Evaluation of low-thermal argon plasma devitalization (LtAPD) for the treatment of cervical intraepithelial neoplasia (CIN) grade 2 versus standard of active surveillance

Short Title	*CINPLASTA*
Protocol Version	*2.0*
Protocol Date	*25.06.2026*
BfArM-identification number § 48 (3) MPDG	*DE-26-0000510067*
Further reference numbers	*pending*
Sponsor	University Hospital Tübingen Geissweg 3 72076 Tübingen Germany
Investigational device	*Low-thermal argon plasma devitalization (LtAPD) treatment*
Comparator	*Sham treatment + active surveillance*
Summary of the revision history	*Version 1.0, 21.04.2026*

CONFIDENTIAL This Clinical Investigation Plan contains confidential information and is intended solely for the guidance of clinical investigation. It may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of the Sponsor.

II. Signature Page

The present clinical investigation plan was subject to critical review and has been approved in the present version by the persons signed.

Sponsor: The University Hospital Tuebingen is sponsor for the purpose of Art. 2 (2) 49. Regulation (EU) No 2017/745 with complementary regulations. The internal responsibility to comply with the obligations of the sponsor in terms of these regulations stays with [redacted]

Date: _____ Signature: _____

Name (block letters): [redacted]

Function: Sponsor´s Delegate

Date: _____ Signature: _____

Name (block letters): _____

Function: Biometrician

III. Declaration of principal investigator

By my signature, I agree to supervise personally the conduct of this investigation at my clinical investigation site and to ensure its conduct in compliance with the clinical investigation plan, informed consent, the applicable European and national laws, the Good Clinical Practice Guidelines and the Declaration of Helsinki. I will train the involved personal accordingly.

Date: _____ Signature: _____

Name (block letters): _____

Function: Principal Investigator

Address of the clinical investigation site: _____

_____

_____

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V. Contacts

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SAE Reporting	[redacted]
Manufacturer of the investigational device and technical support	[redacted]

VI. Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AIN	Anal Intraepithelial Neoplasia
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMBF	Bundesministerium für Bildung und Forschung
CC	Cervical Cancer
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
CI	Coordinating Investigator (Leiter der klinischen Prüfung)
CIN	Cervical Intraepithelial Neoplasia
CIP	Clinical Investigation Plan
CV	Curriculum Vitae
DBL	Data Base Lock
DD	Device Deficiency
DFG	Deutsche Forschungsgemeinschaft
DSMB	Data and Safety Monitoring Board
DVP	Data Validation Plan
EC	Ethics Committee
ECG	Electrocardiogram
ESU	Electrosurgical Units
FIPS	Freiburg Index of Patient Satisfaction
FSI	First Subject In
FU	Follow Up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HPV	Human Papilloma Virus
IB	Investigator's Brochure
IC	Informed Consent
IIT	Investigator Initiated Trial
ISF	Investigator Site File
ITT	Intention to Treat
LDSG	Landesdatenschutzgesetz
LLETZ	Large Loop Excision of the Transformation Zone
LSI	Last Subject In

LSO	Last Subject Out
LtAPD	Low-thermal Argon Plasma Devitalization
MDR	Medical Device Regulation
MPDG	Medizinprodukterecht-Durchführungsgesetz
N.A.	Not Applicable
NIPP	Non-invasive Physical Plasma
PAP	Papanicolaou Test
PEI	Paul-Ehrlich-Institut
PI	Principal Investigator (Hauptprüfer)
PICO	Patient/Population - Intervention - Comparison - Outcome
PP	Per Protocol
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAQ	Sexual Activity Questionnaire
SDV	Source Data Verification
SoA	Schedule of Activities
ST	Standard (Procedure)
TIDieR	Template for Intervention Description and Replication
USADE	Unanticipated Serious Adverse Device Effect
TMF	Trial Master File
VAIN	Vagina Intraepithelial Neoplasia
VIN	Vulva Intraepithelial Neoplasia
ZKS	Zentrum für Klinische Studien

VII. Synopsis

Title	Evaluation of low-thermal argon plasma devitalization (LtAPD) for the treatment of cervical intraepithelial neoplasia (CIN) grade 2 versus standard of active surveillance
Protocol Code	CINPLASTA
Kennnummer der sonstigen klinischen Prüfung (§ 48 (3) MPDG)	*DE-26-0000510067*
Further reference numbers	*pending*
Sponsor	University Hospital Tübingen Geissweg 3 72076 Tübingen Germany
Sponsor delegate	University Hospital Tübingen Department for Women's Health [redacted]
Financing & agreements	*This clinical investigation is funded by the German Federal Ministry of Research, Technology and Space (Bundesministerium für Forschung, Technologie und Raumfahrt, BMFTR) through the DLR Projektträger (DLR-PT), Bonn, Germany, under grant number [redacted]. The grant holder is [redacted], Department of Women's Health (Department für Frauengesundheit), University Hospital Tübingen, Eberhard Karls Universität Tübingen, Germany.* *No confidentiality obligations, publication restrictions, or follow-up costs are associated with this grant. The funder has no role in study design, data collection, data analysis, interpretation of results, or the decision to submit findings for publication.*
Investigational device	*Plasma application system: Low-thermal Argon Plasma Devitalization (LtAPD)*
Comparator	*Sham treatment (application of the inactive LtAPD device without plasma generation) followed by active surveillance according to current clinical guidelines*

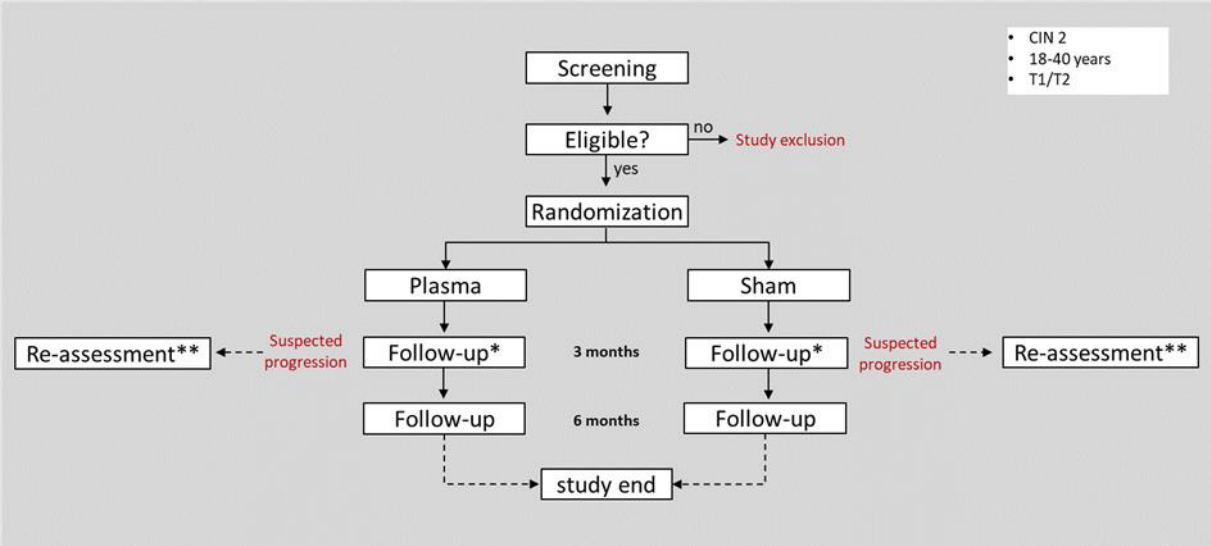
Design of the clinical investigation	*Prospective, multicenter, two-armed, randomized (1:1), single-blinded, sham-controlled clinical investigation with active surveillance as standard of care in the control arm*
Criteria for subject selection	**Inclusion Criteria:** 1. Female sex 2. Age 18 – 40 years at the time of signing the informed consent 3. Histologically confirmed CIN 2 4. Full visibility of the entire transformation zone (Type 1 or Type 2) and entire lesion in colposcopy 5. Ability to understand the nature of the clinical investigation and voluntarily signs the informed consent document prior to any study-related procedures **Exclusion Criteria:** 1. Histologically confirmed CIN other than CIN 2, or indication of (micro-) invasive cervical disease 2. CIN lesions extending to the vaginal vault or suspicion of endocervical disease 3. Current pregnancy or planned pregnancy within the next 6 months 4. Presence of severe local inflammation or active infection 5. Presence of a severe cardiovascular, neurological, psychiatric, endocrine, or hematological disease, immunocompromised condition or malignant tumor of any origin, as judged by the investigator 6. Participation in an interfering clinical study, as judged by the investigator
Number of subjects	264
Subject Population	Women with histologically confirmed cervical intraepithelial neoplasia grade 2 (CIN 2), a high-risk precancerous lesion of the uterine cervix
Intervention/treatment	**LtAPD group:** Single session of LtAPD treatment [redacted] applied to the CIN2 lesion under colposcopic guidance; outpatient, no anesthesia required **Sham group:** Single session of sham treatment (no argon gas delivery and plasma ignition; acoustic signal to maintain blinding) followed by active surveillance according to current clinical guidelines

<table>
<tr><td>Follow-up measures</td><td colspan="2"><u>3 months (V3):</u>
Visit at established gynecologist; PAP-smear sample taken; cytological assessment according to guidelines; immediate colposcopic re-assessment at study center in case of ≥ PAP IVa-p
<u>6 months (V4):</u>
Clinical re-examination at study center; colposcopy with acetic acid and Lugol's iodine staining; PAP-smear; photo documentation; cervical biopsy for histological examination; questionnaires (FIPS, SAQ)
In case of progression to ≥ CIN 3 at any time point: discontinuation of investigational treatment and immediate standard-of-care intervention (LLETZ according to current clinical guidelines). The subject remains in the study for outcome assessment; progression is classified as treatment failure in the primary analysis.</td></tr>
<tr><td rowspan="10">Duration/ Timelines</td><td>Expected total duration of the investigation:</td><td>48 months</td></tr>
<tr><td colspan="2">Expected duration of the subject's participation in the clinical investigation:</td></tr>
<tr><td>Treatment completed:</td><td>1 hour</td></tr>
<tr><td>Follow-up measures completed:</td><td>6 months</td></tr>
<tr><td>FSI (First Subject In):</td><td>Q3-2026</td></tr>
<tr><td>LSI (Last Subject In):</td><td>Q1-2029</td></tr>
<tr><td>LSO (Last Subject Out):</td><td>Q3-2029</td></tr>
<tr><td>DBL (Data Base Lock):</td><td>Q4-2029</td></tr>
<tr><td>Statistical analyses completed:</td><td>Q2-2030</td></tr>
<tr><td>Clinical investigation report completed:</td><td>Q3-2030</td></tr>
<tr><td>Aim of the clinical investigation</td><td colspan="2">To demonstrate the superiority of LtAPD treatment over sham treatment and active surveillance in achieving histopathological remission of CIN 2 after 6 months, and to assess the impact of LtAPD on HPV clearance, cytological remission, and quality of life in women of childbearing age.</td></tr>
</table>

Endpoints of the clinical investigation	Primary endpoints: • Histopathological remission of CIN 2 at 6 months Secondary endpoints: • HPV remission rate at 6 months • Cytological remission of CIN at 6 months • Quality of life, comfort/ discomfort of the treatment procedure and sexual activity • Correlation of electrosurgical unit (ESU) and video data with CIN remission and applied argon plasma Safety endpoint: • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including device-related adverse events
Statistical approach	Efficacy: • histopathological remission rate of CIN 2 Description of the primary efficacy analysis and population: • comparison of the histopathological remission rate of CIN 2 after 6 months in both study groups (logistic regression adjusted for study centers). Safety: • Descriptive statistics safety data (Number of adverse events, Number of device related adverse events/ effects). Secondary endpoints: Descriptive statistics of HPV remission rate after 6 months, cytological remission of CIN after 6 months, quality of life (comfort/discomfort of the treatment procedure and sexual activity), correlation of electrosurgical unit (ESU) and video data with CIN remission and applied argon plasma. After 6 months cytological remission and HPV remission rate, analysed by smear test and p16 immunohistochemical evaluation: i) identical to primary endpoint; ii) before intervention and 6 months after the QoL measures sexual health (SAQ) and patient satisfaction (FIPS) compared for both groups using baseline adjusted analysis of covariance, Mann-Whitney-U test for differences Follow-up minus baseline if data are not normally distributed); iii) During intervention electrical and video data are collected for treatment path visualization and subsequent assessment of plasma homogeneity.

