PHOTODYNAMIC THERAPY FOR A CERVIX DISORDER OR CONDITION

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of the priority of International Application Nos. PCT/CN2024/081168, filed March 12, 2024, and PCT/CN2024/116532, filed September 3, 2024, under 35 U.S.C. 119(a); the disclosure of each of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein is a photodynamic therapy using hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof for treating, preventing, or ameliorating a cervix disorder or condition.

BACKGROUND

[0003] Cervical cancer is the fourth most common cancer in women worldwide, almost exclusively linked to a high-risk human papillomavirus (HPV) infection. Sung *et al.*, *CA Cancer J. Clin.* **2020**, *71*, 209-49; Chen *et al.*, *BMJ Open* **2022**, *12*, e061740. In 2020, 604,000 new cases and 342,000 deaths worldwide were attributed to cervical cancer. Chen *et al.*, *BMJ Open* **2022**, *12*, e061740. A persistent HPV infection increases the risk of carcinogenic progression to cervical precancerous conditions, *e.g.*, high-grade squamous intraepithelial lesion (HSIL), and eventually to cervical cancer if left untreated. Gravitt *et al.*, *Viruses* **2017**, *9*, 267; Usyk *et al.*, *PLoS Pathog.* **2020**, *16*, e1008376. The high-risk types HPV16/HPV18 represent a considerable challenge for host-cell clearance. Hildesheim *et al.*, *JAMA* **2007**, *298*, 743-53. HPV16 reinfection and reappearance of infected viral DNA has been observed in a subset of women. Moscicki *et al.*, *J. Infect. Dis.* **2013**, *208*, 403-12.

[0004] Current treatments for HSIL are limited to invasive surgical procedures, including cryotherapy, electrocauterization, laser vaporization, loop electrosurgical excision procedure (LEEP), and cervical conization. Khan *et al.*, *Obstet. Gynecol.* **2014**, *123*, 1339-43; Hillemanns *et al.*, *Expert Opin. Investig. Drugs* **2015**, *24*, 273-81; Perkins *et al.*, *J. Low. Genit. Tract. Dis.* **2020**, *24*, 102-31; Chen *et al.*, *BMJ Open* **2022**, *12*, e061740. However, these surgical

procedures increase the risk of pre-term labor, low birth weight, premature rupture of membranes, and caesarean section. Kyrgiou *et al.*, *Lancet* **2006**, *367*, 489-98; Arbyn *et al.*, *BMJ* **2008**, *337*, a1284; Simoens *et al.*, *BJOG* **2012**, *119*, 1247-55; Kyrgiou *et al.*, *Cochrane Database Syst. Rev.* **2017**, *11*, CD012847. Additionally, about 16-30% of HSIL patients relapse within six months after an invasive procedure. Repeated surgical interventions are also not recommended. Chen *et al.*, *BMJ Open* **2022**, *12*, e061740.

[0005] Currently, there is no noninvasive alternative for the management of precancerous lesions such as HSIL. Hillemanns *et al.*, *Expert Opin. Investig. Drugs* **2015**, *24*, 273-81; Dadar *et al.*, *Front. Immunol.* **2018**, *9*, 2478; Desravines *et al.*, *Gynecol. Oncol. Rep.* **2020**, *33*, 100608; Xiong *et al.*, *Medicine* **2020**, *99*, e23155. Surgical methods remain the standard of care. Chen *et al.*, *BMJ Open* **2022**, *12*, e061740. Therefore, there is an urgent unmet need for a noninvasive therapy for treating a cervix disorder or condition effectively. Hillemanns *et al.*, *Expert Opin. Investig. Drugs* **2015**, *24*, 273-81; Chen *et al.*, *BMJ Open* **2022**, *12*, e061740.

SUMMARY OF THE DISCLOSURE

[0006] Provided herein is a method of treating, preventing, or ameliorating a cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0007] Also provided herein is a method of treating, preventing, or ameliorating a precancerous cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0008] Additionally, provided herein is a method of treating, preventing, or ameliorating cervical intraepithelial neoplasia in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0009] Furthermore, provided herein is a method of treating, preventing, or ameliorating a high-grade squamous intraepithelial lesion in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0010] Provided herein is a method of treating, preventing, or ameliorating an HPV infection in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0011] Provided herein is a method of inhibiting the replication of HPV in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0012] Provided herein is a method of reducing an HPV proliferation rate in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises

hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0013] Provided herein is a method of eliminating HPV in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0014] Provided herein is a method of clearing HPV in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0015] Provided herein is a method of treating, preventing, or ameliorating a cancerous cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0016] Provided herein is a method of treating, preventing, or ameliorating cervical cancer in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 illustrates an integrated drug- and light-delivery device with a two-part housing in perspective view.

[0018] FIG. 2 is a cross-section elevation through the integrated device of FIG. 1.

DETAILED DESCRIPTION

[0019] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0020] Generally, the nomenclature used herein and the laboratory procedures in medicinal chemistry, biochemistry, biology, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0021] The term "subject" refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject. In one embodiment, the subject is a human.

[0022] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0023] The terms "prevent," "preventing," and "prevention" are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject's risk of acquiring a disorder, disease, or condition.

[0024] The terms "alleviate" and "alleviating" refer to easing or reducing one or more symptoms (*e.g.,* pain) of a disorder, disease, or condition. The terms can also refer to reducing adverse effects associated with an active ingredient. Sometimes, the beneficial effects that a subject derives from a prophylactic or therapeutic agent do not result in a cure of the disorder, disease, or condition.

[0025] The term "contacting" or "contact" is meant to refer to bringing together of a therapeutic agent and a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, or

tissue such that a physiological and/or chemical effect takes place as a result of such contact. Contacting can take place *in vitro*, *ex vivo*, or *in vivo*. In one embodiment, a therapeutic agent is contacted with a biological molecule *in vitro* to determine the effect of the therapeutic agent on the biological molecule. In another embodiment, a therapeutic agent is contacted with a cell in cell culture (*in vitro*) to determine the effect of the therapeutic agent on the cell. In yet another embodiment, the contacting of a therapeutic agent with a biological molecule, cell, or tissue includes the administration of a therapeutic agent to a subject having the biological molecule, cell, or tissue to be contacted.

