Clinical Evaluation Assessment Report

Notified Body: BSI NL

Notified Body Number: 2797

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*(Please note this email is **strictly** for communication between the Expert Panel of the Commission and BSI. Manufacturers should contact their scheme manager with any questions relating to the CEAR)

A1. Assessment Details

A1. Assessment details	
Manufacturer (Name & SRN if available):	AngioDynamics Inc.
Authorised Rep (Name & SRN if available):	AngioDynamics Netherlands BV
Basic UDI-DI	50516840114V
Task Number:	T0016888/T0022241

CEAR Reference Number: CEART0016888/T0022241
TDAR Reference Number: TDART0016888/T0022241

Contents

A2. Assessment Type Details

A2. Assessment Type Details	
Type of Assessment	Initial Conformity Assessment
Certificate Number	MDR 735408
Annex & Section	Annex IX Article 52

A3. Device Details

A3. Device Details	
Device Description	The NanoKnife Procedure involves ablation by means of a series of high voltage DC current pulses between electrodes positions within or around a target. The induced electric field causes electroporation of cells, which increases the permeability of their membranes and ultimately leads to the formation of defects within the lipid bilayer. The result is that the cells are permanently damaged, an outcome which is referred to as Irreversible Electroporation (IRE). The use of high-voltage pulses (500-3000 V) means that a paralytic neuromuscular blockage must be administered in order to prevent/restrict patient movement during pulse delivery. General anaesthesia is therefore required. Additionally, synchronisation of pulse delivery with a patient's heart rhythm (within the refractory period) is required in cases where procedures are conducted within the abdominal or thoracic cavity. In order to achieve this, an external cardiac gating device may be connected to the device.
Variants	N/A - NanoKnife Generator version 3.0 and associated probes (see below) only
Accessories	Single electrode activation probe Single electrode standard probe Probe spacer (class I device) H787203003010 NanoKnife 3.0 Generator H787204001030 Single Electrode Activation Probe, 15 cm

A3. Device Details	
	H787204001040 Single Electrode Probe, 15 cm H787204001050 Single Electrode Activation Probe, 25 cm H787204001060 Single Electrode Probe, 25 cm H787204003015 Single Electrode Probes Spacer (class I device)
Previous Generations	NanoKnife Generator version 2.2 (ceased production as of 12/31/2017)
Novelty	Non-novel
Intended Purpose	Ablation of tissue by cell membrane electroporation
Indications for Use	The NanoKnife System is indicated for the ablation of prostate tissue in patients with intermediate risk prostate cancer.
Contraindications	Ablation procedures using the NanoKnife System are contraindicated in the following cases: • Ablation of lesions in the thoracic area in the presence of implanted cardiac pacemakers or defibrillators • Ablation of lesions in the vicinity of implanted electronic devices or implanted devices with metal parts • Ablation of lesions of the eyes, including the eyelids • Patient history of Epilepsy or Cardiac Arrhythmia Recent history of Myocardial Infarction
Warnings & Precautions	The NanoKnife device has been evaluated for the ablation of prostate tissue in patients with intermediate risk prostate cancer. The use of this device in other organs for other disease states has not been fully evaluated. Clinical Issues (including Arrhythmia, Hypertension, and Thrombus Risks)

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	• Patients with Q-T intervals greater than 500 ms (milliseconds) are at an increased risk for inappropriate energy delivery and arrhythmia. Verification of proper function of a synchronization device before initiating energy delivery is essential in these patients. • Asynchronous energy delivery (90 PPM (Pulses Per Minute)) might trigger atrial or ventricular fibrillation, especially in patients with structural heart disease. Ensure that proper interventions (e.g. defibrillator) and appropriately trained personnel are readily available for dealing with potential cardiac arrhythmias (see Section 6.6). • Using QRS synchronization devices whose output is not compatible with the specifications listed in this manual may result in arrhythmias including ventricular fibrillation. • Adequate precautions should be taken for patients with implantable electrical devices. Note the contraindication in certain patients. • There are potential risks associated with the location of the ablation: near the pericardium (tachycardia), or near the vagus nerve (bradycardia). • Additional patients may be at risk with insufficient muscle blockade or anesthetic analgesia (reflex tachycardia and reflex hypertension); patients with abnormal sinus rhythm prior to an ablation (arrhythmia); patients with a history of hypertension (hypertension); or patients with partial portal venous thrombosis, low central venous pressure (CVP), and a prothrombotic condition (venous thrombosis). Use of Electrodes • Avoid repeated vascular insult during electrode placement. • As anticipated with a needle-related procedure, repeated vascular insult due to multiple insertions into a vessel by an electrode during electrode placement may cause thrombus. • Ensure continuous image guidance during the needle placements. Failure to do so can lead to traumatic injury to surrounding structures. • Care should be taken during electrode placement in areas that require tissue be separated or retracted to avoid surrounding tissue damage.

