		**Phase 1**	**Phase 2**
		p-value	**p-value**
HDAS	$HADS_{depression}$	.355	**0.038**
	$HADS_{anxiety}$	0.068	**0.006**
	$HADS_{total}$	0.340	**0.003**
PCS	PCS_{total}	0.199	**0.004**
	$PCS_{rumination}$	0.667	**0.009**
	$PCS_{magnification}$	0.495	**0.004**
	$PCS_{helplessness}$	**0.048**	**0.039**
SF-36	$SF\text{-}36_{physical\ functioning}$	0.436	**0.025**
	$SF\text{-}36_{role\ limitation\ due\ to\ physical\ health}$	**0.012**	**<0.001**
	$SF\text{-}36_{role\ limitation\ due\ to\ emotional\ health}$	**0.017**	**0.011**
	$SF\text{-}36_{energy\ /\ vitality}$	**0.004**	**<0.001**
	$SF\text{-}36_{emotional\ wellbeing}$	0.326	**0.017**
	$SF\text{-}36_{social\ functioning}$	0.170	**0.004**
	$SF\text{-}36_{pain}$	**<0.001**	**0.043**
	$SF\text{-}36_{general\ health}$	0.144	0.128
	$SF\text{-}36_{health\ change}$	**0.018**	**0.002**

Bolded values represent outcomes that are significantly different prior and after the intervention with p<0.05.

7.1.7 Other reported positive benefits

In addition to the above reported effects, positive benefits have also been reported in qualitative studies, in association with use of the EXOPULSE Mollii Suit. These benefits are improved sleep (Nordström et al., 2019), general relaxation, improved attention, energy levels and concentration (Bourke-Taylor, 2019), as well as included increased mobility, reduced spasticity, reduced use of medication, and problems related to using the treatment concept (Jonasson et al., 2022).

7.2 Performance data from equivalence

7.2.1 Equivalent devices

In this Clinical Evaluation Report, the technical, biological and clinical characteristics of the EXOPULSE Mollii Suit and the EXOPULSE have been compared side-by-side to identify similarities and differences

section (refer to section *4 Equivalence assessment*). In the case a difference between the devices was identified, the potential impact on safety and performance was evaluated in the *Clinical Assessment Plan* and the *Clinical Assessment Report* (refer to *Change record - Technical upgrade of EXOPULSE products*). The overall conclusion from the equivalence comparison was that there is *no significant* difference between the devices in terms of:

- technical characteristics (device design, physical parameters, deployment method and operation principle)
- biological characteristics (clinical condition/purpose, site on the body, target population and intended users)
- clinical characteristics (clinical condition and purpose, site on the body, target population, intended users)

The EXOPULSE Mollii Suit and the EXOPULSE are considered to be equivalent, and the clinical data on safety and performance generated in the present *Clinical Evaluation Report* is applicable for both devices.

7.2.2 Other relevant data on performance

N/A

7.2.3 Summary of performance data on EXOPULSE Mollii Suit

With the identified literature, the following device performance and benefits for the patients, when using the device, could be identified as presented in Table 24:

Table 22. Clinical performance of the device and benefits for the patients.

No.	Description	Source
1	Relaxation of tense and spastic muscles	Bourke-Taylor, 2019 Bakaniene et al., 2018 Flodström et al., 2022 Hedin et al., 2020 Jonasson et al., 2022 Palmcrantz et al., 2020 Nordström and Prellwitz, 2021 Raffalt et al., 2023 Torabi et al., 2018 EXOPULSE Mollii Suit Registry results 2021 (DOC-603)
2	Activation of muscles	Bourke-Taylor, 2019 Bakaniene et al., 2018 Hedin et al., 2020 Hahn et al., 2023 Palmcrantz et al., 2020 Nordström and Prellwitz, 2021 Flodström et al., 2022 Jonasson et al., 2022 Torabi et al., 2018 Raffalt et al., 2023

No.	Description	Source
		EXOPULSE Mollii Suit Registry results 2021 (DOC-603)
3	Increasing local blood circulation	Rubio-Zarapuz et al., 2023 Blood oxygenation internal registration (DOC-506)
4	Symptomatic relief of chronic pain	Bourke-Taylor, 2019 Flodström et al., 2022 Rubio-Zarapuz et al., 2023 Riachi et al., 2019 Riachi et al., 2023 Mattar et al., 2024 EXOPULSE Mollii Suit Registry results 2021 (DOC-603)
5	Anti-fatigue effects, improvements in anxiety and depression in the context of Fibromyalgia	Mattar et al., 2024

