Phase II Single Arm, Open Label Study of Artesunate for the Treatment of Human Papilloma Virus positive High Grade Cervical Intraepithelial Neoplasia (CIN2/3)

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CHIEF INVESTIGATOR (CI):
Professor Sanjeev Krishna MA, MBChB, DPhil, FRCP, ScD, FMedSci
St George's, University of London and Centre for Affordable Diagnostics and Therapeutics
2 Leman St, London,E1 8FA
United Kingdom
Mobile: Email: skrishna@cadt.org.uk

SPONSOR:
Metanoic Health Limited
36 Clarkes Avenue
Worcester Park
Surrey
United Kingdom
Mobile: +44 (0)7798566612 **Email:** clinicaltrials@metanoichealth.com

SPONSOR REPRESENTATIVE:
Name: Dr Isaac John
Mobile:
Email: Isaac.John@metanoichealth.com

Signature Page and Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except in the case of a medical emergency or where departures from the protocol are mutually agreed in writing.

The investigators agree to conduct the trial in compliance with the approved protocol, Malaysian Good Clinical Practice (GCP) and National Pharmaceutical Regulatory Authority (NPRA) Regulations for Clinical Trial Import License (CTIL), the Malaysian Data Protection Act, local governance policy, the Sponsor's SOPs, and other regulatory requirements as stipulated.

This protocol has been written in accordance with the Sponsor's procedure and is intended for use at Malaysian sites only.

Chief Investigator Professor Sanjeev Krishna MA, MBChB, DPhil, FRCP, ScD, FMedSci St George's, University of London and Centre for Affordable Diagnostics and Therapeutics 30 City Road, London England EC1Y 2AB United Kingdom	**Signature**	**Date** **13 November 2024**
Sponsor Representative Dr Isaac John Metanoic Health Limited 36 Clarkes Avenue Worcester Park Surrey United Kingdom	**Signature**	**Date** **13 November 2024**

Acknowledgements and Protocol contributories
This protocol was developed at the European Organisation for Research and Treatment of Cancer (EORTC)- European Society for Medical Oncology (ESMO)- American Association for Cancer Research (AACR) Workshop on Methods in Clinical Cancer Research in June 2022 by Dr Yolanda Augustin in collaboration with Professor Sanjeev Krishna.

Table of Contents

List of abbreviations:

AE	Adverse Event
AUC	Area under the curve
CA	Competent Authority
CADT	Centre for Affordable Diagnostics and Therapeutics
CI	Chief Investigator
CIC	Clinical Investigation Centre
Chk1/Chk2	Checkpoint kinase 1/Checkpoint kinase 2
Cip/Kip	CDK interacting protein/Kinase inhibitory protein
CD31	Cluster of Differentiation 31
CRF	Case Report Form
CT	Computed tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Toxicity Criteria
CTIL	Clinical Trial Import License
DHA	Dihydroartemisinin
DNA	Deoxyribonucleic acid
DDSB	DNA double–strand breaks
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EGFR	Epidermal Growth Factor Receptor
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organisation for Research and Treatment of Cancer
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
g/l	grams per litre
Hb	Haemoglobin
HIF-1α	Hypoxia induced factor - 1α
HPV	Human Papilloma Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ID	Identification
IMP	Investigational Medicinal Product
IIT	Investigator Initiated Trial
IP	Intellectual Property
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number

ITT	Intention to treat
KG	Kilogram
LFT	Liver Function Test
MG	Miligram
ML	Mililitre
MMPs	Metalloproteinases
MOH	Ministry of Health
NCAM	Neural cell adhesion molecule
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMRR	National Medical Research Register
NPRA	National Pharmaceutical Regulatory Agency
NoK	Next of Kin
OD	Once daily
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
PIS	Participant Information Sheet
Plts	Platelets
PO	Oral administration
QC	Quality Control
QOL	Quality of Life
QP	Qualified Person
R&D	Research & Development
REC	Research Ethics Committee
ROS	Reactive Oxygen Species
RSI	Reference Safety Information
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TF	Transferrin
TIMP	Tissue inhibitors of metalloproteinase
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Time to progression
ULN	Upper limit of normal
UM	University of Malaya
UMMC	University Malaya Medical Centre
VEGF	Vascular endothelial growth factor
WCC	White Cell Count
WHO	World Health Organisation

Roles and Responsibilities

Chief Investigator (CI): Professor Sanjeev Krishna, MA, MBChB, DPhil FRCP, ScD, FMedSci
St George's, University of London and Centre for Affordable Diagnostics and Therapeutics
2 Leman St, London,E1 8FA United Kingdom
Mobile:
Email: skrishna@cadt.org.uk

Co-Principal Investigators (PI):

Dr Yolanda Augustin
St George's, University of London and Centre for Affordable Diagnostics and Therapeutics
2 Leman St, London,E1 8FA United Kingdom
Mobile:
Email: yaugustin@cadt.org.uk

Professor Woo Yin Ling
Department of Obstetrics & Gynaecology
Faculty of Medicine, University of Malaya
Lembah Pantai,59100
Kuala Lumpur, Malaysia
Email: ylwoo@ummc.edu.my

Professor Rozita Malik
Department of Oncology,
Faculty of Medicine, University of Malaya
Lembah Pantai,59100
Kuala Lumpur, Malaysia.
Email: rozita@ummc.edu.my

Dr Yong Chee Meng
Hospital Ampang
Jalan Mewah Utara,
Taman Pandan Mewah,
68000 Ampang, Selangor,
Malaysia
Mobile:
Email:

Dr Jamil bin Omar
Institut Kanser Negara
4, Jalan P7, Presint 7, 62250 Putrajaya,
Wilayah Persekutuan,
Malaysia

Mobile:
Email:

Dr Kanddy Loo Chin Yee
Hospital Umum Sarawak
Jalan Hospital, 93586 Kuching,
Sarawak, Malaysia
Mobile:
Email:

Dr Vicknesh Visvalingam
Hospital Selayang
Selayang - Kepong Hwy,
68100 Batu Caves, Selangor, Malaysia
Mobile:
Email:

NeoART Clinical Trial Co-ordinator: Dr Nafeesa Mat Ali
St George's, University of London and Centre for Affordable and Diagnostics and Therapeutics
2 Leman St, London,E1 8FA United Kingdom
Mobile:
Email: nmatali@cadt.org.uk

Pathology Laboratory: Dr Razmin binti Ghazali
Pathology Department ,
Hospital Kuala Lumpur,
Jalan Pahang,
Kuala Lumpur 50586
Wilayah Persekutuan
Mobile:
Email:

Lead Research Pharmacist: Tai Yi Wern
Pharmacy Main Store,
First Floor, Menara Utama,
UMMC, Lembah Pantai, 59100 KL, Malaysia.
Mobile: + 60 (0)7949 2831
Email: ywtai@ummc.edu.my

NeoART Study team emergency number: +60 (0) 172152964

Protocol Summary

<table>
<tr><td>Trial number and full title</td><td>Phase II Single Arm, Open Label Study of Artesunate for the Treatment of Human Papilloma Virus positive High Grade Cervical Intraepithelial Neoplasia (CIN2/3)</td></tr>
<tr><td>Protocol number</td><td>2023-MHL-002</td></tr>
<tr><td>Rationale</td><td>Artesunate belongs to the artemisinin family of sesquiterpene trioxane anti-malarial agents derived from Sweet wormwood (Artemisia annua L.) that have been used in traditional Chinese medicine for centuries to treat a variety of ailments including fever, inflammation and haemorrhage. Artesunate is approved for the treatment of uncomplicated, severe and multidrug-resistant malaria, is on the WHO list of Essential Medicines with an excellent safety profile and is affordable at USD1 per daily dose.

Several comprehensive reviews have examined the evidence for the anti-cancer effects of artemisinins. Pre-clinical studies of artemisinins in cell line and animal models have demonstrated broad anti-cancer activity including pro-apoptotic, anti-proliferative, anti-angiogenesis and anti-metastatic effects. A Phase I dose-escalation study of artesunate vaginal inserts in biopsy-confirmed CIN 2/3 in 28 patients showed that treatment was safe and well tolerated with histologic regression observed in 19/28 (67.9%) subjects and HPV viral clearance in 9/19 subjects (47.4%) (Trimble et al., 2020). In patients who did not experience histological regression, no viral clearance was seen.

NeoART-CIN is a Phase II clinical study evaluating the safety and effectiveness of oral artesunate in patients with CIN2/3, to investigate if a course of treatment with oral artesunate can lead to regression of pre-cancerous changes in the cervix and prevent the development and progression of invasive cancer. Findings from this study will increase our understanding of the effects of artesunate on CIN2/3 and, if confirmatory, inform future clinical studies.</td></tr>
<tr><td>Objective(s) + Endpoint(s)</td><td>Overall objective: To determine the feasibility, safety and preliminary anti-proliferation activity of oral artesunate in Human Papilloma Virus positive (HPV +ve) High Grade Cervical Intraepithelial Neoplasia (CIN2/3).

<table>
<tr><th>Primary Objective</th><th>Primary Endpoints</th></tr>
<tr><td>To determine the effect of artesunate on histologic regression of CIN2/3</td><td>Histological regression of CIN2/3 on colposcopy and biopsy at Day 90</td></tr>
<tr><th>Secondary Objective</th><th>Secondary Endpoints</th></tr>
<tr><td>To determine the effect of artesunate on HPV DNA viral clearance</td><td>HPV DNA viral clearance at Day 90</td></tr>
<tr><td>To determine the effect of artesunate on the vaginome and gut microbiome</td><td>Comparison of vaginome and gut microbiome at Day 0, Day 64 and Day 90</td></tr>
<tr><td>To determine the effects of artesunate on patient safety</td><td>Serious Adverse Event at 90 days using Common Toxicity Criteria (CTCAE V5.0)</td></tr>
<tr><td>To determine the effects of artesunate on patient Quality of Life</td><td>Quality of life using the European Quality of Life–5 Dimensions (EQ-5D) quality of life tool</td></tr>
</table>
</td></tr>
<tr><td>Study design</td><td>Phase II open label single arm study</td></tr>
</table>

Number of patients (statistical design)	A maximum of 28 participants will be enrolled to receive the study intervention. The primary end point is histological regression of CIN2/3 on colposcopy and biopsy at Day 90. Significance level and power: The procedure described above tests the null hypothesis that the response rate is 20 % versus alternating hypotheses that the response rate is 50 %. The significance level (i.e., the probability of rejecting H0 when it is true) is α=0.1 and the power (i.e., 1-beta, the probability of deciding the regimen is active) is 90% when true response rate is 50 %. At the significance level of 0.05, with an equivalence limit of 0.15, a sample size of 24 is required to achieve 90% power when the response rate for the historical control is 0.2 and response rate for the treatment is 0.5. Inflating this sample size by 20% to allow for loss at follow-up would result in a sample size of approximately 28 patients.