A3. Device Details	
	• To avoid risks of infection, always maintain the electrodes' protective packaging (cap, tubes, etc.) when the electrodes are not placed in the patient. • Only electrode probes with intact electrical insulation must be used. Any electrodes with damaged electrical insulation must be discarded immediately and not connected to the NanoKnife Generator. • To preserve the electrode's sterility do not remove the electrodes from the packaging until the User is ready to apply the electrode to the patient. • Do not use the electrodes after the expiration date printed on their packaging. Observe the electrodes manufacturer's specific instructions (e.g., printed on the electrodes' packaging). • Only use AngioDynamics Electrode Probes with the NanoKnife System Generator. • Maintain electrical separation of the electrodes from safety ground by doing the following: - Disconnect any electrode from the Generator that is not applied to the patient. - Avoid any clamping of the electrode's cable, unless explicitly instructed or authorized by the electrode's manufacturer. - Do not connect any devices (e.g., measurement) to the electrodes unless they have been supplied by and specifically indicated for such a use by the manufacturer. Probe spacer warnings Reuse of single-use devices creates a potential risk of patient or user infections. Contamination of the device may lead to injury, illness, or death of the patient. Reprocessing may compromise the integrity of the device and/or lead to device failure.
Intended Patient Population	Men (18 and older) with intermediate risk prostate cancer.
Intended Users	Physicians; (surgeons, interventional radiologists) and Clinical Team Members (nurses, nurse practitioner, physician's assistant, surgical fellow, surgical/radiology technicians).
Risk Class (Class, Rule and Indent):	IIb, Rule 9 (generator and probes); probe spacer is class I and is not subject to assessment

A3. Device Details	
MDR code per (EU 2017 / 2185)	MDA 0312

Section B - Reviewers Involved In the assessment of the clinical review.
B1.Internal Clinical Reviewers

B1: Internal Clinical Reviewers			
Role	**Employee Code**	**Competency Codes Held**	**Medical Practitioner with Experience of the Device**
Clinical Evaluation Specialist (CES)	20135	C730-CS	No
Clinical Evaluation Specialist (CES) – Countersigner (if applicable)	N/A	N/A	N/A
Technical Specialist (TS)	18164	SMD 0312	No
Technical Specialist (TS) – Countersigner (if applicable)	N/A	N/A	N/A
Internal Clinician (IC)	20510	SMD 0312	Yes
Internal Clinician (IC) Countersigner (if applicable)	N/A	N/A	N/A

B2. External Clinical Reviewers

B2. External Clinical Reviewers			
Role	**Employee Code**	**Competency Codes Held**	**Medical Practitioner with Experience of the Device**
External Clinician	N/A	N/A	N/A
Statistician	N/A	N/A	N/A
Where External Reviewers are not considered necessary, please provide a rationale	The IC has confirmed that they have clinical experience of the device or similar devices, or of treating or diagnosing the intended patient population. There is sufficient expertise and knowledge in place internally to complete the assessment.		

Section C – The Clinical Evaluation Report & Plan (including Clinical Development Plan).

C1. Clinical Evaluation Report

CER (Document Number & Rev)	Clinical Evidence Report – AngioDynamics NanoKnife System, P019208.A
CER Update Frequency	Annually
Confirm CER is signed and dated	**CER Signed and Dated**
Confirm Up-to-date CV's provided for each of the CER Evaluators and Appropriate.	**CVs of CER Authors Provided and Accepted**
Confirm Up-to-date DOI's provided for each of the CER Evaluators which are signed and dated by both the evaluator & the manufacturer	**Declaration of Interest Signed, Dated and Acceptable**

C2. Clinical Evaluation Plan

C1. Clinical Evaluation Plan (CEP)	
Clinical Evaluation Plan - Conclusion	The clinical evaluation plan was appropriate: The manufacturer included a clinical development plan, detailing planned/ongoing confirmatory investigations. The manufacturer provided a comprehensive clinical evaluation plan covering all methods to be used to define and support the safety and performance objectives. The clinical evaluation plan has been accepted.