Criteria and measures for temporary halt or early termination	The clinical investigation may be temporarily halted or prematurely terminated based on the following criteria: • Safety: Accumulation of unexpected or disproportionate serious adverse events (SAEs) or unanticipated serious adverse device effects (USADEs) • Efficacy: Overwhelming superiority or demonstrated futility of the investigational treatment based on interim data • Recruitment: Insufficient subject enrollment compromising the validity of the study • New evidence: Emerging external data fundamentally altering the risk-benefit assessment Decisions are made by the sponsor in consultation with the coordinating investigator and the DSMB (DSMB Charta).

Flow Chart



* Cytological assessment according to guidelines at established gynecologist

** ≥PAP IVa-p will immediately be re-assessed by colposcopy ±histology. ≥CIN 3 will be treated by LLETZ according to guidelines

1. Introduction

Cervical cancer is causally linked to persistent infection with high-risk human papillomavirus (HPV) and remains the fourth most common cause of cancer-related death in women worldwide, with approximately 270,000 deaths annually. The majority of cases develop through a well-characterized precancerous continuum of cervical intraepithelial neoplasia (CIN), classified as grades 1 through 3 according to the extent of epithelial involvement.

Current guidelines recommend active surveillance as the standard of care for CIN1 and 2, reserving excisional intervention primarily for CIN 3. However, this conservative approach carries a clinically significant oncological risk: a landmark Danish population-based cohort study of over 20,000 patients demonstrated that women with untreated CIN 2 face an almost fourfold increased long-term risk of developing cervical cancer compared to those receiving immediate treatment [1]. Active surveillance furthermore entails repeated invasive diagnostic procedures at three-month intervals, imposing a substantial psychological and physical burden during an extended period of diagnostic uncertainty [2]. The alternative — excisional treatment by Large Loop Excision of the Transformation Zone (LLETZ) or laser ablation — resolves the oncological risk but introduces a distinct set of iatrogenic complications particularly relevant for young women of reproductive age, including cervical tissue loss, increased risk of preterm birth, major bleeding, and the requirement for anesthesia [3; 4]. With approximately 100,000 LLETZ procedures performed annually in Germany alone, a substantial proportion of which represent overtreatment of lesions that would have regressed spontaneously, the clinical and health-economic burden is considerable. This unresolved tension between the oncological risk of undertreatment and the iatrogenic consequences of overtreatment defines the central clinical problem that CINPLASTA is designed to address.

Low-thermal argon plasma devitalization (LtAPD), generated by high-frequency electrosurgical argon plasma devices, has emerged as a promising tissue-preserving treatment modality for epithelial precancerous lesions. LtAPD exerts its biological effects through reactive oxygen and nitrogen species, inducing DNA damage, cell cycle arrest and apoptosis selectively in dysplastic cells while preserving surrounding stromal tissue, with a demonstrated transmucosal penetration depth of ≥ 270 µm consistently affecting the basal cell layer [5; 6]. Clinical feasibility and preliminary efficacy were established in a monocentric prospective controlled pilot study (CAPCIN, NCT03218436), in which LtAPD application in 63 patients with CIN 1/2 achieved a complete remission rate of 86.2% within 3 months and a statistically significant twofold reduction in high-risk HPV infection at 6 months — comparable to LLETZ — performed entirely on an outpatient basis without anesthesia and without major adverse effects [8]. The CINPLASTA trial is designed to confirm the superiority of LtAPD over sham treatment and active surveillance in a prospective, multicenter, randomized, sham-controlled,

single-blinded setting. If efficacy is confirmed, LtAPD would represent the first curative, non-invasive, tissue-preserving treatment option for CIN 2, directly resolving the current clinical dilemma and forming the evidence base for integration into national and international clinical guidelines.

1.1. Rationale for the design of the clinical investigation

The management of CIN 2 represents an unresolved clinical challenge. Current standard of care — active surveillance — is associated with an almost fourfold increased long-term risk of cervical cancer, while the available excisional alternative (LLETZ) carries significant iatrogenic risks, particularly in women of reproductive age. No curative, non-invasive treatment option currently exists for this indication. The CINPLASTA investigation directly addresses this evidence gap by evaluating LtAPD as a novel therapeutic approach in a confirmatory, randomized, controlled trial.

The design of the clinical investigation is based on the conclusions of a structured clinical evaluation encompassing preclinical, ex vivo, and prior clinical data. At the preclinical level, in vitro studies using dysplastic cervical cell lines demonstrated that LtAPD induces selective, dose-dependent growth retardation, DNA damage, cell cycle arrest, and apoptosis in cancer cells, while sparing benign epithelial cells [5]. Ex vivo and in vivo tissue assessments confirmed transmucosal devitalization of dysplastic areas at penetration depths of ≥ 270 µm, consistently reaching the basal cell layer — the site of CIN origin — without thermal damage to surrounding stromal tissue [6].

At the clinical level, the preceding monocentric, prospective, single-arm feasibility study (CAPCIN, NCT03218436) established the proof-of-concept for LtAPD in CIN treatment. Application of the [redacted] in 63 patients with CIN 1/2 resulted in a complete remission rate of 86.2% within 3 months and a statistically significant twofold reduction in high-risk HPV infection at 6 months, with no serious adverse events and no cases of thermal tissue damage [8]. These results provide the empirical basis for the assumed effect sizes underlying the power calculation of the present investigation.

CINPLASTA represents the confirmatory stage of clinical development. The choice of a prospective, multicenter, randomized (1:1), sham-controlled, single-blinded design reflects the requirement to generate high-quality evidence suitable for regulatory and guideline purposes under MDR Annex XV. A sham-controlled design was selected over an open-label active surveillance comparator to ensure subject blinding and to isolate the treatment effect of LtAPD from placebo and expectation effects. Single blinding — with investigators aware of treatment allocation but subjects blinded — is the maximum feasible blinding level given the nature of the intervention, as investigator awareness is required for safe and targeted plasma application under colposcopic guidance. Multicenter

recruitment across several certified dysplasia centers ensures generalizability of findings and adequate statistical power within the planned recruitment period.

1.2. Risks and clinical benefits of the device to be examined, the clinical procedure and the clinical investigation

Clinical benefits

The LtAPD procedure offers a unique combination of oncological efficacy and procedural safety that directly addresses the current treatment dilemma in CIN 2 management. As a non-invasive, tissue-preserving intervention performed entirely on an outpatient basis without local or general anesthesia, LtAPD avoids the iatrogenic risks associated with excisional procedures — including cervical tissue loss, increased risk of preterm birth, and anesthesia-related complications. The total visit duration is less than one hour, with active tissue treatment requiring only 2–10 minutes. LtAPD demonstrates excellent tolerability, preserves fertility, and reduces the disease-associated psychological burden of prolonged surveillance while maintaining quality of life and sexual health. The procedure can be repeated without limitation if clinically indicated. Upon proof of efficacy, LtAPD is readily transferable to routine outpatient care, with preliminary analyses indicating a 3.8–4.8-fold cost reduction per patient compared to standard excisional treatment.

Risks and foreseeable adverse effects

Based on data from the preceding pilot study (CAPCIN), LtAPD treatment is associated with a low and predictable risk profile. Transient local discomfort or mild to moderate pain may occur during the procedure. Within 24 hours following treatment, minor spotting or increased vaginal discharge have been observed; all events resolved spontaneously without intervention [8]. No serious adverse events attributable to LtAPD have been reported to date. Incorrect application technique — particularly insufficient probe movement — may result in superficial localized thermal tissue effects, which can be mitigated by standardized investigator training prior to study initiation.

1.3. Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be assembled. The DSMB will be composed of independent experts in the field of colposcopy, gynecological dysplasia and clinical epidemiology and an independent biometrician, assessing the progress, safety data and critical efficacy endpoints: [redacted] The mission of the DSMB will be to ensure the ethical conduct of the investigation and to protect the safety interests of subjects in this investigation.

The activities of the DSMB are described in the DSMB Charta.

2. Objectives and hypotheses of the clinical investigation

Primary objective

To demonstrate the superiority of low-thermal argon plasma devitalization (LtAPD) treatment over sham treatment and active surveillance in achieving histopathological remission of CIN 2 after 6 months in women aged 18 to 40 years with histologically confirmed CIN 2 and full visibility of the transformation zone (Type 1 or Type 2).

The primary objective is directly operationalized through the primary endpoint (histopathological remission of CIN 2 at 6 months, assessed by colposcopy-directed biopsy) and is explicitly linked to the subject selection criteria: eligibility requires histologically confirmed CIN 2 (Inclusion Criterion 3), full visibility of the transformation zone Type 1 or Type 2 (Inclusion Criterion 4), and an age of 18 to 40 years (Inclusion Criterion 2), ensuring that the investigation population is representative of the target population for whom the clinical benefit is claimed.

Primary hypothesis

H_0: The histopathological remission rate of CIN 2 at 6 months in the LtAPD group is equal to or lower than in the sham/active surveillance group.

H_1: The histopathological remission rate of CIN 2 at 6 months in the LtAPD group is superior to the sham/ active surveillance group.

The investigation is designed as a superiority trial. A two-sided significance level of $\alpha = 0.05$ and a statistical power of 80% are applied. Based on prior data, a spontaneous remission rate of 50% in the control group and a remission rate of 70% in the LtAPD group are assumed, yielding a clinically relevant absolute difference of 20 percentage points [8; 9; 10].

