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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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## ABSTRACT

**Introduction:** High-risk human papilloma virus (HPV)-associated cervical cancer is the fourth most common cancer in women worldwide. Current treatments of high grade squamous intraepithelial lesion (HSIL) of the cervix are based on invasive surgical interventions, compromising cervical competence and functionality. APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 study further evaluating the efficacy and safety of Cevira®, an integrated drug- and light-delivery device for hexaminolevulinate photodynamic therapy, which shows promise as a novel, non-invasive outpatient therapy for women with HSIL.

**Methods and analysis:** Patients with biopsy-confirmed HSIL histology are invited to participate in the study currently being conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union. The aim is to include at least 384 patients which will be randomised to either Cevira® or placebo group (2:1). All patients will be assessed 3 months after first treatment and a second treatment will be administered in patients who are HPV positive or have at least low grade squamous intraepithelial lesion (LSIL). Primary endpoint is the proportion of the responders 6 months after first treatment. Secondary efficacy and safety endpoints will be assessed at 6 months, and data for secondary performance endpoints of the Cevira® device will be collected at 3 months and 6 months, in case second treatment was administered. All patients in the Cevira® group will be enrolled in an open, long-term extension study for 6 months to collect additional efficacy and safety data (study extension endpoints).

**Ethics and dissemination:** The study was approved by the ethics committee of the Peking Union Medical College Hospital and Hannover Medical University, Germany. Findings will be disseminated through peer review publications and conference presentations.

**Trial registration number:** clinicaltrials.gov NCT04484415


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## Strengths and limitations of this study

- APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 study
- Non-invasive outpatient therapy with Cevira®, as an integrated drug- and light-delivery device for hexaminolevulinate photodynamic therapy, will be evaluated
- This study includes only patients with high grade squamous intraepithelial lesions
- Patients are being recruited from 47 sites in China and 25 sites in Ukraine, Russia and the European Union
- To minimise the risk to the patients in the placebo group, they will be unblinded after 6 months to complete the study

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## INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, almost exclusively linked to infection with high-risk human papillomaviruses (hrHPV) (1). In 2020, 604,000 new cases and 342,000 deaths worldwide were attributed to cervical cancer (2). About 85% of new cases are occurring in developing regions with high HPV prevalence such as Asia, Africa and Eastern Europe (HPV prevalence of 45.5%, 29.6% and 21.4%, respectively (3, 4)). In China, the most prevalent HPV subtypes are HPV16, 52 and 58, while in Europe HPV16, 31 and 33 are more common (5). Notably, all mentioned HPV subtypes belong to the same alpha genotype (6). There are at least 14 high-risk HPV subtypes identified, with HPV16 and HPV18 causing 70% of cervical cancers and pre-cancerous lesions (5, 7).

HPV is transmitted during sexual intercourse with the highest prevalence among sexually active young women. In the vast majority (~90%) infection is spontaneously cleared and induced low grade squamous epithelial lesion (LSIL) or cervical intraepithelial neoplasia (CIN) 1 has low potential to develop into cervical malignancy. Nevertheless, a subset of patients is at risk to develop persistent HPV infection increasing the risk for progression to high grade squamous intraepithelial lesion (HSIL) and eventually cancer (8, 9). Based on histopathological characteristics and the severity of dysplasia, HSIL can be subdivided into CIN 2 and 3, corresponding to moderate and severe dysplasia, respectively (10, 11). Unlike LSIL which usually resolves spontaneously, HSIL mostly requires medical treatment.

Current treatment options for patients with HSIL include excisional and ablative treatment (12). However, these surgical treatments may lead to perinatal complications, including preterm labour, low birth weight and perinatal death, limiting their use in women of reproductive age (13). Surgical treatments lead to a success rate of 85-95% in complete excision of the lesion (14). Recurrences occur as precancerous conditions such as CIN2 or CIN3, however, there is an elevated risk for invasive cervical cancer as well (15, 16). To preserve cervical tissue functionality, repeated surgical interventions are not recommended.

Non-invasive therapies have been developed for the treatment of HSIL and include topical agents (immune-modulators, anti-proliferative medications, antivirals, herbal regimens and probiotics), therapeutic vaccines and biologicals (17-19). However, due to the lack of sufficient clinical evidence, none of them have been accepted by the American Society for Colposcopy



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and Cervical Pathology (ASCCP) and European Federation for Colposcopy (EFC) for the management of cervical cancer and precancerous lesions and surgical methods remain the standard of care (12, 20).

Due to the side-effects associated with surgical treatments and the lack of evidence for most of the current non-invasive therapies, there has been a growing interest in non-invasive photodynamic therapy (PDT) using topically applied photosensitizers for the treatment of CIN (21-26). PDT is based on the accumulation of a photosensitizer or its precursor in the target cells, which upon illumination generates reactive oxygen species (ROS) that eradicate the diseased cells by inducing apoptosis and necrosis while preserving the underlying stroma and thereby the functionality of the cervix (27). For the treatment of CIN, topical hexaminolevulinate hydrochloride (HAL) has been mostly studied as photosensitizer showing promising efficacy and favourable safety results (24, 25). These initial results were confirmed in a Phase 2b study administrating HAL as an ointment via an intravaginal photoactivation device (Cevira®, Photocure ASA, Oslo, Norway) (26).

The objective of APRICITY Phase 3 multicentre, prospective, randomised controlled trial (RCT) is to further evaluate the efficacy and safety of Cevira® compared to placebo in the treatment of patients with cervical histological HSIL (i.e. CIN2/3).

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## METHODS AND ANALYSIS

### Study design

The Phase 3 study is designed as a multicentre, prospective, double-blind RCT enrolling patients with an adequate colposcopy and histology diagnosis of HSIL (clinicaltrials.gov Identifier: NCT04484415) (Figure 1). Randomisation to either Cevira® or placebo (2:1) is stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ or HPV18+Other+). Primary efficacy will be evaluated 6 months after first treatment for both groups. A second treatment will be administered in patients from both treatment groups who at the 3-month assessment have cytology of LSIL or more severe lesion (HSIL or atypical squamous cells-cannot exclude HSIL [ASC-H]) or in patients who are HPV positive. Retreatment visit should be no later than 1 month after the 3-month assessment visit.

All patients in the Cevira® group will be enrolled in an open, long-term extension study following patients for an additional 6 months. To minimise the risk to the patients in the placebo group, they will be unblinded after 6 months to complete the study.

The study will be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union (EU, including Hungary, Romania, Germany, Czech Republic, Slovakia, Poland and Netherlands).

### Study population

In the Phase 2b study, the efficacy of HAL PDT could only be demonstrated in CIN2 patients, probably due to the high spontaneous regression rate in the CIN1 population (26). Based on this outcome, it was decided to only enrol patients with HSIL (CIN2/3) in the present Phase 3 study.

### Eligibility criteria

*Inclusion criteria*

To be included, patients must have biopsy-confirmed HSIL histology determined by a panel of three pathologists from a central laboratory in each region (China, US and Europe), not



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more than 2 months prior to the administration of Cevira® or placebo. Colposcopy should visualise the entire lesion margin and entire cervical transformation zone, including the squamocolumnar junction, to demonstrate that the lesion covers more than 15% of the uterine cervix before biopsy. Additionally, the uterine cervix should have an average diameter of approximately 27 mm to allow application of Cevira®. Only female patients aged 18 years and older will be included. Patients must use a highly effective method of contraception during the entire study and 30 days after study end. Sterilised women or women who are post-menopausal for at least 1 year can be included without use of contraception.

*Exclusion criteria*

Key exclusion criteria are a total lesion area covering over 50% of the cervix (only for biopsy-confirmed CIN3), invasive cervical cancer, adenocarcinoma in situ or other glandular intraepithelial lesions and lesions extending to the cervical canal or vaginal vault. Of note, in certain countries (e.g. Hungary), the ethical review board allowed only the inclusion of HSIL/CIN2 patients and excluded patients diagnosed with CIN3. Additional exclusion criteria are significant vaginal infection or bleeding and porphyria. Furthermore, patients must not be pregnant or breastfeeding.

Prior and during the entire study follow-up, patients are not allowed to use drugs or treatments that may affect efficacy evaluation, i.e., drugs treating HPV, HSIL and tumours as well as regulating immunologic function.

**Interventions**

Cevira® is an integrated combination of 5% HAL in ointment and the drug delivery device Cevira® CL7 (Figure 2A). The drug is administered intravaginally to the cervix by a gynaecologist using the drug delivery device (Figure 2B). The device is a single-use, disposable, LED-based integrated red light source used to photoactivate the drug. The device will automatically switch on the light 5 hours after administration and provide continuous photoactivation of 125 J/cm$^2$ over 4.6 hours before automatically shutting down. The device needs to be removed by the patient once the treatment has been completed between 11 to 24 hours after administration. The placebo ointment contains only vehicle and is similar in



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appearance and consistence to the Cevira® ointment. The placebo device is identical in appearance as the Cevira® CL7 device without providing light.

Treatment in both Cevira® or placebo group must be discontinued if any of the following occurs: consent withdrawal, substantial non-compliance, lost to follow-up, occurrence of a serious adverse event (SAE) possibly related to study treatment, investigator's concern for the patient's health, pregnancy or intention to become pregnant or the investigator's decision to use other appropriate treatments due to disease progression. The patient may request withdrawal due to an adverse event (AE) for which the investigator did not consider removal from the study necessary.

**Outcomes**

The primary endpoint is the proportion of the responders at 6 months after the first treatment, with response being defined as normal histopathology or LSIL histopathology with clearance of baseline HPV. The list of secondary efficacy endpoints, study extension endpoints and safety endpoints can be found in Table 1.

**Table 1: Secondary efficacy, study extension and safety endpoints of the APRICITY Phase 3 study**

| |
|---|
| **Secondary efficacy endpoints** |
| a) The proportion of HPV(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>b) The proportion of HPV16(+) patients with clearance of HPV16 at 6 months after the first treatment<br>c) The proportion of HPV16 and/or HPV18(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>d) The proportion of patients with histologic regression, defined as LSIL or normal histology, at 6 months after the first treatment |
| **Secondary performance/usability endpoints** |
| a) The proportion of gynaecologists successfully inserting the device within 15 minutes<br>b) The proportion of patients with device dislocation or slippage during treatment<br>c) The proportion of patients removing the device outside the specified time |
| **Study extension endpoints** |
| a) The proportion of patients who had LSIL histology and non-clearance of baseline HPV at 6 months, who became responders at 12 months after the first treatment<br>b) The proportion of responders at 6 months who have continued regression at 12 months after the first treatment |



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| **Safety endpoints** |
| --- |
| a) The proportion of patients with AEs up to 6 months after the first treatment<br>b) The proportion of patients with Cevira® 5% HAL ointment-related AEs up to 6 months after the first treatment<br>c) The proportion of patients with Cevira® CL7 device-related AEs up to 6 months after the first treatment<br>d) The proportion of device deficiencies<br>e) The proportion of patients in the treatment group with AEs up to 12 months after the first treatment |

AE, adverse event; HAL, hexaminolevulinate hydrochloride; HPV, human papilloma virus; LSIL, low grade squamous intraepithelial lesion.

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**Assessments**

Study flow and follow-up of assessments are shown in Figure 3. The primary and secondary efficacy assessments will be done 6 months after first treatment and will be based on histology and clinically validated testing for HPV (Cobas, Roche). Colposcopy-directed biopsies will be obtained from all colposcopically-suspicious areas. If there is a normal colposcopy at 6 months or at assessment of study extension endpoints at 12 months, biopsies will be obtained from the original baseline affected area(s) to confirm histologic regression. Two pathologists will independently review the slide(s) from each biopsy in a blinded manner. If there is a discrepancy between the biopsy diagnosis, a third pathologist will review the slide(s). Clinically validated testing of cytology (ThinPrep, Hologic) and HPV (Cobas, Roche) will be used to determine the need for a second treatment.

The secondary performance assessment will be based on the number of gynaecologists successfully inserting the device within 15 minutes, the number of patients with device dislocation or slippage during treatment and the number of patients removing the device outside the specified time. Data will be collected using a patient diary and assessed at 3 months and at 6 months, in case a second treatment was applied. Safety endpoints assessment will be done at 6 months after first treatment. No interim analysis is planned for this study.

Within 24 hours of Cevira® administration, the patients will be contacted telephonically by study personnel, to ensure correct handling of the device and for a safety check. A mandatory patient diary will be used to record the time of device removal and possible AE during use



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and/or after removal of the Cevira® device. To ensure treatment compliance, regular reminders will be provided to the patients to complete the follow-up visits as scheduled.

## Statistical consideration

*Sample size*

The sample size calculation is based on the efficacy results for the HSIL histology population from the Phase 2b study using a significance level of 5% (26). It is assumed that the proportion of patients who will achieve response is 60% in the Cevira® group and 40% in the placebo group. To detect this difference with 90% power, 209 patients need to be included in the Cevira® group and 105 patients in the placebo group using a 2:1 randomisation.

Based on the Phase 2b study results, an 8% error rate of pathological assessment and 10% dropout rate should be considered. Therefore, the total sample size needs to consist of at least 384 patients (256 in Cevira® group and 128 in the placebo group). The aim is to enrol 300 patients in Chinese centres and 84 patients in centres in EU, Ukraine and Russia, with no recruitment goal for the sites. Patients, where the diagnosis for study enrolment was changed from HSIL to not HSIL, will be excluded from the primary efficacy analysis (modified intent-to-treat population, mITT).

*Statistical analysis plan*

To avoid bias, the statistical analysis team will be required to remain blinded throughout the entire study period until primary database lock (primary analyses will be performed when all patients have either completed the 6 month assessments or are early terminated from the study).

The primary efficacy endpoint analysis will be performed on the mITT population and repeated on per protocol (PP) population, which is defined as the subset of patients in the mITT population who had no major protocol violations. Analysis will be done using the Cochran Mantel Haenszel (CMH) test stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ and HPV18+Other+). Estimates and exact 95% confidence intervals for the proportion of patients who achieve response will be calculated overall, for each treatment



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group, for each diagnosis group, for each HPV status group and for each diagnosis group by HPV status subgroup (i.e. for each of the randomisation strata).

The secondary efficacy endpoints on mITT population will be analysed the same as described for the primary endpoint. The study extension endpoints will be summarised using counts and percentages for the extension population. The summary will be presented overall, by CIN diagnosis and by HPV status. The safety analysis will be performed on the safety population. If possible, a distinction will be made between Cevira® 5% HAL ointment-related and Cevira® CL7 device-related AEs.

Two sensitivity analyses will investigate the effect of missing data on the result of the primary endpoint analysis in the mITT population: (1) analysis of all responder data as observed (i.e. no imputations) and (2) analysis after imputing all missing 6-month data as success (responders) in the placebo treatment group and as failure (non-responders) in the Cevira® treatment group. In the safety population, missing values will be treated as missing and will not be substituted.

**Randomisation and blinding method**

The patients will be randomised through an Interactive Web Response System (IWRS) after initial screening by the investigators. The IWRS will generate a randomisation number after the investigator inputs the required information and will then assign a product for the patient. The investigators, study personnel and patients are blinded to the treatment groups as Cevira® and placebo products are identical in packaging. Additionally, the light signal before insertion does not differ between Cevira® and placebo products. If during the blinded part of the study a medical emergency or SAE occurs and the patient's condition requires knowledge of the test medication, the study blind may be broken and reported for that specific patient. After the 6-month assessment, the planned unblinding procedure will be performed by the investigators to decide if patients will continue in the open-label extension study.



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**Data and study monitoring**

An electronic data collection (EDC) system will be used to collect and manage the trial data in this study. Patient data should be entered continuously during the study and within 48 hours after a visit is performed**.** As nonclinical local tolerance studies and previous clinical studies showed an excellent safety profile with only mild to moderate local reactions and few related systemic side effects, no data monitoring committee (DMC) is planned for this study. Nevertheless, all events occurring during the period of observation, reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit, will be documented on the pages provided on the AE form in the electronic case report form (eCRF). Any SAEs for which a causal relationship to the treatment cannot be ruled out, will be documented on the AE form even if they occur after the period of observation. Related AEs and SAEs should be followed up until resolved, or at the latest until database lock. In case of permanent impairment, the event must be followed until the condition stabilises and the investigator considered it medically justifiable to terminate follow-up, or at the latest until database lock.