C3. State of the Art.

Section C2. State of the Art	
State of the Art Conclusion	The literature search demonstrates appropriate use of search terms, databases. The search was broad enough to identify all safety and performance criteria of alternative/benchmark devices. The manufacturer was able to also demonstrate through the guidance published by an International Delphi Consensus Project that IRE is acknowledged as an available therapy, but that HIFU is considered the standard of care in a significant number of focal therapy procedures. The manufacturer has identified all appropriate alternative treatment options for this patient population as part of their state-of-the-art literature search. The exclusion criteria were appropriate and both favourable and unfavourable data was included. The state-of-the-art conclusions are considered acceptable.

C4. Safety, Performance & Benefit-Risk – Claims & Objectives

C4. Safety, Performance & Benefit / Risk – Claims & Objectives (ER 6a, Annex X) (Annex 7)	
Claims & Objectives - Conclusion	The safety objectives are described in Section 2.10 of the CER with references to the state of the art in medicine. The safety objectives are considered appropriate for the subject device in light of its intended purpose/ indications for use.

C4. Safety, Performance & Benefit / Risk – Claims & Objectives (ER 6a, Annex X) (Annex 7)	
	The performance objectives are likewise described in section 2.10 of the CER, again with references to the state of the art in medicine. The performance objectives include post ablation in-field biopsy rate and PSA level reduction. The performance objectives are considered appropriate for the subject device in light of its intended purpose/ indications for use.

C5. Equivalence

C5. Equivalence	
Is the Manufacturer claiming Equivalence? The manufacturer is claiming equivalence.	
Device to which Equivalence is being Claimed (Including Manufacturer and Basic UDI-DI): **NanoKnife model 2.2.0**	
Regulatory Status of device: (Valid MDR Certificate, Valid MDD Certificate or Other)	Previously covered by MDD Certificate – ceased to be placed on the market at the end of 2017
Access to Data:	No concerns – manufacturer is claiming equivalence to their own device
Equivalence Conclusion	The assessment of equivalence has determined that there are no significant differences in safety or performance of the current device and the claimed equivalent device. It is noted that the differences in the presentation of features between NanoKnife 3.0 and NanoKnife 2.2.0 have been accepted: The equivalence argument and justification are provided by the manufacturer on pages 16-21 of the clinical evaluation plan and pages 11-15 of the clinical evaluation report.

C6. Common Specifications, Harmonised Standards or Other Solutions Applied

C6. Common Specifications (CS), Harmonised Standards (HS) or other Solutions Applied.	
Is the Manufacturer claiming compliance to common specifications, harmonised standards or other solutions? No	
Conclusions of Common Specifications, Harmonised Standards and Other Solutions	The manufacturer is not claiming compliance to common specifications, harmonised standards or other solutions, for the purposes of the clinical evaluation.

Section D - Clinical Literature Review on the Device or Equivalent

D1. Clinical Literature Review

D1: Clinical Literature Review	
Conclusions of Clinical Literature Review.	The search criteria of the literature review: • Addressed all device variants, models and accessories • Addressed the same clinical condition The selection criteria of the literature review: • The device under evaluation • The state of the art and all alternative available treatment options. The literature search methodology was described in Appendix 2 of the CER. A systematic literature review was performed for State-of-the-Art and data on the NanoKnife and was found to be acceptable. No concerns were raised regarding the literature search protocol and results. The literature search results (CER appendix D) yielded 22 articles reporting data on IRE.. The appraisal of the clinical data is carried out in a methodological manner and includes consideration of relevance aspects such as appropriate device/intended use, and contribution aspects of quality of data in terms of study design, number of patients, etc. The reviewer raises no concerns in relation to the appraisal methodology.

D1: Clinical Literature Review	
	The reviewer agrees the clinical data is appraised and weighted in a systematic manner for contribution of each data set, considering appropriate factors of suitability and scientific data quality.

Section E. Clinical Investigation (CI) Data

E1. Clinical Investigations and Related Documentation.