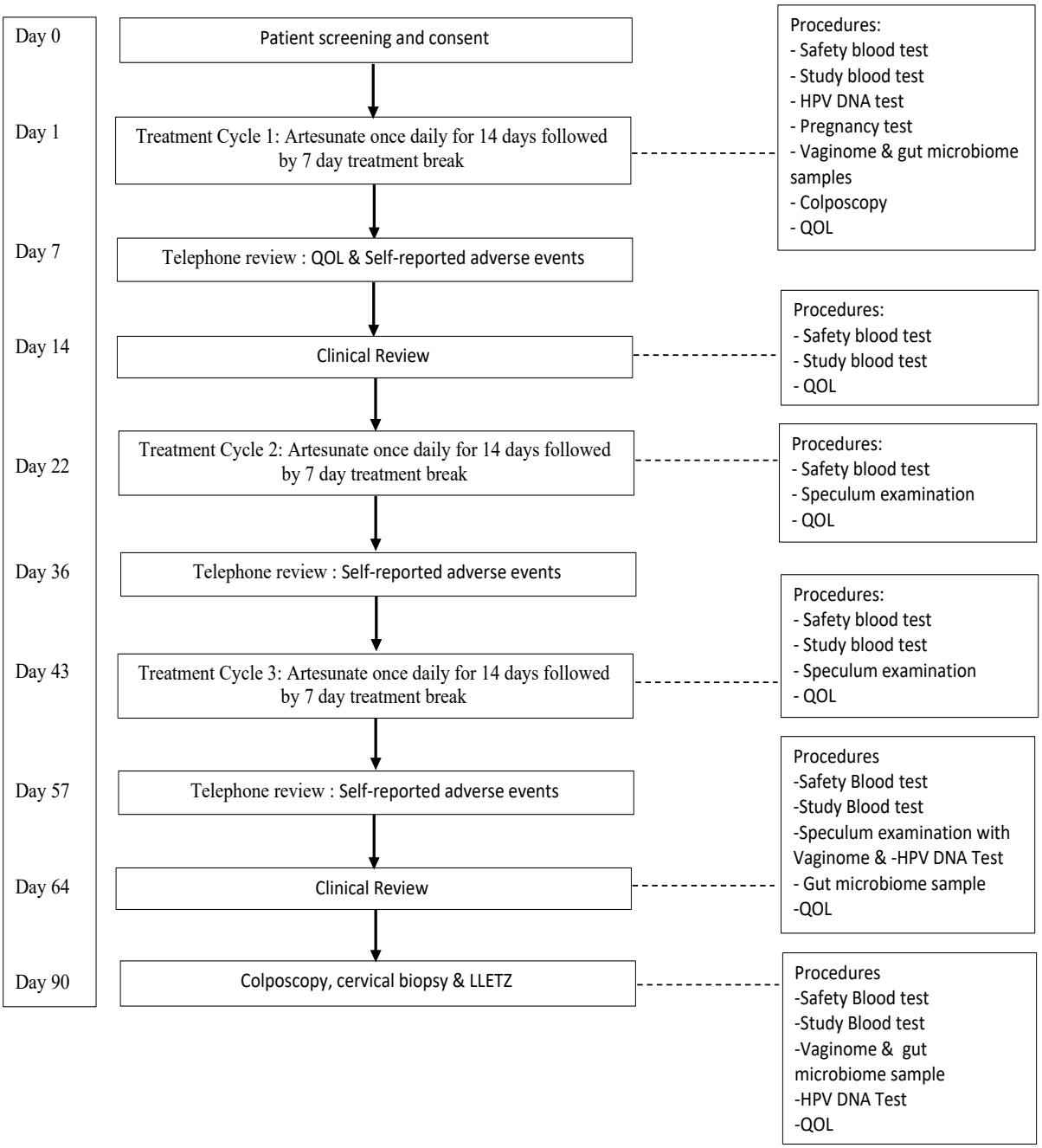
Trial population	<u>Main inclusion criteria</u>
	• Aged 18 or over
	• Histologically proven HPV positive cervical CIN2/3
	• WHO performance status 0-2
	• Adequate full blood count:
	  ○ White Cell Count (WCC) >3.0 x 10^9 /l;
	  ○ Platelets >100 x 10^9/l;
	  ○ Haemoglobin (Hb) >80g/L
	• Adequate renal function:
	  ○ Glomerular Filtration Rate >30ml/min
	• Adequate hepatobiliary function:
	  ○ Total bilirubin < 3 x Upper limit normal
	• Participants of child bearing potential must have a negative pregnancy test < 72 hours prior to initiating study intervention and agree to avoid pregnancy using adequate, medically approved contraceptive precautions for up to 6 weeks after the last dose of study treatment intervention
	• Patient able and willing to provide written, informed consent for the study
	
	<u>Main exclusion criteria</u>
	• Contraindication to the use of artesunate due to hypersensitivity
	• Pregnancy or lactation
	• Weight < 52 kg
	• History of previous CIN
	• Immunocompromised patients

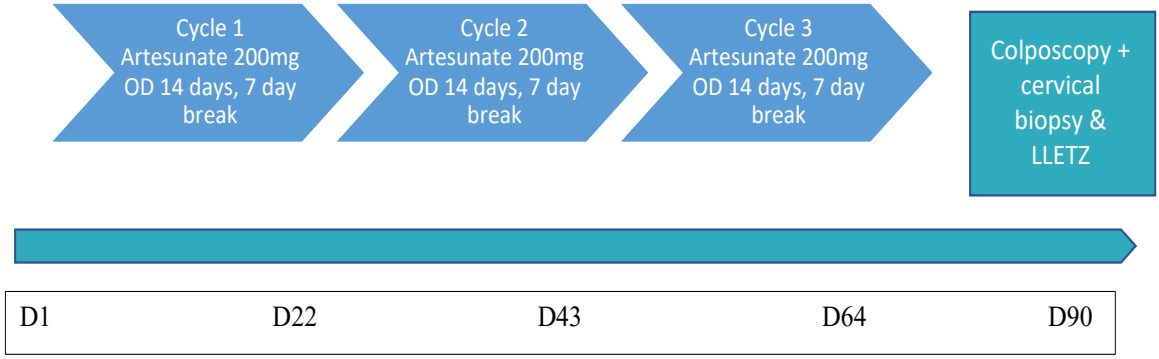
Treatment	Study Intervention: Patients with HPV positive CIN2/3 will receive 3 cycles of oral artesunate 200mg OD prior to standard of care therapeutic large loop excision of transformation zone (LLETZ). Each 21 day treatment cycle will comprise oral artesunate 200mg OD for 14 days followed by a 7 day treatment break.
Reference Treatment	Not applicable.
Statistical analyses	Patients' demographics, baseline characteristics, prior and concomitant medications, treatment exposure, protocol compliance and study withdrawals will be summarized in the intent-to-treat population. For categorical variables, frequency tables (with %) will be presented with descriptive listings of details specified in text fields, where appropriate.

	Continuous variables will be reported using median, range and interquartile range. Primary outcome measure(s) • Histological regression of CIN2/3 on colposcopy and biopsy at Day 90 will be defined as histologic regression to CIN1 or less. This will be described as a response percentage. Secondary outcome measure (s) • HPV DNA viral clearance at Day 90 Viral clearance will be defined as absence of HPV genotoype(s) that were detected at baseline and described as a response percentage. • Vaginome and gut microbiome at Day 1, Day64 and Day 90 Changes in vaginome and gut microbiome will be compared between Day 0, Day 64 and Day 90. • Serious Adverse Events at Day 90 using Common Toxicity Criteria (CTCAE V5.0) Safety assessment will be based on patients who received at least one dose of IMP. Tolerability assessment will be based on the percentage of subjects that complete the designated dosing regimen. • Patient quality of life will analysed using the European Quality of Life–5 Dimensions (EQ-5D) quality of life analysis tool.
Translational research	**Study Assessments:** Patients will have study bloods samples for translational research collected on Day 1, Day 14, Day 64 and Day 90 of the study. HPV DNA will be tested on vaginal sampling Day 1, Day 64 and Day 90 of the study. Vaginome and microbiome samples will be collected on Day 1, Day 64 and Day 90. A laboratory manual has been prepared separate to this protocol.
Quality of Life	European Quality of Life–5 Dimensions (EQ-5D-5L) quality of life tool will be completed on Day 1, Day 7, Day 14, Day 22, Day 43, Day 64 and Day 90 of the study.
Benefit-risk analysis	Cervical cancer represents significant morbidity and mortality globally, particularly in Low and Middle Income Countries (LMICs). The current standard of care in women with pre-cancerous high grade CIN2/3 are surgical or ablative treatments. Although these treatments are generally safe, there remains a small risk of complications such as infection, bleeding, perforation, and cervical stenosis with the most severe late complication being an increased risk of preterm birth and obstetric complications. Following surgical resection, the risk of recurrence with uninvolved margins may range from 8-23% ((Nagai *et al*., 2000 ; Serati *et al*., 2012 ; Fan *et al.,* 2018 ; Verguts *et al.,* 2006). For many women, travel costs, time off work and childcare considerations represent significant barriers to engaging with cervical cancer screening, treatment and follow up. There is an urgent need to develop affordable therapeutics at point-of-need to manage the burden of global oncology. A safe, effective, affordable and convenient oral treatment that results in regression of CIN2/3 and clears HPV infection would represent a significant development in the management of this condition.

	Trial-specific risks and burdens include additional diagnostic, therapeutic and monitoring procedures to ensure safety, tolerability and preliminary antiproliferative effects in this patient population. Patients may not derive any direct benefit from participating in this study. However they will contribute to our scientific and clinical understanding of the potential antiproliferative effects of artesunate in CIN2/3 as we research better treatments for this condition.

Phase II single arm open label study of oral artesunate in Human Papilloma Virus positive High Grade Cervical Intraepithelial Neoplasia (CIN2/3)





1. Objectives and outcome measures of the study

1.1. Study objectives

Primary Objective	**Primary Endpoints**
To determine the effect of artesunate on histologic regression of CIN2/3	Histological regression of CIN2/3 on colposcopy and biopsy at Day 90
Secondary Objective	**Secondary Endpoints**
To determine the effect of artesunate on HPV DNA viral clearance	HPV DNA viral clearance at Day 90
To determine the effect of artesunate on the vaginome and gut microbiome	Vaginome and gut microbiome at Day 0, Day 64 and Day 90
To determine the effects of artesunate on patient safety	Serious Adverse Events at 90 days using Common Toxicity Criteria (CTCAE V5.0)
To determine the effects of artesunate on patient Quality of Life	Patient quality of life using the European Quality of Life–5 Dimensions (EQ-5D) quality of life tool Day 1, Day 7, Day 14, Day 22, Day 43, Day 64 and Day 90.

1.1.1 Primary objective

- To determine the effect of artesunate on histologic regression of CIN2/3.

1.1.2 Secondary objectives

- To determine the effect of artesunate on HPV DNA viral clearance.
- To determine patient safety and tolerability of artesunate.
- To determine the effects of artesunate on patient Quality of Life.