Secondary objectives

To evaluate the effect of LtAPD treatment compared to sham treatment and active surveillance on the following outcomes at 6 months:

- HPV remission rate, assessed by validated HPV testing and p16 immunohistochemical evaluation
- Cytological remission of CIN, assessed by PAP smear
- Patient-reported quality of life, procedural comfort/discomfort, and sexual health, assessed by FIPS and SAQ questionnaires

- Homogeneity and reproducibility of LtAPD application, assessed by correlation of ESU and video data with CIN remission

Safety objective

To characterize the safety profile of LtAPD treatment by documenting the incidence, severity, and causal relationship of adverse events (AEs), serious adverse events (SAEs), and device-related adverse effects (ADEs) throughout the investigation period.

Claimed clinical benefit

Upon demonstration of superiority, LtAPD represents the first curative, non-invasive, tissue-preserving treatment option for CIN 2, directly addressing the current clinical dilemma between oncological undertreatment through active surveillance and iatrogenic overtreatment through excisional procedures. The claimed benefits include histopathological and virological remission without cervical tissue loss, preservation of reproductive health, elimination of anesthesia-related risks, and reduction of disease-associated psychological burden.

3. Design of the clinical investigation with evidence of its scientific robustness and validity

3.1. Type of investigation with rationale for choosing it

CINPLASTA is a prospective, multicenter, two-armed, randomized (1:1), single-blinded, sham-controlled clinical investigation. The prospective design was chosen to generate high-quality evidence suitable for regulatory and guideline purposes under MDR Annex XV, avoiding the inherent limitations of retrospective analyses. The two-armed parallel-group design with 1:1 randomization is the appropriate confirmatory design for a superiority claim, directly comparing the investigational intervention against the current standard of care.

The sham-controlled comparator — consisting of treatment simulation without argon gas and plasma ignition, combined with active surveillance — was selected over an uncontrolled active surveillance arm to ensure subject blinding and to isolate the specific therapeutic effect of LtAPD from non-specific procedural and expectation effects. Active surveillance represents the current evidence-based standard of care for CIN 2 in women of reproductive age and constitutes an ethically justifiable comparator, as it is the recommended clinical management strategy in national and international guidelines. The ethical justification for withholding excisional treatment in the control arm is supported by the well-documented rate of spontaneous regression in this population and the iatrogenic risks associated with LLETZ.

Single blinding — with subjects blinded to treatment allocation but investigators aware — represents the maximum feasible blinding level given the nature of the intervention. Investigator awareness is required for safe, targeted, and homogeneous plasma application under colposcopic guidance. The same acoustic signal, used at study treatment, is used during sham treatment to maintain subject blinding. The multicenter design across five certified dysplasia centers ensures generalizability of findings to the broader target population and supports recruitment within the planned timeframe.

3.2. Measures to minimize bias & manage potential confounding factors

Patient selection:

The reasons for refusal or exclusion of screened subjects will be documented in the screening log, enabling assessment of selection bias and evaluation of the representativeness of the enrolled population.

Allocation:

Treatment allocation will be performed by permuted block randomization with stratification by center, conducted centrally via the electronic data capture system to guarantee concealment of allocation and prevent investigator-driven selection bias.

Treatment:

Uniform, standardized treatment protocols will be applied across all sites. Investigator training and device briefings will be conducted prior to study initiation at each site. Treatment compliance will be monitored through video documentation of each intervention and by on-site clinical monitoring.

Assessment:

Histological evaluation of cervical biopsies at 6-months follow-up (Visit 4) will be performed by an independent, blinded pathologist at each site. Cytological assessment (PAP smear) at 3-months follow-up (Visit 3) and 6-months follow-up (Visit 4) will be evaluated independently. The primary statistical analysis will be performed by an independent biostatistician. Potential confounding by center effects will be addressed through stratified randomization and adjustment for study center in the primary logistic regression model.

Attrition:

The study will be analyzed according to the intention-to-treat (ITT) principle. Missing outcome data will be handled by multiple imputation. A per-protocol (PP) analysis will be conducted as a sensitivity analysis to confirm the primary ITT results.

3.3. Endpoints

Primary endpoint:

Histopathological remission of CIN 2 at 6 months, defined as absence of CIN 2 or higher on colposcopy-directed cervical biopsy at 6-months follow-up. This endpoint was selected as it represents the accepted gold-standard measure of treatment efficacy in cervical dysplasia management, directly reflecting the oncological objective of the investigation and the claimed clinical benefit of the device.

Secondary endpoints:

- HPV remission rate at 6 months, assessed by validated high-risk HPV testing and p16 immunohistochemical evaluation; selected as a virological correlate of treatment success and a predictor of long-term oncological outcome
- Cytological remission of CIN at 6 months, assessed by PAP smear; selected as a complementary, guideline-concordant measure of disease resolution
- Patient-reported quality of life and sexual health at baseline and 6 months, assessed by the Freiburg Index of Patient Satisfaction (FIPS) and the Sexual Activity Questionnaire (SAQ); selected to capture the patient-relevant burden of disease and treatment
- Homogeneity and reproducibility of LtAPD application, assessed by correlation of ESU and video data with CIN remission and applied argon plasma; selected to characterize the technical performance of the device under clinical conditions

Safety endpoint:

Incidence, severity, and causal relationship of adverse events (AEs), serious adverse events (SAEs), and adverse device effects (ADEs) from treatment visit (Visit 2) through 6-month follow-up (Visit 4), assessed according to CTCAE criteria and MDR Art. 2 definitions.

No combined endpoints are defined in this investigation.

3.4. Variables

The primary variable is binary: histopathological remission of CIN 2 (yes/no) at 6 months, assessed by colposcopy-directed biopsy and evaluated by independent blinded histopathology.

Secondary variables include: HPV status (positive/negative) by validated PCR-based high-risk HPV testing and p16 immunohistochemical evaluation; cytological classification (PAP grade) by independent cytology; FIPS and SAQ total scores at baseline / intervention and 6 months; and ESU output parameters and video-based treatment path data recorded during treatment visit (Visit 2).

Safety variables include AE/SAE incidence, CTCAE grade, and causal relationship to the investigational device.

3.5. Definition of completion/ regular end of the clinical investigation

The regular end of the clinical investigation for an individual subject is defined as the last scheduled study visit (6-month follow-up, Visit 4). The end of the clinical investigation as a whole is defined as the last visit of the last subject enrolled, after which the obligation to report to the competent authority is triggered. Following database lock and statistical analysis, the clinical investigation report will be completed and submitted to EUDAMED/DMIDS within the timeframe specified in the publication plan.

4. Study Population

4.1. Investigation population

A total of 264 subjects will be enrolled across five investigational sites. Based on committed recruitment capacities, the expected number of subjects per site over the full recruitment period of 30 months will be on average 53 subjects per site. To achieve this target, approximately 500 subjects will need to be screened for eligibility, based on an estimated eligibility rate and a projected refusal rate of 20%.

The investigation population — women aged 18 to 40 years with histologically confirmed CIN 2 and full colposcopic visibility of the transformation zone — is representative of the clinical target population for whom the investigational device is intended. The age range of 18 to 40 years captures the population at highest risk for CIN 2 (peak incidence between 20 and 24 years) and most directly affected by the competing risks of oncological undertreatment and reproductive harm from excisional overtreatment. Women above 40 years were excluded because family planning is more frequently completed in this age group and the incidence of Type 3 transformation zones increases with age, making LtAPD technically less feasible and the benefit-risk balance less favorable. The restriction to Type 1 and Type 2 transformation zones ensures that the entire lesion is visible and accessible for targeted LtAPD application, which is a prerequisite for oncological completeness of treatment.

4.2. Selection Criteria

4.2.1. Inclusion Criteria

Subjects meeting all the following criteria will be considered for admission to the trial:

1. Female sex
2. Age 18 – 40 years at the time of signing the informed consent.
3. Histologically confirmed CIN 2
4. Full visibility of the entire transformation zone (Type 1 or Type 2) and entire lesion in colposcopy
5. Ability to understand the nature of the clinical investigation and voluntarily signs the informed consent document prior to any study-related procedures.

4.2.2. Exclusion Criteria

Subjects presenting with any of the following criteria will not be included in the trial:

1. Histologically confirmed CIN other than CIN 2, indication of (micro-) invasive disease
2. CIN lesions extending to the vaginal vault or suspicion of endocervical disease
3. Current pregnancy or planned pregnancy within the next 6 months
4. Presence of severe local inflammation or active infection

5. Presence of a severe cardiovascular, neurological, psychiatric, endocrine, or hematological disease, immunocompromised condition or malignant tumor of any origin, as judged by the investigator
6. Participation in any interfering clinical study, as judged by the investigator

4.3. Duration/ Timelines

Expected total duration of the investigation:	48 months
Expected duration of the subject's participation in the clinical investigation:	
Treatment completed:	1 hour
Follow-up measures completed:	6 months
FSI (First Subject In):	Q3-2026
LSI (Last Subject In):	Q1-2029
LSO (Last Subject Out):	Q3-2029
DBL (Data Base Lock):	Q4-2029
Statistical analyses completed:	Q2-2030
Clinical investigation report completed:	Q3-2030

5. Investigational Site(s)

All participating sites are certified dysplasia centers fulfilling the criteria of the Arbeitsgemeinschaft Zervixpathologie und Kolposkopie (AG-CPC).

6. Investigational device

6.1. Identification and description of the device

The investigational medical device used for Low-thermal Argon Plasma Devitalization (LtAPD) treatment in this clinical investigation is the [redacted] with filter, malleable shaft (160 mm), 1 button [redacted].

[redacted]:

[redacted])

All devices and instruments are CE-marked in accordance with the applicable European regulatory framework and are commercially available. [redacted]

[redacted]

Intended purpose (per Instructions for Use): Monopolar coagulation and devitalization of tissue using argon plasma. Indicated for use in open surgery.

Intended purpose in the clinical investigation: Colposcopy-guided, LtAPD treatment of the entire visible transformation zone and colposcopically identified CIN 2 lesion(s) of the uterine cervix. The [redacted]

Target population: Women aged 18 to 40 years with histologically confirmed CIN 2 and full colposcopic visibility of the transformation zone (Type 1 or Type 2).

Traceability: Traceability of all investigational devices will be ensured by recording serial numbers and/or batch numbers for the [redacted] used at each intervention visit. These will be documented in the source data and the eCRF. [redacted] devices will be identified by their device serial numbers, recorded at site initiation and updated in the event of device replacement.

Materials in contact with the human body: During the intervention[redacted] tip and shaft may contact vaginal and cervical mucosa. The [redacted] tip and shaft is composed of biocompatible materials. No medicinal substances, tissues of human or animal origin, or other biologically active substances are incorporated into or released by the investigational device. The argon gas used is medical-grade (purity ≥ 99.998 %) and is not classified as a medicinal medical product.

Training and experience requirements: Safe and homogeneous application of LtAPD requires training in colposcopy and familiarity with the [redacted]. Prior to study initiation at each site, all treating investigators will complete a standardized device training provided by [redacted], including hands-on practice. Documented completion of training is a prerequisite for study initiation at each site.