E1: Clinical Investigations (CI) and Related Documentation
Have Clinical Investigations Been Performed*? Clinical Investigations have NOT been conducted.*

Section F - Other Sources of Data (Including PMS Data)

F1. Other Sources of data

F1: Other Data e.g. PMS Data/PMCF Data	
Type of Data:	Post-market complaint and vigilance data.
CES Conclusions of Data:	The complaint rate is relatively low, stable and acceptably in line with expected complaint rates in risk management. No trends or rates gave cause for concern. While PMS data is understood to have limitations in reporting, the data was considered relevant to the clinical evaluation and is well within the established safety and performance objectives.

Section G - PMS Plan & PMCF Plan.

G1. PMS Plan

G1: PMS Plan	
Conclusions on PMS Plan	Table 5 of the PMS plan describes the methods and procedures for post-market surveillance specific to the subject device. The following passive methods are used: • Complaints and Vigilance • Product Quality Metrics • Literature • Public Database Searches The reviewer agrees the PMS plan for the subject device is acceptable.

G2. PMCF Plan

G2: PMCF Plan	
Conclusions on PMCF Plan	In Section 5 of the PMCF plan, the ongoing PMCF data to be collected is described. There is one ongoing PMCF registry study and one planned RCT comparing the functional outcomes in patients treated with the device under assessment, compared to conventional treatment with either radical prostatectomy or radiation therapy. The data from these studies will be analysed individually and cumulatively toward the safety and performance objectives and acceptance criteria of the device under assessment. Based on the currently available clinical data, the reviewer agrees the PMCF methodologies chosen (registry plus RCT) are appropriate to inform ongoing safety and performance of the subject device. The reviewer concludes that the PMCF plan is acceptable and in line with the associated MDR requirements and MDCG guidance.

Section H - Risk Management & Clinical Evaluation

H1. Risk Management & Clinical Evaluation

H1: Risk Management & Clinical Evaluation	
Conclusions Risk Management & Clinical Evaluation	Clinical risks identified from state of the art and literature are covered within the risk analysis and occurrence rates align. Occurrence rates are quantitative. Complaint rates reported in the CER / PMS report appear to be broadly aligned to or within the occurrence rates in the risk analysis. Residual clinical risks which are deemed to be acceptable after concluding the risk evaluation are weighed against the benefits in the CER and overall acceptability is confirmed. Residual risks are communicated within the IFU.

Section I - Overall Conclusion

I1. Overall Conclusions

I1. Conclusions:	
Benefit/Risk Conclusion:	In Section 5 of the CER, an overall summary of the clinical performance and safety is presented along with a benefit-risk analysis. The reviewer agrees that the manufacturer has evaluated the benefit-risk ratio in a quantitative manner considering the safety and performance data and agrees with the manufacturer's conclusion that an acceptable benefit-risk profile has been demonstrated by the clinical safety and performance data on the subject device. The clinical evaluation plan and report as well as the PMS/PMCF plan supports demonstration of compliance with the relevant General Safety and Performance Requirements of the MDR. The technology is established in the industry clinical practice guidelines and remains a state-of-the-art treatment. The clinical evaluation is based on sufficient clinical data from the literature demonstrating safety and performance of the subject device. A positive benefit-risk ratio is demonstrated. No additional assessment by the notified body is deemed necessary at this time and no particular circumstances have been identified that would warrant a limited period of validity for the certificate. In conclusion, the reviewer provides a positive recommendation for certification of the subject device for a duration of 5 years.
Definitive conclusion on the assessment of the manufacturer's clinical evaluation	Acceptable risk benefit profile demonstrated Acceptability of undesirable side effects have been demonstrated to constitute an acceptable risk when weighed against the performances intended.

Section J - Alignment of Documentation and Labelling

J1. Alignment of Documentation and Labelling

I1: IFU, SSCP, labelling and other information supplied with the device
Information for Users (IFU): NanoKnife 3.0 System User Manual, Rev A, 16955933-21
List of documents reviewed for alignment of information:

I1: IFU, SSCP, labelling and other information supplied with the device

Clinical Evaluation Report
Risk Management Report

Key information	**Alignment**	**Comments (if not aligned):** *Comment on which document that is not aligned and any incorrections or missing information.*
Intended Purpose:	Aligned	
Indication for Use:	Aligned	
Intended patient population:	Aligned	
Intended users:	Aligned	
Limitations:	Aligned	
Contraindications:	Aligned	
Warnings and precautions:	Aligned	
Information supplied for users & other persons:	Aligned	

SSCP –
The SSCP has NOT been validated as part of this assessment.