Study monitoring will be performed in accordance with International Conference on Harmonization (ICH) E6-Good Clinical Practice (GCP)/ISO 14155:2020 as applicable, the sponsor/contract research organisation (CRO) standard operating procedures (SOPs), the protocol, the monitoring plan and applicable local regulations. If missing or inconsistent data not catered for are detected, queries will be issued. Queries may also be generated during the data validation process and shall be resolved immediately before database lock. All study documentation at the investigator site and sponsor site will be archived in accordance with the ICH E6- GCP/ISO 14155:2020 as applicable, EU Regulation 536/2014, 21 CFR 312.62, and the sponsor's quality standards and SOPs. An auditor authorised by the sponsor may audit the investigational site and request access to all source documents, eCRF and other study documentation.



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## Patient and public involvement

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice.

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## ETHICS AND DISSEMINATION

The study was approved by the ethics committee of the Peking Union Medical College Hospital on 2nd of July, 2020 (Nr. KS20202255). Current version of the protocol (No. 2.2) from 31st of July 2021 was also approved on 20th of December 2021 by Hannover Medical University, Germany. It is conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki and all applicable national and international laws, regulations and standards, including archiving of essential documents. Patients agreeing to participate in the study must sign an informed consent form approved according to local regulations. The study site staff member conducting the consent process must also sign the consent form on the same occasion. All amendments to the clinical study protocol should be agreed upon between the sponsor and the investigator and be recorded with a justification for the amendment. The only exceptions are, where necessary to eliminate an immediate hazard to study patients, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). All information concerning drug/device and the sponsor's research and product development is considered confidential and will remain the sole property of the sponsor. A financial agreement will be signed between the sponsor and the investigators and/or the institution involved as required.

Final data analysis and disclosure of contractual agreements will be done by CRO Hangzhou Tigermed Consulting Co., Ltd, which will limit the access of investigators to the final trial dataset. The monitors, auditors, authorised personnel of the sponsor, health authority inspectors or their agents, and authorised members of Independent Ethics Committees/Institutional Review Boards will be given direct access to the source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes and photographs) upon request, provided that patient confidentiality is maintained in accordance with local requirements.

Findings of this study will be disseminated through peer-review publications and conference presentations. No information which could lead to the identification of patients will be included in the dissemination of results.



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## DISCUSSION

Cervical cancer is the most common HPV-related malignancy (7). Given the substantial burden of cervical cancer globally, efforts have been made to develop effective prevention measures, including HPV vaccination and screening programmes in combination with timely and efficient treatment of pre-cancerous lesions (2, 11). Unfortunately, these preventive measures are not equally implemented worldwide, with absent or inadequate screening and vaccination programmes in many low- and middle-income countries who suffer the highest HPV incidence rates. Especially in Eastern Europe and Central Asia, a rapid increase in premature cervical cancer mortality has been reported in recent generations (2). Furthermore, currently available vaccines are expensive and directed against only certain HPV subtypes (4, 11).

PDT has been clinically approved for the treatment of different cancers, including skin cancer, superficial oesophageal cancer and lung cancer (28-30). Due to the lack of adequate non-surgical treatment modalities, the potential of PDT for the treatment of CIN has been investigated in this and previous studies (21-26, 31). The main advantage of PDT for the treatment of CIN is its non-invasiveness, leaving the cervix intact and thereby preserving fertility. Moreover, targeted PDT of CIN is not restricted by HPV subtype causing pre-cancerous lesions and the PDT could be repeated in case of another infection or lesion.

For the treatment of CIN, topical administration of both 5-aminolaevulinic acid (5-ALA) and its esterified derivate HAL have been studied, with HAL being preferred due to its better stability and increased fluorescence at lower doses leading to less systemic exposure (21, 23, 28). As topical administration was perceived to be inconvenient, the integrated light- and drug-delivery device Cevira® was developed (22, 26, 31). The safety and efficacy of Cevira® have been evaluated in a double-blind, placebo-controlled dose-finding Phase 2b study including 262 patients with CIN1/2 randomised to HAL 0.2%, 1% or 5% or placebo, permitting retreatment at 3 months if clinically indicated (26). Based on the outcomes of the Phase 2b, the HAL 5% dose was selected for further evaluation in the Phase 3 study. The HAL 5% dose had a favourable safety profile while being associated with the highest regression rate and oncogenic HPV clearance. However, efficacy could only be demonstrated in patients with CIN2, probably due to a high rate of spontaneous regression in the CIN1 population with most patients being HPV negative. As a result, the present Phase 3 study will only include HSIL



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patients (CIN2/3) ensuring efficacy can be reliably assessed. Due to the local and transient exposure to HAL, side effects were usually self-limiting, mainly including discharge, discomfort and spotting.

The currently available data indicate that Cevira® is easy-to-use for gynaecologists and well-accepted by patients (31). The device results in no patient down-time as it is similar to using a tampon, patients may leave the gynaecologist office immediately after the application and can return to normal daily activities. Additionally, patients can easily remove the device themselves by pulling the string within 24 hours after application. The current Phase 3 study will further evaluate how the use of Cevira® device is perceived by gynaecologists and patients.

In conclusion, Cevira® holds potential to serve high unmet medical need for non-surgical, safe treatment options for patients with HSIL and cervical cancer. Due to its non-invasiveness, Cevira® could be a promising alternative to excisional treatment for young women in reproductive age. Following the encouraging results from the Phase 2b study, the efficacy and safety of Cevira® in patients with HSIL will be further evaluated in the presented APRICITY Phase 3 study currently recruiting patients in China and Europe for a multicentre, prospective, double-blind randomised controlled clinical trial.

**Trial status**

The APRICITY Phase 3 study is currently recruiting patients in China, Ukraine, Russia and Europe. Recruitment started in November 2020 with the aim to enrol at least 384 patients. The process might be interrupted or extended due to the Covid-19 pandemic.

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## Author contributions

FC, LS, YZ, ZY, JH and PH contributed to the experimental design of the study. CD, ZN and CM were involved in study design, outcome definition and ethical approval application. JL is the global PI of the study. PH is the European PI of the study. FC is the Chinese PI of the study. All PIs have contributed to the study protocol amendments. All authors have read, edited and approved the manuscript.

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## Conflict of interest

CD received consulting fees from MSD, GSK, Tesaro and Clovis Oncology and honoraria from MSD and GSK. LH is an employee of Asieris Pharmaceuticals (Shanghai) Co., Ltd. FC, ZN, CM, LS, YZ, ZY, JL and PH have nothing to declare.

## Patient and public involvement

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice.



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## FIGURE LEGENDS

**Figure 1. Overview of the APRICITY Phase 3 study design.**

**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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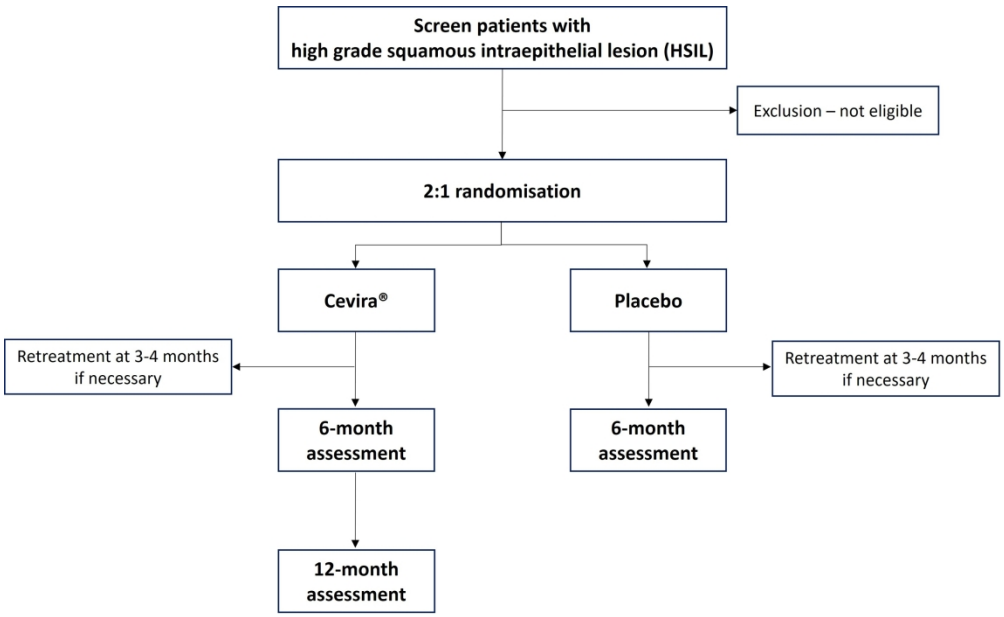


**Figure 1. Overview of the APRICITY Phase 3 study design.**

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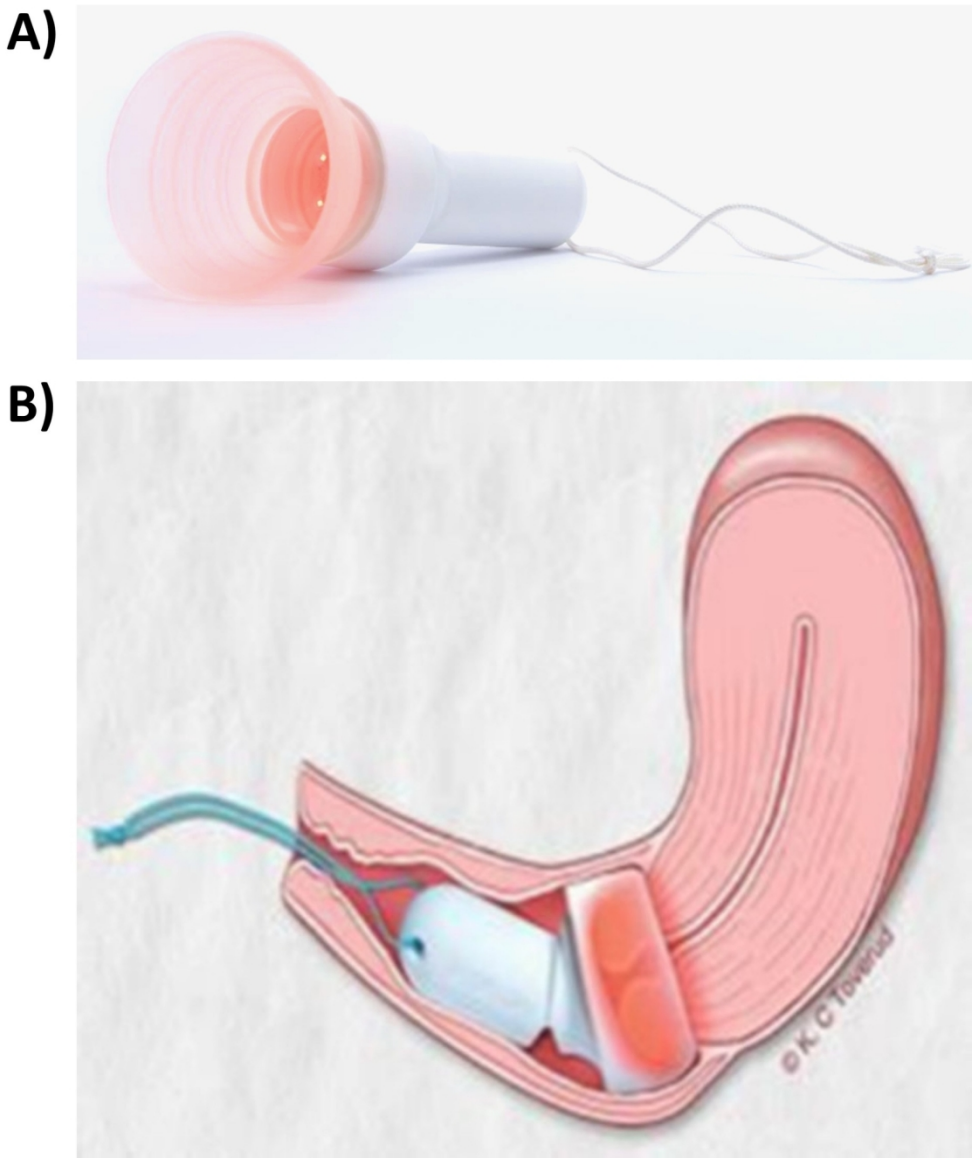


**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

149x175mm (300 x 300 DPI)

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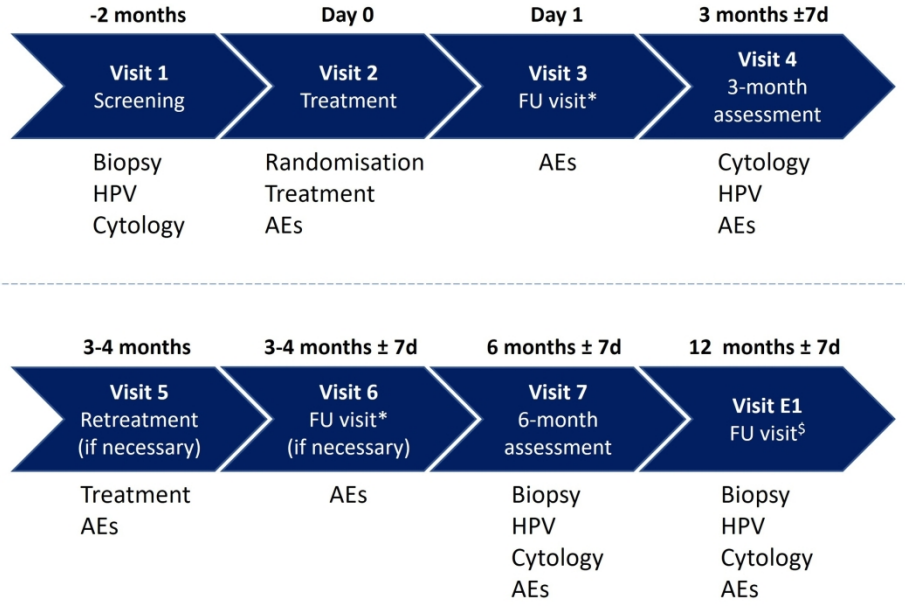


**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

Commented [MR1]: Page 1
Commented [MR2]: Page 2 and Page 6
Commented [MR3]: Page 13
Commented [MR4]: Page 16
Commented [MR5]: Page 4, 5
Commented [MR6]: Page 5
Commented [MR7]: Page 6, Figure 1



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**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | **Commented [MR8]:** Page 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | **Commented [MR9]:** Page 6,7 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | **Commented [MR10]:** Page 7,8 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | **Commented [MR11]:** Page 8,9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | **Commented [MR12]:** Page 9, Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | **Commented [MR13]:** Page 10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | **Commented [MR14]:** Page 10 |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | **Commented [MR15]:** Page 11 |



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| | | | |
|---|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | Commented [MR16]: Page 11 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Commented [MR17]: Page 11 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Commented [MR18]: Page 11 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Commented [MR19]: Page 9,10,12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Commented [MR20]: Page 9,10,12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Commented [MR21]: Page 10,11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Commented [MR22]: Page 9,12 |



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| | | | |
|---|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Commented [MR23]: Page 12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Commented [MR24]: Page 12 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Commented [MR25]: Page 13 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Commented [MR26]: Page 13 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Commented [MR27]: Page 13 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Commented [MR28]: Page 13 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Commented [MR29]: Page 12, 13 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Commented [MR30]: Page 2,13 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |



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**Appendices**

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.



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BMJ Open

# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Infectious diseases, Oncology, Surgery, Reproductive medicine |
| Keywords: | GYNAECOLOGY, Gynaecological oncology < GYNAECOLOGY, OBSTETRICS, Colposcopy < GYNAECOLOGY, Clinical trials < THERAPEUTICS |
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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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## ABSTRACT

**Introduction:** High-risk human papilloma virus (HPV)-associated cervical cancer is the fourth most common cancer in women worldwide. Current treatments of high grade squamous intraepithelial lesion (HSIL) of the cervix are based on invasive surgical interventions, compromising cervical competence and functionality. APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 study further evaluating the efficacy and safety of Cevira®, an integrated drug- and light-delivery device for hexaminolevulinate photodynamic therapy, which shows promise as a novel, non-invasive outpatient therapy for women with HSIL.

**Methods and analysis:** Patients with biopsy-confirmed HSIL histology are invited to participate in the study planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union. The aim is to include at least 384 patients which will be randomised to either Cevira® or placebo group (2:1). All patients will be assessed 3 months after first treatment and a second treatment will be administered in patients who are HPV positive or have at least low grade squamous intraepithelial lesion (LSIL). Primary endpoint is the proportion of the responders 6 months after first treatment. Secondary efficacy and safety endpoints will be assessed at 6 months, and data for secondary performance endpoints of the Cevira® device will be collected at 3 months and 6 months, in case second treatment was administered. All patients in the Cevira® group will be enrolled in an open, long-term extension study for 6 months to collect additional efficacy and safety data (study extension endpoints).