References: For full technical specifications, clinical background, and preclinical and clinical data supporting the use of the device in this investigation, refer to the Investigator Brochure (IB) and the Instructions for Use ([redacted]. The current state of the art in cervical dysplasia management and the proposed clinical benefits of LtAPD are described in Chapter 1 (Introduction and Rationale) of this CIP.

6.2. Further Information on the investigational device, on any comparator and on any other device or medication to be used in the clinical investigation

Investigational device — exposure description:

Each subject assigned to the LtAPD group receives a single session of [redacted]mediated argon plasma treatment at Visit 2. The [redacted] applied under direct colposcopic visualization to the entire transformation zone and all colposcopically identified CIN lesion areas, at a standardized dose of 30 s/cm² (senseAPD mode, Effect 2). Total treatment time is approximately 2–10 minutes. No repetitive treatment is planned within the protocol; the investigational device is applied once per

subject. Additional LtAPD sessions outside the study protocol are not permitted during the investigation period.

Comparator — exposure description:

Subjects assigned to the sham group receive a single session of sham treatment at Intervention Visit (Visit 2) using the [redacted] probe, with identical handling and positioning under colposcopic guidance. In the sham condition, the system is configured such that no plasma-mediated tissue effect is intended. The argon gas flow is not activated. The acoustic signal is emitted to maintain subject blinding.

Following sham treatment, subjects are managed by active surveillance according to current national guidelines for CIN 2, comprising colposcopic re-assessment and PAP smear at 3 months (Visit 3, at the subject's established gynecologist) and full clinical re-assessment including colposcopy, PAP smear, HPV test, and biopsy at 6 months (Visit 4).

Other devices used in the clinical investigation:

The following additional medical devices will be used as part of standard clinical procedures in this investigation, as they are routinely employed in colposcopic practice and do not require specific mention in the IFU of the investigational device:

- Colposcope (standard clinical equipment at each certified dysplasia center; model recorded at site initiation)
- Standard gynecological biopsy forceps (for colposcopy-directed cervical biopsy at Visit 1 and 4)
- Standard cervical spatula / cytobrush (for PAP smear collection at Visits 1, 3, and 4)
- Validated high-risk HPV test system and p16 immunohistochemical evaluation (for HPV testing at Visit 4; specific system recorded at site initiation)

No study-specific medications are required or administered as part of this investigation.

Number of investigational devices [redacted]

[redacted]

6.3. Device accountability

The complete LtAPD system — [redacted]

Receipt and storage: The principal investigator or delegated site staff at each investigational site is responsible for acknowledging receipt of all device shipments and for ensuring that investigational devices are stored under appropriate conditions (room temperature, away from moisture and direct sunlight), in a secure location accessible only to authorized study personnel and used exclusively for study purposes.

Dispensing and documentation: The investigational device is used for the study treatment and is not dispensed to the subject; the procedure is performed exclusively at the investigational site. The treating investigator or delegated site staff documents the following in the source data and eCRF for each subject after treatment: date of use, subject identification number, and the lot number and/or serial number of the [redacted]. The investigator or delegated site staff will also keep accurate records of the quantities of devices received, used, and remaining in stock at the site. Compliance with the investigational treatment will be assessed by count of [redacted] used per subject, cross-referenced against treatment visit (Visit 2) documentation in the eCRF. As the device is applied directly at the investigational site, full accountability can be assumed for all subjects who attend the treatment visit (Visit 2).

Device accountability log: A site-level device accountability log will be maintained at each investigational site, recording: devices received (quantity, lot/serial numbers, date of receipt), devices used (subject ID, date, lot/serial number), and devices remaining in stock. The log will be available for review during monitoring visits and inspections.

Malfunctioning or expired devices: Investigational devices that are expired, damaged, or suspected of malfunction must not be used and must be documented in the device accountability log. Such devices

will be quarantined, labelled, and [redacted] or destroyed according to the site's standard procedures for single-use medical devices, as agreed with the sponsor. Any device-related malfunction occurring during a procedure must be reported as an adverse device effect (ADE) in the eCRF.

End of trial: At the end of the clinical investigation, [redacted]

7. Clinical procedures and diagnostic methods relating to the clinical investigation

7.1. Introduction

All clinical procedures and diagnostic methods performed in the context of this investigation are described below. The Schedule of Activities (SoA) provides a structured overview of all assessments per visit. Detailed visit descriptions are given in sections 7.2–7.4. With the exception of the sham procedure and the systematic video and electrical data recording during the intervention visit, all procedures performed in this investigation correspond to standard clinical practice for the management of CIN 2 at certified dysplasia centers and do not constitute deviations from routine care.

Sponsor activities at the investigational sites — beyond monitoring — include site initiation visits with standardized training for investigators and study nurses/study coordinators, centralized randomization via the electronic data capture system, and centralized quality review of video recordings from all intervention visits.

Several factors are known to potentially affect the results of the investigation or their interpretation. These include the spontaneous regression rate of CIN 2, which is incorporated into the sample size calculation and addressed by the randomized sham-controlled design; HPV genotype and viral load at baseline, which may influence remission rates and will be documented as covariates; prior cervical interventions; smoking status; and immunological status. These factors are addressed through the defined inclusion and exclusion criteria, stratified randomization by center, and adjustment for relevant covariates in the primary statistical model.

The observation period of 6 months was selected as the primary endpoint timepoint based on data from the preceding CAPCIN pilot study, which demonstrated complete remission in 86.2% of treated subjects within 3 months, and on published data on the natural history of CIN 2. Six months provides sufficient time to allow realistic assessment of treatment efficacy while minimizing the oncological risk for subjects in the sham/active surveillance arm, in particular in view of the rescue procedure in case of progression to CIN 3.

Cervical biopsy specimens collected at 6-months follow-up (Visit 4) will be processed, archived, and stored according to local institutional pathology protocols. Residual biomaterial may be used for future exploratory analyses within the scope of a separate ethics application, subject to separate informed consent.

7.1.1. Schedule of Activities

Detailed information is provided below.

	Screening [a]	**Intervention: LtADP Treatment or Sham**	**FU 3 months** *(Visit at gynecologist)*	**FU 6 months** *(Visit at study center)*
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**
	Day - 60 to -1	*Day 0*	*+/- 10 days*	*+/- 10 days*
Written Informed Consent	X			
Inclusion/ Exclusion Criteria	X			
Demographics	X			
Medical history	X			
Clinical examination by colposcopy	X			X
HPV-Test	X [b]			X
PAP-smear sample	X		X [e, f]	X [e]
Randomization	X [c]			
Record video data		X		
Record electrical data		X [d]		
Photo documentation				X
Cervical lip biopsy	X			X
Questionnaires				
Freiburg Index of Patient Satisfaction (FIPS)		X		X
Sexual Activity Questionnaire (SAQ)	X			X
Adverse Events		X	X	X

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 60 days prior to Day 0 may be used; such tests do not need to be repeated for screening, unless otherwise indicated.
[b] HPV-testing within 183 days prior to Day 0 may be used.
[c] Randomization will take place day -5 to day 0 before intervention.
[d] Only for LtAPD group.
[e] When result is ≥ PAP IVa-p subject will immediately be re-assessed by colposcopy ± histology at study center; result ≥ CIN 3 will be treated by LLETZ according to guidelines.

[f] Cytological assessment according to guidelines at established gynecologist.

7.1.2. Deviation from normal clinical practice

The sham procedure at treatment visit (Visit 2) — consisting of application of the [redacted]

7.2. Entry

7.2.1. Subject´s Informed Consent

The subject must be informed both in writing and verbally by the investigator before any study-specific procedure is performed. Each subject will be informed about the modalities of the clinical investigation in accordance with the provided subject information. It must also be made clear to the subject that she can withdraw from the investigation at any time without needing to provide reasons and that she will not be in any way disadvantaged as a result of withdrawal. The subject will be given sufficient time to consider participation in the clinical investigation and can ask for additional advice if needed. Informed consent from the subject will be obtained using a form approved by the responsible ethical committee (EC). The subject and informing investigator must each personally date and sign the informed consent form with an integrated declaration on data privacy protection, whereby the physician must not sign before the subject. The original signed documents will be part of the investigator's site file and retained with it and a copy included the insurance policy of the investigation will be handed to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject. The informed consent process is documented in the

subject records. The subjects will be informed as soon as possible if new information may influence her decision to participate in the investigation. The communication of this information should be documented in the subject chart.

7.2.2. Screening (Visit 1)

Screening will be performed within 60 days prior to intervention. After having signed the informed consent, subjects will undergo all assessments listed below:

- Clinical examination by colposcopy
- PAP-smear sample
- HPV-test
- Questionnaire: Sexual Activity Questionnaire (SAQ)

Subjects undergo a clinical examination by colposcopy and visual inspection using acetic acid and Lugol's iodine staining to delineate the CIN lesion(s) and transformation zone. A PAP-smear sample is taken for cytological assessment and a colposcopy-directed cervical biopsy is obtained for histopathological evaluation. A HPV-test is performed. Medical history and demographics are recorded. The questionnaire, Sexual Activity Questionnaire (SAQ), will be given to subjects to evaluate the state of quality of life and sexual activity. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 60 days prior to Day 0 may be used; such tests do not need to be repeated for screening, unless otherwise indicated.
Subject will be informed to use highly effective methods during treatment and for 7 months after the end of treatment (adequate: combined hormonal contraception

associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner1, sexual abstinence2). The participants using hormonal contraceptives should use a barrier method as well.

1) Vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

2) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

The investigator will review all information obtained from the screening procedures. Subjects who fulfil all the inclusion criteria and none of the exclusion criteria will be eligible to participate in the investigation. Screening failures (i.e. screened subjects not in compliance with all criteria; will not be randomized) are to be excluded and the reason will be recorded in the subject records.

Information of subject's investigation participation can be provided to the subject's general practitioner and gynecologist if the subject agreed.

7.2.3. Enrollment

If the subject meets all inclusion criteria and no exclusion criteria, she can be enrolled. The subject number will be used for the subject throughout the study.

7.2.4. Randomization

The randomization of each participant will be conducted by the study site via electronic interaction. Subjects will be randomized after completion of testing for inclusion/exclusion criteria. Randomization is performed centrally via the electronic data capture system and can take place day -5 to day 0 before start of intervention. Randomized subjects who withdraw from the study before intervention will not be replaced.

7.2.5. Blinding/Unblinding

This investigation is designed as a single-blinded study. Subjects are blinded to their treatment allocation throughout the investigation; investigators, treating physicians, and study staff are aware of the allocated treatment. Blinding of subjects is maintained through the use of a sham procedure that is identical in appearance and handling to the active LtAPD treatment, with argon gas flow and an acoustic signal used to simulate plasma ignition. Subjects are explicitly informed during the consent process that they may be allocated to either the LtAPD or the sham group, and that they will not be informed of their allocation during the investigation period.

Since investigators and study staff are not blinded to treatment allocation, formal unblinding of the investigator is not applicable in this investigation.