1.2 Outcome measures

1.2.1 Primary outcome measure

- Histological regression of CIN2/3 on colposcopy and biopsy at Day 90.
    - Histological regression will be defined as histologic regression to CIN1 or less.

1.2.2 Secondary outcome measures

- HPV DNA viral clearance at Day 90.
    - Viral clearance will be defined as absence of HPV genotoype (s) detected at baseline.
- Vaginome and gut microbiome at Day 1, Day 64 and Day 90.
    - Changes in vaginome and gut microbiome will be compared between Day 1, Day 64 and Day 90.
- Serious Adverse Events at Day 90 using Common Toxicity Criteria (CTCAE V5.0).
    - Safety assessment will be based on patients who received at least one dose of IMP.
- Tolerability assessment will be based on the percentage of subjects that complete the designated dosing regime.

- Patient quality of life using the European Quality of Life–5 Dimensions (EQ-5D) quality of life tool Day 1, Day 7, Day 14, Day 22, Day 43, Day 64 and Day 90.

2. Background and Introduction

2.1 Background Disease Information

Cervical cancer is the 4th most common form of cancer in women globally (Sung *et al*., 2020). It is a significant cause of morbidity and mortality with over half a million new cases and over 300,000 deaths per year despite being preventable and curable if detected early and managed effectively. Low and Middle Income Countries (LMICs) are disproportionately affected with 80% of cases and 90% of cervical cancer related deaths occurring in low resource settings. There is an urgent need to develop affordable therapeutics to manage this burden of global oncology. For many women, travel costs, time off work and childcare considerations represent significant barriers to engaging with cervical cancer screening, treatment and follow up (McPherson *et al*., 2020 ; Majid *et al*., 2019).

The World Health Organisation (WHO) cervical cancer elimination strategy has set a target to eliminate cervical cancer as a public health problem (target incidence <4/100,000 population) (WHO 2020). To be on track to achieve this by the end of the century, draft targets are that 90% of girls should be vaccinated against HPV by the age of 15 years, 70% of all women aged 30 to 49 years should have at least 2 high precision screening tests 10 years apart and 90% of screen positive women, as well as 90% of women with cancer, should receive treatment by 2030. Countries are called to meet the 90-70-90 targets by 2030 in order to work towards cervical cancer elimination. It is estimated that over 62 millions deaths due to cervical cancer could be prevented in the next 100 years through the implementation of this strategy alongside HPV vaccination.

Whilst survival rates from colorectal, breast, prostate, cervical and lung cancer are improving in high income countries (HICs) due to a combination of early detection and more effective treatments, cancer death rates in LMICs are unfortunately increasing. This is in part because many lifesaving cancer treatments remain unaffordable for patients in LMICs where cancer remains a neglected disease. Novel drug development takes on average 10-15 years to go from bench to clinic at an average cost of USD1 billion. Repurposing of 'old' drugs for new indications can shorten this pathway substantially with significant cost savings (Nosengo 2016 ; Bertolini *et al*., 2015).

In Malaysia, cervical cancer is the fourth leading cause of cancer related morbidity and mortality amongst women with an annual incidence of 1700 in 2018 (MyScan 2018). At present, only around 25% of women participate in regular cervical screening and many patients present with advanced disease with 5 year overall survival around 52 % (MyScan 2018). There is an urgent need for effective, safe and affordable treatments to improve survival.

Chronic infections are a major contributor to the development of around 20% of certain cancers (Plummer *et al*., 2016). Some pathogenic agents disrupt signaling that controls proliferation and cell growth, exert effects on immune-modulation and cause persistent inflammation that can lead to cancer. The majority of cervical cancers are caused by persistent infection with high-risk oncogenic types of Human Papillomavirus (HPV) (Walboomers *et al*., 1999). There are over 100 types of HPV, of which 14 are classified as high-risk oncotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) (WHO 2021 ; Sanjose *et al*., 2010). Two HPV types (16 and 18) cause 70% of cervical

cancers and pre-cancerous cervical lesions. HPV is also responsible for a significant proportion of vaginal, vulval, anal and oropharyngeal cancers (Roden *et al*. 2018 ; Otter *et al*., 2019)

The prevention of cervical cancer requires vaccination against the most oncogenic types of HPV (at least types 16 and 18) for pre-adolescents and screening of adult women to enable detection and treatment of pre-cancerous abnormalities. Infection with HPV is ubiquitous and in the majority of cases is resolved by the host within 1- 2 years (Schiffman *et al*., 2007 ; Maucort-Boulch *et al*., 2010). However, in around 10-20% of women, for reasons that remain unclear, persistent infection results in chronic inflammation, which can then progress to pre-cancerous lesions and cancer. High-risk HPV infections leading to cervical cancer require the production of both HPV E6 and E7 oncoproteins (Pal *et al*., 2020). Sustained expression of the viral E6 and E7 oncogenes are required to drive the transformation and growth of cancerous lesions.

The average time from initial HPV infection to the development of invasive CIN is 10-30 years (Fan *et al*., 2016 ; Rodriguez *et al*., 2010 ; WHO 2020). Although estimates vary, around 20–40% of CIN2-3 will undergo spontaneous regression with around 30% of high-grade dysplasia (CIN2-3) progressing to cancer (Verguts *et al*., 2006). At present, the standards of care in women with CIN2-3 are surgical or ablative treatments (WHO 2020). Although these treatments are generally safe, there remains a small risk of complications such as infection, bleeding, perforation, and cervical stenosis with the most severe late complication being an increased risk of preterm birth and obstetric complications (Heinonen *et al*., 2013). Following surgical resection, the risk of recurrence with uninvolved margins may range from 8-23% (Nagai *et al*., 2000 ; Serati *et al*., 2012 ; Fan *et al*., 2018 ; Verguts *et al*., 2006).

Whilst the WHO Cervical Cancer Elimination strategy is resulting in an increase in cervical screening in many LMICs, diagnostic follow up and treatment pathways also requiring strengthening. A safe, effective, affordable and convenient oral treatment that results in regression of CIN2/3 and clears HPV infection would represent a significant development in the management of this condition.

2.2 Background Therapeutic Information

Artesunate is derived from a plant called Sweet Wormwood (*Artemisia annua* L. / 'Qing Hao'), which has been used for more than two thousand years in traditional Chinese medicine to treat a variety of ailments (Augustin *et al*., 2020 ; Krishna *et al*., 2008). Pre-clinical studies of artemisinins in cell line and animal models have demonstrated broad anti-cancer activity including pro-apoptotic, anti-proliferative, anti-angiogenesis and anti-metastatic effects (Augustin *et al*., 2020; Krishna *et al*., 2014 ; Ho *et al*., 2014).

Artesunate, artemether and arteether are derivatives of artemisinin that are converted into their active metabolite dihydroartemisinin (DHA). Artesunate is approved for the treatment of uncomplicated and multidrug-resistant malaria and is on the WHO list of Essential Medicines (WHO., 2015). Artesunate has a hemisuccinate group which confers substantial water-solubility and high oral bioavailability and therefore a convenient oral route of administration. Artesunate has a good safety and tolerability profile, having been used to treat tens of millions of adults and children globally (Hien *et al.,* 1994 ; Kremsner *et al.,* 2004).

The dose of artesunate for the study will be 200 mg per oral (PO) once daily (OD) for fourteen days per treatment cycle. There are no data on the most appropriate dose of artesunate in cancer in humans. This dose has been chosen by a consensus among medical experts experienced with using artesunate for the treatment of malaria and following published results from a pilot feasibility and

safety study of neodajuvant oral artesunate in patients with colorectal cancer (Krishna *et al*. 2015).

The daily dose of artesunate used in combination treatments to treat uncomplicated *Plasmodium falciparum* malaria is 4 mg/kg, given over three days. When given as monotherapy for uncomplicated falciparum malaria the total dose is approximately 20 mg/kg, over seven to ten days. For curative courses in severe malaria, the total doses of artesunate (parenteral and oral combined) can reach 24 mg/kg. The daily dose of artesunate for a patient in this study will be between 2 mg/kg and 4 mg/kg, depending on the weight of the participant (ranging between 52-110 kg). At daily doses of 6 mg/kg the dose limiting side effect of artesunate is neutropenia.

Artesunate Chemical Structure

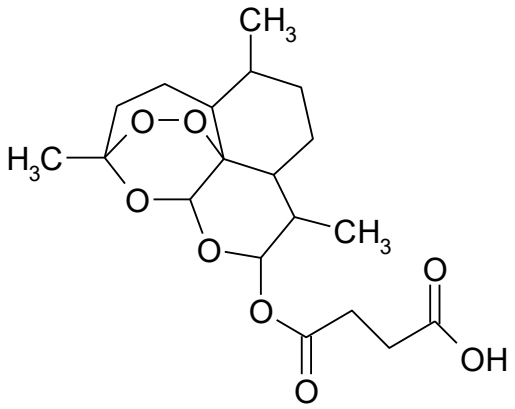


Figure 1: Chemical structure of Artesunate

The molecular formula: C_{19} H_{28} O_8
The relative molecular mass: 384.43
Chemical Name: [3R-(3R*)]- Butanedioic acid mono (Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl) ester.
Chemical Abstracts Service (CAS) registry number: 88495-63-0

Metabolite

Artesunate is extensively hydrolysed by plasma esterases and possibly CYP2A6. Its main metabolite, dihydroartemisinin (DHA) is metabolised through glucuronidation (WHOPAR., 2011).

Elimination

The plasma half-life of artesunate is 3-29 minutes whilst its active metabolite DHA has a plasma half-life of 40 to 95 minutes (WHOPAR., 2011). Artesunate has a renal mode of excretion.

The effect of food

The effect of food consumption with artesunate has been studied. When healthy volunteers consumed artesunate fixed dose combinations with a high fat meal, the Cmax and AUC (0-t) of artesunate decreased by 66% and 13% respectively, compared to fasting. The Cmax and AUC (0-t) of the active metabolite dihydroartemisinin (DHA) decreased by 48% and 5% respectively with a high-fat meal, compared to fasting (WHOPAR., 2011). Patients should take the study medication after a light meal.

Pre-clinical models examining the anti-cancer effects of artemisinins

Carcinogenesis in humans is a complex process and 8 key hallmarks have been well described (Hanahan & Weinberg, 2011). These include sustained proliferative signaling, evasion of cell death and growth suppression, induction of angiogenesis, invasion and metastasis, reprogramming energy metabolism and evasion of immune destruction (Hanahan & Weinberg, 2011). In the last three decades, artemisinins have shown potent and broad anticancer properties in a range of cell lines and animal models, supporting the hypothesis that artemisinins have the potential to be developed as an effective anti-cancer therapy (Fig 2). Several comprehensive reviews have examined the evidence for the anti-cancer effects of artemisinins (Efferth, 2017a; Ho *et al*., 2014; Krishna *et al*., 2008). Multiple potential mechanisms of action include anti-proliferative effects through cell-cycle disruption, reactive oxygen species(ROS) -induced DNA damage, induction of apoptosis, anti-angiogenesis, immunomodulation and induced radiosensitivity.