**Ethics and dissemination:** The study was approved by the ethics committee of the Peking Union Medical College Hospital and Hannover Medical University, Germany. Findings will be disseminated through peer review publications and conference presentations.

**Trial registration number:** clinicaltrials.gov NCT04484415


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## Strengths and limitations of this study

- Currently, there is a high need for non-invasive treatments of HSIL and other HPV-related diseases
- APRICITY is the first large scale multicentre, prospective, double-blind, randomised controlled Phase 3 trial, evaluating a non-invasive outpatient hexaminolevulinate photodynamic therapy delivered through an integrated drug- and light-delivery device (Cevira®)
- The study has an international set-up, planning to include 47 sites in China and 25 sites in Ukraine, Russia and the European Union
- The most important limitation is the potential for spontaneous regression of CIN2 lesions in the placebo group, which could underestimate the trial results

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## INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, almost exclusively linked to infection with high-risk human papillomaviruses (hrHPV) (1). In 2020, 604,000 new cases and 342,000 deaths worldwide were attributed to cervical cancer. Of these new cases and deaths, about 90% are occurring in low- and middle-income countries due to the lack organised screening (1, 2). In China, the most prevalent HPV subtypes are HPV16, 52 and 58, while in Europe HPV16, 31 and 33 are more common (3). Notably, all mentioned HPV subtypes belong to the same alpha genotype (4). There are at least 14 high-risk HPV subtypes identified, with HPV16 and HPV18 causing 70% of cervical cancers and pre-cancerous lesions (3, 5).

HPV is transmitted during sexual intercourse with the highest prevalence among sexually active young women. In the vast majority (~90%) infection is spontaneously cleared and induced low grade squamous epithelial lesion (LSIL) or cervical intraepithelial neoplasia (CIN) 1 has low potential to develop into cervical malignancy. Nevertheless, a subset of patients is at risk to develop persistent HPV infection increasing the risk for progression to high grade squamous intraepithelial lesion (HSIL) and eventually cancer (6, 7). Based on histopathological characteristics and the severity of dysplasia, HSIL can be subdivided into CIN 2 and 3, corresponding to moderate and severe dysplasia, respectively (8, 9). Unlike LSIL which usually resolves spontaneously, the guidelines for cervical cancer screening generally recommend medical treatment for women with HSIL (10). Although in women of childbearing age, CIN2 lesions often regress spontaneously, not requiring immediate intervention (11, 12).

Current treatment options for patients with HSIL include excisional and ablative treatment (13). However, these surgical treatments may lead to perinatal complications, including preterm labour, low birth weight and perinatal death, limiting their use in women of reproductive age (14). Surgical treatments lead to a success rate of 85-95% in complete excision of the lesion (15). Recurrences occur as precancerous conditions such as CIN2 or CIN3, however, there is an elevated risk for invasive cervical cancer as well (16, 17). To preserve cervical tissue functionality, repeated surgical interventions are not recommended but no good tissue alternatives are available for the treatment of high-grade CIN.



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Non-invasive therapies have been developed for the treatment of HSIL and include topical agents (immune-modulators, anti-proliferative medications, antivirals, herbal regimens and probiotics), therapeutic vaccines and biologicals (18-20). However, due to the lack of sufficient clinical evidence, none of them have been accepted by the American Society for Colposcopy and Cervical Pathology (ASCCP) and European Federation for Colposcopy (EFC) for the management of cervical cancer and precancerous lesions and surgical methods remain the standard of care (13, 21).

Due to the side-effects associated with surgical treatments and the lack of evidence for most of the current non-invasive therapies, there has been a growing interest in non-invasive photodynamic therapy (PDT) using topically applied photosensitizers for the treatment of CIN (22-27). PDT is based on the accumulation of a photosensitizer or its precursor in the target cells, which upon illumination generates reactive oxygen species (ROS) that eradicate the diseased cells by inducing apoptosis and necrosis while preserving the underlying stroma and thereby the functionality of the cervix (28). For the treatment of CIN, topical hexaminolevulinate hydrochloride (HAL) has been mostly studied as photosensitizer showing promising efficacy and favourable safety results (25, 26). These initial results were confirmed in a Phase 2b study administrating HAL as an ointment via an intravaginal photoactivation device (Cevira®, Photocure ASA, Oslo, Norway) (27).

The objective of APRICITY Phase 3 multicentre, prospective, randomised controlled trial (RCT) is to further evaluate the efficacy and safety of Cevira® compared to placebo in the treatment of patients with cervical histological HSIL (i.e. CIN2/3).



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## METHODS AND ANALYSIS

### Study design

The Phase 3 study is designed as a multicentre, prospective, double-blind RCT enrolling patients with an adequate colposcopy and histology diagnosis of HSIL (clinicaltrials.gov Identifier: NCT04484415) (Figure 1). Randomisation to either Cevira® or placebo (2:1) is stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ or HPV18+Other+). Primary efficacy will be evaluated 6 months after first treatment for both groups. A second treatment will be administered in patients from both treatment groups who at the 3-month assessment have cytology of LSIL or more severe lesion (HSIL or atypical squamous cells-cannot exclude HSIL [ASC-H]) or in patients who are HPV positive. Retreatment visit should be no later than 1 month after the 3-month assessment visit.

All patients in the Cevira® group will be enrolled in an open, long-term extension study following patients for an additional 6 months. To minimise the risk to the patients in the placebo group, they will be unblinded after 6 months to complete the study. Patients with persistent high-grade CIN after 6 months will receive surgical treatment regardless of study group.

The study is planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union (EU, including Hungary, Romania, Germany, Czech Republic, Slovakia, Poland and Netherlands).

### Study population

In the Phase 2b study, the efficacy of HAL PDT could only be demonstrated in CIN2 patients, probably due to the high spontaneous regression rate in the CIN1 population (27). Based on this outcome, it was decided to only enrol patients with HSIL (CIN2/3) in the present Phase 3 study.



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**Eligibility criteria**

*Inclusion criteria*

To be included, patients must have biopsy-confirmed HSIL histology determined by a panel of three pathologists from a central laboratory in each region (China, US and Europe), not more than 2 months prior to the administration of Cevira® or placebo. Colposcopy should visualise the entire lesion margin and entire cervical transformation zone, including the squamocolumnar junction, to demonstrate that the lesion covers more than 15% of the uterine cervix before biopsy. Additionally, the uterine cervix should have an average diameter of approximately 27 mm to allow application of Cevira®. Only female patients aged 18 years and older (maximum age 85 years) will be included. Patients must use a highly effective method of contraception during the entire study and 30 days after study end. Sterilised women or women who are post-menopausal for at least 1 year can be included without use of contraception.

*Exclusion criteria*

Key exclusion criteria are a total lesion area covering over 50% of the cervix (only for biopsy-confirmed CIN3), invasive cervical cancer, adenocarcinoma in situ or other glandular intraepithelial lesions and lesions extending to the cervical canal or vaginal vault. Of note, in certain countries (e.g. Hungary), the ethical review board allowed only the inclusion of HSIL/CIN2 patients and excluded patients diagnosed with CIN3. Additional exclusion criteria are significant vaginal infection or bleeding, current severe pelvic inflammatory disease, history of toxic shock syndrome, known allergies to hexaminolevulinate and/or silicone, use of heart pacemaker and porphyria. Furthermore, patients must not be pregnant or breastfeeding.

Prior and during the entire study follow-up, patients are not allowed to use drugs or treatments that may affect efficacy evaluation, i.e., drugs treating HPV, HSIL and tumours as well as regulating immunologic function. In addition, patients who previously received surgical treatment, have incomplete cervical structure and have recurrent HSIL or patients who received other treatment after the confirmed diagnosis of HSIL are excluded from the study. Furthermore, patients may not participate in other therapeutic clinical trials using investigational agents either concurrently or within the last 30 days. Lastly, patients are



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excluded if they are not deemed suitable in the investigator's opinion or if the patient has a conflict of interest that would interfere with the study conduct.

**Interventions**

Cevira® is an integrated combination of 5% HAL in ointment and the drug delivery device Cevira® CL7 (Figure 2A). The drug is administered intravaginally to the cervix by a gynaecologist using the drug delivery device (Figure 2B). The device is a single-use, disposable, LED-based integrated red light source used to photoactivate the drug. The device will automatically switch on the light 5 hours after administration and provide continuous photoactivation of 125 J/cm$^2$ over 4.6 hours before automatically shutting down. The device needs to be removed by the patient once the treatment has been completed between 11 to 24 hours after administration. The placebo ointment contains only vehicle and is similar in appearance and consistence to the Cevira® ointment. The placebo device is identical in appearance as the Cevira® CL7 device without providing light. The investigators and staff at each site are trained on at least five occasions in the study procedures before study start through standard intervention procedure videos upon which each investigator should perform the intervention before opening the study site.

Treatment in both Cevira® or placebo group must be discontinued if any of the following occurs: consent withdrawal, substantial non-compliance, lost to follow-up, occurrence of a serious adverse event (SAE) possibly related to study treatment, investigator's concern for the patient's health, pregnancy or intention to become pregnant or the investigator's decision to use other appropriate treatments due to disease progression. The patient may request withdrawal due to an adverse event (AE) for which the investigator did not consider removal from the study necessary.

**Outcomes**

The primary endpoint is the proportion of the responders at 6 months after the first treatment, with response being defined as normal histopathology or LSIL histopathology with



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clearance of baseline HPV. The list of secondary efficacy endpoints, study extension endpoints and safety endpoints can be found in Table 1.

**Table 1: Secondary efficacy, study extension and safety endpoints of the APRICITY Phase 3 study**

| |
|---|
| **Secondary efficacy endpoints** |
| a) The proportion of HPV(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>b) The proportion of HPV16(+) patients with clearance of HPV16 at 6 months after the first treatment<br>c) The proportion of HPV16 and/or HPV18(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>d) The proportion of patients with histologic regression, defined as LSIL or normal histology, at 6 months after the first treatment |
| **Secondary performance/usability endpoints** |
| a) The proportion of gynaecologists successfully inserting the device within 15 minutes<br>b) The proportion of patients with device dislocation or slippage during treatment<br>c) The proportion of patients removing the device outside the specified time |
| **Study extension endpoints** |
| a) The proportion of patients who had LSIL histology and non-clearance of baseline HPV at 6 months, who became responders at 12 months after the first treatment<br>b) The proportion of responders at 6 months who have continued regression at 12 months after the first treatment |
| **Safety endpoints** |
| a) The proportion of patients with AEs up to 6 months after the first treatment<br>b) The proportion of patients with Cevira® 5% HAL ointment-related AEs up to 6 months after the first treatment<br>c) The proportion of patients with Cevira® CL7 device-related AEs up to 6 months after the first treatment<br>d) The proportion of device deficiencies<br>e) The proportion of patients in the treatment group with AEs up to 12 months after the first treatment |

AE, adverse event; HAL, hexaminolevulinate hydrochloride; HPV, human papilloma virus; LSIL, low grade squamous intraepithelial lesion.

**Assessments**

Study flow and follow-up of assessments are shown in Figure 3. The primary and secondary efficacy assessments will be done 6 months after first treatment and will be based on histology and clinically validated testing for HPV (Cobas, Roche). To standardise the procedure, investigators will all receive a colposcopy operation manual. Colposcopy-directed biopsies will be obtained from all colposcopically-suspicious areas. If there is a normal colposcopy at 6



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months or at assessment of study extension endpoints at 12 months, biopsies will be obtained from the original baseline affected area(s) to confirm histologic regression. Two pathologists will independently review the slide(s) from each biopsy in a blinded manner. If there is a discrepancy between the biopsy diagnosis, a third pathologist will review the slide(s). Clinically validated testing of cytology (ThinPrep, Hologic) and HPV (Cobas, Roche) will be used to determine the need for a second treatment.

The secondary performance assessment will be based on the number of gynaecologists successfully inserting the device within 15 minutes, the number of patients with device dislocation or slippage during treatment and the number of patients removing the device outside the specified time. Data will be collected using a patient diary and assessed at 3 months and at 6 months, in case a second treatment was applied. Safety endpoints assessment will be done at 6 months after first treatment. No interim analysis is planned for this study.

Within 24 hours of Cevira® administration, the patients will be contacted telephonically by study personnel, to ensure correct handling of the device and for a safety check. A mandatory patient diary will be used to record the time of device removal and possible AE during use and/or after removal of the Cevira® device. To ensure treatment compliance, regular reminders will be provided to the patients to complete the follow-up visits as scheduled.

## Statistical consideration

*Sample size*

The sample size calculation is based on the efficacy results for the HSIL histology population from the Phase 2b study using a significance level of 5% (27). It is assumed that the proportion of patients who will achieve response is 60% in the Cevira® group and 40% in the placebo group. To detect this difference with 90% power, 209 patients need to be included in the Cevira® group and 105 patients in the placebo group using a 2:1 randomisation.

Patients for whom the diagnosis for study enrolment was changed from HSIL to not HSIL upon confirmation of the diagnosis by a panel of three expert gynaecological pathologists from three independent institutions, will be excluded from the primary efficacy analysis (modified intent-to-treat population, mITT). Based on the Phase 2b study results, an 8% error



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rate of pathological assessment and 10% dropout rate should be considered. Therefore, the total sample size needs to consist of at least 384 patients (256 in Cevira® group and 128 in the placebo group). The aim is to enrol 300 patients in Chinese centres and 84 patients in centres in EU, Ukraine and Russia, with no recruitment goal for the sites.

*Statistical analysis plan*

To avoid bias, the statistical analysis team will be required to remain blinded throughout the entire study period until primary database lock (primary analyses will be performed when all patients have either completed the 6 month assessments or are early terminated from the study).

The primary efficacy endpoint analysis will be performed on the mITT population and repeated on per protocol (PP) population, which is defined as the subset of patients in the mITT population who had no major protocol violations. Analysis will be done using the Cochran Mantel Haenszel (CMH) test stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ and HPV18+Other+). Estimates and exact 95% confidence intervals for the proportion of patients who achieve response will be calculated overall, for each treatment group, for each diagnosis group, for each HPV status group and for each diagnosis group by HPV status subgroup (i.e. for each of the randomisation strata).

The secondary efficacy endpoints on mITT population will be analysed the same as described for the primary endpoint. The study extension endpoints will be summarised using counts and percentages for the extension population. The summary will be presented overall, by CIN diagnosis and by HPV status. The safety analysis will be performed on the safety population. If possible, a distinction will be made between Cevira® 5% HAL ointment-related and Cevira® CL7 device-related AEs.

Two sensitivity analyses will investigate the effect of missing data on the result of the primary endpoint analysis in the mITT population: (1) analysis of all responder data as observed (i.e. no imputations) and (2) analysis after imputing all missing 6-month data as success (responders) in the placebo treatment group and as failure (non-responders) in the Cevira® treatment group. In the safety population, missing values will be treated as missing and will not be substituted.



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**Randomisation and blinding method**

The patients will be randomised through an Interactive Web Response System (IWRS) after initial screening by the investigators. The IWRS will generate a randomisation number after the investigator inputs the required information and will then assign a product for the patient. The investigators, study personnel and patients are blinded to the treatment groups as Cevira® and placebo products are identical in packaging. Additionally, the light signal before insertion does not differ between Cevira® and placebo products. If during the blinded part of the study a medical emergency or SAE occurs and the patient's condition requires knowledge of the test medication, the study blind may be broken and reported for that specific patient. After the 6-month assessment, the planned unblinding procedure will be performed by the investigators to decide if patients will continue in the open-label extension study.

**Data and study monitoring**

An electronic data collection (EDC) system will be used to collect and manage the trial data in this study. Patient data should be entered continuously during the study and within 48 hours after a visit is performed**.** As nonclinical local tolerance studies and previous clinical studies showed an excellent safety profile with only mild to moderate local reactions and few related systemic side effects, no data monitoring committee (DMC) is planned for this study. Nevertheless, all events occurring during the period of observation, reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit, will be documented on the pages provided on the AE form in the electronic case report form (eCRF). Any SAEs for which a causal relationship to the treatment cannot be ruled out, will be documented on the AE form even if they occur after the period of observation. Related AEs and SAEs should be followed up until resolved, or at the latest until database lock. In case of permanent impairment, the event must be followed until the condition stabilises and the investigator considered it medically justifiable to terminate follow-up, or at the latest until database lock.