Subject-level unblinding — i.e., disclosure of treatment allocation to the subject — is not required for safety reasons, as the sham procedure carries no tissue effect and poses no safety risk. Nevertheless, if a subject requests disclosure of her treatment allocation for reasons of personal wellbeing or medical necessity, this may be performed by the principal investigator at any time. Any such disclosure will be documented in the eCRF, including the date, reason, and requesting party.

In the event of premature termination of the entire investigation, treatment allocation for all enrolled subjects may be disclosed following database lock and prior to final analysis, at the discretion of the sponsor and coordinating investigator in consultation with the DSMB. Individual subject allocation data are held centrally in the electronic randomization system and are accessible to the sponsor and coordinating investigator at any time.

Following completion of the 6-month follow-up visit (Visit 4), each subject will be informed of their treatment allocation as part of the end-of-study communication.

7.2.6. Concomitant Medication and Treatments

No concomitant medications are required as part of this investigation. The following concomitant treatments are prohibited during the investigation: any concurrent excisional or ablative treatment of the cervix (LLETZ, laser conization, cryotherapy) outside the protocol-defined rescue procedure; participation in any other interventional clinical investigation. All other concomitant medications and treatments are permitted and will be documented in the patient´s medical record and eCRF.

On the day of the intervention visit (Visit 2), subjects are advised to avoid sexual intercourse, tampon use, and bathing in public or open waters. These restrictions apply to the day of the procedure only and are consistent with standard post-interventional recommendations following outpatient gynecological procedures. No restrictions apply from the following day onwards. Subjects will be informed of these recommendations as part of the informed consent process and in the subject information leaflet.

7.3. Treatment Phase

7.3.1. Description of subjects' treatment visit (Visit 2)

The treatment visit takes place at the investigational site on an outpatient basis on the day of the intervention. Prior to the procedure, the cervix is re-examined by colposcopy with acetic acid and Lugol's iodine staining to confirm the extent of the transformation zone and CIN lesion(s) to be treated. The procedure is performed without local infiltrative or general anesthesia. Topical anesthetical sprays might be applied for sensitive patients. Subjects randomized to the LtAPD group receive a single session of low-thermal argon plasma devitalization (LtAPD) applied to the CIN2 lesion at visible transformation zone under colposcopic guidance, using the Argon Plasma [redacted] module at an application rate of 30 s/cm², using a reusable silicone electrode mat. [redacted] For larger lesions more

application cycles may be used on top. The probe is passed over the target tissue in defined brush strokes to ensure homogeneous coverage and prevent localized thermal effects. Electrical device parameters are recorded throughout the procedure for quality assurance purposes.

Subjects randomized to the sham group undergo an identical procedure in terms of probe positioning and handling under colposcopic guidance. In the sham condition, no argon gas is delivered; an acoustic signal is used to simulate active plasma treatment and maintain subject blinding. No tissue effect is produced.

Video documentation of the intervention is recorded in both groups. Following the procedure, subjects complete the Freiburg Index of Patient Satisfaction (FIPS) questionnaire. Adverse events are documented. Subjects receive standardized post-procedural instructions: on the day of the procedure, sexual intercourse, tampon use, and bathing in public or open waters should be avoided; no restrictions apply from the following day.

Subjects will be instructed to make an appointment at her gynecologist for a PAP smear sample within the time window for 3 months follow-up, asking her to report the appointed date to the investigational site.

7.3.2. Premature termination of clinical investigation for a subject (subject withdrawal)

Reasons for premature termination for an individual subject are:

1. Death
2. Withdrawal of consent
3. Subject lost to follow-up
4. Major protocol violation (e.g. enrolling ineligible patients, ICF not obtained)
5. Progression of disease (including ≥PAP IVa-p or ≥CIN 3)
6. If, in the investigator's opinion, continuation of the investigation would be detrimental to the subject's well-being
7. Noncompliance with protocol requirements

The PI decides about withdrawal of subjects from investigational treatment in case of occurrence of criteria mentioned above. In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. In case of withdrawal of a subject after own request, the reason should be determined and documented.

All examinations scheduled for the last investigation day will be performed and documented as far as possible. These subjects will enter the regular follow-up of the investigation, unless the subject has withdrawn her consent to any further study-related procedure. If a subject may / will be withdrawn

from all investigation-related procedures (including follow-up visits) (e.g. at her own request), this will not result in any disadvantages for the subject.

All ongoing Adverse Events (AEs)/ Serious Adverse Events (SAEs) of withdrawn subjects must be followed-up until no more signs and symptoms are verifiable or the subject is on stable condition.

Premature termination should be avoided. In case of a premature termination of the study, reasons/circumstances and if applicable the final status must be documented. If the subject does not withdraw the consent for further follow-up, she should be followed-up as planned.

A final assessment visit for the relevant safety data will be always offered to the subject.

7.3.3. Premature closure of an investigational site

Premature closure of an investigational site has to be considered if:

- The recruitment rate is not sufficient
- The conduct of the study is not compliant with the protocol (or the legal regulations),
- The data quality is not sufficient

The premature closure of a site will be decided by the sponsor.

Site principal investigators may terminate his/her participation in the study. If this occurs, they should provide a written statement of the reasons for terminating participation and should provide the sponsor with all available and up-to-date study data.

The sponsor may also decide to terminate participation of an investigator or investigational site for the following reasons:

- Breach of agreement
- Serious non-compliance to protocol or the legal regulations
- Insufficient subject recruitment

If a participating site closes, or is closed, prior to termination of the whole investigation, the sponsor expects that data from subjects already entered into the investigation will be reported as per protocol. Details on further treatment and follow-up of subjects on study have to be discussed with the site principal investigator.

7.3.4. Premature termination of the investigation

The investigation may be prematurely terminated, if in the opinion of the sponsor and coordinating investigator there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigators.

In case of the following situations, a premature termination of the investigation has to be considered

- Substantial changes in risk-benefit considerations
- Overwhelming superiority or demonstrated futility of the investigational treatment based on interim data
- New insights from other investigations
- Insufficient recruitment rate

The DSMB will monitor the study conduct and the safety aspects of the investigation on a regular basis, and will give recommendations to the coordinating investigator/ the sponsor whether to stop the investigation or to change the investigation protocol. The sponsor will then decide on the actions to be taken.

7.4. Follow up

7.4.1. Three Months follow up (Visit 3)

3 months after intervention subjects should have a visit at their gynecologist, as being instructed at treatment visit. A PAP smear sample is taken for cytological assessment according to the gynecologist's standard procedures. For early knowledge about any occurring events, the (principal) investigator or study nurse/study coordinator will contact the gynecologist after the subject's appointment date. The gynecologist should send the result of the PAP-smear to study center, respectively the (principal) investigator or study nurse/study coordinator should request the result of the subject for documentation.

If the cytological result is ≥ PAP IVa-p, the subject will be immediately re-assessed by colposcopy with or without directed biopsy at the investigational site. If progression to CIN 3 or higher is histologically confirmed, the subject will discontinue investigational treatment and receive standard-of-care excisional treatment (LLETZ) without delay. The subject remains in the ITT population and the event is classified as treatment failure in the primary analysis.

7.4.2. Six Months follow up (Visit 4)

Subjects will have an outpatient visit 6 months after intervention at investigational site. During that visit, subjects undergo clinical re-examination by colposcopy with acetic acid and Lugol's iodine staining; photo documentation is performed. A PAP smear sample is taken for cytological assessment, a HPV test is performed, and a colposcopy-directed cervical biopsy is obtained for histopathological evaluation. Cervical biopsy specimens collected will be processed and evaluated by an independent blinded pathologist; archived and stored according to local institutional pathology protocols. Subjects complete two questionnaires: the Freiburg Index of Patient Satisfaction (FIPS), and the Sexual Activity

Questionnaire (SAQ). Adverse events are documented. 6-month follow-up constitutes the regular end of the investigation for the individual subject per protocol.

No follow-up obligations beyond 6 months follow-up (Visit 4) exist for subjects who complete the investigation per protocol, with the exception of relevant ongoing adverse events, in the opinion of the investigator, that have not resolved at the time of Visit 4.

7.4.3. Subjects lost to follow up

Every effort will be made to complete follow-up for all enrolled subjects. Before a subject is classified as lost to follow-up, a minimum of three documented contact attempts must be made using different communication channels — by telephone, email, and postal mail — over a period of at least four weeks. All contact attempts, including unsuccessful ones, must be documented in the source data and the eCRF, including the date, method, and outcome of each attempt. If a subject cannot be contacted despite these efforts, she will be classified as lost to follow-up and this will be recorded in the eCRF with the date of last known contact. Subjects lost to follow-up will not be replaced; their data will be included in the intention-to-treat analysis and missing outcome data will be handled by multiple imputation as described in the statistical analysis plan.

7.5. Regular end of the investigation for individual subject

The regular end for a subject enrolled in this investigation is defined as the last investigational visit.

7.5.1. Regular end of the investigation for individual subject

The regular end of the clinical investigation for an individual subject is defined as the completion of 6-month follow-up (Visit 4), including all scheduled assessments. Subjects who complete 6-months follow-up are considered to have completed the investigation per protocol.

7.5.2. Plan for treatment or care after regular end of the investigation

No additional medical care obligations arise specifically from participation in this clinical investigation, as all procedures performed are consistent with standard clinical practice for the management of CIN 2. The investigational intervention and follow-up assessments do not introduce medical conditions or risks requiring post-study care beyond routine clinical management.

Following completion of 6-month follow-up, subjects will be advised by the investigator to continue participation in the national cervical cancer prevention program and to attend routine gynecological follow-up at their established gynecologist in accordance with current guidelines. Subjects in whom CIN 2 has not resolved at 6-months follow-up will receive clinical management according to current

national guidelines for persistent CIN 2, at the discretion of the treating gynecologist. Subjects allocated to the sham group will be informed of their treatment allocation at the end of the 6-month follow up (Visit 4) and will be offered the opportunity to receive LtAPD treatment outside the study context, depending on clinical indication and device availability at that time.

8. Quality control and quality assurance

8.1. Monitoring

Monitoring for this study is provided by the Zentrum für Klinische Studien Tübingen (ZKS Tübingen). The monitoring will be conducted according to ZKS Tübingen internal Standard Operating Procedures (SOPs). The monitoring timelines include, for all centers, initiation visit, regular monitor visits during the course of the trial as well as a close out visit. Usually, Monitoring will end with the last visit after full documentation of the last patient enrolled (close out visit). All investigators agree that the monitors regularly visit the trial site, assure that the monitors will receive appropriate support in their activities and will have access to all trial-related documents.

The aims of the monitoring visits are as follows:

- Check informed consent documents
- Monitor trial subject safety (occurrence and documentation/reporting of Serious Adverse Events (SAEs), Device Deficiency and Adverse Events (AEs)).
- Check completeness and accuracy of entries on the eCRFs.
- Validate entries on the eCRFs against those in the source documents (source data verification (SDV)).
- Check the Device Accountability
- Check the storage conditions of the MP
- Evaluate the progress of the trial
- Evaluate compliance with the trial protocol
- Assess whether the trial is being performed according to GCP at the trial site
- Discuss with the investigator aspects of trial conduct and any deficiencies found
- A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems.