The clinical data presented in the present *Clinical Evaluation Report* supports the intended use of the EXOPULSE devices. The conclusions are based on data from clinically validated tests performed of more than 400 patients in total. In general, the strongest data is derived from the registry (observational study), in which some of the test of mobility, balance and quality of life are highly significant with large effect sizes. The significant results can be explained by a stringent patient selection, appropriate follow-up times, outcome measures for the specific aetiologies.
Moreover, the report concludes that EXOPULSE devices are equivalent, thus the clinical data of EXOPULSE Mollii Suit is also applicable for EXOPULSE and comply with the general safety and performance requirements.

In summary, the evidence presented herein, along with the scientific background of the EXOPULSE device technology, suggest that the device relax tense and spastic muscles, activate muscles, improve local blood circulation and relieve chronic pain symptoms in patients with CP, MS, stroke, fibromyalgia and other neurologic disorders that may cause similar symptoms, as well as anti-fatigue effects, improvements in anxiety and depression in the context of fibromyalgia.

To further expand the clinical data on the EXOPULSE devices and further strengthen the safety and performance of the device, the manufacturer aims at conducting and/or outsourcing several RCT's as described in the *PMCF Plan – EXOPULSE Devices*. The target populations will be CP, MS, stroke, chronic pain (fibromyalgia and back pain) patients, in which spasticity, muscle activation, blood circulation and/or pain relief, among other outcomes, will be measured.

7.3 Data on safety

7.3.1 Published safety data for the device under evaluation

When performing a literature search on published clinical trials on the EXOPULSE Mollii Suit in PubMed and Cochrane, no relevant adverse events were found. The same results were obtained when searching in the national adverse event databases. Like with all electrical stimulation devices, side effects such as

skin irritations or rashes from use of the EXOPULSE Mollii Suit, may occur but at a low frequency (see *Risk Management Report EXOPULSE Mollii* and *Risk Management Report EXOPULSE* for more information on severity and probability scores).

7.3.2 Safety data for the device under evaluation

The following number of post-market events have been reported for the EXOPULSE Mollii Suit during 2016-2022:

Table 23. Number of post-market events that have been reported during 2016-2022.

Year	Complaints	Safety Critical	Injuries	Sales number
2016-2020 (EXOPULSE Mollii Control Unit and Body Garments)	611	9	7	2568
2021-2022 (EXOPULSE Mollii Control Unit)	107	0	2	987
2021-2022 (EXOPULSE Mollii Body Garments)	90	0	2 (same injuries as above)	3506

Between 2021 and 2022, 987 EXOPULSE Mollii Control Units and 3 506 EXOPULSE Body Garments were distributed. 107 complaints on the EXOPULSE Mollii Control Units and 90 complaints on the EXOPULSE Body Garments were received, out of which 2 in total were safety relevant. The total number of reported safety relevant complaint during the period was low (0.2% for EXOPULSE Mollii Control Unit and 0.06% for EXOPULSE Body Garments) in relation to the number of distributed units.

The majority of the complaints reported are related to the quality of the product, e.g., dysfunctional zippers or BSI arms on the control units, which are not expected to lead to patient injuries. The identified injuries in the present and previous reports include epilepsy, skin irritations or burns which are already considered in the risk management report. Moreover, skin irritations- and burns are well known side effects from the use of other types of electrical stimulation devices.

Design features that would pose special safety concern are identified in the *Risk Management Report* and deemed to be of a similar kind to those that can be found in other electrotherapeutic devices with similar treatment modalities. There are no specific risks identified related to EXOPULSE Mollii Suit. The risk management confirms the adequacy of the information materials supplied by the manufacturer, including if risk mitigation measures are correctly addressed in the IFU.

7.3.3 Published data for similar devices

The literature review on TENS and NMES resulted in numerous clinical trials on performance. However, only a few (15 in total) reported adverse events and/or negative side effects caused by transcutaneous electrical nerve stimulation or neuromuscular electrical nerve stimulation. The most commonly reported event being skin irritations or discomfort.