Study monitoring will be performed in accordance with International Conference on Harmonization (ICH) E6-Good Clinical Practice (GCP)/ISO 14155:2020 as applicable, the sponsor/contract research organisation (CRO) standard operating procedures (SOPs), the



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protocol, the monitoring plan and applicable local regulations. If missing or inconsistent data not catered for are detected, queries will be issued. Queries may also be generated during the data validation process and shall be resolved immediately before database lock. All study documentation at the investigator site and sponsor site will be archived in accordance with the ICH E6- GCP/ISO 14155:2020 as applicable, EU Regulation 536/2014, 21 CFR 312.62, and the sponsor's quality standards and SOPs. An auditor authorised by the sponsor may audit the investigational site and request access to all source documents, eCRF and other study documentation.

**Patient and public involvement**

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice.

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## ETHICS AND DISSEMINATION

The study was approved by the ethics committee of the Peking Union Medical College Hospital on 2nd of July, 2020 (Nr. KS20202255). Current version of the protocol (No. 2.2) from 31st of July 2021 was also approved on 20th of December 2021 by Hannover Medical University, Germany. It is conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki and all applicable national and international laws, regulations and standards, including archiving of essential documents. Patients agreeing to participate in the study must sign an informed consent form approved according to local regulations. The study site staff member conducting the consent process must also sign the consent form on the same occasion. All amendments to the clinical study protocol should be agreed upon between the sponsor and the investigator and be recorded with a justification for the amendment. The only exceptions are, where necessary to eliminate an immediate hazard to study patients, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). All information concerning drug/device and the sponsor's research and product development is considered confidential and will remain the sole property of the sponsor. A financial agreement will be signed between the sponsor and the investigators and/or the institution involved as required.

Final data analysis and disclosure of contractual agreements will be done by CRO Hangzhou Tigermed Consulting Co., Ltd, which will limit the access of investigators to the final trial dataset. The monitors, auditors, authorised personnel of the sponsor, health authority inspectors or their agents, and authorised members of Independent Ethics Committees/Institutional Review Boards will be given direct access to the source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes and photographs) upon request, provided that patient confidentiality is maintained in accordance with local requirements.

Findings of this study will be disseminated through peer-review publications and conference presentations. No information which could lead to the identification of patients will be included in the dissemination of results.



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## DISCUSSION

Cervical cancer is the most common HPV-related malignancy (5). Given the substantial burden of cervical cancer globally, efforts have been made to develop effective prevention measures, including HPV vaccination and screening programmes in combination with timely and efficient treatment of pre-cancerous lesions (2, 9). Unfortunately, these preventive measures are not equally implemented worldwide, with absent or inadequate screening and vaccination programmes in many low- and middle-income countries who suffer the highest HPV incidence rates. Especially in Eastern Europe and Central Asia, a rapid increase in premature cervical cancer mortality has been reported in recent generations (2). Furthermore, currently available vaccines are expensive and directed against only certain HPV subtypes (9, 29).

PDT has been clinically approved for the treatment of different cancers, including skin cancer, superficial oesophageal cancer and lung cancer (30-32). Due to the lack of adequate non-surgical treatment modalities, the potential of PDT for the treatment of CIN has been investigated in this and previous studies (22-27, 33). The main advantage of PDT for the treatment of CIN is its non-invasiveness, leaving the cervix intact and thereby preserving fertility. Moreover, targeted PDT of CIN is not restricted by HPV subtype causing pre-cancerous lesions and the PDT could be repeated in case of another infection or lesion.

For the treatment of CIN, topical administration of both 5-aminolaevulinic acid (5-ALA) and its esterified derivate HAL have been studied, with HAL being preferred due to its better stability and increased fluorescence at lower doses leading to less systemic exposure (22, 24, 30). As topical administration was perceived to be inconvenient, the integrated light- and drug-delivery device Cevira® was developed (23, 27, 33). The safety and efficacy of Cevira® have been evaluated in a double-blind, placebo-controlled dose-finding Phase 2b study including 262 patients with CIN1/2 randomised to HAL 0.2%, 1% or 5% or placebo, permitting retreatment at 3 months if clinically indicated (27). Based on the outcomes of the Phase 2b, the HAL 5% dose was selected for further evaluation in the Phase 3 study. The HAL 5% dose had a favourable safety profile while being associated with the highest regression rate and oncogenic HPV clearance. However, efficacy could only be demonstrated in patients with CIN2, probably due to a high rate of spontaneous regression in the CIN1 population with most patients being HPV negative. As a result, the present Phase 3 study will only include HSIL



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patients (CIN2/3) ensuring efficacy can be reliably assessed. Due to the local and transient exposure to HAL, side effects were usually self-limiting, mainly including discharge, discomfort and spotting.

The currently available data indicate that Cevira® is easy-to-use for gynaecologists and well-accepted by patients (33). The device results in no patient down-time as it is similar to using a tampon, patients may leave the gynaecologist office immediately after the application and can return to normal daily activities. Additionally, patients can easily remove the device themselves by pulling the string within 24 hours after application. The current Phase 3 study will further evaluate how the use of Cevira® device is perceived by gynaecologists and patients.

In conclusion, Cevira® holds potential to serve high unmet medical need for non-surgical, safe treatment options for patients with HSIL and cervical cancer. Due to its non-invasiveness, Cevira® could be a promising alternative to excisional treatment for young women in reproductive age. Following the encouraging results from the Phase 2b study, the efficacy and safety of Cevira® in patients with HSIL will be further evaluated in the presented APRICITY Phase 3 study currently recruiting patients in China and Europe for a multicentre, prospective, double-blind randomised controlled clinical trial.

**Trial status**

The APRICITY Phase 3 study is currently recruiting patients in China, Ukraine, Russia and Europe. Recruitment started in November 2020 with the aim to enrol at least 384 patients. However, study start-up had to be delayed in Ukraine and Russia. In addition, the process might be interrupted or extended due to the Covid-19 pandemic.

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## Author contributions

FC, LS, YZ, ZY, JH and PH contributed to the experimental design of the study. CD, ZN and CM were involved in study design, outcome definition and ethical approval application. JL is the global PI of the study. PH is the European PI of the study. FC is the Chinese PI of the study. All PIs have contributed to the study protocol amendments. All authors have read, edited and approved the manuscript.

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## Conflict of interest

CD received consulting fees from MSD, GSK, Tesaro and Clovis Oncology and honoraria from MSD and GSK. LH is an employee of Asieris Pharmaceuticals (Shanghai) Co., Ltd. FC, ZN, CM, LS, YZ, ZY, JL and PH have nothing to declare.

## Patient and public involvement

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study and did assess the burden of participating in the study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice. All other study results will be disseminated to the participants on demand.



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## FIGURE LEGENDS

**Figure 1. Overview of the APRICITY Phase 3 study design.**

**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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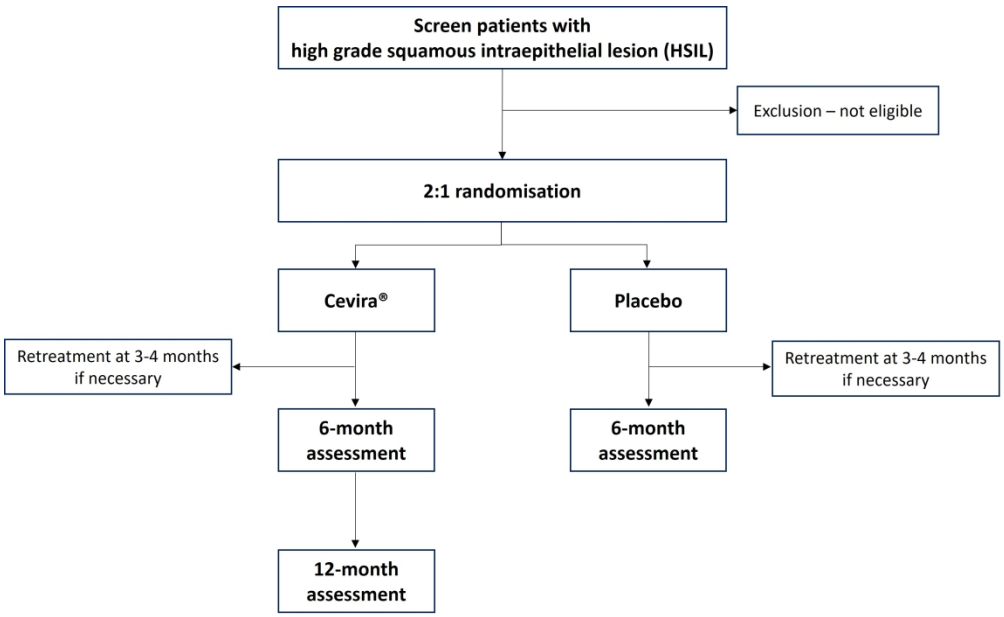


**Figure 1. Overview of the APRICITY Phase 3 study design.**

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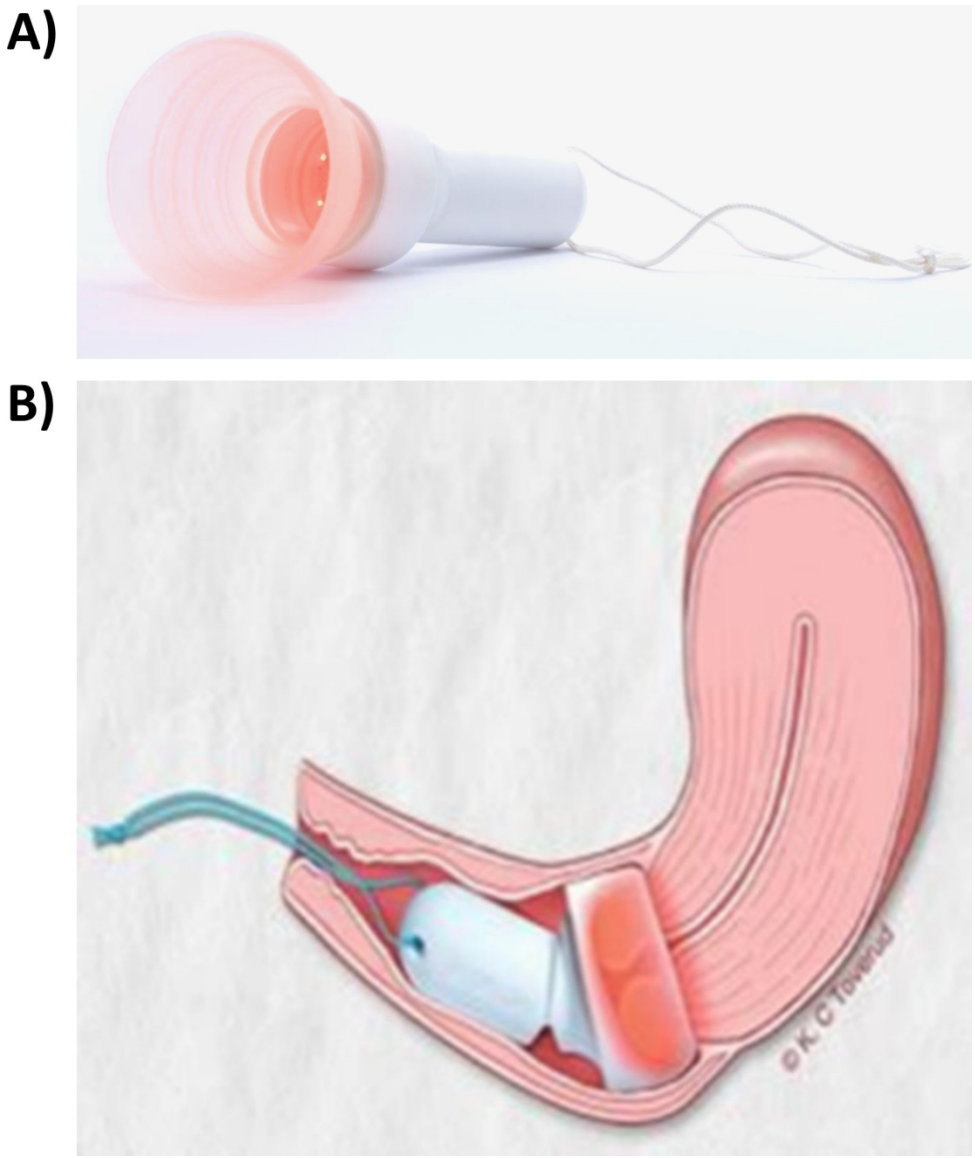


**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

149x175mm (330 x 330 DPI)

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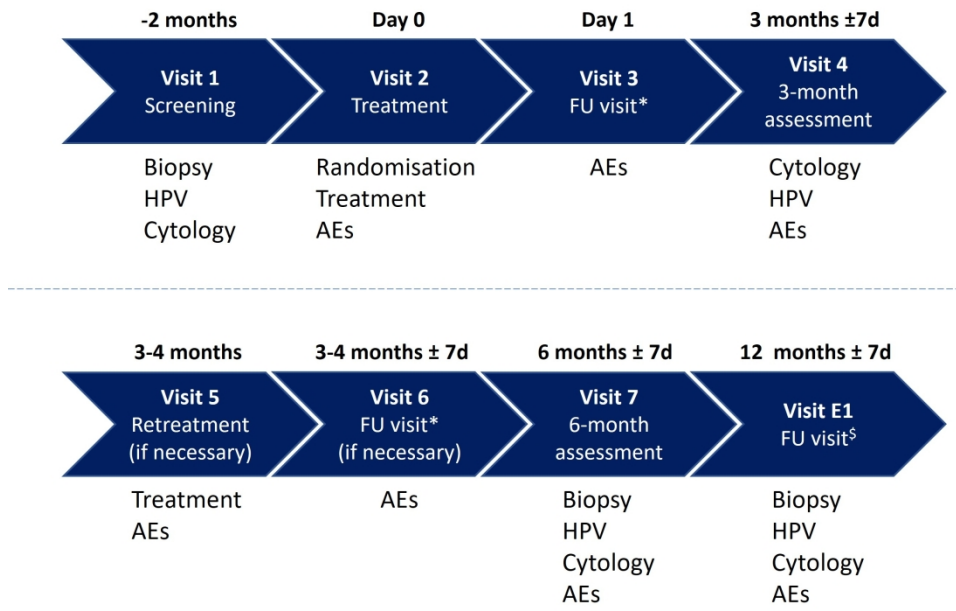


**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

215x134mm (330 x 330 DPI)

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

Commented [MR1]: Page 1
Commented [MR2]: Page 2 and Page 6
Commented [MR3]: Page 13
Commented [MR4]: Page 16
Commented [MR5]: Page 4, 5
Commented [MR6]: Page 5
Commented [MR7]: Page 6, Figure 1



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**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | **Commented [MR8]:** Page 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | **Commented [MR9]:** Page 6,7 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | **Commented [MR10]:** Page 7,8 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | **Commented [MR11]:** Page 8,9 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | **Commented [MR12]:** Page 9, Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | **Commented [MR13]:** Page 10 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | **Commented [MR14]:** Page 10 |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | **Commented [MR15]:** Page 11 |



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| | | | |
|---|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | Commented [MR16]: Page 11 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Commented [MR17]: Page 11 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Commented [MR18]: Page 11 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Commented [MR19]: Page 9,10,12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Commented [MR20]: Page 9,10,12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Commented [MR21]: Page 10,11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Commented [MR22]: Page 9,12 |



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| | | | |
|---|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Commented [MR23]: Page 12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Commented [MR24]: Page 12 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Commented [MR25]: Page 13 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Commented [MR26]: Page 13 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Commented [MR27]: Page 13 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Commented [MR28]: Page 13 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Commented [MR29]: Page 12, 13 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Commented [MR30]: Page 2,13 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |



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**Appendices**

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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## ABSTRACT

**Introduction:** High-risk human papilloma virus (HPV)-associated cervical cancer is the fourth most common cancer in women worldwide. Current treatments of high grade squamous intraepithelial lesion (HSIL) of the cervix are based on invasive surgical interventions, compromising cervical competence and functionality. APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 study further evaluating the efficacy and safety of Cevira®, an integrated drug- and light-delivery device for hexaminolevulinate photodynamic therapy, which shows promise as a novel, non-invasive outpatient therapy for women with HSIL.

**Methods and analysis:** Patients with biopsy-confirmed HSIL histology are invited to participate in the study planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union. The aim is to include at least 384 patients which will be randomised to either Cevira® or placebo group (2:1). All patients will be assessed 3 months after first treatment and a second treatment will be administered in patients who are HPV positive or have at least low grade squamous intraepithelial lesion (LSIL). Primary endpoint is the proportion of the responders 6 months after first treatment. Secondary efficacy and safety endpoints will be assessed at 6 months, and data for secondary performance endpoints of the Cevira® device will be collected at 3 months and 6 months, in case second treatment was administered. All patients in the Cevira® group will be enrolled in an open, long-term extension study for 6 months to collect additional efficacy and safety data (study extension endpoints).