8.2. Audits/ Inspections

In addition to the monitoring activities, audits can be conducted by the sponsor or assigned auditors. These audits may include checking the whole course of the study, documentation, trial center, investigators and the monitor.

The competent regulatory authorities may also conduct inspections.

With his/her participation in the study, the investigator agrees to support the activities of the auditor/inspector, provide her/him with direct access to the source documents, study documentation and give her/him the opportunity to audit/inspect the study site, laboratory facilities, storage of the investigational product, etc.

8.3. Data management

8.3.1. Case Report Form (CRF)

The trial Case Report Form (CRF) is the primary data collection instrument for the trial. All data requested on the CRF must be recorded. All missing data must be explained.

Electronic CRFs

For this project, electronic Case Report Forms (eCRFs) will be used. The Clinical Data Management System [“secuTrial(r)”] will be used for data capture, processing and storage of study data. Data entry is performed at the investigational site by clinical staff after having received training and a user manual for the electronic CRF. Training and the user manual will detail procedures to be followed in case of technical problems. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

The Clinical Trial Data Management System (CDMS) is validated and changes are tracked via an audit trail.

Authorized clinical staff at the investigational site will enter the data into the eCRF using this access controlled, audit-trailed, ICH-GCP compliant, validated system. Entered data will be subjected to plausibility checks directly implemented in the eCRF, monitoring and medical review. Implausible or missing data will be queried. Database lock will be performed after completion of data entry, data cleaning and a final data review.

The correctness of entries in CRFs will be confirmed by dated signature of an authorized investigator. The principal site investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against source data. The principal site investigator has to

verify the eCRFs via dated signature/electronic signature at defined times in the course of the study and after completion of the eCRF. The investigator's signature should take place in regular and meaningful intervals.

8.3.2. Clinical Data Management Systems (CDMS)

The selected CDMS-Software secuTrial® and the associated Oracle-Database used to save the information are located in the European judicial area administered on server of the software manufacturer interActive Systems (iAS) GmbH, Glogauer Straße 19, 10999 Berlin.

Availability and technical specification are regulated by a hosting contract between iAS and the UKT.

This hosting contract was checked and approved by the responsible staff of the department of "UKT-IT Sicherheit" and "UKT-Datenschutz".

The access to the electronic database of the CINPLASTA Trial uses an encrypted connection and the URL can be called 24/7 to enter data or to modify data.

8.3.3. Data protection

8.3.3.1. Controllership

Responsible for data processing according to Art. 4 para. 7 and Art. 26 EU General Data Protection Regulation (GDPR) are the University Hospital Tübingen for the Medical Faculty of the University of Tübingen and the participating trial sites. Internally responsible for data processing in the trial is the Sponsor´s delegate. In case of questions regarding the use or processing of the data of trial participants and members of the investigating team, the Sponsor´s delegate should be contacted in the first instance. Responsibilities and processes between the joint controllers are regulated in a contract in accordance with Art. 26 para. 1 GDPR.

Data subjects are informed about the processing of their personal data in accordance with Art. 13 and, if applicable, Art. 14 GDPR as part of the informed consent or the information for the investigating team. This also includes information about the controller(s) of the processing.

The legal basis for the processing of personal (also pseudonymized) data of the trial participants is Art. 6 para. 1 lit. a and Art. 9 para. 2 lit. a GDPR in conjunction with the informed consent of the data subjects.

8.3.3.2. Records of processing activities and data protection impact assessment

An entry in the hospital's record of processing activities and a data protection impact assessment are available for the trial. The design of the processing of personal data in the context of the trial complies with the standard specifications of the University Hospital Tübingen and the Faculty of Medicine on the processing principles pursuant to Art. 5 para. 1 GDPR and the technical and organizational measures for processing security (pursuant to Art. 32 GDPR).

Only data specified in this protocol and required for this clinical trial will be collected. The data will be collected from the trial participants and from their medical records, e.g. patient files [delete as appropriate/otherwise: and with co-treatment/pre-treatment institutions and medical doctors].

After completion of the trial, data will be stored for 10 years and then deleted or destroyed.

8.3.3.3. Withdrawal of consent

Data subjects can withdraw their consent to participate in the trial and the associated data processing at any time. Insofar as this is possible beyond retention obligations, the data will be deleted, otherwise anonymized by discarding the pseudonym assignment. Data that has already been analyzed will not be deleted.

8.3.3.4. Principles relating to processing of personal data

Trial sites are contractually obliged to comply with the GDPR and other data protection regulations, in particular with regard to ensuring appropriate technical and organizational measures for processing security (Art. 32 GDPR).

The data of trial participants are processed pseudonymously as far as possible; the assignment to the identity of the person concerned or their patient ID is only accessible to the investigator and his team at the trial site as well as to authorized persons within the scope and for the purpose of verifying the collected trial data (auditors, monitors).

The trial participant data is processed exclusively for the clinical trial described. The trial participant data will only be passed on to the recipients as described in the participant information (e.g. to the sponsor or monitors, auditors). If data is transferred to recipients in third countries, the participants will be informed of this and of the guarantees in place. Explicit consent may be obtained for the transfer of data to recipients in third countries. Only pseudonymized data is transmitted via cryptographically protected transmission.

8.3.4. Storage and archiving of data

According to the applicable regulations (MDR Anhang XV, Kap. III (3)) essential trial documents (e.g. CRF) will be archived for 10 years. After archiving has expired, the data will be destroyed in a data protection compliant manner.

9. Statistical planning and analyses

9.1. Definition of analysis population

The primary confirmatory analyses will be based on the intention-to-treat population (ITT), which will include all randomized patients. Only patients who withdraw their consent to the analysis of their complete (ante and retrograde) data or drop out before treatment will be excluded from ITT. The per-protocol population (PP) will be a subset of the ITT. Patients in the intervention group who fulfil one of the following criteria will be excluded from the PP: i) inclusion in contradiction to one of the in- or exclusion criteria; ii) by randomization assigned therapy is not received according to protocol; iii) no evaluation of primary outcome at 6 months. For the control group, patients will only be considered PP if the study arm decision was made due to medical necessity under active surveillance. The PP is the secondary analysis population with the aim to confirm the results of the ITT-analysis.

Regarding estimands, intercurrent events will be very rare. It is not to be expected that patients will die during the follow up period, however, theoretically patients might develop a cervix carcinoma in this period. These patients will be classified as no response, i.e. failure in the primary analysis. Deviation from therapeutic scheme except for early drop outs are due to the short-term intervention, not realistic.

9.1.1. Sample size and power consideration

From the literature [5-7] we expect a spontaneous remission rate in the control group of maximal 50%. Furthermore, we expect a remission rate of 70% for patients in the intervention group. This is based on prior data with 75 % remission after NIPP in 58 patients [5]. This leads to 103 evaluable patients for each group. To adjust for study center, we need 105 evaluable patients per group. Assuming conservatively 20% drop outs, we will need to recruit 264 patients. This refers to a type one error of 0.05 (two-sided) and a power of 80%.

Compliance / Rate of loss to follow up: Drop outs are assumed conservatively by 20%. Therefore, we will need to recruit 264 patients.

9.2. Analysis of primary variables

A logistic regression model adjusted for study center using binary coding for study arm will be applied to the primary outcome “remissions”. Missing outcome data will be simulated using multiple imputation (500 samples, covariates age, and if applicable, assessment at 3 months).

9.3. Analysis of secondary variables

The PP is the secondary analysis population with the aim to confirm the results of the ITT-analysis. Descriptive analysis includes mean, standard deviation, minimum, maximum, quartiles (continuous variables), and absolute and relative frequencies (categorical data).

The secondary endpoints will be analyzed as follows: i) After 6 months cytological remission and HPV remission rate, analyzed by smear test: identical to primary endpoint; ii) before intervention and 6 months after the QoL measures sexual health (SAQ) and patient satisfaction (FIPS) compared for both groups using baseline adjusted analysis of covariance, Mann-Whitney-U test for differences FU minus base-line if data are not normally distributed); iii) During intervention electrical and video data are collected for treatment path visualization and subsequent assessment of plasma homogeneity.

All statistical tests concerning the secondary endpoints will be done for descriptive purposes. The p-values will be given without adjustment for multiple testing and are interpreted non confirmatory.

9.4. Subgroup analysis

No subgroup analysis is planned.

9.5. Interim analysis

No interim analysis is planned.

9.6. Stopping rules

In the study protocol stopping rules (Chapter 7.3.4.) will be defined to determine whether the study should be terminated early. These rules are established to ensure participant safety, maintain ethical standards, and preserve scientific integrity. They will be based on several factors, such as overwhelming efficacy, futility (the trial is unlikely to achieve its objectives), or safety concerns due to adverse effects. Stopping rules help prevent exposing participants to unnecessary risks or ineffective treatments. They also ensure that resources are used efficiently and that beneficial treatments can be made available sooner. A Data Safety Monitoring Board (DSMB) will be implemented to oversee these stopping rules.

Safety analyses will include frequency tabulations and line listings for AEs and SAEs separately for study arms, as treated. All confirmatory analyses will be fully specified in the trial protocol. Other details of the statistical analysis will be fixed at the latest in the Statistical Analysis Plan (SAP), to be prepared during blind review before data base lock.

9.7. Biometric report

The biostatistical DPT will provide a statistical report including descriptive, confirmatory and exploratory analyses.

10. Safety

Assessment of adverse events will be based on Common Terminology Criteria for Adverse Events (CTCAE), version 6.0. The grade refers to the severity of the AE. The CTCAE displays grades 1 to grade 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL or mild/moderate impact on normal daily activity.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL or severe impact on age appropriate normal daily activity (pediatric).

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

10.1. Definitions

10.1.1. Adverse Event - AE (MDR Art. 2 (57))

“Adverse event” means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

10.1.2. Adverse Device Effect - ADE (ISO 14155,3.1)

AE related to the use of an investigational device (German: unerwünschte Wirkung des Produkts).

10.1.3. Serious Adverse Event - SAE (MDR Art. 2 (58))

“Serious adverse event” means any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the subject, that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalization or prolongation of patient hospitalization,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

(c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

10.1.4. Device Deficiency - DD (MDR Art. 2 (59))

“Device deficiency” means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

10.1.5. Serious Adverse Device Effect - SADE (ISO 14155,3.44)

ADE that has resulted in any of the consequences characteristic of a serious adverse event (German: schwerwiegende, unerwünschte Wirkung des Produkts).

10.1.6. Unanticipated Serious Adverse Device Effect - USADE (ISO 14155,3.51)

SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (German: unvorhersehbare, schwerwiegende, unerwünschte Wirkung des Produkts).

10.1.7. Suspected Serious Incident (MDR Art. 2 (65))

“Suspected serious incident" means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer, and any undesirable side-effect, which directly or indirectly led, might have led or might lead to any of the following:

1. the death of a patient, user or other person,
2. the temporary or permanent serious deterioration of the state of health of a patient, user or other person,
3. a serious risk to public health.