The large number of publications on TENS and NMES found in PubMed and Cochrane, the relatively few adverse events and relatively mild severity of incidents reported on TENS, NMES and EXOPULSE Mollii Suit, suggest that the devices under evaluation are considered to be safe for use for the intended use described in the present *Clinical Evaluation Report.*

7.3.4 Risk analysis from the actual device

After all the measures taken had been implemented, not a single risk remained in the unacceptable area of the risk graph. The remaining residual risk for the individual risks listed in the risk analysis, was assessed as acceptable, after taking into account all the results of the risk assessment, as defined in the *Risk Management Plan*. Considering the residual risk assessment of the individual risks, the remaining overall residual risk is considered acceptable for all risks as defined in the risk management plan.

7.3.5 Other relevant data

7.3.5.1 Human factors Usability Engineering Report Results

Human factors validation studies have been conducted for the EXOPULSE Mollii Suit and EXOPULSE and the conclusions are summarized below:

EXOPULSE Mollii Suit	**EXOPULSE**
A human factors validation study has been conducted by an external party in a simulated-use format in which intended users performed the tasks that are necessary to use the EXOPULE Mollii Suit as intended (IRV-001 HFEUE Report). The conclusion from the report was that the EXOPULSE Mollii Suit was found to be safe and effective for the intended users, uses, and use environments. *Human Factors Engineering & Usability*	Human factors specialists observed participants as they performed various tasks and documented difficulties and use errors. The results of the study were analysed to identify root causes of any difficulties or use errors observed during testing. The conclusion of the evaluation conducted is that the EXOPULSE was found to be safe and effective for the intended users, uses and use environments with a mandatory onboarding process for intended users with a certified HCP and fitting session. *Usability Evaluation Summary Report* (DOC-1555)

Engineering Report for EXOPULSE Mollii (DOC-75)	

7.3.5.2 Effects of long-term use

Regarding potential negative side effects of long-term use of the EXOPULSE Mollii Suit, no such events have been reported from either of the two clinical trials which have been conducted over a period of six months (Torabi et al., 2018 and Hedin et al., 2020). Use of the device over an even longer period is not expected to result in any additional side effects.

7.3.5.3 Published safety data from the equivalent devices

In this clinical evaluation, no data on safety from equivalent devices is presented.

7.3.6 Summary of safety data

With the identified literature, the following risks for the patients, when using the EXPULSE Mollii Suit could be identified:

Table 24. Clinical safety of the device and risks for the patients.

Clinical risk	**Identified in documentation**			**Published studies**		**Published AE and internal databases**	
	Risk analysis (Yes/No)	Category / Frequency	IFU (Yes/No)	Identified (Yes/No) /reference	Frequency (n/total observations), severity	Identified	Frequency, severity
Skin irritation/ Burns/ Blisters/ Rashes	Yes	N/A	Yes	Yes	0 hits	MHRA, Swissmedic, BfARM, TGA System for Australian Recall Actions, TGA Database of Adverse Event Notifications and MAUDE	0 hits

Detailed description of hazards, nature of harm, probability, duration of harmful events, and risk mitigation are to be found in the risk analysis. Here, the focus is on information provided by the literature.

7.3.6.1 Side effects

Electrical stimulation devices have been on the market for several decades and the side effects are well known and relatively few when used in accordance with the intended use and as prescribed by the health care professional. However, as with all electrical stimulation devices, care must be taken to ensure good contact between the electrodes and the skin, as poor contact in rare cases may lead to skin irritations, rashes, or blisters under the site of the electrodes.

7.3.6.2 Other special populations

The EXOPULSE devices can be used by both children from the age of 2 years and adults, according to the same procedure. However, the stimulation settings are individually adjusted to fit each individual and are based on height, weight, body composition, age, severity of symptoms, size of the stimulated muscle etc. This means that a special population like children, will receive stimulation with the same parameters 20 Hz and 20 V, but with lower intensity (pulse width) compared to adults, according to a defined protocol.

The performance and safety data (for state of the art and for the device under evaluation) presented in this clinical evaluation and the available literature is evaluated on both children and adults. Frequency, type and adverse reactions in children are expected to be the same as in adults. There is no limitation on use of the device in children, as long as the patient fulfils the indications and contraindications specified in the IFU.

7.3.6.3 Adequacy of claims with identified data

Considering evidence gathered to perform this review on EXOPULSE devices, it is concluded that there is sufficient data to support the clinical performance and safety claims for the devices (see table below).