**Ethics and dissemination:** The study was approved by the ethics committee of the Peking Union Medical College Hospital and Hannover Medical University, Germany. Findings will be disseminated through peer review publications and conference presentations.

**Trial registration number:** clinicaltrials.gov NCT04484415


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## Strengths and limitations of this study

- APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 trial, evaluating hexaminolevulinate photodynamic therapy (Cevira®) in HSIL patients
- The study has an international set-up, planning to include 47 sites in China and 25 sites in Ukraine, Russia and the European Union
- The most important limitation is the potential for spontaneous regression of CIN2 lesions in the placebo group, which could underestimate the trial results

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## INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, almost exclusively linked to infection with high-risk human papillomaviruses (hrHPV) (1). In 2020, 604,000 new cases and 342,000 deaths worldwide were attributed to cervical cancer. Of these new cases and deaths, about 90% are occurring in low- and middle-income countries due to the lack organised screening (1, 2). In China, the most prevalent HPV subtypes are HPV16, 52 and 58, while in Europe HPV16, 31 and 33 are more common (3). Notably, all mentioned HPV subtypes belong to the same alpha genotype (4). There are at least 14 high-risk HPV subtypes identified, with HPV16 and HPV18 causing 70% of cervical cancers and pre-cancerous lesions (3, 5).

HPV is transmitted during sexual intercourse with the highest prevalence among sexually active young women. In the vast majority (~90%) infection is spontaneously cleared and induced low grade squamous epithelial lesion (LSIL) or cervical intraepithelial neoplasia (CIN) 1 has low potential to develop into cervical malignancy. Nevertheless, a subset of patients is at risk to develop persistent HPV infection increasing the risk for progression to high grade squamous intraepithelial lesion (HSIL) and eventually cancer (6, 7). Based on histopathological characteristics and the severity of dysplasia, HSIL can be subdivided into CIN 2 and 3, corresponding to moderate and severe dysplasia, respectively (8, 9). Unlike LSIL which usually resolves spontaneously, the guidelines for cervical cancer screening generally recommend medical treatment for women with HSIL (10). Although in women of childbearing age, CIN2 lesions often regress spontaneously, not requiring immediate intervention (11, 12).

Current treatment options for patients with HSIL include excisional and ablative treatment (13). However, these surgical treatments may lead to perinatal complications, including preterm labour, low birth weight and perinatal death, limiting their use in women of reproductive age (14). Surgical treatments lead to a success rate of 85-95% in complete excision of the lesion (15). Recurrences occur as precancerous conditions such as CIN2 or CIN3, however, there is an elevated risk for invasive cervical cancer as well (16, 17). To preserve cervical tissue functionality, repeated surgical interventions are not recommended but no good tissue alternatives are available for the treatment of high-grade CIN.



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Non-invasive therapies have been developed for the treatment of HSIL and include topical agents (immune-modulators, anti-proliferative medications, antivirals, herbal regimens and probiotics), therapeutic vaccines and biologicals (18-20). However, due to the lack of sufficient clinical evidence, none of them have been accepted by the American Society for Colposcopy and Cervical Pathology (ASCCP) and European Federation for Colposcopy (EFC) for the management of cervical cancer and precancerous lesions and surgical methods remain the standard of care (13, 21).

Due to the side-effects associated with surgical treatments and the lack of evidence for most of the current non-invasive therapies, there has been a growing interest in non-invasive photodynamic therapy (PDT) using topically applied photosensitizers for the treatment of CIN (22-27). PDT is based on the accumulation of a photosensitizer or its precursor in the target cells, which upon illumination generates reactive oxygen species (ROS) that eradicate the diseased cells by inducing apoptosis and necrosis while preserving the underlying stroma and thereby the functionality of the cervix (28). For the treatment of CIN, topical hexaminolevulinate hydrochloride (HAL) has been mostly studied as photosensitizer showing promising efficacy and favourable safety results (25, 26). These initial results were confirmed in a Phase 2b study administrating HAL as an ointment via an intravaginal photoactivation device (Cevira®, Photocure ASA, Oslo, Norway) (27).

The objective of APRICITY Phase 3 multicentre, prospective, randomised controlled trial (RCT) is to further evaluate the efficacy and safety of Cevira® compared to placebo in the treatment of patients with cervical histological HSIL (i.e. CIN2/3).



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## METHODS AND ANALYSIS

### Study design

The Phase 3 study is designed as a multicentre, prospective, double-blind RCT enrolling patients with an adequate colposcopy and histology diagnosis of HSIL (clinicaltrials.gov Identifier: NCT04484415) (Figure 1). Randomisation to either Cevira® or placebo (2:1) is stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ or HPV18+Other+). Primary efficacy will be evaluated 6 months after first treatment for both groups. A second treatment will be administered in patients from both treatment groups who at the 3-month assessment have cytology of LSIL or more severe lesion (HSIL or atypical squamous cells-cannot exclude HSIL [ASC-H]) or in patients who are HPV positive. Retreatment visit should be no later than 1 month after the 3-month assessment visit.

All patients in the Cevira® group will be enrolled in an open, long-term extension study following patients for an additional 6 months. To minimise the risk to the patients in the placebo group, they will be unblinded after 6 months to complete the study. Patients with persistent high-grade CIN after 6 months will receive surgical treatment regardless of study group.

The study is planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union (EU, including Hungary, Romania, Germany, Czech Republic, Slovakia, Poland and Netherlands).

### Study population

In the Phase 2b study, the efficacy of HAL PDT could only be demonstrated in CIN2 patients, probably due to the high spontaneous regression rate in the CIN1 population (27). Based on this outcome, it was decided to only enrol patients with HSIL (CIN2/3) in the present Phase 3 study.



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**Eligibility criteria**

*Inclusion criteria*

To be included, patients must have biopsy-confirmed HSIL histology determined by a panel of three pathologists from a central laboratory in each region (China, US and Europe), not more than 2 months prior to the administration of Cevira® or placebo. Colposcopy should visualise the entire lesion margin and entire cervical transformation zone, including the squamocolumnar junction, to demonstrate that the lesion covers more than 15% of the uterine cervix before biopsy. Additionally, the uterine cervix should have an average diameter of approximately 27 mm to allow application of Cevira®. Only female patients aged 18 years and older (maximum age 85 years) will be included. Patients must use a highly effective method of contraception during the entire study and 30 days after study end. Sterilised women or women who are post-menopausal for at least 1 year can be included without use of contraception.

*Exclusion criteria*

Key exclusion criteria are a total lesion area covering over 50% of the cervix (only for biopsy-confirmed CIN3), invasive cervical cancer, adenocarcinoma in situ or other glandular intraepithelial lesions and lesions extending to the cervical canal or vaginal vault. Of note, in certain countries (e.g. Hungary), the ethical review board allowed only the inclusion of HSIL/CIN2 patients and excluded patients diagnosed with CIN3. Additional exclusion criteria are significant vaginal infection or bleeding, current severe pelvic inflammatory disease, history of toxic shock syndrome, known allergies to hexaminolevulinate and/or silicone, use of heart pacemaker and porphyria. Furthermore, patients must not be pregnant or breastfeeding.

Prior and during the entire study follow-up, patients are not allowed to use drugs or treatments that may affect efficacy evaluation, i.e., drugs treating HPV, HSIL and tumours as well as regulating immunologic function. In addition, patients who previously received surgical treatment, have incomplete cervical structure and have recurrent HSIL or patients who received other treatment after the confirmed diagnosis of HSIL are excluded from the study. Furthermore, patients may not participate in other therapeutic clinical trials using investigational agents either concurrently or within the last 30 days. Lastly, patients are



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excluded if they are not deemed suitable in the investigator's opinion or if the patient has a conflict of interest that would interfere with the study conduct.

**Interventions**

Cevira® is an integrated combination of 5% HAL in ointment and the drug delivery device Cevira® CL7 (Figure 2A). The drug is administered intravaginally to the cervix by a gynaecologist using the drug delivery device (Figure 2B). The device is a single-use, disposable, LED-based integrated red light source used to photoactivate the drug. The device will automatically switch on the light 5 hours after administration and provide continuous photoactivation of 125 J/cm$^2$ over 4.6 hours before automatically shutting down. The device needs to be removed by the patient once the treatment has been completed between 11 to 24 hours after administration. The placebo ointment contains only vehicle and is similar in appearance and consistence to the Cevira® ointment. The placebo device is identical in appearance as the Cevira® CL7 device without providing light. The investigators and staff at each site are trained on at least five occasions in the study procedures before study start through standard intervention procedure videos upon which each investigator should perform the intervention before opening the study site.

Treatment in both Cevira® or placebo group must be discontinued if any of the following occurs: consent withdrawal, substantial non-compliance, lost to follow-up, occurrence of a serious adverse event (SAE) possibly related to study treatment, investigator's concern for the patient's health, pregnancy or intention to become pregnant or the investigator's decision to use other appropriate treatments due to disease progression. The patient may request withdrawal due to an adverse event (AE) for which the investigator did not consider removal from the study necessary.

**Outcomes**

The primary endpoint is the proportion of the responders at 6 months after the first treatment, with response being defined as normal histopathology or LSIL histopathology with



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clearance of baseline HPV. The list of secondary efficacy endpoints, study extension endpoints and safety endpoints can be found in Table 1.

**Table 1: Secondary efficacy, study extension and safety endpoints of the APRICITY Phase 3 study**

| |
|---|
| **Secondary efficacy endpoints** |
| a) The proportion of HPV(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>b) The proportion of HPV16(+) patients with clearance of HPV16 at 6 months after the first treatment<br>c) The proportion of HPV16 and/or HPV18(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>d) The proportion of patients with histologic regression, defined as LSIL or normal histology, at 6 months after the first treatment |
| **Secondary performance/usability endpoints** |
| a) The proportion of gynaecologists successfully inserting the device within 15 minutes<br>b) The proportion of patients with device dislocation or slippage during treatment<br>c) The proportion of patients removing the device outside the specified time |
| **Study extension endpoints** |
| a) The proportion of patients who had LSIL histology and non-clearance of baseline HPV at 6 months, who became responders at 12 months after the first treatment<br>b) The proportion of responders at 6 months who have continued regression at 12 months after the first treatment |
| **Safety endpoints** |
| a) The proportion of patients with AEs up to 6 months after the first treatment<br>b) The proportion of patients with Cevira® 5% HAL ointment-related AEs up to 6 months after the first treatment<br>c) The proportion of patients with Cevira® CL7 device-related AEs up to 6 months after the first treatment<br>d) The proportion of device deficiencies<br>e) The proportion of patients in the treatment group with AEs up to 12 months after the first treatment |

AE, adverse event; HAL, hexaminolevulinate hydrochloride; HPV, human papilloma virus; LSIL, low grade squamous intraepithelial lesion.

**Assessments**

Study flow and follow-up of assessments are shown in Figure 3. The primary and secondary efficacy assessments will be done 6 months after first treatment and will be based on histology and clinically validated testing for HPV (Cobas, Roche). To standardise the procedure, investigators will all receive a colposcopy operation manual. Colposcopy-directed biopsies will be obtained from all colposcopically-suspicious areas. If there is a normal colposcopy at 6



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months or at assessment of study extension endpoints at 12 months, biopsies will be obtained from the original baseline affected area(s) to confirm histologic regression. Two pathologists will independently review the slide(s) from each biopsy in a blinded manner. If there is a discrepancy between the biopsy diagnosis, a third pathologist will review the slide(s). Clinically validated testing of cytology (ThinPrep, Hologic) and HPV (Cobas, Roche) will be used to determine the need for a second treatment.

The secondary performance assessment will be based on the number of gynaecologists successfully inserting the device within 15 minutes, the number of patients with device dislocation or slippage during treatment and the number of patients removing the device outside the specified time. Data will be collected using a patient diary and assessed at 3 months and at 6 months, in case a second treatment was applied. Safety endpoints assessment will be done at 6 months after first treatment. No interim analysis is planned for this study.

Within 24 hours of Cevira® administration, the patients will be contacted telephonically by study personnel, to ensure correct handling of the device and for a safety check. A mandatory patient diary will be used to record the time of device removal and possible AE during use and/or after removal of the Cevira® device. To ensure treatment compliance, regular reminders will be provided to the patients to complete the follow-up visits as scheduled.

## Statistical consideration

*Sample size*

The sample size calculation is based on the efficacy results for the HSIL histology population from the Phase 2b study using a significance level of 5% (27). It is assumed that the proportion of patients who will achieve response is 60% in the Cevira® group and 40% in the placebo group. To detect this difference with 90% power, 209 patients need to be included in the Cevira® group and 105 patients in the placebo group using a 2:1 randomisation.

Patients for whom the diagnosis for study enrolment was changed from HSIL to not HSIL upon confirmation of the diagnosis by a panel of three expert gynaecological pathologists from three independent institutions, will be excluded from the primary efficacy analysis (modified intent-to-treat population, mITT). Based on the Phase 2b study results, an 8% error



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rate of pathological assessment and 10% dropout rate should be considered. Therefore, the total sample size needs to consist of at least 384 patients (256 in Cevira® group and 128 in the placebo group). The aim is to enrol 300 patients in Chinese centres and 84 patients in centres in EU, Ukraine and Russia, with no recruitment goal for the sites.

*Statistical analysis plan*

To avoid bias, the statistical analysis team will be required to remain blinded throughout the entire study period until primary database lock (primary analyses will be performed when all patients have either completed the 6 month assessments or are early terminated from the study).

The primary efficacy endpoint analysis will be performed on the mITT population and repeated on per protocol (PP) population, which is defined as the subset of patients in the mITT population who had no major protocol violations. Analysis will be done using the Cochran Mantel Haenszel (CMH) test stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ and HPV18+Other+). Estimates and exact 95% confidence intervals for the proportion of patients who achieve response will be calculated overall, for each treatment group, for each diagnosis group, for each HPV status group and for each diagnosis group by HPV status subgroup (i.e. for each of the randomisation strata).

The secondary efficacy endpoints on mITT population will be analysed the same as described for the primary endpoint. The study extension endpoints will be summarised using counts and percentages for the extension population. The summary will be presented overall, by CIN diagnosis and by HPV status. The safety analysis will be performed on the safety population. If possible, a distinction will be made between Cevira® 5% HAL ointment-related and Cevira® CL7 device-related AEs.

Two sensitivity analyses will investigate the effect of missing data on the result of the primary endpoint analysis in the mITT population: (1) analysis of all responder data as observed (i.e. no imputations) and (2) analysis after imputing all missing 6-month data as success (responders) in the placebo treatment group and as failure (non-responders) in the Cevira® treatment group. In the safety population, missing values will be treated as missing and will not be substituted.



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**Randomisation and blinding method**

The patients will be randomised through an Interactive Web Response System (IWRS) after initial screening by the investigators. The IWRS will generate a randomisation number after the investigator inputs the required information and will then assign a product for the patient. The investigators, study personnel and patients are blinded to the treatment groups as Cevira® and placebo products are identical in packaging. Additionally, the light signal before insertion does not differ between Cevira® and placebo products. If during the blinded part of the study a medical emergency or SAE occurs and the patient's condition requires knowledge of the test medication, the study blind may be broken and reported for that specific patient. After the 6-month assessment, the planned unblinding procedure will be performed by the investigators to decide if patients will continue in the open-label extension study.

**Data and study monitoring**

An electronic data collection (EDC) system will be used to collect and manage the trial data in this study. Patient data should be entered continuously during the study and within 48 hours after a visit is performed**.** As nonclinical local tolerance studies and previous clinical studies showed an excellent safety profile with only mild to moderate local reactions and few related systemic side effects, no data monitoring committee (DMC) is planned for this study. Nevertheless, all events occurring during the period of observation, reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit, will be documented on the pages provided on the AE form in the electronic case report form (eCRF). Any SAEs for which a causal relationship to the treatment cannot be ruled out, will be documented on the AE form even if they occur after the period of observation. Related AEs and SAEs should be followed up until resolved, or at the latest until database lock. In case of permanent impairment, the event must be followed until the condition stabilises and the investigator considered it medically justifiable to terminate follow-up, or at the latest until database lock.

Study monitoring will be performed in accordance with International Conference on Harmonization (ICH) E6-Good Clinical Practice (GCP)/ISO 14155:2020 as applicable, the sponsor/contract research organisation (CRO) standard operating procedures (SOPs), the



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protocol, the monitoring plan and applicable local regulations. If missing or inconsistent data not catered for are detected, queries will be issued. Queries may also be generated during the data validation process and shall be resolved immediately before database lock. All study documentation at the investigator site and sponsor site will be archived in accordance with the ICH E6- GCP/ISO 14155:2020 as applicable, EU Regulation 536/2014, 21 CFR 312.62, and the sponsor's quality standards and SOPs. An auditor authorised by the sponsor may audit the investigational site and request access to all source documents, eCRF and other study documentation.