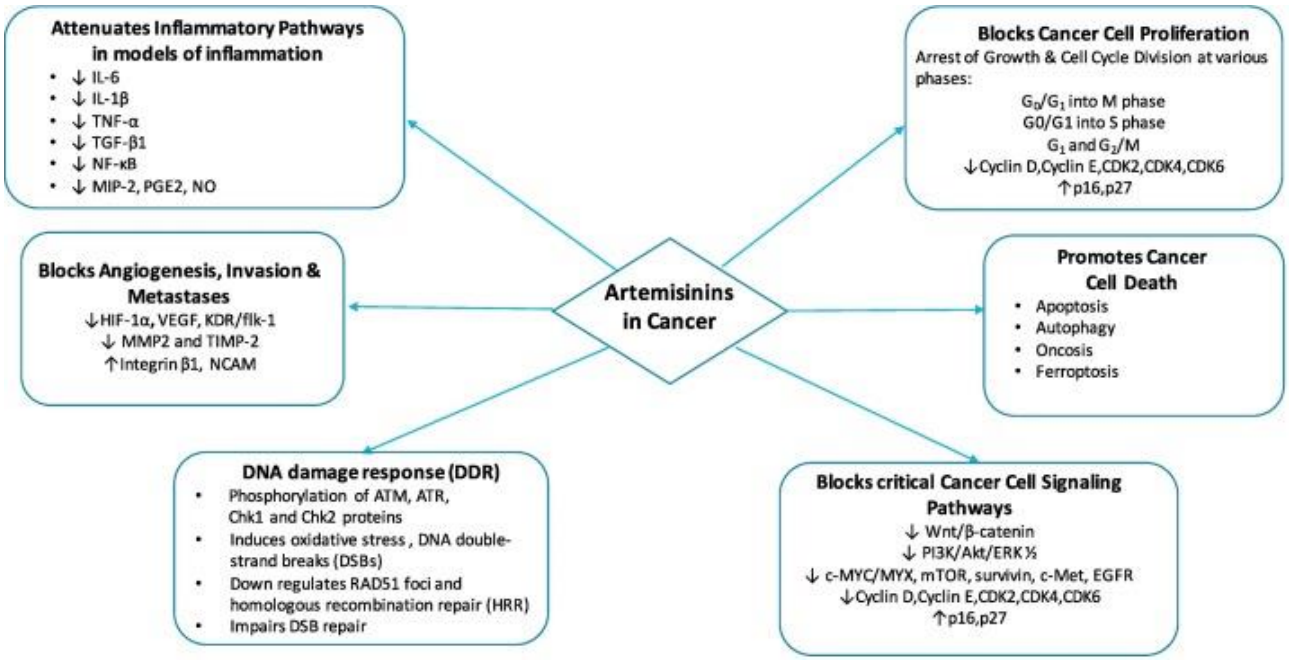


Fig. 2. Artemisinins: multiple modes of action against cancer CDK2/4/6; Cyclin dependent kinase 2/4/6:mTOR; mammalian target of rapamycin: EGFR;epidermal growth factor: HIF---1α; Hypoxia Inducible Factor 1 alpha:VEGF; Vascular endothelial growth factor: KDR/flk---1;kinase insert domain receptor MMP2; Matrix Metallopeptidase 2: TIMP---2; Tissue inhibitor of metalloproteinases 2: NCAM; Neural Cell Adhesion Molecule: IL---6;interleukin---6: IL---1β; Interleukin---1β: TNF---α; Tumour necrosis factor---α: TGF---β1; Transforming growth factor beta 1: NF---κB; nuclear factor kappa---light---chain--- enhancer of activated B cells: MIP---2; Macrophage Inflammatory Protein 2: PGE2; Prostaglandin E2: NO;Nitric Oxide. (Reproduced from Augustin et al. 2020)

The active metabolite of artemisinin, dihydroartemisinin (DHA), has also displayed antineoplastic effects on cervical, breast, glioma, colon, lung, ovarian and pancreatic cancer cell lines (Disbrow et al., 2005 ; Singh & Lai., 2001 ; Kim *et al.,* 2006 ; Lu *et al.,* 2011 ; Mu *et al.,* 2007 ; Chen *et al.*, 2009 ; Hooft van Huijsduijnen., 2013).

Artesunate has been shown to promiscuously target multiple critical biological pathways and over 300 specific artesunate targets using a chemical proteomics approach with artemisinin-based activity probes (Wang *et al*., 2017). Cellular functions associated with these target proteins include growth and proliferation, cell death and survival, protein synthesis, fatty acid metabolism, cellular movement, free radical scavenging and energy metabolism. Pleiotropic alkylation targets in different cell lines raise questions about which ones are key to anticancer effects of artemisinins, and which ones may be bystanders to the main anticancer pathways. In depth mechanism of action studies in various cancer models are needed to better understand the nature of specific molecular targets in different cellular environments.

The exact underlying mechanism of artesunate anti-proliferative effects remain to be elucidated but include actions on cell cycle proteins that control transit through cell cycle G1 phase restriction, induction of apoptosis, inhibition of NF-kB, antioangiogenic and antimetastatic effects. Iron-mediated endoperoxide bridge cleavage and the formation of toxic free radicals are thought to be key mechanisms underlying the anti-cancer effects of artesunate (Efferth *et al*., 2003, 2004). Cancer cells are highly proliferative, requiring a heavy iron load which acts as a cofactor in the synthesis of deoxyriboses prior to cell division (Daniels *et al.*, 2012). Artemisinins induce cellular damage via the formation of reactive oxygen species (ROS) such as hydroxyl and superoxide anion radicals. When free iron is available, artemisinins are converted into a highly potent alkylating radical, capable of inducing direct oxidative damage in cancer cells (Efferth *et al*., 2003, 2004). Cancer cells frequently overexpress the transferrin (TF) receptor. Increased antitumor activity has been observed in human liver hepatocellular carcinoma and lung adenocarcinoma cell lines with increased TF receptor adducts (Yang *et al*., 2014). Artemisinin–transferrin conjugates have been shown to possess higher anti-cancer efficacy than artemisinins alone (Lai *et al.*, 2009 ; Nakase *et al.*, 2008, 2009). For example, a DHA–transferrin conjugate has demonstrated at least 280 times more potent anti-cancer activity in breast cancer cells compared to normal breast cells (Xie *et al.*, 2009).

Artesunate has been shown to induce radiosensitivity in cervical cancer cell lines by inducing apoptosis and G2/M cell cycle arrest (Luo *et al*., 2014). Radiosensitisation with artesunate has also been shown in glioblastoma cell lines by diminishing expression of the anti-apoptotic protein survivin (Reichert *et al*., 2012) and lung cancer cell lines by increasing nitrous oxide production and associated signal transduction pathways, to induce cell cycle arrest in G2/M phase (Zhao *et al*., 2011).

Disbrow et al (2005) found that dihydroartemisinin (DHA) and artesunate displayed strong cytotoxic effects on HPV-immortalized and transformed cervical cells in vitro, inducing apoptosis through activation of the mitochondrial caspase pathway. Apoptosis appeared to be independent of p53 activation and did not appear to be the result of drug-induced reductions in viral oncogene expression.

Inflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-1β (IL-1β),Nuclear factor kappa B (NF-κB). Nitric Oxide (NO) and Tumour Necrosis Factor alpha (TNFα) are key regulators of cancer development (Fishbein et al., 2020). Chronic inflammation in a key characteristic of carcinogenesis and inflammation in the tumour microenvironment leads to the release of pro-inflammatory cytokines and triggers oxidative stress, DNA damage and uncontrolled cell proliferation (Fishbein et al., 2020; Kay et al., 2019). Artesunate has shown to be a potent inhibitor of IL-6, NO, TNF- α and NF-κB in other disease models of inflammation and sepsis (Sordi et al., 2017 ; Khan et al., 2018; Liu et al., 2018; Wan & Li, 2017; Zhao et al., 2017).

Clinical evidence of antiproliferative activity in CIN2/3 and cervical squamous cell cancer

In a Phase I dose-escalation study of artesunate vaginal inserts in biopsy confirmed CIN 2/3 in 28 patients showed that treatment was safe and well tolerated with histological regression observed in 19/28 (68%) subjects and HPV viral clearance in 9/19 subjects (47%) (Trimble *et al.*, 2020). Twenty-eight patients received 1, 2, or 3 five-day treatment cycles at study weeks 0, 2, and 4, respectively, prior to a planned, standard-of-care resection at study week 15. The mean time to regression was shorter in subjects who received 2 or 3 treatment cycles (12.9 weeks, n = 10) compared to the group that received one treatment cycle only (20.4 weeks, n = 9). In patients undergoing histological regression, 9 of the 19 (47.4%) subjects also underwent clearance of HPV

genotypes detected at baseline. In 3 of the 9 subjects, viral clearance was documented concurrently with histological regression whilst in 6 subjects, histological regression preceded viral clearance (range 8 - 35 weeks). Time to viral clearance was longer in subjects treated with one cycle (mean 27.5 weeks, n = 9) compared to those who had received either 2 or 3 treatment cycles (mean 16.5 weeks, n = 10). No subjects underwent viral clearance prior to histological regression. Viral clearance did not occur in any subject who had persistent CIN2/3 at the end of the study. Of note, all residual CIN2/3 lesions were limited to the endocervical glandular compartment, not involving the ectocervix. The authors concluded that intravaginal artesunate pessaries were likely to exert their effects through topical contact that may not penetrate the endocervical compartment (Trimble *et al.,* 2020). This provides further rational for testing an oral, systemic formulation in our study.

In a separate Phase I study, oral and intravenous artesunate were safe when systemically administered and displayed cytotoxic effects on human solid tumours including HPV positive tumours (Deeken *et al.,*2018). A small open label pilot study of dihydroartemisinin (the major active metabolite of artesunate) in 10 patients with advanced cervical cancer reported a reduction in Ki67 proliferation, p53, EGFR and CD31 and symptomatic benefit (Jansen *et al.,* 2011).

3. Trial Design

This is a Phase II single arm, open label study of artesunate to determine the feasibility, safety and preliminary anti-proliferation activity of oral artesunate in HPV +ve High Grade Cervical Intraepithelial Neoplasia (CIN2/3). Patients with HPV positive CIN2/3 will receive 3 cycles of oral artesunate 200mg OD prior to standard of care therapeutic large loop excision transformation zone (LLETZ). Each 21 day treatment cycle will comprise oral artesunate 200mg OD for 14 days followed by a 7 day treatment break. Patients will be followed up clinically after each cycle of treatment till standard of care large loop excision transformation zone (LLETZ) at 90 days. Colposcopy and cervical biopsy to assess histological regression will be performed at 90 days. A cervical sample to test for HPV DNA clearance will also be collected. A vaginal swab will also be collected for vaginome analysis and a faecal sample collected for microbiome analysis.