[0026] The term "therapeutically effective amount" or "effective amount" is meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" or "effective amount" also refers to the amount of a compound that is sufficient to elicit a biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0027] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of a subject (*e.g.*, a human) without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, and commensurate with a reasonable benefit/risk ratio. *See*, *e.g.*, *Remington: The Science and Practice of Pharmacy*, 23rd ed.; Adejare Ed.; Academic Press, 2020; *Handbook of Pharmaceutical Excipients*, 9th ed.; Sheskey *et al.*, Eds.; Pharmaceutical Press, 2020; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Synapse Information Resources, 2007; *Pharmaceutical Preformulation and Formulation*, 1st ed.; Gibson Ed.; CRC Press, 2015.

[0028] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, or 3 standard deviations. In certain embodiments, the term "about" or "approximately" means within 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0029] The term "semi-solid" or "quasi-solid" refers to a physical state that shares certain properties with both a solid and liquid. For example, a semi-solid has the ability to support its own weight and hold its shape; and also has the ability to conform to the shape of a container and flow under pressure.

Method of Treatment

[0030] In one embodiment, provided herein is a method of treating, preventing, or ameliorating a cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0031] In certain embodiments, the cervix disorder or condition is a disorder or condition associated with a human papillomavirus (HPV) infection. In certain embodiments, the cervix disorder or condition is a precancerous disorder or condition.

[0032] In one embodiment, provided herein is a method of treating, preventing, or ameliorating a precancerous cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0033] In certain embodiments, the cervix disorder or condition is a precancerous disorder or condition associated with an HPV infection. In certain embodiments, the precancerous disorder or condition is associated with a high-risk HPV infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the precancerous cervix disorder or condition is associated with an HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is associated with an HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 16 or HPV 18 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 16 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 18 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 31 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 33 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 35 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 39 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 45 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 51 infection. In certain embodiments, the precancerous disorder or condition is associated

with an HPV 52 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 56 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 58 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 59 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 66 infection. In certain embodiments, the precancerous disorder or condition is associated with an HPV 68 infection.

[0034] In certain embodiments, the precancerous cervix disorder or condition is cervical adenocarcinoma in situ, cervical intraepithelial neoplasia (CIN), or squamous intraepithelial lesion (SIL). In certain embodiments, the precancerous cervix disorder or condition is cervical adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is CIN, which is also known as cervical dysplasia.

[0035] In one embodiment, provided herein is a method of treating, preventing, or ameliorating CIN in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0036] In certain embodiments, the precancerous cervix disorder or condition is cervical intraepithelial neoplasia 1 (CIN1), cervical intraepithelial neoplasia 2 (CIN2), or cervical intraepithelial neoplasia 3 (CIN3). In certain embodiments, the precancerous cervix disorder or condition is CIN1. In certain embodiments, the precancerous cervix disorder or condition is CIN2 or CIN3. In certain embodiments, the precancerous cervix disorder or condition is CIN2. In certain embodiments, the precancerous cervix disorder or condition is CIN3.

[0037] In certain embodiments, the precancerous cervix disorder or condition is SIL. In certain embodiments, the precancerous cervix disorder or condition is low-grade squamous intraepithelial lesion (LSIL) or high-grade squamous intraepithelial lesion (HSIL). In certain embodiments, the precancerous cervix disorder or condition is LSIL. In certain embodiments, the precancerous cervix disorder or condition is HSIL. In certain embodiments, the precancerous cervix disorder or condition is HSIL with no cervical invasive cancer. In certain embodiments, the precancerous cervix disorder or condition is HSIL with no adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is HSIL with neither cervical invasive cancer nor adenocarcinoma in situ.

[0038] In certain embodiments, the precancerous cervix disorder or condition is histologically confirmed HSIL. In certain embodiments, the precancerous cervix disorder or condition is histologically confirmed HSIL with no cervical invasive cancer. In certain embodiments, the precancerous cervix disorder or condition is histologically confirmed HSIL with no adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is histologically confirmed HSIL with neither cervical invasive cancer nor adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is histologically confirmed CIN3 with a lesion area of no more than about 50%.

[0039] In one embodiment, provided herein is a method of treating, preventing, or ameliorating HSIL in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0040] In certain embodiments, the precancerous cervix disorder or condition is histologic HSIL. In certain embodiments, the precancerous cervix disorder or condition is biopsy-confirmed HSIL.

[0041] In certain embodiments, the precancerous cervix disorder or condition is persistent. In certain embodiments, the cervix disorder or condition is persistent cervical adenocarcinoma in situ, persistent CIN, or persistent SIL. In certain embodiments, the precancerous cervix disorder or condition is persistent cervical adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN1, persistent CIN2, or persistent CIN3. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN1. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN2 or persistent CIN3. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN2. In certain embodiments, the precancerous cervix disorder or condition is persistent CIN3. In certain embodiments, the precancerous cervix disorder or condition is persistent SIL. In certain embodiments, the precancerous cervix disorder or condition is persistent LSIL or persistent HSIL. In certain embodiments, the precancerous cervix disorder or condition is persistent LSIL. In certain embodiments, the precancerous cervix disorder or condition is persistent HSIL. In certain embodiments, the precancerous cervix disorder or condition is persistent histologic HSIL. In certain embodiments, the precancerous cervix disorder or condition is persistent biopsy-confirmed HSIL.

[0042] In certain embodiments, the precancerous cervix disorder or condition is recurrent. In certain embodiments, the cervix disorder or condition is recurrent cervical adenocarcinoma in situ, recurrent CIN, or recurrent SIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent cervical adenocarcinoma in situ. In certain embodiments, the precancerous cervix disorder or condition is recurrent CIN. In certain embodiments, the precancerous cervix disorder or condition is recurrent CIN1, recurrent CIN2, or recurrent CIN3. In certain embodiments, the precancerous cervix disorder or condition is recurrent CIN1. In certain embodiments, the precancerous cervix disorder or condition is recurrent CIN2 or recurrent CIN3. In certain embodiments, the precancerous cervix disorder or condition is recurrent CIN2. In certain embodiments, the precancerous cervix disorder or condition is

recurrent CIN3. In certain embodiments, the precancerous cervix disorder or condition is recurrent SIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent LSIL or recurrent HSIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent LSIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent HSIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent histologic HSIL. In certain embodiments, the precancerous cervix disorder or condition is recurrent biopsy-confirmed HSIL.

[0043] In certain embodiments, the precancerous cervix disorder or condition is an HPV infection.