The statements (claims) made regarding EXOPULSE devices' safety and performance were confirmed. The list of claims made by management is available in the *Claims Matrix* and Section 2.7 Device claims in this *Clinical Evaluation Report*.

Table 25. Overview of the clinical claims for the EXOPULSE Mollii Suit.

Claim / Description	Justified through evidence (Yes / No)
Claim 1: Relaxation of tense and spastic muscles This claim is supported by data obtained directly from the EXPOPULSE Mollii Suit, which is equivalent to the EXOPULSE, and confirmed by data from literature on similar devices.	Yes
Claim 2: Activation of muscles This claim is supported by data obtained directly from the EXPOPULSE Mollii Suit, which is equivalent to the EXOPULSE, and confirmed by data from literature on similar devices	Yes
Claim 3: Increasing local blood circulation This claim is supported by data obtained directly from the EXPOPULSE Mollii Suit, which is equivalent to the EXOPULSE, and confirmed by data from literature on similar devices	Yes
Claim 4: Symptomatic relief of chronic pain	Yes

Claim / Description	Justified through evidence (Yes / No)
This claim is supported by data obtained directly from the EXPOPULSE Mollii Suit, which is equivalent to the EXOPULSE, and confirmed by data from literature on similar devices	
Claim 5: Analgesic and anti-fatigue effects, improvements in anxiety and depression in the context of Fibromyalgia This claim is supported by data obtained directly from the EXPOPULSE Mollii Suit.	Yes
The claims highlighted in green can be confirmed with own device data; the claims highlighted in yellow cannot be confirmed; the claims highlighted in red are wrong.	

The results of the assessment of the product claims will be forwarded to the person responsible for the product's market strategy.

7.4 Device literature and Instructions for use

The device literature and IFU's are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact on the use of the medical device. Risks from the risk analysis have been addressed in the IFU's according to Section 2.5 Warnings and precautions in instructions for use.

8 Benefit-risk-summary

The EXOPULSE Mollii Suit has been marketed since 2012 whereas the EXOPULSE has an anticipated market launch in 2024. In the context of this report, clinical evidence was obtained by analysing relevant published articles with clinical data obtained from similar devices on the market and from the devices under evaluation. This clinical evaluation aimed to determine whether there is sufficient data to continue to support the intended use, the clinical performance, and the safety of device.

The current evaluation provides evidence of the effectiveness of electrical stimulation for relaxation of tense and spastic muscles, activation of muscles, improved local blood circulation and relief of chronic pain symptoms. Given that transcutaneous electrical nerve stimulation and neuromuscular electrical stimulation, are two relatively safe interventions with acceptable adverse event profiles and that there is evidence for effectiveness in the above-mentioned intended use, the devices under evaluation may be used to improve function in patients with chronic pain, CP, MS, stroke, fibromyalgia and other neurological disorders that may cause such symptoms. It may also be used as an additive therapeutic method in combination with other treatments.

Compliance with essential safety and performance requirements has been demonstrated. The functional principle of electrical stimulation has been well established on the market for several decades and is described in the literature as a recognized state of the art.

All clinical performance claims are supported by the data analysed in this clinical evaluation in regard to the intended use of the devices. Through the literature review, clinical data identified different adverse events associated with the method. All events are judged predictable and already considered as possible to occur within the device's IFU.

Regarding benefit and safety assessment, available documentation and clinical literature have been reviewed. The devices have been shown to be effective for the intended use and at the same time, are associated with relatively mild side effects. The safety-relevant complaint rate for the currently marketed device EXOPULSE Mollii Suit is to be considered as very low. Reports on the device in adverse event databases were not identified.

Moreover, the EXOPULSE devices have several advantages compared to the alternative treatment options identified in the present report – the method is non-pharmacological and non-invasive, and the clinical effect from repeated use is long-lasting compared to alternative treatments such as botulinum toxin injections.

While rounded together, all available documentation and clinical literature reviewed for this evaluation demonstrate that the devices under evaluation have an established safe use. As indirectly demonstrated by the increase in number EXOPULSE Mollii Suit units sold per year since 2012, together with the supported intended use, the performance, clinical claims and acceptable safety level expectation, the device confirms the interest in relaxing tense and spastic muscles, activating muscles, improving local blood circulation and in symptomatic relief of chronic pain. However additional randomized controlled trials would be beneficial to further increase the patient number and improve the statistical power.