**Patient and public involvement**

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study and did not assess the burden of participating in the study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice. All other study results will be disseminated to the participants on demand.

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## ETHICS AND DISSEMINATION

The study was approved by the ethics committee of the Peking Union Medical College Hospital on 2nd of July, 2020 (Nr. KS20202255). Current version of the protocol (No. 2.2) from 31st of July 2021 was also approved on 20th of December 2021 by Hannover Medical University, Germany. It is conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki and all applicable national and international laws, regulations and standards, including archiving of essential documents. Patients agreeing to participate in the study must sign an informed consent form approved according to local regulations. The study site staff member conducting the consent process must also sign the consent form on the same occasion. All amendments to the clinical study protocol should be agreed upon between the sponsor and the investigator and be recorded with a justification for the amendment. The only exceptions are, where necessary to eliminate an immediate hazard to study patients, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). All information concerning drug/device and the sponsor's research and product development is considered confidential and will remain the sole property of the sponsor. A financial agreement will be signed between the sponsor and the investigators and/or the institution involved as required.

Final data analysis and disclosure of contractual agreements will be done by CRO Hangzhou Tigermed Consulting Co., Ltd, which will limit the access of investigators to the final trial dataset. The monitors, auditors, authorised personnel of the sponsor, health authority inspectors or their agents, and authorised members of Independent Ethics Committees/Institutional Review Boards will be given direct access to the source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes and photographs) upon request, provided that patient confidentiality is maintained in accordance with local requirements.

Findings of this study will be disseminated through peer-review publications and conference presentations. No information which could lead to the identification of patients will be included in the dissemination of results.



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## DISCUSSION

Cervical cancer is the most common HPV-related malignancy (5). Given the substantial burden of cervical cancer globally, efforts have been made to develop effective prevention measures, including HPV vaccination and screening programmes in combination with timely and efficient treatment of pre-cancerous lesions (2, 9). Unfortunately, these preventive measures are not equally implemented worldwide, with absent or inadequate screening and vaccination programmes in many low- and middle-income countries who suffer the highest HPV incidence rates. Especially in Eastern Europe and Central Asia, a rapid increase in premature cervical cancer mortality has been reported in recent generations (2). Furthermore, currently available vaccines are expensive and directed against only certain HPV subtypes (9, 29).

PDT has been clinically approved for the treatment of different cancers, including skin cancer, superficial oesophageal cancer and lung cancer (30-32). Due to the lack of adequate non-surgical treatment modalities, the potential of PDT for the treatment of CIN has been investigated in this and previous studies (22-27, 33). The main advantage of PDT for the treatment of CIN is its non-invasiveness, leaving the cervix intact and thereby preserving fertility. Moreover, targeted PDT of CIN is not restricted by HPV subtype causing pre-cancerous lesions and the PDT could be repeated in case of another infection or lesion.

For the treatment of CIN, topical administration of both 5-aminolaevulinic acid (5-ALA) and its esterified derivate HAL have been studied, with HAL being preferred due to its better stability and increased fluorescence at lower doses leading to less systemic exposure (22, 24, 30). As topical administration was perceived to be inconvenient, the integrated light- and drug-delivery device Cevira® was developed (23, 27, 33). The safety and efficacy of Cevira® have been evaluated in a double-blind, placebo-controlled dose-finding Phase 2b study including 262 patients with CIN1/2 randomised to HAL 0.2%, 1% or 5% or placebo, permitting retreatment at 3 months if clinically indicated (27). Based on the outcomes of the Phase 2b, the HAL 5% dose was selected for further evaluation in the Phase 3 study. The HAL 5% dose had a favourable safety profile while being associated with the highest regression rate and oncogenic HPV clearance. However, efficacy could only be demonstrated in patients with CIN2, probably due to a high rate of spontaneous regression in the CIN1 population with most patients being HPV negative. As a result, the present Phase 3 study will only include HSIL



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patients (CIN2/3) ensuring efficacy can be reliably assessed. Due to the local and transient exposure to HAL, side effects were usually self-limiting, mainly including discharge, discomfort and spotting.

The currently available data indicate that Cevira® is easy-to-use for gynaecologists and well-accepted by patients (33). The device results in no patient down-time as it is similar to using a tampon, patients may leave the gynaecologist office immediately after the application and can return to normal daily activities. Additionally, patients can easily remove the device themselves by pulling the string within 24 hours after application. The current Phase 3 study will further evaluate how the use of Cevira® device is perceived by gynaecologists and patients.

In conclusion, Cevira® holds potential to serve high unmet medical need for non-surgical, safe treatment options for patients with HSIL and cervical cancer. Due to its non-invasiveness, Cevira® could be a promising alternative to excisional treatment for young women in reproductive age. Following the encouraging results from the Phase 2b study, the efficacy and safety of Cevira® in patients with HSIL will be further evaluated in the presented APRICITY Phase 3 study currently recruiting patients in China and Europe for a multicentre, prospective, double-blind randomised controlled clinical trial.

**Trial status**

The APRICITY Phase 3 study is currently recruiting patients in China, Ukraine, Russia and Europe. Recruitment started in November 2020 with the aim to enrol at least 384 patients. However, study start-up had to be delayed in Ukraine and Russia. In addition, the process might be interrupted or extended due to the Covid-19 pandemic.

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## Acknowledgments

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## Author contributions

FC, LS, YZ, ZY, JH and PH contributed to the experimental design of the study. CD, ZN and CM were involved in study design, outcome definition and ethical approval application. JL is the global PI of the study. PH is the European PI of the study. FC is the Chinese PI of the study. All PIs have contributed to the study protocol amendments. All authors have read, edited and approved the manuscript.

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## Conflict of interest

CD received consulting fees from MSD, GSK, Tesaro and Clovis Oncology and honoraria from MSD and GSK. LH is an employee of Asieris Pharmaceuticals (Shanghai) Co., Ltd. FC, ZN, CM, LS, YZ, ZY, JL and PH have nothing to declare.

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## FIGURE LEGENDS

**Figure 1. Overview of the APRICITY Phase 3 study design.**

**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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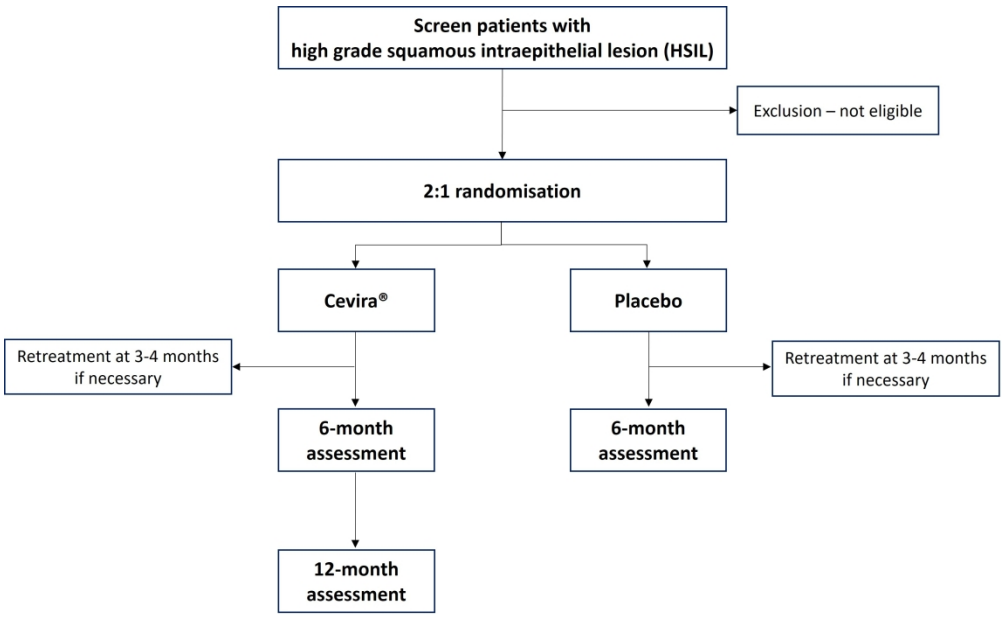


**Figure 1. Overview of the APRICITY Phase 3 study design.**

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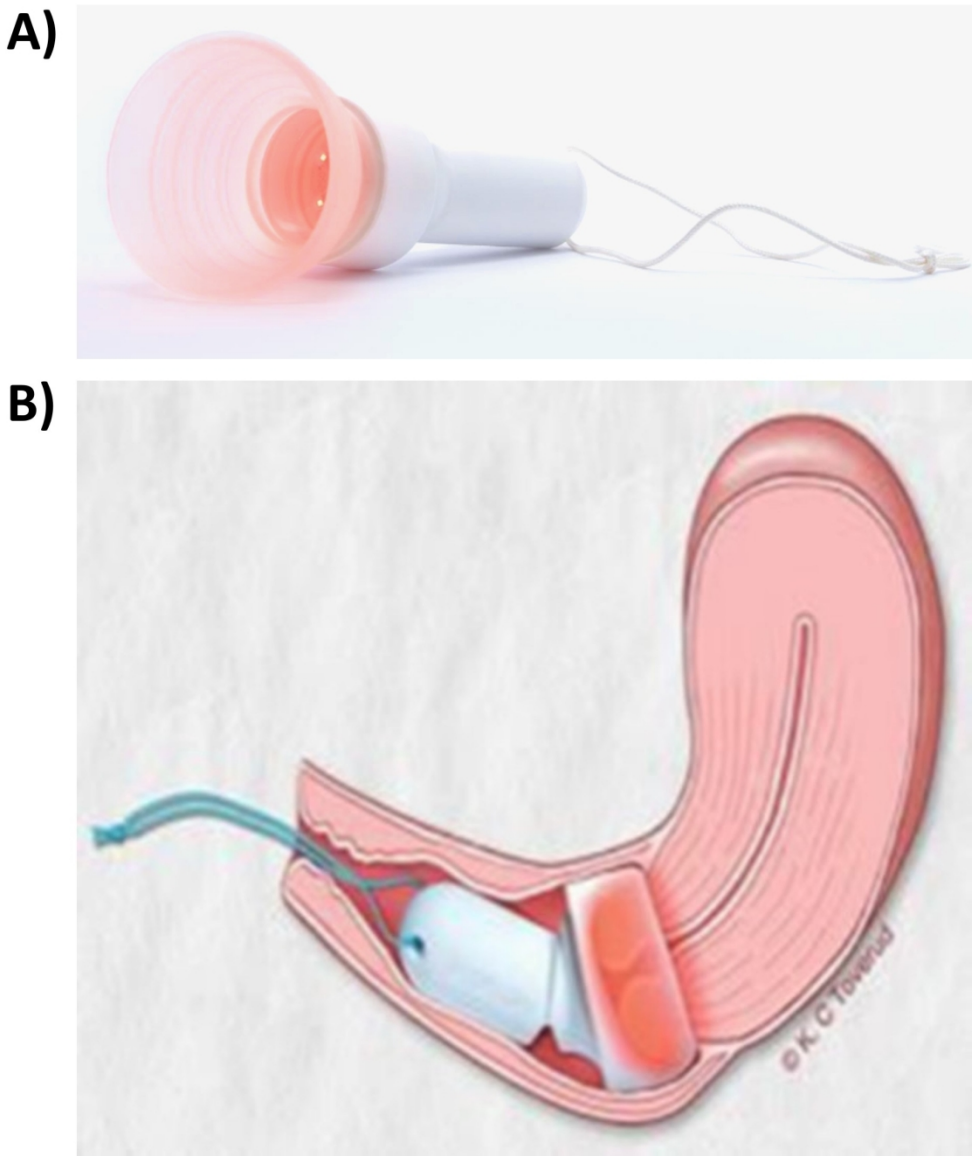


**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

149x175mm (330 x 330 DPI)

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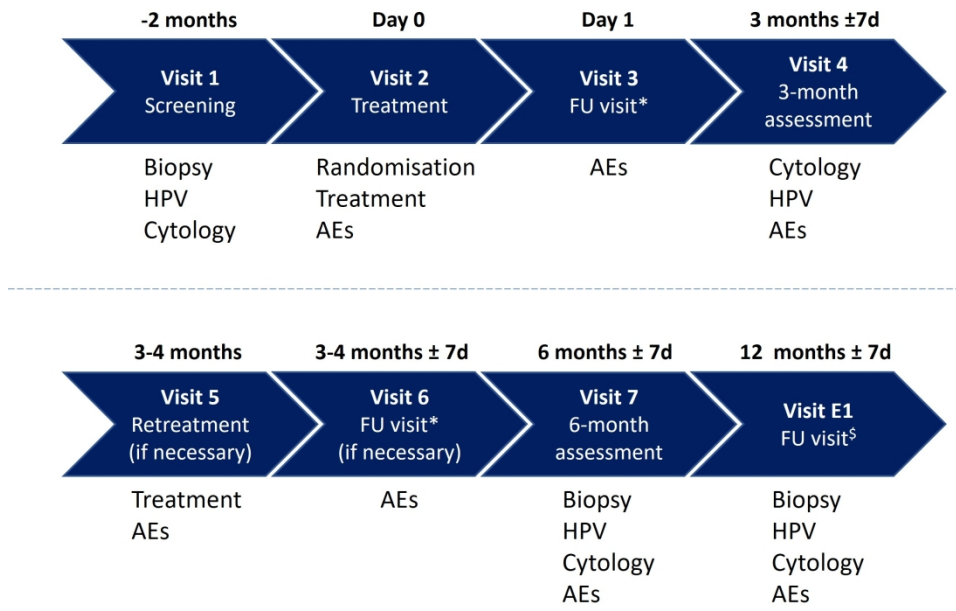


**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry |
| | 2b | All items from the World Health Organization Trial Registration Data Set |
| Protocol version | 3 | Date and version identifier |
| Funding | 4 | Sources and types of financial, material, and other support |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors |
| | 5b | Name and contact information for the trial sponsor |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
| | 6b | Explanation for choice of comparators |
| Objectives | 7 | Specific objectives or hypotheses |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |

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Commented [MR2]: Page 2, Page 6
Commented [MR3]: Page 14
Commented [MR4]: Page 17
Commented [MR5]: Page 4, Page 5
Commented [MR6]: Page 5
Commented [MR7]: Page 6, Figure 1



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**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | Commented [MR8]: Page 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Commented [MR9]: Page 7, Page 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | Commented [MR10]: Page 8 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | Commented [MR11]: Page 8, Page 9, Table 1 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Commented [MR12]: Page 9, Page 10, Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | Commented [MR13]: Page 10, Page 11 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | Commented [MR14]: Page 10 |

**Methods: Assignment of interventions (for controlled trials)**

Allocation:

| | | | |
|---|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | Commented [MR15]: Page 12 |



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| | | | |
|---|---|---|---|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | Commented [MR16]: Page 12 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | Commented [MR17]: Page 12 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | Commented [MR18]: Page 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | Commented [MR19]: Page 12, Page 13, Page 14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | Commented [MR20]: Page 12, Page 13, Page 14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | Commented [MR21]: Page 11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Commented [MR22]: Page 12, Page 13, Page 14 |



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|---|---|---|---|
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | Commented [MR23]: Page 12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Commented [MR24]: Page 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | Commented [MR25]: Page 14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Commented [MR26]: Page 14 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Commented [MR27]: Page 14 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | Commented [MR28]: Page 14 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Commented [MR29]: Page 13, Page 14 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | Commented [MR30]: Page 2, Page 14 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |



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**Appendices**

| | | |
|---|---|---|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

Commented [MR31]: Submitted separately

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.



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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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# A multicentre, prospective, randomised controlled trial to evaluate hexaminolevulinate photodynamic therapy (Cevira®) as a novel treatment in patients with high grade squamous intraepithelial lesion: APRICITY Phase 3 study protocol

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## ABSTRACT

**Introduction:** High-risk human papilloma virus (HPV)-associated cervical cancer is the fourth most common cancer in women worldwide. Current treatments of high grade squamous intraepithelial lesion (HSIL) of the cervix are based on invasive surgical interventions, compromising cervical competence and functionality. APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 study further evaluating the efficacy and safety of Cevira®, an integrated drug- and light-delivery device for hexaminolevulinate photodynamic therapy, which shows promise as a novel, non-invasive outpatient therapy for women with HSIL.