[0044] In one embodiment, provided herein is a method of treating, preventing, or ameliorating an HPV infection in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0045] In certain embodiments, the precancerous cervix disorder or condition is a low-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a high-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 16

or HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 16 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 31 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 35 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 39 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 45 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 51 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 52 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 56 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 59 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 66 infection. In certain embodiments, the precancerous cervix disorder or condition is an HPV 68 infection.

[0046] In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent low-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent high-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 16 or HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 16 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 31 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 35 infection. In certain embodiments, the precancerous cervix

disorder or condition is a persistent HPV 39 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 45 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 51 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 52 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 56 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 59 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 66 infection. In certain embodiments, the precancerous cervix disorder or condition is a persistent HPV 68 infection.

[0047] In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent low-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent high-risk HPV infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 16 or HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 16 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 18 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 31 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 33 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 35 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 39 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 45 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 51 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 52 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 56 infection. In

certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 58 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 59 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 66 infection. In certain embodiments, the precancerous cervix disorder or condition is a recurrent HPV 68 infection.

[0048] In one embodiment, provided herein is a method of inhibiting the replication of HPV in an HPV-positive subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contract of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0049] In another embodiment, provided herein is a method of reducing an HPV proliferation rate in an HPV-positive subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0050] In yet another embodiment, provided herein is a method of eliminating HPV in an HPV-positive subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contract of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0051] In still another embodiment, provided herein is a method of clearing HPV in an HPV-positive subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0052] In certain embodiments, the HPV is low-risk HPV. In certain embodiments, the HPV is high-risk HPV. In certain embodiments, the HPV is HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68. In certain embodiments, the HPV is HPV 16, HPV 31, or HPV 33. In certain embodiments, the HPV is HPV 16, HPV 52, or HPV 58. In certain embodiments, the HPV is HPV 16 or HPV 18. In certain embodiments, the HPV is HPV 16. In certain embodiments, the HPV is HPV 18. In certain embodiments, the HPV is HPV 31. In certain embodiments, the HPV is HPV 33. In certain embodiments, the HPV is HPV 35. In certain embodiments, the HPV is HPV 39. In

certain embodiments, the HPV is HPV 45. In certain embodiments, the HPV is HPV 51. In certain embodiments, the HPV is HPV 52. In certain embodiments, the HPV is HPV 56. In certain embodiments, the HPV is HPV 58. In certain embodiments, the HPV is HPV 59. In certain embodiments, the HPV is HPV 58. In certain embodiments, the HPV is HPV 66. In certain embodiments, the HPV is HPV 58. In certain embodiments, the HPV is HPV 68.

[0053] In certain embodiments, the cervix disorder or condition is a cancerous cervix disorder or condition.

[0054] In one embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of a cancerous cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contract of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0055] In certain embodiments, the cancerous cervix disorder or condition is a cancerous cervix disorder or condition associated with an HPV infection. In certain embodiments, the cancerous cervix disorder or condition is associated with a high-risk HPV infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 16 or HPV 18 infection. In certain embodiments, the cervix cancerous disorder or

condition is associated with an HPV 16 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 18 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 31 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 33 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 35 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 39 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 45 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 51 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 52 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 56 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 58 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 59 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 66 infection. In certain embodiments, the cancerous cervix disorder or condition is associated with an HPV 68 infection.

[0056] In certain embodiments, the cervix disorder or condition is cervical cancer. In certain embodiments, the cervical cancer is associated with an HPV infection.

[0057] In one embodiment, provided herein is a method of treating, preventing, or ameliorating one or more symptoms of cervical cancer in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) contacting the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix thereafter with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

[0058] In certain embodiments, the cervical cancer is associated with a high-risk HPV infection. In certain embodiments, the cervical cancer is associated with an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, or HPV 68 infection. In certain embodiments, the cervical cancer is associated with an HPV 16, HPV 31, or HPV 33 infection. In certain embodiments, the cervical cancer is associated with an HPV 16, HPV 52, or HPV 58 infection. In certain embodiments, the cervical cancer is associated with an HPV 16 or HPV 18 infection. In certain embodiments, the cervical cancer is associated with an HPV 16 infection. In certain embodiments, the cervical cancer is associated with an HPV 18 infection. In certain embodiments, the cervical cancer is associated with an HPV 31 infection. In certain embodiments, the cervical cancer is associated with an HPV 33 infection. In certain embodiments, the cervical cancer is associated with an HPV 35 infection. In certain embodiments, the cervical cancer is associated with an HPV 39 infection. In certain embodiments, the cervical cancer is associated with an HPV 45 infection. In certain embodiments, the cervical cancer is associated with an HPV 51 infection. In certain embodiments, the cervical cancer is associated with an HPV 52 infection. In certain embodiments, the cervical cancer is associated with an HPV 56 infection. In certain embodiments, the cervical cancer is associated with an HPV 58 infection. In certain embodiments, the cervical cancer is associated with an HPV 59 infection. In certain embodiments, the cervical cancer is associated with an HPV 66 infection. In certain embodiments, the cervical cancer is associated with an HPV 68 infection.

[0059] In certain embodiments, the cervical cancer is squamous cell carcinoma or adenocarcinoma. In certain embodiments, the cervical cancer is squamous cell carcinoma. In certain embodiments, the cervical cancer is adenocarcinoma. In certain embodiments, the cervical cancer is stage I, II, III, or IV. In certain embodiments, the cervical cancer is stage I. In certain embodiments, the cervical cancer is stage IA, IA1, IA2, IB, IB1, IB2, or IB3. In certain embodiments, the cervical cancer is stage IA. In certain embodiments, the cervical cancer is IA1. In certain embodiments, the cervical cancer is stage IA2. In certain embodiments, the cervical cancer is stage IB. In certain embodiments, the cervical cancer is stage IB1. In certain embodiments, the cervical cancer is stage IB2. In certain embodiments, the cervical cancer is stage IB3. In certain embodiments, the cervical cancer is stage II. In certain embodiments, the cervical cancer is stage IIA, IIA1, IIA2, or IIB. In certain embodiments, the cervical cancer is

stage IIA. In certain embodiments, the cervical cancer is stage IIA1, In certain embodiments, the cervical cancer is stage IIA2. In certain embodiments, the cervical cancer is stage IIB. In certain embodiments, the cervical cancer is stage III. In certain embodiments, the cervical cancer is stage IIIA, IIIB, or IIIC. In certain embodiments, the cervical cancer is stage IIIA. In certain embodiments, the cervical cancer is stage IIIB. In certain embodiments, the cervical cancer is stage IIIC. In certain embodiments, the cervical cancer is stage IV. In certain embodiments, the cervical cancer is stage IVA or IVB. In certain embodiments, the cervical cancer is stage IVA. In certain embodiments, the cervical cancer is stage IVB.