In conclusion, enough clinical data was collected to support the safe use and general performance of the devices. The identified data are in line with current knowledge/the state of the art, are scientifically sound, cover all aspects of the intended purpose and the clinical benefit, and address all products foreseen by the manufacturer, which include the medical devices and their sizes and settings. Based on the findings from the literature, clinical data as well as the risk analysis, it can be inferred that the probability of a patient experiencing a substantial benefit outweighs the probability of suffering harm due to residual risks of the devices. All gathered information indicates an acceptable safety profile and that the benefits of the devices outweigh the risks and that the benefit-risk ratio therefore is acceptable.

9 Conclusions

The clinical evaluation confirms that:

- the EXOPULSE devices comply with the current knowledge/ state-of-the-art technology,
- the EXOPULSE devices are adequate for their intended purposes,
- the EXOPULSE devices are suitable for the intended users and the usability aspects, and
- the clinical benefits for the patients are achieved and the benefit from the use of the EXOPULSE devices outweighs possible adverse effects.

Identified, reviewed, assessed and analysed clinical data were evaluated adequately to provide evidence of conformity of the EXOPULSE devices with the Regulation (EU) 2017/745. The identified data are in line with the current knowledge/ the state of the art, are scientifically sound, cover all aspects of the intended purpose and address all products foreseen by the manufacturer. Based on the findings of the literature, clinical data as well as the risk analysis, it can be inferred that the probability of a patient experiencing a substantial benefit when using the medical devices outweighs the probability of suffering harm due to a residual risk. Considering the available evidence identified in the clinical evaluation, further clinical investigations are not necessary. However, the *PMCF Plan* will define the processes which are the result of the *Clinical Evaluation Report* in order to further generate the PMCF data which will be presented in the *PMCF Report*.

In summary, the clinical safety, performance, and the clinical benefit of the EXOPULSE devices were demonstrated with this clinical evaluation. The report demonstrates that the EXOPULSE devices comply with the relevant general safety and performance requirements 1 and 8 of ANNEX I (Regulation (EU) 2017/745).

10 Declaration of interest and qualifications of authors

The declarations of interest and CV's of the authors and reviewers of the clinical evaluation are stored by Human Resources at ENN and/or in the eQMS of ENN; or in the Clinical Research & Services department by Ottobock.

11 Planned update

The next planned update of the *Clinical Evaluation Report* will be created prior to March 31, 2025 or when a significant change has been made affecting the validated status of the devices (*SSOP840 Clinical Evaluation* (DOC-165)).

12 Abbreviations

Terms	Explanation
BBS	Berg balance scale
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BPI	Brief Pain Inventory
CP	Cerebral palsy

Terms	Explanation
eQMS	Electronic Quality Management System
FGA	Functional Gait Assessment
FIQ	Fibromyalgia Impact Questionnaire
HADS	Hospital Anxiety and Depression Scale
IFU	Instructions For Use
MAUDE	Manufacturer and User Facility Device Experience
MDD	Medical Device Directive
MDR	Medical Device Regulation (Regulation (EU) 2017/745)
MEDDEV	European medical device guidelines
10-MWT	10 Metre Walking Test
MS	Multiple sclerosis
NCBI	National Center for Biotechnology Information
NMES	Neuromuscular Electrical Stimulation
PBS	Pediatric Balance Scale
PCS	Pain Catastrophizing Scale
PMCF	Post-market Clinical Follow-Up
PMS	Post-market surveillance
SF-36	Short Form 36 Health Survey
TENS	Transcutaneous Electrical Nerve Stimulation
TGA	Therapeutic Goods Administration
TUG	Timed Up and Go
VAS	Visaul Analogue Scale
WMFT	Wolf Motor Function Test

13 Team

Team	
Name / Function	**Responsibilities**
Reinhard Wolkerstorfer *PRRC*	Responsible for regulatory compliance
Sanna Dünesius *Clinical Project Manager*	Author of the clinical evaluation
Sarah Schröder *Clinical Project Manager*	Reviewer of the clinical evaluation

Dr. Marten Jakob *Director CRS Duderstadt*	Reviewer of the clinical evaluation
Dr. Milana Mileusnic *Director CRS Vienna*	Approver of the clinical evaluation