**Methods and analysis:** Patients with biopsy-confirmed HSIL histology are invited to participate in the study planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union. The aim is to include at least 384 patients which will be randomised to either Cevira® or placebo group (2:1). All patients will be assessed 3 months after first treatment and a second treatment will be administered in patients who are HPV positive or have at least low grade squamous intraepithelial lesion (LSIL). Primary endpoint is the proportion of the responders 6 months after first treatment. Secondary efficacy and safety endpoints will be assessed at 6 months, and data for secondary performance endpoints of the Cevira® device will be collected at 3 months and 6 months, in case second treatment was administered. All patients in the Cevira® group will be enrolled in an open, long-term extension study for 6 months to collect additional efficacy and safety data (study extension endpoints).

**Ethics and dissemination:** The study was approved by the ethics committee of the Peking Union Medical College Hospital and Hannover Medical University, Germany. Findings will be disseminated through peer review publications and conference presentations.

**Trial registration number:** clinicaltrials.gov NCT04484415


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## Strengths and limitations of this study

- APRICITY is a multicentre, prospective, double-blind, randomised controlled Phase 3 trial, evaluating hexaminolevulinate photodynamic therapy (Cevira®) in HSIL patients
- The study has an international set-up, planning to include 47 sites in China and 25 sites in Ukraine, Russia and the European Union
- The most important limitation is the potential for spontaneous regression of CIN2 lesions in the placebo group, which could underestimate the trial results

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## INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, almost exclusively linked to infection with high-risk human papillomaviruses (hrHPV) (1). In 2020, 604,000 new cases and 342,000 deaths worldwide were attributed to cervical cancer. Of these new cases and deaths, about 90% are occurring in low- and middle-income countries due to the lack organised screening (1, 2). In China, the most prevalent HPV subtypes are HPV16, 52 and 58, while in Europe HPV16, 31 and 33 are more common (3). Notably, all mentioned HPV subtypes belong to the same alpha genotype (4). There are at least 14 high-risk HPV subtypes identified, with HPV16 and HPV18 causing 70% of cervical cancers and pre-cancerous lesions (3, 5).

HPV is transmitted during sexual intercourse with the highest prevalence among sexually active young women. In the vast majority (~90%) infection is spontaneously cleared and induced low grade squamous epithelial lesion (LSIL) or cervical intraepithelial neoplasia (CIN) 1 has low potential to develop into cervical malignancy. Nevertheless, a subset of patients is at risk to develop persistent HPV infection increasing the risk for progression to high grade squamous intraepithelial lesion (HSIL) and eventually cancer (6, 7). Based on histopathological characteristics and the severity of dysplasia, HSIL can be subdivided into CIN 2 and 3, corresponding to moderate and severe dysplasia, respectively (8, 9). Unlike LSIL which usually resolves spontaneously, the guidelines for cervical cancer screening generally recommend medical treatment for women with HSIL (10). Although in women of childbearing age, CIN2 lesions often regress spontaneously, not requiring immediate intervention (11, 12).

Current treatment options for patients with HSIL include excisional and ablative treatment (13). However, these surgical treatments may lead to perinatal complications, including preterm labour, low birth weight and perinatal death, limiting their use in women of reproductive age (14). Surgical treatments lead to a success rate of 85-95% in complete excision of the lesion (15). Recurrences occur as precancerous conditions such as CIN2 or CIN3, however, there is an elevated risk for invasive cervical cancer as well (16, 17). To preserve cervical tissue functionality, repeated surgical interventions are not recommended but no good tissue alternatives are available for the treatment of high-grade CIN.



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Non-invasive therapies have been developed for the treatment of HSIL and include topical agents (immune-modulators, anti-proliferative medications, antivirals, herbal regimens and probiotics), therapeutic vaccines and biologicals (18-20). However, due to the lack of sufficient clinical evidence, none of them have been accepted by the American Society for Colposcopy and Cervical Pathology (ASCCP) and European Federation for Colposcopy (EFC) for the management of cervical cancer and precancerous lesions and surgical methods remain the standard of care (13, 21).

Due to the side-effects associated with surgical treatments and the lack of evidence for most of the current non-invasive therapies, there has been a growing interest in non-invasive photodynamic therapy (PDT) using topically applied photosensitizers for the treatment of CIN (22-27). PDT is based on the accumulation of a photosensitizer or its precursor in the target cells, which upon illumination generates reactive oxygen species (ROS) that eradicate the diseased cells by inducing apoptosis and necrosis while preserving the underlying stroma and thereby the functionality of the cervix (28). For the treatment of CIN, topical hexaminolevulinate hydrochloride (HAL) has been mostly studied as photosensitizer showing promising efficacy and favourable safety results (25, 26). These initial results were confirmed in a Phase 2b study administrating HAL as an ointment via an intravaginal photoactivation device (Cevira®, Photocure ASA, Oslo, Norway) (27).

The objective of APRICITY Phase 3 multicentre, prospective, randomised controlled trial (RCT) is to further evaluate the efficacy and safety of Cevira® compared to placebo in the treatment of patients with cervical histological HSIL (i.e. CIN2/3).

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## METHODS AND ANALYSIS

### Study design

The Phase 3 study is designed as a multicentre, prospective, double-blind RCT enrolling patients with an adequate colposcopy and histology diagnosis of HSIL (clinicaltrials.gov Identifier: NCT04484415) (Figure 1). Randomisation to either Cevira® or placebo (2:1) is stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ or HPV18+Other+). Primary efficacy will be evaluated 6 months after first treatment for both groups. A second treatment will be administered in patients from both treatment groups who at the 3-month assessment have cytology of LSIL or more severe lesion (HSIL or atypical squamous cells-cannot exclude HSIL [ASC-H]) or in patients who are HPV positive. Retreatment visit should be no later than 1 month after the 3-month assessment visit.

All patients in the Cevira® group will be enrolled in an open, long-term extension study following patients for an additional 6 months. To minimise the risk to the patients in the placebo group, they will be unblinded after 6 months to complete the study. Patients with persistent high-grade CIN after 6 months will receive surgical treatment regardless of study group.

The study is planned to be conducted at 47 sites in China and 25 sites in Ukraine, Russia and the European Union (EU, including Hungary, Romania, Germany, Czech Republic, Slovakia, Poland and Netherlands).

### Study population

In the Phase 2b study, the efficacy of HAL PDT could only be demonstrated in CIN2 patients, probably due to the high spontaneous regression rate in the CIN1 population (27). Based on this outcome, it was decided to only enrol patients with HSIL (CIN2/3) in the present Phase 3 study.



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**Eligibility criteria**

*Inclusion criteria*

To be included, patients must have biopsy-confirmed HSIL histology determined by a panel of three pathologists from a central laboratory in each region (China, US and Europe), not more than 2 months prior to the administration of Cevira® or placebo. Colposcopy should visualise the entire lesion margin and entire cervical transformation zone, including the squamocolumnar junction, to demonstrate that the lesion covers more than 15% of the uterine cervix before biopsy. Additionally, the uterine cervix should have an average diameter of approximately 27 mm to allow application of Cevira®. Only female patients aged 18 years and older (maximum age 85 years) will be included. Patients must use a highly effective method of contraception during the entire study and 30 days after study end. Sterilised women or women who are post-menopausal for at least 1 year can be included without use of contraception.

*Exclusion criteria*

Key exclusion criteria are a total lesion area covering over 50% of the cervix (only for biopsy-confirmed CIN3), invasive cervical cancer, adenocarcinoma in situ or other glandular intraepithelial lesions and lesions extending to the cervical canal or vaginal vault. Of note, in certain countries (e.g. Hungary), the ethical review board allowed only the inclusion of HSIL/CIN2 patients and excluded patients diagnosed with CIN3. Additional exclusion criteria are significant vaginal infection or bleeding, current severe pelvic inflammatory disease, history of toxic shock syndrome, known allergies to hexaminolevulinate and/or silicone, use of heart pacemaker and porphyria. Furthermore, patients must not be pregnant or breastfeeding.

Prior and during the entire study follow-up, patients are not allowed to use drugs or treatments that may affect efficacy evaluation, i.e., drugs treating HPV, HSIL and tumours as well as regulating immunologic function. In addition, patients who previously received surgical treatment, have incomplete cervical structure and have recurrent HSIL or patients who received other treatment after the confirmed diagnosis of HSIL are excluded from the study. Furthermore, patients may not participate in other therapeutic clinical trials using investigational agents either concurrently or within the last 30 days. Lastly, patients are



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excluded if they are not deemed suitable in the investigator's opinion or if the patient has a conflict of interest that would interfere with the study conduct.

**Interventions**

Cevira® is an integrated combination of 5% HAL in ointment and the drug delivery device Cevira® CL7 (Figure 2A). The drug is administered intravaginally to the cervix by a gynaecologist using the drug delivery device (Figure 2B). The device is a single-use, disposable, LED-based integrated red light source used to photoactivate the drug. The device will automatically switch on the light 5 hours after administration and provide continuous photoactivation of 125 J/cm$^2$ over 4.6 hours before automatically shutting down. The device needs to be removed by the patient once the treatment has been completed between 11 to 24 hours after administration. The placebo ointment contains only vehicle and is similar in appearance and consistence to the Cevira® ointment. The placebo device is identical in appearance as the Cevira® CL7 device without providing light. The investigators and staff at each site are trained on at least five occasions in the study procedures before study start through standard intervention procedure videos upon which each investigator should perform the intervention before opening the study site.

Treatment in both Cevira® or placebo group must be discontinued if any of the following occurs: consent withdrawal, substantial non-compliance, lost to follow-up, occurrence of a serious adverse event (SAE) possibly related to study treatment, investigator's concern for the patient's health, pregnancy or intention to become pregnant or the investigator's decision to use other appropriate treatments due to disease progression. The patient may request withdrawal due to an adverse event (AE) for which the investigator did not consider removal from the study necessary.

**Outcomes**

The primary endpoint is the proportion of the responders at 6 months after the first treatment, with response being defined as normal histopathology or LSIL histopathology with



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clearance of baseline HPV. The list of secondary efficacy endpoints, study extension endpoints and safety endpoints can be found in Table 1.

**Table 1: Secondary efficacy, study extension and safety endpoints of the APRICITY Phase 3 study**

| |
|---|
| **Secondary efficacy endpoints** |
| a) The proportion of HPV(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>b) The proportion of HPV16(+) patients with clearance of HPV16 at 6 months after the first treatment<br>c) The proportion of HPV16 and/or HPV18(+) patients with clearance of baseline HPV at 6 months after the first treatment<br>d) The proportion of patients with histologic regression, defined as LSIL or normal histology, at 6 months after the first treatment |
| **Secondary performance/usability endpoints** |
| a) The proportion of gynaecologists successfully inserting the device within 15 minutes<br>b) The proportion of patients with device dislocation or slippage during treatment<br>c) The proportion of patients removing the device outside the specified time |
| **Study extension endpoints** |
| a) The proportion of patients who had LSIL histology and non-clearance of baseline HPV at 6 months, who became responders at 12 months after the first treatment<br>b) The proportion of responders at 6 months who have continued regression at 12 months after the first treatment |
| **Safety endpoints** |
| a) The proportion of patients with AEs up to 6 months after the first treatment<br>b) The proportion of patients with Cevira® 5% HAL ointment-related AEs up to 6 months after the first treatment<br>c) The proportion of patients with Cevira® CL7 device-related AEs up to 6 months after the first treatment<br>d) The proportion of device deficiencies<br>e) The proportion of patients in the treatment group with AEs up to 12 months after the first treatment |

AE, adverse event; HAL, hexaminolevulinate hydrochloride; HPV, human papilloma virus; LSIL, low grade squamous intraepithelial lesion.

**Assessments**

Study flow and follow-up of assessments are shown in Figure 3. The primary and secondary efficacy assessments will be done 6 months after first treatment and will be based on histology and clinically validated testing for HPV (Cobas, Roche). To standardise the procedure, investigators will all receive a colposcopy operation manual. Colposcopy-directed biopsies will be obtained from all colposcopically-suspicious areas. If there is a normal colposcopy at 6



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months or at assessment of study extension endpoints at 12 months, biopsies will be obtained from the original baseline affected area(s) to confirm histologic regression. Two pathologists will independently review the slide(s) from each biopsy in a blinded manner. If there is a discrepancy between the biopsy diagnosis, a third pathologist will review the slide(s). Clinically validated testing of cytology (ThinPrep, Hologic) and HPV (Cobas, Roche) will be used to determine the need for a second treatment.

The secondary performance assessment will be based on the number of gynaecologists successfully inserting the device within 15 minutes, the number of patients with device dislocation or slippage during treatment and the number of patients removing the device outside the specified time. Data will be collected using a patient diary and assessed at 3 months and at 6 months, in case a second treatment was applied. Safety endpoints assessment will be done at 6 months after first treatment. No interim analysis is planned for this study.

Within 24 hours of Cevira® administration, the patients will be contacted telephonically by study personnel, to ensure correct handling of the device and for a safety check. A mandatory patient diary will be used to record the time of device removal and possible AE during use and/or after removal of the Cevira® device. To ensure treatment compliance, regular reminders will be provided to the patients to complete the follow-up visits as scheduled.

## Statistical consideration

*Sample size*

The sample size calculation is based on the efficacy results for the HSIL histology population from the Phase 2b study using a significance level of 5% (27). It is assumed that the proportion of patients who will achieve response is 60% in the Cevira® group and 40% in the placebo group. To detect this difference with 90% power, 209 patients need to be included in the Cevira® group and 105 patients in the placebo group using a 2:1 randomisation.

Patients for whom the diagnosis for study enrolment was changed from HSIL to not HSIL upon confirmation of the diagnosis by a panel of three expert gynaecological pathologists from three independent institutions, will be excluded from the primary efficacy analysis (modified intent-to-treat population, mITT). Based on the Phase 2b study results, an 8% error



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rate of pathological assessment and 10% dropout rate should be considered. Therefore, the total sample size needs to consist of at least 384 patients (256 in Cevira® group and 128 in the placebo group). The aim is to enrol 300 patients in Chinese centres and 84 patients in centres in EU, Ukraine and Russia, with no recruitment goal for the sites.

*Statistical analysis plan*

To avoid bias, the statistical analysis team will be required to remain blinded throughout the entire study period until primary database lock (primary analyses will be performed when all patients have either completed the 6 month assessments or are early terminated from the study).

The primary efficacy endpoint analysis will be performed on the mITT population and repeated on per protocol (PP) population, which is defined as the subset of patients in the mITT population who had no major protocol violations. Analysis will be done using the Cochran Mantel Haenszel (CMH) test stratified by CIN diagnosis (CIN2 or CIN3) and HPV status (HPV-, HPV16+ and HPV18+Other+). Estimates and exact 95% confidence intervals for the proportion of patients who achieve response will be calculated overall, for each treatment group, for each diagnosis group, for each HPV status group and for each diagnosis group by HPV status subgroup (i.e. for each of the randomisation strata).

The secondary efficacy endpoints on mITT population will be analysed the same as described for the primary endpoint. The study extension endpoints will be summarised using counts and percentages for the extension population. The summary will be presented overall, by CIN diagnosis and by HPV status. The safety analysis will be performed on the safety population. If possible, a distinction will be made between Cevira® 5% HAL ointment-related and Cevira® CL7 device-related AEs.

Two sensitivity analyses will investigate the effect of missing data on the result of the primary endpoint analysis in the mITT population: (1) analysis of all responder data as observed (i.e. no imputations) and (2) analysis after imputing all missing 6-month data as success (responders) in the placebo treatment group and as failure (non-responders) in the Cevira® treatment group. In the safety population, missing values will be treated as missing and will not be substituted.



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**Randomisation and blinding method**

The patients will be randomised through an Interactive Web Response System (IWRS) after initial screening by the investigators. The IWRS will generate a randomisation number after the investigator inputs the required information and will then assign a product for the patient. The investigators, study personnel and patients are blinded to the treatment groups as Cevira® and placebo products are identical in packaging. Additionally, the light signal before insertion does not differ between Cevira® and placebo products. If during the blinded part of the study a medical emergency or SAE occurs and the patient's condition requires knowledge of the test medication, the study blind may be broken and reported for that specific patient. After the 6-month assessment, the planned unblinding procedure will be performed by the investigators to decide if patients will continue in the open-label extension study.