4. Patient Selection Criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to entering the participant.

The eligibility criteria have been carefully considered and are standard to ensure both the safety of the participants and that the trial results can be appropriately used to make future treatment decisions for other patients with similar disease or medical condition. It is therefore vital exceptions are not made to the following detailed selection criteria.

Deviations from the eligibility criteria are considered to be protocol violations and may be reported to the NPRA as a serious breach.

All participants that are screened for inclusion into the study must be entered onto the Sponsor screening log and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the Sponsors Subject ID log and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. PPUM001.

4.1 Inclusion criteria

- Aged 18 or over
- Histologically proven HPV positive cervical CIN2/3
- WHO performance status 0-2
- Adequate full blood count:
    - White Cell Count (WCC) >3.0 x 109 /l;
    - Platelets >100 x 109/l;
    - Haemoglobin (Hb) >80g/L
- Adequate renal function:
    - Glomerular Filtration Rate >30ml/min
- Adequate hepatobiliary function:
    - Total bilirubin < 3 x Upper limit normal

- Female participants of child bearing potential must have a negative pregnancy test < 72 hours prior to initiating study intervention and agree to avoid pregnancy using adequate, medically approved contraceptive precautions for up to 6 weeks after the last dose of study treatment intervention
- Patient able and willing to provide written, informed consent for the study

4.2 Exclusion criteria

- Contraindication to the use of artesunate due to hypersensitivity
- Pregnancy or lactation
- Weight < 52 kg
- History of previous CIN
- Immunocompromised patients

4.3 Subject Recruitment Process

Participant recruitment at any site will only commence once evidence of the following are in place in the Sponsor site file.

- Relevant ethics committee and NPRA approval
- Delegation of Duties and Sponsorship Agreement signed by the CI
- Final sponsorship (following evidence of Pharmacy green light) issued by the Sponsor representative

All sites participating in the trial will also be asked to provide a copy of the signed Clinical Trial Agreement (CTA) and Confirmation of Capacity and Capability.

Once the trial initiation procedure is completed the Sponsor will issue the 'Open to recruitment' letter. All participants who wish to enter the study will be fully screened and consented by the Principal Investigator, or one of the qualified clinicians involved in the study as Clinical Co-investigator.

NeoART-CIN aims to recruit participants over 24 months with 3 months follow-up. We aim to recruit 2-3 participants to the study per month to meet our recruitment target.

5. Study Interventions and Concomitant Therapy

5.1 Drug information

5.1.1 Drug Administration

Patients with HPV positive CIN2/3 will receive 3 cycles of oral artesunate 200mg OD prior to therapeutic large loop excision transformation zone (LLETZ). Each treatment cycle comprises 21 days, with oral artesunate 200mg OD given for 14 days followed by a 7 day treatment break.

5.1.2 Premedication

No premedication is required.

5.1.3 Patient Monitoring

Baseline temperature, blood pressure, heart rate, oxygen saturations and electrocardiogram will be recorded prior to commencing the IMP. Baseline temperature, blood pressure, heart rate, oxygen saturations will be repeated at each study visit whilst on IMP or as requested by the PI as clinically indicated.

5.1.4 Treatment duration

Patients with HPV positive CIN2/3 will receive 3 cycles of oral artesunate 200mg OD prior to therapeutic large loop excision transformation zone (LLETZ). A treatment cycle comprises 21 days, with oral artesunate 200mg OD given for 14 days followed by a 7 day treatment break.

5.1.5 Dose and schedule modifications

No dosage modifications will be undertaken. Any Grade 3/4 reaction (according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) which occurs in any patient and is deemed related to the IMP by the treating investigator will result in that patient's trial treatment being discontinued. If patients develop Grade 3 neutropenia or more (according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) they should be managed with granulocyte colony stimulating factor (GCSF) supplied via routine hospital pharmacy in accordance with local policy and prescribing practice. The study drug will be stopped and they will continue to be monitored until their full blood count recovers. They will not be recommenced on the study drug but will continue to be followed up within the trial.

5.1.6 Packaging and storage conditions

Study medication will be provided in bottles. One bottle will provide 28 tablets – sufficient for the duration of 1 cycle of treatment. The product labelling will be fully compliant with both Appendix E: Labelling Requirements of the Rules and guidance for Malaysian-Guideline-for-Application-of-CTIL-and-CTX-7.1-Edition and the protocol submitted and authorised by the NPRA.

5.1.7 Pregnancy

Artesunate is teratogenic in animal models and is contraindicated in the first trimester of pregnancy in humans. Pregnant women with malaria nevertheless are exposed to artesunate when no alternatives are available for treatment and studies published to date do not indicate an increased risk of teratogenicity. Pregnant women will not be recruited and participants will be required to use effective methods of medical contraception during the study. Women of child bearing age will be required to undergo a pregnancy test within 72 hours prior to commencing the study and must consent to adequate contraceptive methods from the time of consent and for up to 6 weeks following the end of IMP treatment.

5.1.8 Adverse events associated with artesunate

Artesunate has a good safety profile and has been taken by millions of patients worldwide for malaria. In data taken from studies of malaria, serious side-effects are extremely rare. However the average treatment duration of artesunate in malaria is 3-5 days. In our Phase II study, the treatment duration of 14 days for 3 cycles represents a prolonged duration of treatment compared to conventional treatment for malaria and therefore requires close pharmacovigilance.

The Summary of Product Characteristics for Artesunate provided to sites lists the potential side

effects. The reference safety information document provided to sites lists the adverse events considered by the Sponsor as being 'expected'.

5.1.9 Source of IMP

Bulk artesunate 100 mg tablets are manufactured by HCM- Medical under license according to Good Manufacturing Practice (GMP).

Artesunate is packaged into bottles containing 28 tablets. Package labelling was performed under controlled conditions to ensure no cross contamination. HCM- Medical performed the controlled labelling operation.

Each botttle has a label affixed in accordance with Appendix E: Labelling Requirements of the Rules and guidance for Malaysian-Guideline-for-Application-of-CTIL-and-CTX-7.1-Edition

The named Qualified Person (QP) at HCM- Medical will issue a QP release certificate. The full IMP batch will be delivered, accompanied by the QP batch release certificate to the study sites.

Upon instruction from the Sponsor, HCM-Medical will arrange an appropriate delivery to each participating trial site of sufficient artesunate. Shipment will be under temperature-controlled conditions and the recipient pharmacy department at each site will be required to confirm by return of a completed delivery note as instructed that correct shipment conditions have been maintained. A copy of the QP release will be provided to each site to file in the Pharmacy Site File (PSF).

Full IMP accountability will be maintained at all participating site pharmacy departments or Clinical Research centres.

The IMP artesunate 100 mg tablets must be stored below 25°C. Temperature records are to be maintained with daily minimum/maximum readings via a calibrated/certificated thermometer. The records will be available for monitoring visit purposes and either a copy of those records or a signed statement of compliance will be placed in the Pharmacy Site File (PSF) following the end of IMP treatment phase.

5.1.10 Accountability procedures for the IMP

Each participating site's pharmacy department or research centre will be responsible for maintaining and updating the IMP Accountability Log, filed in the pharmacy site file. All used/unused IMP(s) will be returned to the site pharmacy. If a research pharmacist is not available at the study site, a qualified study coordinator that is not part of the investigator's team can perform this task.

IMP(s) destruction will be conducted, following verification by the Clinical Trials Monitor and agreement by the Sponsor, in accordance with local pharmacy practice. Destruction records will be maintained and filed in the PSF.

5.2 Concomitant therapy

There are no reports of negative drug interactions with artesunate to date. Concomitant medication details will be collected at baseline and any changes recorded at subsequent study visits. The CI will monitor the international literature for drug interactions and report any emerging data to the study sponsor and as part of the annual Development Safety Update Report (DSUR). The study protocol and concomitant medication allowed on study will be updated accordingly.

If patients develop Grade 3 neutropenia or more (according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0) they should be managed with granulocyte colony stimulating factor (GCSF) supplied via routine hospital pharmacy in accordance with local policy and prescribing practice.

5.3 Withdrawal criteria

Patients may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons :

- Unacceptable treatment toxicity or an adverse event
- Investigator decides that it is in the best interests of the patient to terminate his/her participation in the study
- Poor patient compliance and/or major protocol deviation
- Intercurrent illness that prevents further protocol treatment

Withdrawal of consent from the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/study participation a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

Temporary discontinuations of study medication are not permitted. If a patient decides to discontinue treatment then the patient's decision should be documented on the Subject Tracking log, CRF and the IMP returned to the study site Pharmacy or research centre. Participants should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. However if the participant confirms they do not wish to participate in the scheduled follow up data collection visits then data that has already been collected should be kept and analysed according to the ITT principle for all participants who stop follow up early. Patients withdrawn from the study will continue to be followed up according to the study protocol to the scheduled date of study completion, or to recovery or stabilisation of a followed-up Adverse Events (AE), whichever comes last. Routine medical and surgical care of withdrawn participants will continue as planned. The investigator will make every effort to contact the participant in the case of non attendance to a planned review appointment. Participants who stop the trial follow up early will not be replaced.

Participants who develop CTCAE v5.0 Grade 3 or 4 serious adverse effects related to artesunate will be withdrawn from the study treatment but will continue in the study to enable an intention to treat analysis.

There will be a 24 hour emergency card provided to each participant when they receive their IMP dispensed from pharmacy. The 24 hour emergency card will contain the contact details of the local PI and site team in addition to a NeoART-CIN 24 hour emergency telephone number.

All PIs and research team members will have appropriate experience and knowledge of the target patient population. All team members will have demonstrated experience in clinical research and Good Clinical Practice (GCP).

The Chief Investigator (CI) and the CI delegate will construct a Trial Master File and ensure that all essential trial documents are stored safely and securely. The trial will be subject to monitoring in accordance with the Sponsor risk-based monitoring plan. The purpose of the monitoring is to ensure the safety, rights and well being of the trial participants are upheld and that any risk to the trial data is minimised.

5.4 Assessment of compliance

If vomiting occurs during the course of treatment, the dose should not be retaken on the same day. The occurrence and frequency of any vomiting during the reporting period must be noted in the adverse events log and CRF. Each treatment cycle will comprise artesunate 200mg once a day for 14 days followed by a 7 day break. Patients will receive 3 cycles of treatment. At each treatment cycle, an assessment of medication compliance will be made by the principal investigator or delegated research team member on Day 7, Day 14, Day 22, Day 43 and Day 64 based on verbal answers given to direct questioning. This data will be entered into the Case Report Form. Following completion of the patient's IMP treatment period any unused medication will be returned to the site pharmacy department or research centre for the IMP accountability log to be updated. Patients who take the study drug for < 8 days in a 14 day treatment period will be considered 'non-compliant'. All patients will continue to be followed up according to the study protocol regardless of compliance.

5.5 Overdose of Trial medication

In the event of an overdose of trial medication the patient should attend the Accident and Emergency and be urgently reviewed by a member of the research team during working hours or the on-call Medical Officer. A thorough medical history and events leading to the overdose should be documented as well as a complete physical examination including blood pressure monitoring. Blood tests should be performed including full blood count, urea and electrolytes and liver function tests. There is no antidote or documented role for gastric lavage. The overdose should be documented in the participants medical notes and CRF. The Adverse Event log and the Serious Adverse Events (SAE) reporting form should be completed. The completed SAE form should be emailed to the Sponsor in accordance with the protocol.