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15 Accompanying documents

Document	ID
Biological Evaluation Plan of EXOPULSE Mollii	DOC-60
Blood oxygenation internal registration	DOC-506
BOM datasheets and certificates - EXOPULSE Body Garments	DOC-3135
Change record - technical upgrade of EXOPULSE products	DOC-799
Claims Matrix	DOC-228
Classification (EU) EXOPULSE	DOC-844
Classification (EU) for EXOPULSE Apps	DOC-3870
Classification EXOPULSE Mollii Suit (EU)	DOC-53
Clinical Evaluation Plan EXOPULSE Devices	DOC-39
Electrode size groups	DOC-1703
EXOPULSE UDI Master List	DOC-1778
EXOPULSE Garments Design Specification	DOC-1840
EXOPULSE Suit 9.3 - Stimulation	DOC-11
EXOPULSE Active - Stimulation Algorithm	DOC-1129
EXOPULSE IFU	DOC-691
EXOPULSE Mollii Suit Registry results 2021	DOC-603
Human Factors Engineering & Usability Engineering Report for EXOPULSE Mollii	DOC-75
IFU EXOPULSE Mollii - EN	DOC-52
Intended Use - EXOPULSE	DOC-606

Document	ID
Intended Use EXOPULSE Body Garments (MDR)	DOC-293
Intended Use EXOPULSE MOLLII Control Unit (MDR)	DOC-125
Intended Use for EXOPULSE Apps	DOC-3867
Part A - Description of the device - EXOPULSE Apps	DOC-3853
Part A Description of the device EXOPULSE	DOC-2047
Part A Description of the device EXOPULSE Mollii Control Unit	DOC-170
PMCF Plan - EXOPULSE Device	DOC 103
PMCF Report - EXOPULSE Devices	DOC-104
PSUR EXOPULSE Mollii 2021-2022	DOC-924
QM100 Quality Manual	DOC-339
Risk analysis worksheet EXOPULSE	DOC-605
Risk Analysis Worksheet EXOPULSE Mollii	DOC-58
Risk Management Plan EXOPULSE	DOC-846
Risk Management Plan EXOPULSE Mollii	DOC-56
Risk Management Report EXOPULSE	DOC-3159
Risk Management Report EXOPULSE Mollii	DOC-57
SSOP840 Clinical Evaluation	DOC-165
Technical Documentation EXOPULSE Body Garment	DOC-962
UDI Master list EXOPULSE Mollii Suit	DOC-20
Usability Evaluation Summary Report	DOC-1555

16 Appendix

Appendix A - List of excluded literature (DOC-504)

Appendix B - List of complaints 2016-2022 (DOC-593)

Appendix C - Full text articles (DOC-4319)

Appendix D - N.A.

Appendix E - Evaluation criteria (DOC-505)

Appendix F - N.A.

Appendix G - List of included literature (DOC-916)

Appendix H - Literature search on alternative treatments (DOC-2998)

Clinical Evaluation Report EXOPULSE Devices (DOC-84) Ver. 6

Approved By:

(CO-844) update of clinical evaluation report Exopulse devices

Description

update of studies results on fibromyalgia (Mattar et al. 2024); changes list of team members; removal of chapter 17 which included preliminary data that was later published in Mattar et al. 2024

Justification

update of studies results on fibromyalgia (Mattar et al. 2024); changes list of team members; removal of chapter 17 which included preliminary data that was later published in Mattar et al. 2024

Assigned To:	Initiated By:	Priority:	Impact:
Milana Mileusnic	Milana Mileusnic	High	Minor

Version History:

Author	Effective Date	CO#	Ver.	Status
Milana Mileusnic	December 13, 2024 10:18 AM CET	CO-844	6	Published
Sarah Schröder	May 21, 2024 2:00 PM CEST	CO-623	5	Superseded
Mimi Westerlund	May 13, 2024 6:25 PM CEST	CO-615	4	Superseded
Mimi Westerlund	February 16, 2024 9:13 AM CET	CO-494	3	Superseded
Mimi Westerlund	March 31, 2023 9:23 PM CEST	CO-197	2	Superseded
Matilda Ekman	September 19, 2022 6:07 PM CEST	CO-72	1	Superseded
Matilda Ekman	July 6, 2022 5:19 PM CEST	Not Available	0	Superseded