[0060] In certain embodiments, the cervical cancer is persistent. In certain embodiments, the cervical cancer is persistent squamous cell carcinoma or persistent adenocarcinoma. In certain embodiments, the cervical cancer is persistent squamous cell carcinoma. In certain embodiments, the cervical cancer is persistent adenocarcinoma. In certain embodiments, the persistent cervical cancer is stage I, II, III, or IV. In certain embodiments, the persistent cervical cancer is stage I. In certain embodiments, the persistent cervical cancer is stage IA, IA1, IA2, IB, IB1, IB2, or IB3. In certain embodiments, the persistent cervical cancer is stage IA. In certain embodiments, the persistent cervical cancer is stage IA1. In certain embodiments, the persistent cervical cancer is stage IA2. In certain embodiments, the persistent cervical cancer is stage IB. In certain embodiments, the persistent cervical cancer is stage IB1. In certain embodiments, the persistent cervical cancer is stage IB2. In certain embodiments, the persistent cervical cancer is stage IB3. In certain embodiments, the persistent cervical cancer is stage II. In certain embodiments, the persistent cervical cancer is stage IIA, IIA1, IIA2, or IIB. In certain embodiments, the persistent cervical cancer is stage IIA. In certain embodiments, the persistent cervical cancer is stage IIA1. In certain embodiments, the persistent cervical cancer is stage IIA2. In certain embodiments, the persistent cervical cancer is stage IIB. In certain embodiments, the persistent cervical cancer is stage III. In certain embodiments, the persistent cervical cancer is stage IIIA, IIIB, or IIIC. In certain embodiments, the persistent cervical cancer is stage IIIA. In certain embodiments, the persistent cervical cancer is stage IIIB. In certain embodiments, the persistent cervical cancer is stage IIIC. In certain embodiments, the persistent cervical cancer is stage IV. In certain embodiments, the persistent cervical cancer is stage IVA or IVB. In certain embodiments, the persistent cervical cancer is stage IVA. In certain embodiments, the persistent cervical cancer is stage IVB.

[0061] In certain embodiments, the cervical cancer is recurrent. In certain embodiments, the cervical cancer is recurrent squamous cell carcinoma or recurrent adenocarcinoma. In certain embodiments, the cervical cancer is recurrent squamous cell carcinoma. In certain embodiments, the cervical cancer is recurrent adenocarcinoma. In certain embodiments, the recurrent cervical cancer is stage I, II, III, or IV. In certain embodiments, the recurrent cervical cancer is stage I. In certain embodiments, the recurrent cervical cancer is stage IA, IA1, IA2, IB, IB1, IB2, or IB3. In certain embodiments, the recurrent cervical cancer is stage IA. In certain embodiments, the recurrent cervical cancer is stage IA1. In certain embodiments, the recurrent cervical cancer is stage IA2. In certain embodiments, the recurrent cervical cancer is stage IB. In certain embodiments, the recurrent cervical cancer is stage IB1. In certain embodiments, the recurrent cervical cancer is stage IB2. In certain embodiments, the recurrent cervical cancer is stage IB3. In certain embodiments, the recurrent cervical cancer is stage II. In certain embodiments, the recurrent cervical cancer is stage IIA, IIA1, IIA2, or IIB. In certain embodiments, the recurrent cervical cancer is stage IIA. In certain embodiments, the recurrent cervical cancer is stage IIA1. In certain embodiments, the recurrent cervical cancer is stage IIA2. In certain embodiments, the recurrent cervical cancer is stage IIB. In certain embodiments, the recurrent cervical cancer is stage III. In certain embodiments, the recurrent cervical cancer is stage IIIA, IIIB, or IIIC. In certain embodiments, the recurrent cervical cancer is stage IIIA. In certain embodiments, the recurrent cervical cancer is stage IIIB. In certain embodiments, the recurrent cervical cancer is stage IIIC. In certain embodiments, the recurrent cervical cancer is stage IV. In certain embodiments, the recurrent cervical cancer is stage IVA or IVB. In certain embodiments, the recurrent cervical cancer is stage IVA. In certain embodiments, the recurrent cervical cancer is stage IVB.

[0062] In certain embodiments, the cervical cancer is refractory and/or relapsed. In certain embodiments, the cervical cancer is refractory. In certain embodiments, the cervical cancer is relapsed. In certain embodiments, the cervical cancer is metastatic. In certain embodiments, the cervical cancer is unresectable.

[0063] In certain embodiments, the cervical cancer is drug-resistant. In certain embodiments, the cervical cancer is multidrug-resistant. In certain embodiments, the cervical cancer is resistant to a chemotherapy. In certain embodiments, the cervical cancer is resistant to

an immunotherapy. In certain embodiments, the cervical cancer is resistant to a standard therapy for the cancer.

[0064] In certain embodiments, the administering step in a method provided herein is administering intravaginally to the ectocervix of the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0065] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate and a pharmaceutically acceptable excipient. In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate, a triglyceride, and a thickener.

[0066] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises a pharmaceutically acceptable salt of hexyl 5-aminolevulinate and a pharmaceutically acceptable excipient. In certain embodiments, the semi-solid pharmaceutical composition described herein comprises a pharmaceutically acceptable salt of hexyl 5-aminolevulinate, a triglyceride, and a thickener.

[0067] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises a pharmaceutically acceptable salt of hexyl 5-aminolevulinate in an amount ranging from about 1 to about 10% by weight, a triglyceride in an amount ranging from about 70 to about 85% by weight, and a thickener in an amount ranging from about 10 to about 20% by weight.

[0068] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises a pharmaceutically acceptable salt of hexyl 5-aminolevulinate in an amount of about 5% by weight, a triglyceride in an amount of about 77% by weight, and a thickener in an amount of about 18% by weight.

[0069] Suitable acids for use in the preparation of a pharmaceutically acceptable salt of hexyl 5-aminolevulinate described herein include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzene-sulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid,

camphorsulfonic acid, (+)-(1*S*)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, undecylenic acid, and valeric acid.

[0070] In certain embodiments, the pharmaceutically acceptable salt of hexyl 5-amino-levulinate in the semi-solid pharmaceutical composition described herein is hexyl 5-aminolevulinate hydrochloride. In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride and a pharmaceutically acceptable excipient.