5.6 List of criteria for premature discontinuation of the study

The study may be discontinued prematurely by the Sponsor, the Data Monitoring Committe(DMC) or the Chief Investigator (CI) if:

- As a result of the interim analysis or any other event during the study there is significant doubt based on statistical evaluation as to the risk/benefit ratio
- The aim of the study has become outdated or is no longer of interest
- There is a serious breach by the investigator of a fundamental obligation under this agreement, including but not limited to breach of the Study Protocol, breach of the applicable laws and regulations or breach of the ICH guidelines for Good Clinical Practice

In all cases the relevant ethics committee and NPRA will be informed in accordance with statutory guidance.

5.7 Lost to Follow up

For all participants that consent and are enrolled in the trial, information in relation to their Next of Kin (NoK) details will be confirmed as correct and current in the patient medical records to facilitate ease of contact throughout the study and data collection period. Following a missed scheduled visit, effort to contact the participant and/or Next of Kin on up to 3 occasions over a 7-10 day period should be made. Each occasion will be documented in the medical notes and on the Telephone log.

5.8 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. The last study visit is at Day 90, when patient attends for colposcopy and standard of care LLETZ. A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit as shown in the Schedule of Assessment.

6. Clinical Evaluation, Laboratory Tests, Follow-Up

6.1 Before treatment start

The following information will be recorded for all subjects up to 7 days prior to starting study treatment on D1(-7 days):

- Demographic details: Date of consent, enrolment, age, ethnicity, HPV vaccination status
- Clinical data: symptomatology, weight, height, vital signs
- Colposcopy findings (within 28 days of study commencement)
- Histology: routine histological grading (within 28 days of study commencement)
- HPV DNA oncotyping (within 28 days of study commencement)
- Concomitant medication: all non-study drugs taken will be recorded

D1 of study

- Baseline safety blood tests full blood count (FBC), Urea and Elelctrolytes (U&E), Liver Function Tests (LFTs) will be conducted at D1
- Baseline study blood tests (plasma, Peripheral Blood Mononuclear Cell (PBMC)) will be collected at D1
- Vaginome and gut microbiome samples will be collected at D1
- Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D))

6.2 During treatment

D7, D14, D22, D36, D43, D57

- Telephone consultation on D7, D36, D57
- Clinical Assessment on D14, D22, D43
- Speculum examination on D22,D43
- Concomitant medication on D14, D22, D43

- Patient self reported adverse events
- Safety blood test – FBC, U&E, LFT on D14, D22, D43,
- Study blood tests (plasma & PBMC) on D14
- Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D)) D7, D14, D22, D43

6.3 After the end of treatment (Follow-up)

Following the end of IMP treatment x 3 cycles, patients will undergo the following:

Day 64 (+ 3 days)

- Clinical Review
- Speculum examination
- Safety blood test – FBC, U&E, LFT
- Study blood tests (plasma & PBMC)
- HPV DNA oncotyping
- Vaginome and gut microbiome samples
- Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D))

Day 90 (+ 14 days)

- Clinical Assessment
- Safety blood test – FBC, U&E, LFT
- Study blood test (plasma & PBMC)
- Colposcopy & endocervical biopsy
- HPV DNA oncotyping
- Vaginome and gut microbiome sampling
- Large Loop Excision Transformation Zone
- Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D))

6.4 Summary table

Study Procedures	**Screening prior to study entry**	**D1 Clinical review prior to start of medication**	**D7 Telephone consultation**	**D14 Clinical Review**	**D22 Clinical Review**	**D36 Telephone consultation**	**D43 Clinical Review**	**D57 Telephone consultation**	**D64 (+3 days) Clinical Review**	**D90 (+14 days) Clinical Review**
Consent	**X**									
Medical History	**X**	**X**		**X**	**X**		**X**		**X**	**X**
Clinical Examination	**X**	**X**			**X**		**X**		**X**	**X**
Telephone consultation review			**X**			**X**		**X**		
Toxicity Assessment			**X**	**X**	**X**		**X**		**X**	**X**
Concomitant medication check		**X**	**X**	**X**	**X**		**X**		**X**	
Patient self-reported events (diary card)			**X**	**X**	**X**		**X**		**X**	**X**
Vital signs		**X**		**X**	**X**		**X**		**X**	**X**
Pregnancy Test		**X**								
Study medication check				**X**			**X**		**X**	
Safety Blood Test (FBC/renal/ liver profile)		**X**		**X**	**X**		**X**		**X**	**X**
Study Blood test		**X**		**X**					**X**	**X**
Speculum examination					**X**		**X**		**X**	
Colposcopy examination + Cervical Biopsy		**X**								**X**
HPV Test		**X**							**X**	**X**
Vaginome + gut microbiome sample		**X**							**X**	**X**
Large Loop Excision Transformation Zone (LETTZ)										**X**
QOL Tools (EuroQol EQ-5D)		**X**	**X**	**X**	**X**		**X**		**X**	**X**

7. Pharmacovigilance

7.1 Safety/Toxicity

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events. This study will use the Common Terminology Criteria for Adverse Events (CTCAE V5.0) for adverse event reporting.

The AE monitoring period will commence on Day 1 of the study (start of IMP) till Day 90 of the study. Adverse events will be assessed by the worst grade and per CTCAE term from first dose until 30 days after last dose of study treatment.

7.2 Reference Safety Information

A NeoART-CIN Reference Safety Information document based upon the Summary Product Characteristics for artesunate (WHOPAR., 2017) forms the Reference Safety Information for this study. Section 4.8 of the Summary Product Characteristics for artesunate (WHOPAR., 2017) lists the following potential side effects. The adverse events are listed by body system, organ class and absolute frequency. They are generally not based on adequately sized randomized controlled trials but on published literature data generated mostly during post-approval use. When frequency estimates are available they are defined as follows: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (< 1/10,000).

Very Common	**Common**	**Uncommon**	**Rare**
Blood and lymphatic disorders			
		Neutropenia Low reticulocyte count	
Cardiac disorders			
		Bradycardia	
Gastrointestinal disorders			
		Mild GI disturbances	
Hepato-biliary disorders			
		Elevated liver enzymes	
General disorders			
			Hypersensitivity (allergic reactions)

7.3 Serious adverse events

Serious adverse events or adverse drug ractions are defined by the *Malaysian Guideline for Safety Reporting of Investigational Products* and *Malaysian Guideline for Good Clinical Practice, 3rd Edition, Item 1.56.*

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL.

Adverse Event (AE) — Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing conditions should only be reported as an adverse event if the condition worsens by at least 1 CTCAE grade. As the IMP has a short half-life, we would expect drug clearance within 24 hours of stopping the IMP.

As part of pharmacovigilance, adverse event data will be collected from the day 1 of IMP dose until 30 days following the end of the IMP treatment schedule.

Adverse Reaction (AR) — All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) — *any untoward medical occurrence that at any dose:*

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity or
- Is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered “serious”.

Suspected Unexpected Serious Adverse Reaction (SUSAR) — an Adverse Reaction which is classed in nature as both serious and unexpected

An ‘Unexpected Adverse Reaction’ is when both the nature and severity of the event is not consistent with the reference safety information available for the IMP in question.

7.4 Investigator responsibilities relating to safety reporting

All Adverse Events whether serious or not will be recorded in the hospital notes in the first instance. A record will also be kept in the participant’s CRF and the Sponsor’s AE Log. In the event of a mildly deranged blood test or clinical observation of no clinical significance to the patient (for example a mildly elevated liver function test or a mildly elevated blood pressure reading in a participant with known hypertension taking prescribed antihypertensive medication), the local PI will be informed and will sign and date the participants CRF. However it will not be necessary to complete an AE CRF or the Sponsor’s AE Log for these minor events.

SAEs or serious adverse reactiosn (SAR)s must be notified to the sponsor as soon as the investigator becomes aware of the event (within 24 hours). Refer to SOP and ensure the completed SAE report form is sent to the sponsor via E-mail.

The sponsor will notify all SUSARs to the NPRA electronically and the relevant ethics committee.

The sponsor will inform the NPRA and relevant ethics committee of SUSARs as soon as possible, but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies. Any additional information will be reported within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products. Follow-up information should be actively sought and follow-up reports should be submitted to the NPCB when it becomes available.

Serious, unexpected ADRs that are not fatal or life-threatening must be notified to the NPCB as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. Follow-up information should be actively sought and follow-up reports should be submitted to the NPCB when it becomes available.

Causality Assessment — All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.

Definitely — there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably — there is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Possibly — there is some evidence to suggest a causal relationship (*e.g.* the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient's clinical condition, other concomitant events).

Unlikely — there is little evidence to suggest there is a causal relationship (*e.g.* the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (*e.g*. the participant's clinical condition, or other concomitant treatments).

Unrelated — there is no evidence of any causal relationship.

Not Assessable — Note if this description is used the sponsor will assume the event is related to the IMP until follow up information is received from the investigator to confirm a definitive causality assessment.

Any SUSAR assessed as related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Expectedness should be based solely on the available Reference Safetu Information (RSI) for the

IMP and will be described using following categories :

Expected — an AE that is classed in nature as serious and which is consistent with the information about the IMP listed in the RSI or clearly defined in this protocol.

Unexpected — an AE that is classed in nature as serious and which is not consistent with the information about the IMP listed in the RSI.

The completed AE Log will be sent to Sponsor upon request and/or every 2 months.

The Chief Investigator (CI) will respond to any SAE queries raised by the Sponsor as soon as possible. Follow up reports must continually be completed within acceptable time-frames and sent to the sponsor as detailed above until the reportable event is considered resolved.

Notification of deaths

All deaths will be reported to the Sponsor irrespective of whether the death is related to disease progression, the IMP or an unrelated event.

7.5 Development Safety Update Reports (DSURs)

The CI or the CI delegate will prepare the DSUR, using the Sponsor's template and in accordance with the Sponsor's SOP. It will be reviewed by the Sponsor and when necessary be referred to an independent committee (*i.e*. Research Governance Safety Sub Committee). The CI or the CI delegate will provide to the relevant ethics committee and the Sponsor will provide to NPCB the prepared DSUR annually within the defined reporting timelines.

7.6 Annual Progress Reports (APRs)

The CI or the CI delegate will prepare the APR in accordance with SOP. Following review by the Sponsor, the CI or the CI delegate will send to the relevant ethics committee the reviewed report. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the ethics committee, until the trial is declared ended

7.7 Pregnancy

Artesunate is teratogenic in animal models and is contraindicated in the first trimester of pregnancy in humans. Pregnant women with malaria nevertheless are exposed to artesunate when no alternatives are available for treatment and studies published to date do not indicate an increased risk of teratogenicity. Pregnant women will not be recruited and participants will be required to use effective methods of medical contraception during the study. Women of child bearing age will be required to undergo a pregnancy test within 72 hours prior to commencing the study and must consent to adequate contraceptive methods from the time of consent and for up to 6 weeks following the end of IMP treatment.