Section K - Final versions of Documents

Documentation Assessed (Final Versions)	
CER (Document Number & Rev)	Clinical Evidence Report – AngioDynamics NanoKnife System, P019208.A
Clinical Evaluation Plan (Document Number & Rev)	Clinical Evaluation Plan – Nanoknife, P018964.A
IFU (Document Number & Rev)	NanoKnife 3.0 System User Manual, Rev A
Draft SSCP (Document Number & Rev)	N/A
PSUR (Document Number & Rev)	N/A
Others:	NanoKnife 3.0 Generator Risk Management Report, P018136, Revision A

Appendices

Appendix II – CECP (Clinical Evaluation Consultation Procedure)

Appendix II: Clinical evaluation consultation procedure for certain class III and class IIb devices (Article 54)
Is the device a class III implant or class IIb active device intended to administer and/or remove a medicinal substance (Rule 12)? *No - Article 54 NOT Applicable*
Is the procedure required by Article 54(1) to be applied? Choose an item. ☐ Renewal of a certificate issued under the MDR; ☐ The device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, and the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device; ☐ The principles of the clinical evaluation of the device type or category have been addressed in a CS referred to in Article 9 and the notified body confirms that the clinical evaluation of the manufacturer for this device is in compliance with the relevant CS for clinical evaluation of that kind of device; ☐ AIMDD/MDD certified devices with no modifications that adversely affect the benefit-risk ratio at the time of MDR application. **Further information and Justification for selection of Why Article 54 (1) does not apply:**
Relevant scientific panel and associated competence area(s)

Appendix II: Clinical evaluation consultation procedure for certain class III and class IIb devices (Article 54)			
☐	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☐ Joint replacements (hip, knee, shoulder)	
		☐ Spinal devices	
		☐ Non-articulating devices, rehabilitation	
		☐ Other	
☐	**Circulatory system: cardiovascular / lymphatic system**	☐ Prosthetic heart valves and devices for heart valve repair	
		☐ Cardiovascular stents (metallic and bioresorbable) and vascular prostheses	
		☐ Active implantable cardiac devices and electrophysiological devices	
		☐ Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices)	
		☐ Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts (and left ventricular assist devices)	
		☐ Other	
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices	
☐	**Neurology**	☐ Central and peripheral nervous system devices	
		☐ Implants for hearing and vision (sensory recovery)	
		☐ Neurosurgical devices	
		☐ Other	
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes (e.g. insulin delivery systems and closed-loop systems, continuous glucose monitoring) Implantable systems	
☐	**General and plastic surgery, dentistry**	☐ Surgical implants and general surgery	
		☐ Plastic surgery and wound care	
		☐ Maxillofacial surgery	
		☐ Dentistry (devices for dentistry (oral surgery, implantology, dental materials incl.))	
		☐ Other	
☐	**Obstetrics & gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology and reproductive medicine	

Appendix II: Clinical evaluation consultation procedure for certain class III and class IIb devices (Article 54)			
☐	**Gastroenterology & hepatology**	☐Devices for gastroenterology and hepatology	
☐	**Nephrology & urology**	☐ Devices for nephrology and urology	
☐	**Ophthalmology**	☐ Devices for ophthalmology	

Conclusions for Certain Class III and IIb devices to be considered by the Expert Panel

Novel Aspects:

Benefit-risk determination:

Consistency of clinical evidence with intended purpose and PMCF:

Appendix III – Article 61 (10)

Appendix III: Where demonstration of conformity based on clinical data is not deemed appropriate (Article 61(10))
Article 61 (10) Choose an item.

Appendix III: Where demonstration of conformity based on clinical data is not deemed appropriate (Article 61(10))	
Justification for using Article 61(10):	
CER (Document Number & Rev)	**N/A**
CER Update Frequency	**N/A**
Confirm CER is signed and dated	Choose an item.
Confirm Up-to-date CV's provided for each of the CER Evaluators and Appropriate.	Choose an item.
Confirm Up-to-date DOI's provided for each of the CER Evaluators which are signed and dated by both the evaluator & the manufacturer	Choose an item.
Conclusions On Article 61 (10) Assessment	

Appendix IV – Article 61 (2) Voluntary Clinical Consultation on Clinical Development Strategy.

Appendix IV: The voluntary clinical consultation on the clinical development strategy (Article 61(2))
L1: **The manufacturer did NOT undertake the voluntary clinical consultation on the clinical development strategy (Article 61(2** **Expert Panel consultation reference:** **Expert Panel recommendations:**