[0071] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount ranging from about 1 to about 10% by weight, a triglyceride in an amount ranging from about 70 to about 85% by weight, and a thickener in an amount ranging from about 10 to about 20% by weight.

[0072] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount of about 5% by weight, a triglyceride in an amount of about 77% by weight, and a thickener in an amount of about 18% by weight.

[0073] In certain embodiments, the pharmaceutically acceptable salt of hexyl 5-amino-levulinate in the semi-solid pharmaceutical composition described herein is hexyl 5-aminolevulinate hydrochloride. In certain embodiments, the semi-solid pharmaceutical

composition described herein comprises hexyl 5-aminolevulinate hydrochloride and a pharmaceutically acceptable excipient.

[0074] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount ranging from about 1 to about 10% by weight, a triglyceride in an amount ranging from about 70 to about 85% by weight, and a thickener in an amount ranging from about 10 to about 20% by weight.

[0075] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount of about 5% by weight, a triglyceride in an amount of about 77% by weight, and a thickener in an amount of about 18% by weight.

[0076] In certain embodiments, the triglyceride in the pharmaceutical composition described herein comprises medium chain triglycerides. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is tricaprylin, tricaproin, triheptanoin, caprylic/capric triglyceride, caprylic/capric/linoleic triglyceride, or caprylic/capric/succinic triglyceride. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is tricaprylin. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is tricaproin. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is triheptanoin. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is caprylic/capric triglyceride. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is caprylic/capric/linoleic triglyceride. In certain embodiments, the triglyceride in the pharmaceutical composition described herein is caprylic/capric/succinic triglyceride. Additional triglycerides suitable for use in the pharmaceutical composition described herein include those described in US 9,326,964 B2, the disclosure of which is incorporated herein by reference in its entirety.

[0077] In certain embodiments, the thickener in the pharmaceutical composition described herein is beeswax, yellow wax, white beeswax, carnauba wax, castor wax, cetyl alcohol, stearyl alcohol, cetostearyl alcohol (cetearyl alcohol), arachidyl alcohol, behenyl alcohol, palmitic acid, or stearic acid. In certain embodiments, the thickener in the pharmaceutical composition

described herein is beeswax. In certain embodiments, the thickener in the pharmaceutical composition described herein is yellow wax. In certain embodiments, the thickener in the pharmaceutical composition described herein is white beeswax. In certain embodiments, the thickener in the pharmaceutical composition described herein is carnauba wax. In certain embodiments, the thickener in the pharmaceutical composition described herein is castor wax. In certain embodiments, the thickener in the pharmaceutical composition described herein is cetyl alcohol. In certain embodiments, the thickener in the pharmaceutical composition described herein is stearyl alcohol. In certain embodiments, the thickener in the pharmaceutical composition described herein is cetostearyl alcohol. In certain embodiments, the thickener in the pharmaceutical composition described herein is arachidyl alcohol. In certain embodiments, the thickener in the pharmaceutical composition described herein is behenyl alcohol. In certain embodiments, the thickener in the pharmaceutical composition described herein is palmitic acid. In certain embodiments, the thickener in the pharmaceutical composition described herein is stearic acid. Additional thickeners suitable for use in the pharmaceutical composition described herein include those described in US 9,326,964 B2, the disclosure of which is incorporated herein by reference in its entirety.

[0078] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride, caprylic/capric triglycerides, and stearic acid.

[0079] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount ranging from about 1 to about 10% by weight, caprylic/capric triglycerides in an amount ranging from about 70 to about 85% by weight, and stearic acid in an amount ranging from about 10 to about 20% by weight.

[0080] In certain embodiments, the semi-solid pharmaceutical composition described herein comprises hexyl 5-aminolevulinate hydrochloride in an amount of about 5% by weight, caprylic/capric triglycerides in an amount of about 77% by weight, and stearic acid in an amount of about 18% by weight.

[0081] In certain embodiments, the semi-solid pharmaceutical composition described herein is a cream, gel, lotion, ointment, or paste. In certain embodiments, the semi-solid pharmaceutical composition described herein is a cream. In certain embodiments, the semi-solid pharmaceutical

composition described herein is a gel. In certain embodiments, the semi-solid pharmaceutical composition described herein is a lotion. In certain embodiments, the semi-solid pharmaceutical composition described herein is an ointment. In certain embodiments, the semi-solid pharmaceutical composition described herein is a paste.

[0082] In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 25 to about 50 °C, from about 25 to about 45 °C, from about 30 to about 42 °C, from about 32 to about 41 °C, or from about 35 to about 40 °C; wherein the drop point is determined according to the procedure as described in European Pharmacopoeia 6.0, Section 2.217, the disclosure of which is incorporated herein by reference in its entirety. In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 25 to about 50 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 25 to about 45 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 30 to about 42 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 32 to about 41 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point ranging from about 35 to about 40 °C.

[0083] In certain embodiments, the pharmaceutical composition described herein has a drop point of about 35, about 36, about 37, about 38, about 39, or about 40 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 35 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 36 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 37 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 38 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 39 °C. In certain embodiments, the pharmaceutical composition described herein has a drop point of about 40 °C.

[0084] In certain embodiments, the pharmaceutical composition described herein is stable for at least for about six months at 25 °C and 60% relative humidity. In certain embodiments, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, or no less than about 99.5% of the initial amount of hexyl 5-

aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 95% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 96% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 97% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 98% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 99% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months. In certain embodiments, no less than about 99.5% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about six months.

[0085] In certain embodiments, the pharmaceutical composition described herein is stable for at least for about nine months at 25 ºC and 60% relative humidity. In certain embodiments, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, or no less than about 99.5% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months. In certain embodiments, no less than about 95% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months. In certain embodiments, no less than about 96% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months. In certain embodiments, no less than about 97% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months. In certain embodiments, no less than about 98% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about

nine months. In certain embodiments, no less than about 99% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months. In certain embodiments, no less than about 99.5% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 25 °C and 60% relative humidity for a period of about nine months.

[0086] In certain embodiments, the pharmaceutical composition described herein is stable for at least for about three months at 40 °C and 75% relative humidity. In certain embodiments, no less than about 90%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, or no less than about 99.5% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 90% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 95% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 96% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 97% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 98% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 99% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months. In certain embodiments, no less than about 99.5% of the initial amount of hexyl 5-aminolevulinate remains after the pharmaceutical composition is stored at 40 °C and 75% relative humidity for a period of about three months.