8. Translational Research / Pharmacodynamic Studies

For instructions on processing and storage of study bloods, vaginome and gut microbiome samples please refer to the study lab manual.

9. Data Collection Tool

All data will be handled in accordance with the Data Protection Act. The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only will be used for identification. The Sponsor Subject ID log can be used to cross reference participant's identifiable information.

Case Report Forms will be designed by the CI and the CI delegate and the final version will be approved by the Sponsor.

It is the Investigator's responsibility to ensure the The Staff Delegation of Responsibilities Log is completed and all data entered and recorded in the CRFs are accurate. The Staff Delegation of Responsibilities Log will identify all trial personnel responsible for data collection, entry, handling and managing the trial Redcap database. Basic demographic and clinical information will be gathered at the time of the initial interview and by review of the medical notes if needed.

All laboratory analysis should be reviewed by the PI and where results reported are not within the normal range the PI must clearly annotate 'Not clinically Significant' or 'Clinically significant' and sign and date the results. The relevant results should be carefully transcribed to the Case Report Forms.

In order to ensure completeness of data collected, participants will be contacted by the research team (telephone call/letter) in the event of missing data such as patient quality of life questionnaires.

9.1 Incidental findings

Incidental findings arising during the study will be discussed with the medical and research team involved in the patients care. The medical and research team will always act in the patient's best interest and take appropriate clinical action in accordance with good clinical practice.

9.2 Data handling and analysis

Data will be stored in anonymised form in a password-protected database. We will use a customised study database storage programme. Study documentation will be stored for fifteen years after the completion of the study. Quality Control will be applied at each stage of data handling to ensure that all data are reliable and are processed correctly.

10. Statistical Considerations

10.1 Statistical design

Sample size

This is a Phase II open label, single arm study to investigate the activity of oral artesunate in patients with high grade intraepithelial neoplasia CIN2/3 prior to treatment with large loop excision

transformation zone (LLETZ). The primary end point is histological regression of CIN2/3 on colposcopy and biopsy at Day 90.

Significance level and power: The procedure described above tests the null hypothesis that the response rate is 20 % versus alternating hypotheses that the response rate is 50 %. The significance level (i.e., the probability of rejecting H0 when it is true) is α=0.1 and the power (i.e., 1-beta, the probability of deciding the regimen is active) is 90% when true response rate is 50 %.

At the significance level of 0.05, with an equivalence limit of 0.15, a sample size of 24 is required to achieve 90% power when the response rate for the historical control is 0.2 and response rate for the treatment is 0.5.

Inflating this sample size by 20% to allow for loss at follow-up would result in approximately 28 patients. We believe that 28 patients represents a feasible and achievable target given our time and financial considerations.

10.1.1 Interim analyses / Decision rules

An interim analysis reviewing feasibility and tolerability will be performed once 10% (n = 3) and 50% (n = 14) of patients have completed their day 90 assessments. No early conclusions will be drawn.

10.1.2 Accrual and Duration of Study

The estimated accrual for this study is 3 patients a month. Thus, patient accrual is expected to be completed within 24 months. An additional 6 months is required to allow the response data to mature.

10.2 Statistical Analysis

The study outcome measures are listed in chapter 2. The methods used to evaluate them are detailed in this section. The statistical analysis will be performed using *SAS® and Graphpad software*.

10.2.1 Analysis populations

- Intention-to-treat population: All patients will analysed according treatment allocation.
- Per protocol population: All patients who meet the eligibility criteria and have started their allocated treatment (at least 8 out of 14 doses in cycle 1 of their treatment plan).

Safety population: All patients who have started protocol treatment (e.g., at least one dose of the study drug).

10.2.2 Patient disposition, data recording and display

Patients' demographics, baseline characteristics, prior and concomitant medications, treatment exposure, protocol compliance and study withdrawals will be summarized in the intent-to-treat population. For categorical variables, frequency tables (with %) will be presented with descriptive listings of details specified in text fields, when appropriate. Continuous variables will be reported using median, range and interquartile range.

A CONSORT diagram will be used to document the flow of patients through the various stages of the study. The number of patients included in the various analysis populations will be presented in a table and reasons for exclusions will be detailed in listings.

10.2.3 Safety

Safety analyses will be performed on the safety population. Patients will be analysed according to the treatment actually started, regardless of duration or compliance with treatment.

Periods

- “Baseline” is defined as the period from before study entry to first day of protocol treatment administration. For patients who never started treatment, the baseline period is assumed to end on the day of enrolment.
- "On treatment " is defined as the time on study after baseline (i.e., starting on the first day of protocol treatment administration) to and including 30 days after the day of last protocol treatment administration.
- "Follow-up period" is defined as the period that follows the on-treatment period until the end of the follow up. For patients who never started treatment, the follow-up period is assumed to start on the day of enrolment.

10.2.3.1 Safety analyses

Tables on AEs will report

- all AEs irrespective of their relationship to treatment
- the AEs related to the treatment (excluding those declared not reasonably possibly related to the treatment, but including those with relationship not assessable).

The worst grade of the AEs per patient and per CTCAE term over each period will be tabulated by treatment arm. The percentage of patients on each treatment arm presenting severe treatment-related AE (grade ≥ 3), of patients reported to have died of toxicity and that of patients who stopped treatment due to toxicity will also be calculated and the 95% confidence interval will be presented.

For the reporting of SAEs:

- the study safety overview table will list the number of reported SAE terms, SAR terms and SUSAR terms per treatment arm and the number of reported death and toxic death cases;
- line listings of SAEs and of SARs will be provided;
- the number of SAEs and SARs per System Organ Class and Preferred Term will be tabulated

10.2.4 Study outcome measures

Primary outcome measure(s)

- Histological regression of CIN2/3 on colposcopy and biopsy at Day 90 will be defined as histologic regression to CIN1 or less. This will be described as a response percentage.

Secondary outcome measures

- HPV DNA viral clearance at Day 90
  Viral clearance will be defined as absence of HPV genotype (s) detected at baseline and described as a response percentage.

- Vaginome and gut microbiome at Day 0, Day 64 and Day 90
  Changes in vaginome and gut microbiome will be compared between Day 0 and Day 90.

- Serious Adverse Events at Day 90 using Common Toxicity Criteria (CTCAE V5.0)
  Safety assessment will be based on patients who received at least one dose of IMP.
  Tolerability assessment will be based on the percentage of subjects that complete the designated dosing regimen.
- Patient quality of life using the European Quality of Life–5 Dimensions (EQ-5D) quality of life tool D7, D14, D22, D43, D64, D90.

Toxicity assessments

The proportion of patients experiencing grade 3 or 4 toxicity will be assessed using CTCAE V5.0.

Quality of life

The functional and symptomatic quality of life questionnaires (EuroQol EQ-5D) will be examined by calculating the differences in measurements from baseline. The standard EuroQol EQ-5D recommended methods will be used to calculate function and symptomatic scores. The nature of the variable which quantifies this score will be investigated and summary statistics will be presented for values at baseline and post treatment.

Exploratory outcome measures

Vaginome and gut microbiome

Exploratory analyses will be conducted on patient vaginome and microbiome analysis comparing Day 1 with Day 90.

11. Committees Involved In The Trial

Appropriate oversight mechanisms will be put in place for the trial.

1. Trial Management Group (TMG) – will include those individuals responsible for the day-to-day management of the trial, such as the CI, statistician, trial manager, research nurse, data manager, Clinical Trial Monitor/Sponsor representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Management Group as informed by the TSC

2. Trial Steering Committee (TSC) - provides overall supervision of the trial and ensures that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Trial Steering Committee should agree the trial protocol and any protocol amendments and provide advice to the Investigators on all aspects of the trial. A Trial Steering Committee may have members who are independent of the Investigators, in particular an independent chairperson. The TSC will discharge its safety assessment of the study to the DMC. The TSC will advise the Sponsor directly of

any decision regarding any change to study status in accordance with the NeoART-CIN TSC Charter.

All formally constituted trial groups/committees will be provided with a charter that sets out group composition, quorum requirements, responsibilities, structure of meetings, processes for decision making and reaching consensus.

12. Direct Access To Source Data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, relevant ethics committee review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

13. Site Approval And Ongoing Regulatory Compliance

Before any site can enrol patients into the trial, the Sponsor will be in possession of the relevant ethics committee approval. The site will have a fully executed Clinical Trial Agreement and have received the Open to Recruitment letter issued by the Sponsor. The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and by the regulatory authorities as appropriate and which was given a favourable opinion by the relevant ethics committee and registration with National Medical Research Registration (NMRR).

The Chief Investigator will be provided (via the Sponsor) with file indexes Trial Master File (TMF) index and Investigator Site File (ISF) index for use with SOP 'Preparation and Maintenance of the TMF'. The CI will be responsible for the maintenance of the TMF and will delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the relevant ethics committee and the NPRA are notified that the trial has finished. If the trial is ended prematurely, those reports will be made within 15 days after the end of the trial. Refer to SOP 'End of study declaration'.

The CI will supply an End of Study report of the clinical trial to the NPRA and relevant ethics committee within one year after the end of the trial. The Sponsor will provide the End of study Report template.

14. Monitoring Plan For The Trial

The CI will be requested to complete the Feasibility Questionnaire and forward to the Sponsor to facilitate appropriatecosting and Sponsorship in Principle to be issued prior to the relevant ethics application and NMRR registration. The trial will be monitored according to the risk based monitoring plan agreed by the Sponsor and CI. The investigator's team determine the initial project risk assessment and justify change as the study progresses. The PI at each collaborating site in addition to site monitoring visits will be required to complete self-monitoring form(s) and must return the forms to the Sponsor for review and action. Failure for any PI to comply with requests for

on behalf of the Sponsor may be escalated in accordance with Escalation Procedure ; the site may also be selected for a GCP audit.

It is the Sponsor's Clinical Research Associate' s (CRA) responsibility to ensure that any findings identified in any monitoring report are actioned appropriately and in a timely manner and that any violations of GCP or the protocol will be reported to the CI and Sponsor. Any serious breach will be handled according to Serious Breach Reporting.

Any urgent safety measures at either the CI or a PI site must be reported by that site, as per Malaysian Regulations. The CI and/or the CI delegate will be provided with a copy of the study monitoring plan during the Site Initiation Visit (SIV).

15. Finance

The Malaysian Federal Government, Selangor State Government, charitable and philanthropic donations provided financial support for the study.

16. Insurance And Indemnity

Metanoic Health Limited, United Kingdom as the study Sponsor holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that participating sites have been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. Metanoic Health Limited will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to Metanoic Health Limited upon request.

Participants may be able to claim compensation for injury caused by participation in this Trial without the need to prove negligence on the part of Metanoic Health Limited or another party.