10.1.8. Serious Public Health Threat (MDR Art. 2 (66))

“Serious public health threat” means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

10.2.List of non-reportable adverse events with justification

#	non-reportable AE	Justification
1	Vaginal discharge	Standard occurrence / Normal for LtAPD treatment
2	Spotting / Smear bleeding	Standard occurrence / Normal for LtAPD treatment
3	Mild discomfort	Standard occurrence / Normal for LtAPD treatment

10.3.List of adverse events of special interest (AESI)

N. A.

10.4.List of foreseeable adverse events & expected adverse device effects together with their probable frequency, alleviation or treatment

#	foreseeable AE	probable frequency	alleviation or treatment
1	Vaginal discharge	100 %	N. A.
2	Spotting / Smear bleeding	50-100 %	N. A.
3	Mild discomfort	50-100 %	NSAR analgesics

#	expected ADE	probable frequency	alleviation or treatment
1	Skin burns	<1 %	Wound care
2	Treatment of unintended skin area	<1 %	Active surveillance

10.5.Procedures and timelines for reporting

10.5.1. Reporting Period for AEs and DDs

The time frame for the principal investigator to report serious adverse events and product deficiencies to the sponsor and, if required, to the ethics committee(s) and regulatory authority extends from the start of the intervention until 6 months follow-up.

10.5.2. Documentation, Assessment and Reporting of Reporting of Adverse Events

10.5.2.1. by the (Principal) Investigator

All SAE reports and reports of device defects (that could have led to serious adverse events in the absence of appropriate measures or intervention or under less favorable circumstances) (initial and follow-up reports), must be sent, even if they are incomplete, immediately, to representative of the Sponsor:

Zentrum für Klinische Studien Tübingen (ZKS Tübingen)

[redacted]

[redacted]

Device deficiencies are recorded in the source data and eCRF

The (principal) investigator or delegated site staff must document adverse events and device deficiencies that occur during the observation period set in this protocol in the source data and on the pages provided in the case report form. Additional instructions may be provided in the investigator site file and in the case report form itself. Adverse events (whether serious or non-serious) must be documented on the “adverse event” page of the case report form. If the adverse event is serious, the investigator must complete, in addition to the “adverse event” page in the case report form, a “serious adverse event report form” at the time when the serious adverse event is detected. The initial report must be as complete as possible.

The (principal) investigator needs to assess whether it is a reportable event. In the case, that the conclusion is that it is a reportable event, the (principal) investigator shall **immediately (i.e. within 24 hours)** report the event to the sponsor (or the vigilance department delegated by the sponsor, if applicable).

Reportable events according to MPDG § 63 are:

- any SAE
- any DD that could have led to SAEs in the absence of appropriate measures or intervention or under less favorable circumstances.

If not, all information is initially available to the (principal) investigator, the report must still be made on the basis of the state of knowledge. As soon as new information on the SAE becomes known, a follow-up report must be sent to the sponsor (or the vigilance department delegated by the sponsor, if applicable). As soon as new information on the SAE becomes available, a follow-up notification must be sent to the sponsor.

The (principal) investigator will report at least the following information to the sponsor (using the respective reporting form):

- person affected: subject, user or another person
- the date when he/she or any employee was first aware of the report and
- the terms according to the actual “Common Terminology Criteria for Adverse Events (CTCAE)-List” (version 6.0) (one term per event)

- reason of the seriousness
- severity (e.g. using CTCAE grading)
- causal relationship between the event and the investigational device/comparator/procedure (not related, possible, probable, causal relationship)
- action taken in relation to the intervention (device application not changed, temporarily discontinued, withdrawn, unknown, not applicable)
- treatment of the event
- outcome (recovered/resolved, not recovered/not resolved/ongoing, recovered/resolved with sequalae, fatal, unknown)
- onset / resolution date
- location of the device
- action taken / treatment

Follow-up of initial report:

Information not available at the time of the initial report (e.g. end date for the adverse event or laboratory values received after the report) must be documented on a “Serious Adverse Event” form with the box “Follow-up” checked under “Report type”.

All patients who have adverse events, whether considered associated with the use of the investigational device or not, must be monitored to determine the outcome as far as possible. The clinical course of the adverse event will be followed up according to accepted standards of medical practice even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist’s report should be supplied, if possible.

The sponsor will identify missing information for each SAE / DD report and will require follow up information in regular intervals from the investigators until all queries are resolved or no further information can be reasonably expected. All responses to queries and supply of additional information by the investigator should follow the same reporting route and timelines as the initial report.

Besides reporting SAEs and DDs as mentioned above, the (principal) investigator shall also document any adverse events, and DD. In addition, the BfArM continues to expect the quarterly summary SAE / DD assessment.

Any report needs to be filed in the Investigator Site File (ISF).

10.5.2.2. by the Sponsor

The sponsor shall maintain complete records of:

- SAEs
- DDs that could have led to SAEs in the absence of appropriate action or intervention or under less favorable circumstances
- any new findings related to any of the above events.

The sponsor documents each of the above-mentioned events in a continuous list/ in a vigilance database.

This documentation must be filed completely in the Trial Master File (TMF).

The sponsor vigilance department confirms receipt of the report from the (principal) investigator and checks it for completeness. Incomplete or unclear information is supplemented by a query to the reporting site.

Sponsors assessment of the reported events

All reported events will be subject to a second assessment by the trial Sponsor or authorized second assessors.

The second assessor will fill out a 'Second Assessment Form' for each reported event containing:

- Event serious yes/no
- Causal relationship between event and the investigational device procedure
- [redacted]Expectedness according to the reference document device manual (Investigator`s Brochure: [redacted]
- Statement if the benefit / risk assessment for the trial did change as a result of event.

Causality assessment (MDCG 2020-10/1)

The relationship between the use of the medical device and the occurrence of each adverse event will be assessed and categorized by the sponsor and the investigators.

During causality assessment activity, clinical judgement will be used and the relevant documents, such as the Clinical Investigation Plan will be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there.

The above considerations apply also to the serious adverse events occurring in the comparison group.

Each SAE will be classified according to four different levels of causality:

- Not related (excluded from reporting in accordance with MDR Art. 80(2))

Reportable events in accordance with MDR Art. 80(2) / related:

- Possible
- Probable
- Causal relationship

The **sponsor and the investigators** will assess the relationship of the serious adverse event to the investigational device, the comparator and the investigation procedure.

Reportable events:

According to MDR Article 80 and MPDG § 64 MPDG the sponsor shall report to the "Federal Institute for Drugs and Medical Devices (BfArM) **without delay**

- any SAE which has a causal relationship with the investigational device, the comparator or the investigational procedure, or where a causal relationship appears to be reasonably possible
- any DD which could have led to serious adverse events in the absence of appropriate measures or intervention or under less favorable circumstances
- any new knowledge relating to an event in accordance with the above points.

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

According to MPAMIV § 3 and MDR Article 80 (5) and (6) the sponsor must report to BfArM **without delay (see table "condition to reporting to BfArM)**:

- suspected serious incidents
- *in case of additional invasive and / or burdensome procedures:* SAEs, where a causal relationship between the serious adverse event and the preceding investigational procedure has been established (this includes SAEs associated with the procedure for use of the investigational device or any of the additional invasive and / or burdensome procedures).

Until reporting via the central European database EUDAMED or the German Medical Devices Information System (DMIDS) is possible, see the reporting form and instruction on the BfArM homepage. For SAEs or device deficiencies (DD) from German trial sites, the SAE / DD individual notification form of the BfArM must still be used.

"Without delay" means:

- For all reportable events which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: **Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.** This includes events that are of significant and unexpected nature such that they become alarming as a potential public health hazard. It also includes the possibility of multiple deaths occurring at short intervals.

- For any other reportable events as described above or a new finding/update to it: **Immediately, but not later than 7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

All reported SAEs and device deficiencies, regardless of a causal relationship to the investigational device, the comparator or the procedure, as well as the summary evaluation of SAEs, are sent to the BfArM on a quarterly basis (see the following table):

Condition for reporting to BfArM	Country in which the SAE / DD occurred	Timeline for reporting to BfArM	Form
(a) any serious adverse event that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is **reasonably possible**; (b) any **device deficiency** that **might have led** to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate; (c) any new findings in relation to any event referred to in points (a) and (b).	Germany	immediately	Individual report **German SAE Report Form** PDF, 1MB, File does not meet accessibility standards Please send to ✉ **mpsae@bfarm.de**
	all other countries where the clinical investigation is performed	immediately	Summary table **MDCG SAE Report Table** Please document all SAE cumulatively in the same Excel spreadsheet. Please send to ✉ **mpsae@bfarm.de**
all reportable SAEs / DDs* and in addition SAEs / DDs* that are included in Endpoints according to the CIP *In the case of clinical investigations according to Art. 74 (1) MDR incidents instead of DDs have to be reported.	all	quarterly	Summary evaluation of SAEs / DDs or incidents **Evaluation** docx, 25KB, File does not meet accessibility standards **Annex 3.1 complication rates** XLSX, 43KB, File does not meet accessibility standards Please send to ✉ **mpsae@bfarm.de** Please observe our **Notes** PDF, 485KB, File does not meet accessibility standards

10.6.Other

10.8.1. Reporting of pregnancy

Subjects should use a save method of contraception method during the time they participate in the study (e.g. oral contraception (“the pill”), condom, diaphragm or other drug-based contraception („the pill” as patch) or sexual abstinence). Should a participant become pregnant while taking part in the clinical trial, the pregnancy of the subject must be reported to the sponsor vigilance department. Although pregnancy itself is not considered an adverse event or a serious adverse event, the pregnant participant should be followed until at least the end of the pregnancy. The (principal) investigator must collect all information to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of birth defects, congenital abnormalities, or maternal and/or newborn complications. Any occurrences due to pregnancy that result in an SAE should also be reported.

11. Regulatory considerations

11.1.Amendments to the CIP

All planned substantial changes will be submitted for approval to EC and will be reported to the competent authority as protocol amendments.

11.2.Deviations from the CIP

Any deviation from the study protocol will be documented in the deviation log outlining the reason of the deviation and its consequence for the patient`s safety. The principal investigator is responsible to inform the sponsor about the deviations and measures. Corrective and preventive actions are determined and implemented by the principal investigator and the sponsor.

11.3.Statement of compliance

11.3.1. Regulatory Compliance

The procedures set out in this CIP, pertaining to the conduct, evaluation and documentation of this investigation, are designed to ensure that all persons involved in the investigation act in compliance with

- the ethical principles originating in the Declaration of Helsinki (applicable version)
- the principles of the Good Clinical Practice Clinical for investigations of medical devices for human subjects (ISO 14155 applicable version)
- The following applicable Union law:
    - Regulation (EU) 2017/745 on Medical Devices

General Data Protection Regulation (GDPR)

- The following applicable national law:
    - Medical Device Law Implementation Act (MPDG)

11.3.2. Approval of CIP and Subsequent Amendments

Before the start of the investigation, the CIP, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) and must be reported to the competent authority (BfArM). A written favorable opinion of the EC and an approval by/notification to the competent authority are a prerequisite for initiation of this investigation. Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted for approval to EC and the competent authority in writing as CIP amendments.