[0087] In certain embodiments, the pharmaceutical composition described herein is administered intravaginally to the subject with an integrated drug- and light-delivery device. In

certain embodiments, the pharmaceutical composition described herein is administered intravaginally to the subject's ectocervix with an integrated drug- and light-delivery device. In certain embodiments, the pharmaceutical composition described herein is administered intravaginally to the subject with an integrated drug- and light-delivery device, which is independently operational once placed within the vagina. In certain embodiments, the integrated device is a single-use and disposable device. In certain embodiments, the integrated device automatically switches on the LED lamp system to emit light from the concave treatment surface onto the ectocervix continuously over the second predetermined time period before automatically shutting down. In certain embodiments, the integrated device comprises a concave treatment surface that is complementary to the convex shape of the ectocervix, which automatically switches on the LED lamp system to emit light from the concave treatment surface onto the ectocervix continuously over the second predetermined time period before automatically shutting down. In certain embodiments, the integrated device is one described in US 10,485,985 B2 or US 10,874,875 B2, the disclosure of each of which is incorporated herein by reference in its entirety.

[0088] In certain embodiments, the integrated device is an integrated drug- and light-delivery device illustrated in FIGS. 1 and 2. As shown in FIG. 1, the housing comprises a first housing part **2** and a second housing part **4**. The first housing part **2** has a chamber **6** for holding a power source **41**, an opening part **8** for joining to the second housing part **4**, and one or more holes **32** at the rearward end of the chamber **6** for attaching cord(s) for removing the device from the vagina after use.%The chamber **6** is generally cylindrical, reflecting the shape of the power source **41** that it encases. The opening part **8** has two main parts, a neck part **10** at the end of the chamber **6** and a coupling part **12** extending away from the neck part **10**.

[0089] The second housing part **4** has a flexible outer portion **14** that forms a hollow frustoconical shape extending away from the first housing part **2** and outwardly from the front of the device. Circumferential ribs **16** provide strength for the flexible outer portion **14** and also aid in the folding movement of the flexible outer portion **14** for securing the device within the vagina when in use.

[0090] As illustrated FIG. 2, the first housing part **2** encloses a power source **41** (*e.g.*, a battery) in the chamber **6**. The power source **41** is held in a cradle **20**. The chamber **6** has a shape and size that is complementary to the shape and size of the cradle **20** and power source **41**. The power source **41** is electrically coupled to an LED lamp system **22** that is held on the second housing part **4**. The LED lamp system **22** comprises LEDs **45** and a control circuit molded on a circuit board **24**.

[0091] The neck part **10** has inner shoulders formed across the opening of the chamber **6** and outer shoulders across the width of the coupling part **12**. The shoulders form a slot shaped hole **26**, allowing the wires that connect the cradle **20** to the LED lamp system **22** to pass through. The lens **34** has an outer concave treatment surface **36**, which faces forward in use and is for placement against the ectocervix. The outer treatment surface **36** also serves as a drug carrying area for delivering the pharmaceutical composition to the ectocervix. The LEDs **45** direct light forward through the lens **34** and out *via* the concave treatment surface **36** to the ectocervix. The first housing part **2** connects to the second housing part **4** *via* the coupling part **12** of the first housing part **2** and a corresponding coupling part **30** on the second housing part **4**.

[0092] In certain embodiments, the integrated device comprises a housing molded from a resilient material and adapted to be fully inserted and secured in the vagina, the housing enclosing an LED lamp system **22** and a power source **41** for powering the LED lamp system **22**; wherein the device is independently operational while located in the vagina; and wherein the housing comprises a concave treatment surface **36**, which serves as a drug carrying area for delivering the pharmaceutical composition to the cervix.

[0093] In certain embodiments, the integrated comprises:

a housing comprising a separate first housing part **2** for holding a power source **41** for powering a LED lamp system **22**, and a separate second housing part **4** for holding the LED lamp system **22**, wherein:

(a) the first housing part **2** comprises:

a chamber **6** comprising the power source **41**;

an opening part **8** to the chamber **6**, which comprises a first coupling part **12**; and

an electrical coupling passing from the power source **41** to the LED lamp system **22** in the second housing part **4**; and

(b) the second housing part **4** comprises:

a flexible outer portion **14**, which is frustoconical in shape that forms a continuous surface extending away from the first housing part **2** and outwardly from the front of the device;

a concave treatment surface **36**, which serves as a drug carrying area for delivering the pharmaceutical composition to the cervix;

the LED lamp system **22** arranged to emit light from the concave treatment surface **36** onto the cervix; and

a second coupling part **30**;

wherein the first coupling part **12** on the first housing part **2** is arranged to join to and form a seal with the second coupling part **30** on the second housing part **4**, thereby forming a joint and closing the chamber; and

wherein the device, when in use, is fully inserted and secured in the vagina and is independently operational while located in the vagina.

[0094] In certain embodiments, the first housing part **2** is molded from a resilient material. In certain embodiments, the first housing part **2** is molded from a medical grade opaque silicone. In certain embodiments, the second housing part **4** is molded from a resilient material. In certain embodiments, the first housing part **4** is molded from a medical grade silicone. In certain embodiments, the second housing part **4** is molded from a material that is at least partially transparent to light emitted from the LED lamp system **22**, when the device is in use, the light exits *via* a treatment surface **36** on the second housing part **4** and illuminates a treatment area on the subject.

[0095] In certain embodiments, the resilient material of the first housing part **2** is sized to fit the chamber tightly around the power source **41**. In certain embodiments, the opening part **8** allows for an electrical coupling to pass from the power source **41** to the LED lamp system **22**. In certain embodiments, the opening part **8** can be deformed for inserting and/or removing the power source **41** into or from the first housing part **2**. In certain embodiments, the opening part **8** comprises a neck part **10** for holding the power source **41** within the chamber **6**. In certain

embodiments, the neck part **10** is a resilient narrowing of the entrance to the chamber **6** to a size less than the width of the power source **41** to thereby hold the power source **41** within the chamber **6**. In certain embodiments, the resilient material of the chamber **6** is sized to fit tightly around the power source **41**.