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of Metanoic Health Limited immediately. Failure to alert Metanoic Health Limited without delay and to comply with requests for information by the sponsor or any designated parties may lead to a lack of insurance cover for the incident.

17. Intellectual Property and Development Policy

Unless otherwise specified in agreements, the following guidelines shall apply : All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding :

1) pre-existing IP related to clinical procedures of any participating hospital.
2) pre-existing IP related to analytical procedures of any external laboratory.

All contributors shall assign their rights in relation to all Intellectual Property Rights and in all Know How, not excluded above, to the Sponsor and at the request and expense of the Sponsor, shall

execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

All contributors shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake such Know How as confidential information jointly owned between it and the Sponsor.

Nothing in this section shall be construed so as to prevent or hinder the medical professional team from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

Transfer of ownership of Intellectual Property and Know How from Sponsor will be arranged through the principal funding and coordinating agency in Malaysia (based on funding for the study coming from the Malaysian Federal Government and Selangor State Government).

18. Publication Policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Chief Investigator (CI) in the first instance, in discussion with Sponsor.

18.1 Before the official completion of the Trial

All publications associated with this trial will be discussed with the Sponsor but duties regarding publication will be delegated to the Chief Investigator. Any disputes regarding authorship will be discussed and settled by the Trial Steering Committee. Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

18.2 Up to 180 days after the official completion of the Trial

During this period the Chief Investigator (CI) shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

Insofar as compatible with the policies of the publication outlet and good academic practice, the

other Investigators shall be listed according to contributions and/or under a Trial title such as NeoART-CIN.

Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.

Members of the Steering Group will be acknowledged as co-authors.

18.3 Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least thirty (30) days prior to submission for publication, public dissemination, or review by a publication committee. In exceptional circumstances this should be expedited. Sponsor's reasonable comments shall be reflected.

19. Statement Of Compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the Malaysian country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP, and the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version).

This study will be conducted in compliance with the protocol approved by the relevant ethics committee and according to GCP standards, and Malaysia Clinical Trials Regulations. No major deviations from the protocol will be implemented without the prior review and approval of the Sponsor except where it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the Sponsor and the relevant ethics committee as soon as possible.

20. List of Protocol Appendices

Appendix 1	Protocol Amendment/Revision History
Appendix 2	Summary chart of study assessments
Appendix 3	Quality of Life Questionnaire EuroQol EQ-5D-5L
Appendix 4	Common Terminology Criteria for Adverse Events (CTCAE V5.0)

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Appendix 1. Protocol amendment /Revision History

Protocol Version and Date	Amended text Section details and change
Version 2.0 16 January 2023	Replaced HPV +ve in the Protocol title with Human Papilloma Virus positive replaced on page 1 Added Protocol ID: 2023 - MHL- 002 Added NMRR number: RSCH ID-22-04943-NW0 Added Protocol Version: Version 2.0 Date 16 January 2023 Chief Investigator Professor Sanjeev Krishna MA, MBChB, DPhil, FRCP, ScD, FMedSci St George's, University of London and Centre for Affordable Diagnostics and Therapeutics 30 City Road, London England EC1Y 2AB United Kingdom Mobile: +44 (0)7931901724 Email: skrishna@cadt.org.uk Added SPONSOR: Metanoic Health Limited 36 Clarkes Avenue Worcester Park Surrey United Kingdom Mobile: +44 (0)7798566612 Email: info@metanoichealth.com SPONSOR REPRESENTATIVE: Name: Dr Isaac John Mobile: +44 (0) 7798566612 Email: Isaac.John@metanoichealth.com Removed SPONSOR'S PROJECT NUMBER: 02.0154 <INSERT> ETHICS COMMITTEE ID: <INSERT> NMRR NUMBER: RSCH ID-22-04943-NW0 PROTOCOL VERSION: 1.0 Dated 12 December 2022

	SPONSOR: Centre For Affordable Diagnostics And Therapeutics SPONSOR REPRESENTATIVE: Name: Dr Yolanda Augustin Phone: +447894319056 Email: yaugustin@cadt.org.uk Protocol identification number / code / Registration n° (if applicable) Study Coordinator: Dr Nafeesa Mat Ali Phone: +44 7872101116 e-mail: nmatali@cadt.org.uk
Version 2.0 16 January 2023	Removed This protocol was developed at the EORTC-ESMO-AACR Workshop on Methods in Clinical on page 2 Cancer Research. Removed Chief Investigator and Co-Investigator list on page 2 Replaced with Signature Page and Statement on page 2 The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except in the case of a medical emergency or where departures from the protocol are mutually agreed in writing. The investigators agree to conduct the trial in compliance with the approved protocol, Malaysian Good Clinical Practice (GCP) and National Pharmaceutical Regulatory Authority (NPRA) Regulations for Clinical Trial Import License (CTIL), the Malaysian Data Protection Act, local governance policy, the Sponsor's SOPs, and other regulatory requirements as stipulated. This protocol has been written in accordance with the Sponsor's procedure and is intended for use at Malaysian sites only. Replaced with Acknowledgements and Protocol contributories
Version 2.0 16 January 2023	Added Roles and Responsibility on Page 9-11
Version 2.0 16 January 2023	Added Protocol summary Study Assessments: Patients will have study bloods samples for translational research collected on Day 1, Day 14, Day 64 and Day 90 of the study. HPV DNA will be tested on vaginal sampling Day 1, Day 64 and Day 90 of the study. Vaginome and microbiome samples will be collected on Day 1 and Day 90. A laboratory manual has been prepared separate to this protocol.

	European Quality of Life–5 Dimensions (EQ-5D-5L) quality of life tool will be completed on Day 1, Day 7, Day 14, Day 22, Day 43, Day 64 and Day 90 of the study.
Version 2.0 16 January 2023	Amended Schematic design of trial
Version 2.0 16 January 2023	Added In a separate Phase I study, oral and intravenous artesunate were safe when systemically administered and displayed cytotoxic effects on human solid tumours including HPV positive tumours (Deeken et al.,2018). A small open label pilot study of dihydroartemisinin (the major active metabolite of artesunate) in 10 patients with advanced cervical cancer reported a reduction in Ki67 proliferation, p53, EGFR and CD31 and symptomatic benefit (Jansen et al., 2011) on page 23
Version 2.0 16 January 2023	Added This is a Phase II single arm, open label study of artesunate to determine the feasibility, safety and preliminary anti-proliferation activity of oral artesunate in HPV +ve High Grade Cervical Intraepithelial Neoplasia (CIN2/3). Patients with HPV positive CIN2/3 will receive 3 cycles of oral artesunate 200mg OD prior to standard of care therapeutic large loop excision transformation zone (LLETZ). Each 21 day treatment cycle will comprise oral artesunate 200mg OD for 14 days followed by a 7 day treatment break. Patients will be followed up clinically after each cycle of treatment till standard of care large loop excision transformation zone (LLETZ) at 90 days. Colposcopy and cervical biopsy to assess histological regression will be performed at 90 days. A cervical sample to test for HPV DNA clearance will also be collected. A vaginal swab will also be collected for vaginome analysis, and a faecal sample collected for microbiome analysis on page 23 3. Trial design
Version 2.0 16 January 2023	Replaced Pamoja BV with HCM-Medical in 5.1.9 Source of IMP
Version 2.0 16 January 2023	Added The CI will monitor the international literature for drug interactions and report any emerging data to the study sponsor and as part of the annual Development Safety Update Report (DSUR). The study protocol and concomitant medication allowed on study will be updated accordingly to 5.2 Concomitant theraphy
Version 2.0 16 January 2023	Removed D14 from 6.2 During treatment D7, D14, D22, D43 • Speculum examination on D22,D43 Added D7 to • Patient self reported adverse events on D7,D14, D22, D43 Added plasma & PBMC • Study blood tests (plasma & PBMC) on D14 Added D22

	• Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D)) D7, D14, D22, D43 Added Study blood tests (plasma & PBMC) and Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D)) D64 to 6.3 After the end of treatment (Follow-up) and Following the end of IMP treatment x 3 cycles, patients will undergo the following: Added Quality of Life Tool (European Quality of Life–5 Dimensions (EQ-5D)) to Day 90 (+ 14 days)
Version 2.0 16 January 2023	Amended 6.4 Summary table
Version 3.0 6 January 2024	Front page Changed version to 3.0 and Date 6 January 2024 Changes Sponsor's email clinicaltrials@metanoichealth.com
Version 3.0 6 January 2024	Signature Page and Statement Added signature and date 6 January 2024
Version 3.0 6 January 2024	Protocol synopsis Amended Protocol number 2023-MHL-002
Version 3.0 6 January 2024	Removed Professor Adeeba Kamarulzaman Department of Medicine Faculty of Medicine, University of Malaya Lembah Pantai,59100 Kuala Lumpur, Malaysia. Email: adeeba@ummc.edu.my Dr Zatul Akmar binti Ahmad Hospital UiTM KS359 Pintu Utama UiTM, 42300, Selangor, Malaysia, Mobile: +60 (0)193839020 Email: drzatul@gmail.com
Version 3.0 6 January 2024	Schematic design trial Removed Day 14, 22, 43 and 64
Version 3.0 6 January 2024	4.3 Subject Recruitment Process Changed 'NeoART-CIN aims to recruit participants between 1st of August 2023 -31st of July 2024. We aim to recruit 2-3 participants to the study per month to meet our recruitment target' to NeoART-CIN aims to recruit participants over 12-18 months. We aim to recruit 2-3 participants to the study per month to meet our recruitment target.
Version 3.0 6 January 2024	15. Finance Added 'The Malaysian Federal Government'
Version 3.0 6 January 2024	17. Intellectual Properties and Development Policy Added

	'Transfer of ownership of Intellectual Property and Know How from Sponsor will be arranged through the principal funding and coordinating agency in Malaysia (based on funding for the study coming from the Malaysian Federal Government and Selangor State Government).'
Version 3.0 6 January 2024	Added Appendix 1. Protocol amendment /Revision History
Version 4.0 1 May 2024	Added 1.2.2 Secondary outcome measures Vaginome and gut microbiome at Day 1, Day 64 and Day 90. Changes in vaginome and gut microbiome will be compared between Day 1, Day 64 and Day 90. 6.3 Added Vaginome and gut microbiome samples will be collected at D64
Version 4.0 1 May 2024	Changed 1 June 2024 to 'NeoART-CIN aims to recruit participants over 24 months with 3 months follow-up. We aim to recruit 2-3 participants to the study per month to meet our recruitment target.'
Version 5.0 13 November 2024	Changed Schematic drawing to add telephone review on D36 and D57
Version 5.0 13 November 2024	Added telephone review on D36 and D57, removed D7, D4, D22 and D43 from patient self-reported adverse event. Updated the 6.2 Summary Table
Version 5.0 13 November 2024	**Removed** Dr Nik Ahmad Nik Abdullah Hospital Raja Perempuan Zainab II Bandar Kota Bharu, 15586 Kota Bharu, Kelantan, Malaysia **Mobile:** +60 (0)13-9336161 **Email:** nikahmadkb@me.com