11.3.3. Insurance

Each subject is insured against any health impairment occurring as a result of participation in the clinical investigation in accordance with the provisions of the Medical Device Law Implementation Act (MPDG). The insurers maximum coverage is €500,000 per insured individual participating in this clinical trial. The insurance is covered by:

[redacted]

[redacted]nd valid throughout the conduct of the investigation including follow-up for each individual subject. Accidents on the way to and from the study visits are covered by the insurance. A copy of the insurance policy and conditions are distributed to the subject upon enrollment and the subject is advised to adhere to the conditions of the insurance policy to safeguard a valid subject insurance.

11.3.4. Financing

This clinical investigation is funded by the German Federal Ministry of Research, Technology and Space (Bundesministerium für Forschung, Technologie und Raumfahrt, BMFTR) through the DLR Projektträger (DLR-PT), Bonn, Germany, under [redacted].The grant holder is [redacted] Department of Women's Health (Department für Frauengesundheit), University Hospital Tübingen, Eberhard Karls Universität Tübingen, Germany.

12. Publications

This clinical investigation has been registered in the following public accessible database: ClinicalTrials.gov

The clinical investigation report together with the summary easily understandable to the intended user will be submitted to EUDAMED within one year of the end of the clinical investigation or within three months of the early termination or temporary halt.

13. Bibliography

Regulation 745/2017 on Medical Devices

Medical Devices Implementation Act

European General Data Protection Regulation (GDPR)

Radiation Protection Act

Medizinprodukte-Anwendermelde- und Informationsverordnung (MPAMIV)

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2 *Dominiak-Felden G, Cohet C, Atrux-Tallau S et al.* Impact of human papillomavirus-related genital diseases on quality of life and psychosocial wellbeing: results of an observational, health-related quality of life study in the UK. BMC Public Health 2013; 13: 1065

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4 *Peto J, Gilham C, Deacon J et al.* Cervical HPV infection and neoplasia in a large population-based prospective study: the Manchester cohort. BR J Cancer 2004; 91: 942-953

5 *Marzi J, Stope MB, Henes M, Koch A, Wenzel T, Holl M, et al.* Noninvasive physical plasma as innovative and tissue-preserving therapy for women positive for cervical intraepithelial neoplasia. Cancers 2022; 14: 1933. doi: 10.3390/cancers14081933

6 Wenzel T, Carvajal Berrio DA, Reisenauer C, Layland S, Koch A, Wallwiener D, et al. Trans-mucosal efficacy of non-thermal plasma treatment on cervical cancer tissue and human cervix uteri by a next generation electrosurgical argon plasma device. Cancers 2020; 12: 267. doi: 10.3390/cancers12020267

7 https://clinicaltrials.gov/study/NCT03218436

8 Weiss M, Arnholdt M, Hissnauer A, et al. Tissue-preserving treatment with non-invasive physical plasma of cervical intraepithelial neoplasia-a prospective controlled clinical trial. Front Med (Lausanne). 2023; 10: 1242732

9 Castle PE, et al. Evidence for Frequent Regression of Cervical Intraepithelial Neoplasia-Grade 2. Obstet Gynecol. 2009 January; 113(1): 18–25. doi:10.1097/AOG.0b013e31818f5008

10 Tainio K, et al. Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis. BMJ 2018; 360: k499 | doi: 10.1136/bmj.k499

14. Correlation table

MDR Annex XV, Chapter II	ISO 14155 Annex A	Chapters in this CIP
3.1.1.	A.1.2	Title page V. Abbreviations
3.1.2. 3.1.3 3.1.4	A.1.3 A.1.4	III. Contacts IV. Roles, responsibilities and qualifications of the various kinds of investigators VI. Synopsis Outsourced: Signature Page & Prüfgruppenbeschreibung
3.1.5.	A.1.5	VI. Synopsis
3.2	A.2	6.1 Identification and description of the device
3.4.	A.3	1.1. Rationale for the design of the clinical investigation
3.5.	A.5	2. Objectives and hypotheses of the clinical investigation
3.6.1	A.6.1	3. Design of the clinical investigation with evidence of its scientific robustness and validity
3.6.2	A6.2	6.2. Further Information on the investigational device, on any comparator and on any other device or medication to be used in the clinical investigation
3.6.3	A6.3 A15	4. Subjects
3.6.4	A.6.1	3. Design of the clinical investigation with evidence of its scientific robustness and validity
3.6.5	A.6.4	7.1 Introduction to Clinical procedures and diagnostic methods relating to the clinical investigation
3.6.6	A6.5	8.1 Monitoring plan
3.7	A.7	9. Statistical planning and analyses
3.8	A.8	8.3. Data management
3.9	A.9	11.1 Amendments of the CIP
3.10	A.10	11.2 Deviations from the CIP
3.11	A.11	6.3 Device accountability
3.12	A.12	11.3 Statement of compliance
3.13	A.13	7.2.1 Subject´s informed consent
3.14	A14	10. Safety
3.15	A.16 A.6.3	7.4 Follow-up
3.16	A.16	7.5.1. Plan for treatment or care after regular end of the investigation
3.17	A.17	12. Publications
3.18	A.2	6.1 Identification and description of the device
3.19	A.18	13 Bibliography

15. Appendices

15.1.Questionnaires

15.1.1. Freiburg Index of Patient Satisfaction

German version of Freiburg Index of Patient Satisfaction (FIPS).

Freiburger Index für Patientenzufriedenheit

Bitte geben Sie im Folgenden an, wie Sie die bei Ihnen durchgeführte Behandlung einschätzen.

Bitte lesen Sie zuerst alle Fragen durch und beantworten Sie dann jede Frage für sich.

Vielen Dank!

1) Ich habe die Behandlung selbst als wenig belastend empfunden

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
trifft voll und ganz zu	trifft zu	trifft eher zu	trifft eher nicht zu	trifft nicht zu	trifft überhaupt nicht zu

2) Ich habe mich nach der Behandlung rasch erholt

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
trifft voll und ganz zu	trifft zu	trifft eher zu	trifft eher nicht zu	trifft nicht zu	trifft überhaupt nicht zu

3) Die Behandlung war aus meiner Sicht ein Erfolg

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
trifft voll und ganz zu	trifft zu	trifft eher zu	trifft eher nicht zu	trifft nicht zu	trifft überhaupt nicht zu

4) Ich würde die Behandlung wieder durchführen lassen

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
trifft voll und ganz zu	trifft zu	trifft eher zu	trifft eher nicht zu	trifft nicht zu	trifft überhaupt nicht zu

5) Insgesamt bewerte ich die Behandlung als ...

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
hervorragend	sehr gut	gut	befriedigend	schlecht	sehr schlecht

Weitere Kommentare:

Dtsch Med Wochenschr 2012; 137: 419-424. M. Schoenthaler et al., Der Freiburger Index für Patientenzufriedenheit

15.1.2. Sexual Activity Questionnaire

German version of Sexual Activity Questionnaire (SAQ).

Sexual Activity Questionnaire (SAQ)

Sexualaktivitäts-Fragebogen

- STRENG VERTRAULICH! -

Teil 1: Sexuelle Aktivität

Die folgenden Fragen sind sehr sensibel und persönlich.
Bitte seien Sie versichert, dass Ihre Antworten auf diese Fragen streng vertraulich behandelt werden.

1. Sind Sie aktuell verheiratet oder haben Sie eine intime Beziehung mit jemandem? ☐ Ja ☐ Nein
2. Haben Sie in den letzten 6 Monaten Ihren Sexualpartner gewechselt? ☐ Ja ☐ Nein
3. Sind Sie zurzeit mit jemandem sexuell aktiv? ☐ Ja ☐ Nein

*Wenn **Ja**,*	*Wenn **Nein**,*
füllen Sie bitte	*füllen Sie bitte*
***Teil 3** aus.*	***Teil 2** aus.*

Teil 2: Gründe für sexuelle Inaktivität

Ich bin zurzeit nicht sexuell aktiv, weil …

(Bitte kreuzen Sie alle Antworten an, die auf Sie zutreffen.)

a) Ich habe im Moment keinen Partner ☐
b) Ich bin zu müde ☐
c) Mein Partner ist zu müde ☐
d) Ich habe kein Interesse an Sex ☐
e) Mein Partner hat kein Interesse an Sex ☐
f) Ich habe ein physisches Problem, das sexuelle Beziehungen schwierig oder unangenehm macht ☐
g) Mein Partner hat ein physisches Problem, das sexuelle Beziehungen schwierig oder unangenehm macht ☐
h) Andere Gründe *(bitte beschreiben Sie)* ☐

_____

1

Quality of Life Research 1996; 5: 81-90. K. Thirlaway et al., The Sexual Activity Questionnaire

Sexual Activity Questionnaire (SAQ)

- STRENG VERTRAULICH! -

Teil 3: Sexualfunktion

Bitte lesen Sie jede der folgenden Fragen genau durch und kreuzen Sie das Kästchen an, das am besten Ihre sexuellen Gefühle und Erfahrungen während des vergangenen Monats angibt.

Während des vergangenen Monats:

	sehr	ziemlich	ein wenig	überhaupt nicht
1. War „Sex haben" ein wichtiger Teil Ihres Lebens in diesem Monat?	☐	☐	☐	☐
2. Haben Sie die sexuelle Aktivität diesen Monat genossen?	☐	☐	☐	☐
3. Waren Sie im Allgemeinen zu müde, um Sex zu haben?	☐	☐	☐	☐
4. Haben Sie sich diesen Monat gewünscht mit Ihrem/Ihren Partner(n) Sex zu haben?	☐	☐	☐	☐
5. Wie häufig haben Sie diesen Monat während sexueller Beziehungen Scheidentrockenheit bemerkt?	☐	☐	☐	☐
6. Haben Sie in diesem Monat Schmerz oder Unwohlsein während der Penetration gefühlt?	☐	☐	☐	☐
7. Haben Sie sich im Allgemeinen diesen Monat nach sexueller Aktivität befriedigt gefühlt?	☐	☐	☐	☐
	5 mal oder mehr	**3-4 mal**	**1-2 mal**	**überhaupt nicht**
8. Wie oft waren Sie in diesem Monat sexuell aktiv?	☐	☐	☐	☐
	viel mehr	**etwas mehr**	**ungefähr gleich**	**weniger als gewöhnlich**
9. Wie ist diese Häufigkeit an sexueller Aktivität im Vergleich zu dem, was für Sie normal ist, einzuordnen?	☐	☐	☐	☐
	sehr	**ziemlich**	**ein wenig**	**überhaupt nicht**
10. Waren Sie mit der Häufigkeit an sexueller Aktivität diesen Monat zufrieden?	☐	☐	☐	☐

Weitere Kommentare:

Vielen Dank für die Beantwortung dieser Fragen.

Quality of Life Research 1996; 5: 81-90. K. Thirlaway et al., The Sexual Activity Questionnaire