[0096] In certain embodiments, the power source **41** is sealed within the housing such that the housing is fluid tight in use, and optionally a sealing media is used at the joint between the first and second housing parts **2** and **4**. In certain embodiments, the opening part **8** has a coupling part **12** arranged to join to and form a seal with a complementary shaped coupling part **30** on the second housing part **4**. In certain embodiments, one of the two coupling parts **12** and **30** is arranged to be stretched to place it around the other of the two coupling parts **12** and **30**, thereby using the elasticity of the resilient material to hold the two housing parts **2** and **4** together.

[0097] In certain embodiments, the treatment surface **36** has a size and/or shape adapted for complementary fit with the treatment area on the subject. In certain embodiments, the treatment surface **36** has a size and/or shape adapted for complementary fit with the ectocervix of the subject. In certain embodiments, when in use, the device provides light with a fluence rate/irradiance no greater than 50 mW/cm^2.

[0098] In certain embodiments, the pharmaceutical composition described herein is administered intravaginally to the subject by applying a therapeutically effective amount of the pharmaceutical composition to the concave treatment surface **36** of an integrated drug- and light-delivery device and then placing the device inside the vagina with the concave treatment surface **36** contacting the ectocervix.

[0099] In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 10 to about 500, from about 20 to about 250, from about 50 to about 200, from about 50 to about 150, or from about 75 to about 125 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 10 to about 500 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 20 to about

250 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 50 to about 200 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 50 to about 150 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 75 to about 125 mg hexyl 5-aminolevulinate per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, or about 125 mg hexyl 5-aminolevulinate per treatment.

[00100] In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 10 to about 500, from about 20 to about 250, from about 50 to about 200, from about 50 to about 150, or from about 75 to about 125 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 10 to about 500 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 20 to about 250 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 50 to about 200 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 50 to about 150 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is ranging from about 75 to about 125 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, or about 125 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 75 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 80

mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 85 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 90 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 95 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 100 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 105 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 110 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 115 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 120 mg hexyl 5-aminolevulinate hydrochloride per treatment. In certain embodiments, the therapeutically effective amount of the pharmaceutical composition described herein is about 125 mg hexyl 5-aminolevulinate hydrochloride per treatment.

[00101] The pharmaceutical composition described herein can be administered at once or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the subject being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the subject's need and the professional judgment of the person administering or supervising the administration of the pharmaceutical composition.

[00102] In certain embodiments, the first predetermined period is ranging from about 0.5 to about 24 hours, from about 1 to 12 hours, from about 2 to 10 hours, from about 4 to 8 hours, or from about 4 to 6 hours. In certain embodiments, the first predetermined period is ranging from

about 0.5 to about 24 hours. In certain embodiments, the first predetermined period is ranging from about 1 to 12 hours. In certain embodiments, the first predetermined period is ranging from about 2 to 10 hours. In certain embodiments, the first predetermined period is ranging from about 4 to 8 hours. In certain embodiments, the first predetermined period is ranging from about 4 to 6 hours. In certain embodiments, the first predetermined period is about 4, about 5, about 6, about 7, or about 8 hours. In certain embodiments, the first predetermined period is about 5.

[00103] In certain embodiments, the second predetermined period is ranging from about 0.5 to about 24 hours, from about 1 to 12 hours, from about 2 to 10 hours, from about 4 to 8 hours, or from about 4 to 5 hours. In certain embodiments, the second predetermined period is ranging from about 0.5 to about 24 hours. In certain embodiments, the second predetermined period is ranging from about 1 to 12 hours. In certain embodiments, the second predetermined period is ranging from about 2 to 10 hours. In certain embodiments, the second predetermined period is ranging from about 4 to 8 hours. In certain embodiments, the second predetermined period is ranging from about 4 to 5 hours. In certain embodiments, the second predetermined period is about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours. In certain embodiments, the second predetermined period is about 4.6 hours.

[00104] In certain embodiments, the wavelength is ranging from about 500 to about 1,000 nm, from about 600 to about 850 nm, from about 600 to about 800 nm, from about 600 to about 690 nm, from about 630 to about 670 nm, or from about 630 to about 640 nm. In certain embodiments, the wavelength is ranging from about 500 to about 1,000 nm. In certain embodiments, the wavelength is ranging from about 600 to about 850 nm. In certain embodiments, the wavelength is ranging from about 600 to about 800 nm. In certain embodiments, the wavelength is ranging from about 600 to about 690 nm. In certain embodiments, the wavelength is ranging from about 630 to about 670 nm. In certain embodiments, the wavelength is ranging from about 630 to about 640 nm. In certain embodiments, the wavelength is about 630, about 631, about 632, about 633, about 634, about 635, about 636, about 637, about 638, about 639, or 640 nm. In certain embodiments, the wavelength is about 635 nm.

[00105] In certain embodiments, the fluence rate/irradiance is ranging from about 1 to about 50 mW/cm^2, from about 2 to about 25 mW/cm^2, from about 3 to about 15 mW/cm^2, or from about 5 to about 10 mW/cm^2. In certain embodiments, the fluence rate/irradiance is ranging from about 1 to about 50 mW/cm^2. In certain embodiments, the fluence rate/irradiance is ranging from about 2 to about 25 mW/cm^2. In certain embodiments, the fluence rate/irradiance is ranging from about 3 to about 15 mW/cm^2. In certain embodiments, the fluence rate/irradiance is ranging from about 5 to about 10 mW/cm^2. In certain embodiments, the fluence rate/irradiance is about 5, about 6, about 7, about 8, about 9, or about 10 mW/cm^2.

[00106] In certain embodiments, the irradiating step is performed to deliver a fluence in an amount ranging from about 10 to about 500 J/cm^2, from about 20 to about 250 J/cm^2, from about 50 to about 200 J/cm^2, or from about 100 to about 150 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount ranging from about 10 to about 500 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount ranging from about 20 to about 250 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount ranging from about 50 to about 200 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount ranging from about 100 to about 150 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount of about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, or about 150 J/cm^2. In certain embodiments, the irradiating step is performed to deliver a fluence in an amount of about 125.

[00107] In certain embodiments, the pharmaceutical composition described herein is administered once a week, twice a month, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or once a year. In certain embodiments, the pharmaceutical composition described herein is administered once a week. In certain embodiments, the pharmaceutical composition described herein is administered twice a month. In certain embodiments, the pharmaceutical composition described herein is administered once a month. In certain embodiments, the pharmaceutical composition described herein is administered once every two months. In certain embodiments, the pharmaceutical composition described herein is administered once every three months. In certain embodiments, the pharmaceutical composition described herein is administered once

every four months. In certain embodiments, the pharmaceutical composition described herein is administered once every five months. In certain embodiments, the pharmaceutical composition described herein is administered once every six months. In certain embodiments, the pharmaceutical composition described herein is administered once a year.