**Data and study monitoring**

An electronic data collection (EDC) system will be used to collect and manage the trial data in this study. Patient data should be entered continuously during the study and within 48 hours after a visit is performed**.** As nonclinical local tolerance studies and previous clinical studies showed an excellent safety profile with only mild to moderate local reactions and few related systemic side effects, no data monitoring committee (DMC) is planned for this study. Nevertheless, all events occurring during the period of observation, reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit, will be documented on the pages provided on the AE form in the electronic case report form (eCRF). Any SAEs for which a causal relationship to the treatment cannot be ruled out, will be documented on the AE form even if they occur after the period of observation. Related AEs and SAEs should be followed up until resolved, or at the latest until database lock. In case of permanent impairment, the event must be followed until the condition stabilises and the investigator considered it medically justifiable to terminate follow-up, or at the latest until database lock.

Study monitoring will be performed in accordance with International Conference on Harmonization (ICH) E6-Good Clinical Practice (GCP)/ISO 14155:2020 as applicable, the sponsor/contract research organisation (CRO) standard operating procedures (SOPs), the



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protocol, the monitoring plan and applicable local regulations. If missing or inconsistent data not catered for are detected, queries will be issued. Queries may also be generated during the data validation process and shall be resolved immediately before database lock. All study documentation at the investigator site and sponsor site will be archived in accordance with the ICH E6- GCP/ISO 14155:2020 as applicable, EU Regulation 536/2014, 21 CFR 312.62, and the sponsor's quality standards and SOPs. An auditor authorised by the sponsor may audit the investigational site and request access to all source documents, eCRF and other study documentation.

**Patient and public involvement**

Patients and general public were not involved in the design, conduct, reporting or dissemination plans of the presented study and did not assess the burden of participating in the study. Patients will receive HPV and colposcopy test results from their provider, as part of routine practice. All other study results will be disseminated to the participants on demand.

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## ETHICS AND DISSEMINATION

The study was approved by the ethics committee of the Peking Union Medical College Hospital on 2nd of July, 2020 (Nr. KS20202255). Current version of the protocol (No. 2.2) from 31st of July 2021 was also approved on 20th of December 2021 by Hannover Medical University, Germany. It is conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice (ICH-GCP), the Declaration of Helsinki and all applicable national and international laws, regulations and standards, including archiving of essential documents. Patients agreeing to participate in the study must sign an informed consent form approved according to local regulations. The study site staff member conducting the consent process must also sign the consent form on the same occasion. All amendments to the clinical study protocol should be agreed upon between the sponsor and the investigator and be recorded with a justification for the amendment. The only exceptions are, where necessary to eliminate an immediate hazard to study patients, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). All information concerning drug/device and the sponsor's research and product development is considered confidential and will remain the sole property of the sponsor. A financial agreement will be signed between the sponsor and the investigators and/or the institution involved as required.

Final data analysis and disclosure of contractual agreements will be done by CRO Hangzhou Tigermed Consulting Co., Ltd, which will limit the access of investigators to the final trial dataset. The monitors, auditors, authorised personnel of the sponsor, health authority inspectors or their agents, and authorised members of Independent Ethics Committees/Institutional Review Boards will be given direct access to the source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes and photographs) upon request, provided that patient confidentiality is maintained in accordance with local requirements.

Findings of this study will be disseminated through peer-review publications and conference presentations. No information which could lead to the identification of patients will be included in the dissemination of results.



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## DISCUSSION

Cervical cancer is the most common HPV-related malignancy (5). Given the substantial burden of cervical cancer globally, efforts have been made to develop effective prevention measures, including HPV vaccination and screening programmes in combination with timely and efficient treatment of pre-cancerous lesions (2, 9). Unfortunately, these preventive measures are not equally implemented worldwide, with absent or inadequate screening and vaccination programmes in many low- and middle-income countries who suffer the highest HPV incidence rates. Especially in Eastern Europe and Central Asia, a rapid increase in premature cervical cancer mortality has been reported in recent generations (2). Furthermore, currently available vaccines are expensive and directed against only certain HPV subtypes (9, 29).

PDT has been clinically approved for the treatment of different cancers, including skin cancer, superficial oesophageal cancer and lung cancer (30-32). Due to the lack of adequate non-surgical treatment modalities, the potential of PDT for the treatment of CIN has been investigated in this and previous studies (22-27, 33). The main advantage of PDT for the treatment of CIN is its non-invasiveness, leaving the cervix intact and thereby preserving fertility. Moreover, targeted PDT of CIN is not restricted by HPV subtype causing pre-cancerous lesions and the PDT could be repeated in case of another infection or lesion.

For the treatment of CIN, topical administration of both 5-aminolaevulinic acid (5-ALA) and its esterified derivate HAL have been studied, with HAL being preferred due to its better stability and increased fluorescence at lower doses leading to less systemic exposure (22, 24, 30). As topical administration was perceived to be inconvenient, the integrated light- and drug-delivery device Cevira® was developed (23, 27, 33). The safety and efficacy of Cevira® have been evaluated in a double-blind, placebo-controlled dose-finding Phase 2b study including 262 patients with CIN1/2 randomised to HAL 0.2%, 1% or 5% or placebo, permitting retreatment at 3 months if clinically indicated (27). Based on the outcomes of the Phase 2b, the HAL 5% dose was selected for further evaluation in the Phase 3 study. The HAL 5% dose had a favourable safety profile while being associated with the highest regression rate and oncogenic HPV clearance. However, efficacy could only be demonstrated in patients with CIN2, probably due to a high rate of spontaneous regression in the CIN1 population with most patients being HPV negative. As a result, the present Phase 3 study will only include HSIL



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patients (CIN2/3) ensuring efficacy can be reliably assessed. Due to the local and transient exposure to HAL, side effects were usually self-limiting, mainly including discharge, discomfort and spotting.

The currently available data indicate that Cevira® is easy-to-use for gynaecologists and well-accepted by patients (33). The device results in no patient down-time as it is similar to using a tampon, patients may leave the gynaecologist office immediately after the application and can return to normal daily activities. Additionally, patients can easily remove the device themselves by pulling the string within 24 hours after application. The current Phase 3 study will further evaluate how the use of Cevira® device is perceived by gynaecologists and patients.

In summary, Cevira® holds potential to serve high unmet medical need for non-surgical, safe treatment options for patients with HSIL and cervical cancer. Due to its non-invasiveness, Cevira® could be a promising alternative to excisional treatment for young women in reproductive age. Following the encouraging results from the Phase 2b study, the efficacy and safety of Cevira® in patients with HSIL will be further evaluated in the presented APRICITY Phase 3 study currently recruiting patients in China and Europe for a multicentre, prospective, double-blind randomised controlled clinical trial.

**Trial status**

The APRICITY Phase 3 study is currently recruiting patients in China, Ukraine, Russia and Europe. Recruitment started in November 2020 with the aim to enrol at least 384 patients. However, study start-up had to be delayed in Ukraine and Russia. In addition, the process might be interrupted or extended due to the Covid-19 pandemic.

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## Acknowledgments

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## Author contributions

FC, LS, YZ, ZY, JH and PH contributed to the experimental design of the study. CD, ZN and CM were involved in study design, outcome definition and ethical approval application. JL is the global PI of the study. PH is the European PI of the study. FC is the Chinese PI of the study. All PIs have contributed to the study protocol amendments. All authors have read, edited and approved the manuscript.

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## Conflict of interest

CD received consulting fees from MSD, GSK, Tesaro and Clovis Oncology and honoraria from MSD and GSK. LH is an employee of Asieris Pharmaceuticals (Shanghai) Co., Ltd. FC, ZN, CM, LS, YZ, ZY, JL and PH have nothing to declare.

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## FIGURE LEGENDS

**Figure 1. Overview of the APRICITY Phase 3 study design.**

**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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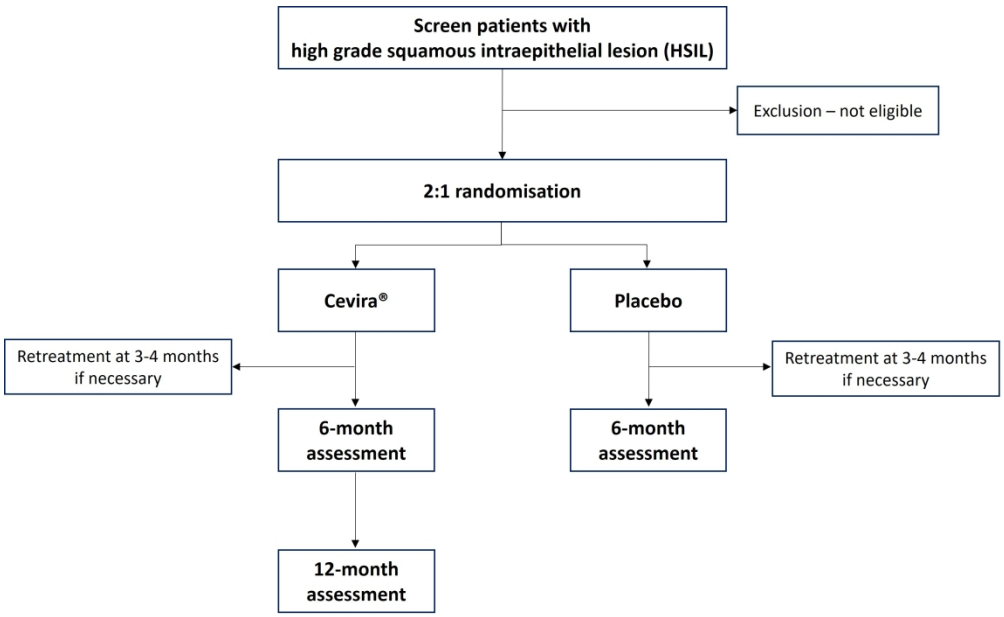


**Figure 1. Overview of the APRICITY Phase 3 study design.**

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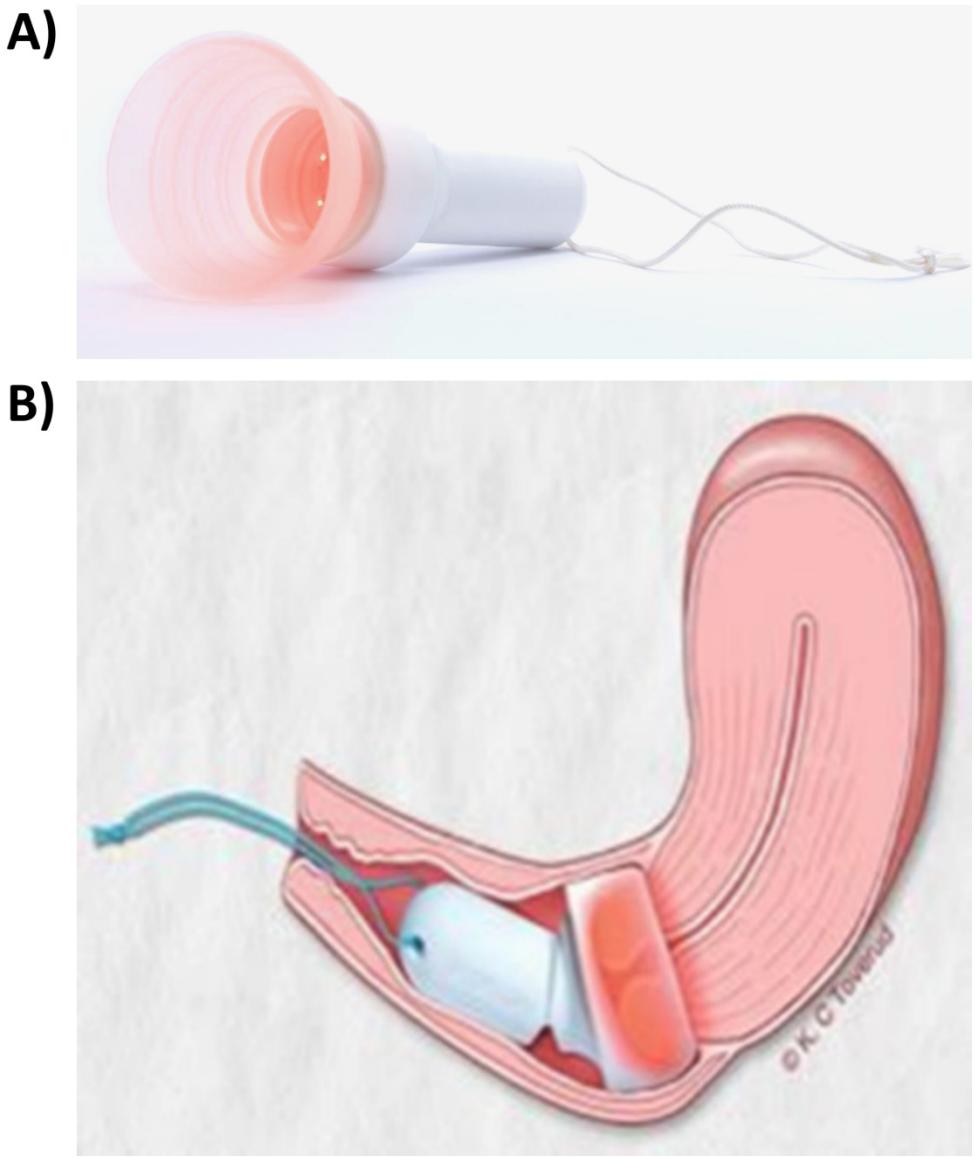


**Figure 2. Cevira® (Photocure ASA, Oslo, Norway).** A) Cevira® CL7 drug delivery device with integrated red light source. B) Ointment and device are administered intravaginally by the gynaecologist to the cervix of the HSIL patient. HSIL, high grade squamous intraepithelial lesion.

149x175mm (330 x 330 DPI)

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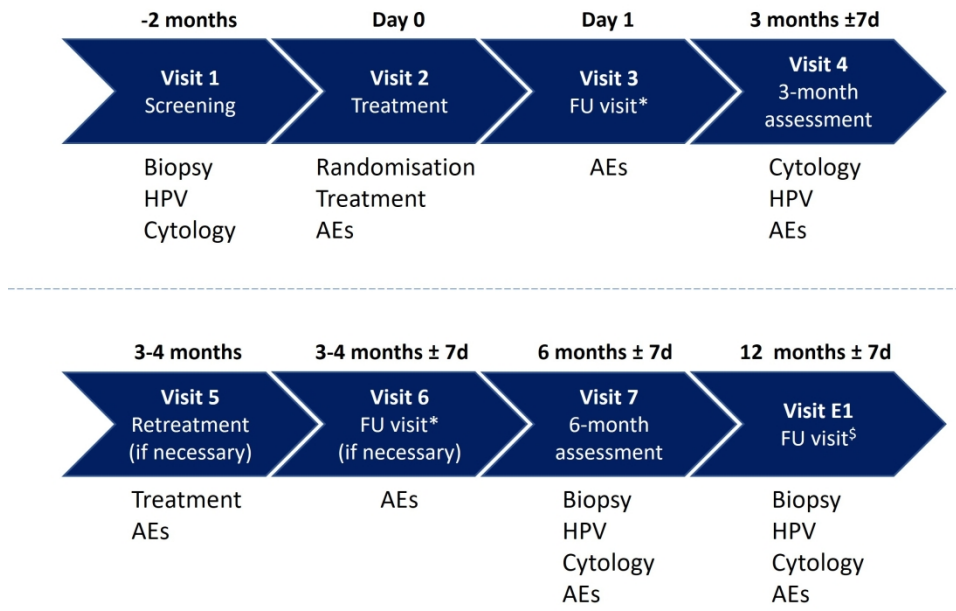


**Figure 3. Study flow and assessments of the APRICITY Phase 3 study.** AEs, adverse events; FU, follow-up; HPV, human papilloma virus; * Performed by telephone calls. $ Only treatment group.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | ItemNo | Description | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2, 6 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | 2, 6-10, 14, 16, 17 |
| Protocol version | 3 | Date and version identifier | 14 |
| Funding | 4 | Sources and types of financial, material, and other support | 17 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | NA |
| | 5b | Name and contact information for the trial sponsor | NA |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | NA |
| **Introduction** | | | |

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| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4, 5 |
| | 6b | Explanation for choice of comparators | 6 |
| Objectives | 7 | Specific objectives or hypotheses | 5 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6, Figure 1 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7, 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | 8 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7, 8 |

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| | | | |
|---|---|---|---|
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 8, 9, Table 1 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 9, 10, Figure 3 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10, 11 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 10 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 12 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 12 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 12 |



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| | | | |
|---|---|---|---|
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 12 |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12-14 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | NA |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12-14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 11 |
| **Methods: Monitoring** | | | |



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| | | | |
|---|---|---|---|
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 12-14 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 10 |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 12 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 13 |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 14 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 14 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 14 |

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| | | | |
|---|---|---|---|
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | NA |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13, 14 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | NA |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 2, 14 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | NA |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | NA |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Supp. material |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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