[00108] In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a female human.

[00109] In certain embodiments, the subject is a female subject of about 10 to about 80 years of age, about 10 to about 70 years of age, about 20 to about 60 years of age, about 20 to about 50 years of age, or about 20 to about 40 years of age. In certain embodiments, the subject is a female subject of about 10 to about 80 years of age. In certain embodiments, the subject is a female subject of about 10 to about 70 years of age. In certain embodiments, the subject is a female subject of about 20 to about 60 years of age. In certain embodiments, the subject is a female subject of about 20 to about 50 years of age. In certain embodiments, the subject is a female subject of about 20 to about 40 years of age. In certain embodiments, the subject is a female subject of about 20 to about 30 years of age. In certain embodiments, the subject is a female subject of about 30 to about 40 years of age. In certain embodiments, the subject is a female subject of childbearing age.

[00110] In certain embodiments, the subject has not received any treatment for a cervix disorder or condition. In certain embodiments, the subject has received a prior treatment for a cervix disorder or condition. In certain embodiments, the subject has received a prior invasive treatment for a cervix disorder or condition. In certain embodiments, the subject has received a prior invasive surgical treatment for a cervix disorder or condition.

[00111] In certain embodiments, the subject has failed a prior treatment for a cervix disorder or condition. In certain embodiments, the subject has failed a prior invasive treatment for a cervix disorder or condition. In certain embodiments, the subject has failed a prior invasive surgical treatment for a cervix disorder or condition.

[00112] In certain embodiments, the subject has failed more than one prior treatment for a cervix disorder or condition. In certain embodiments, the subject has failed more than one prior

invasive treatment for a cervix disorder or condition. In certain embodiments, the subject has failed more than one prior invasive surgical treatment for a cervix disorder or condition.

[00113] In certain embodiments, provided herein is a kit which, when used by a medical practitioner, can simplify the administration of an appropriate amount of the pharmaceutical composition described herein. In certain embodiments, the kit provided herein includes an integrated drug- and light-delivery device and a pharmaceutical composition described herein.

[00114] The disclosure will be further understood by the following non-limiting example.

EXAMPLES

Example 1

Storage Stability Determination

[00115] A semi-solid pharmaceutical composition comprising hexyl 5-aminolevulinate hydrochloride (5% by weight), MIGLYOL® 812 (caprylic/capric triglycerides) (77% by weight), and stearic acid (18% by weight) was prepared according to the procedures as described in US 9,326,964 B2, the disclosure of which is incorporated herein by reference in its entirety. The pharmaceutical composition was determined according to the procedure as described in European Pharmacopoeia 6.0, Section 2.217 to have a drop point of 39 °C. The pharmaceutical composition was stored at 25 °C/60% RH and 40 °C/75% RH. At each time point, three samples were taken from the pharmaceutical composition and quantitated for hexyl 5-aminolevulinate by HPLC. The results are summarized in Table 1.

TABLE 1

Duration	**Relative Content of Hexyl 5-Aminolevulinate**	
	25 °C/60% RH	**40 °C/75% RH**
0	100%	
1 month	101%	
2 months	98%	100%
6 months	99%	101%
9 months	103%	

Example 2

Photodynamic Therapy Treatment of Cervical Histologic HSIL and an HPV Infection

[00116] In a double blind, randomized, placebo-controlled, multi-center global phase 3 study, about 402 subjects with cervical histologic HSIL were enrolled from 7 countries (China, Hungary, Germany, Czech Republic, Slovakia, Poland, and Netherlands). Eligible subjects were randomized to either a photodynamic therapy (PDT) treatment group or a placebo group in a 2:1 ratio. Each subject received either a hexyl 5-hexaminolevulinate hydrochloride (HAL-HCl) ointment (5% by weight) as described in Example 1 or a placebo no more than twice in 6 months. In the treatment group, the HAL-HCl ointment was administered intravaginally by a gynecologist using an integrated drug- and light-delivery device, which was a single-use, disposable, LED-based integrated red-light source. For intravaginal administration, the gynecologist first spread the HAL-HCl ointment evenly over the treatment surface of the integrated device and then placed it into the vagina and positioned it correctly on the cervix. The device automatically switched on the light 5 hours after administration and provided continuous irradiation at the surface of the cervix for 4.6 hours to deliver a fluence (a total dose) of 125 J/cm^2 before automatically shutting down. The placebo device was identical in appearance to the integrated device without providing light. The subjects were instructed not to remove the integrated device earlier than 11 hours after administration, but to remove it within 24 hours (a cord was attached to the device to ensure easy removal). If an abnormality (*e.g.*, LSIL or more severe (ASC-H or HSIL), or HPV positive) in histology or cytology was found in the 3-month after the first treatment, the subjects received a second treatment.

[00117] The primary endpoint was a response rate (RR, normal histology or LSIL histology with baseline HPV clearance) six months after first treatment. Secondary endpoints were proportions of the HPV, HPV16, HPV16 and/or 18 positive subjects with baseline HPV clearance six months after first treatment and proportions of the subjects with histologic regression (LSIL or normal histology six months after first treatment). Clearance of baseline HPV for a subject was defined as an HPV genotype with a positive result at baseline (*i.e.*, at the time of the enrollment) that had a negative result for the same HPV genotype six months after first treatment, resulting in a "negative HPV rate," that is, a lower percentage of the subjects within a group testing positive for HPV, which, in turn, leads to a "HPV positive rate decreased,"

that is, a lower prevalence of active HPV infections within the group of subjects. All samples were reviewed by an independent adjudication panel of three pathologists. The results are summarized in Table 1, where mITT represents a modified intention-to-treat analysis population, which is a subset of the population diagnosed with HSIL by an independent adjudication panel of three pathologists in all randomized subjects. The median follow-up time was 185 days for the mITT population.

[00118] In the mITT population, as shown in Table 2, the proportion of responders in the PDT treatment group (41%) was statistically significantly higher than that in the placebo group (22%). The clearance rates in the PDT treatment group were 32% for HPV16 and 31% for HPV16 and/or HPV18. In contrast, the clearance rates in the placebo group were only 17% for HPV16 and only 15% for HPV16 and/or HPV18. In the per-protocol (PP) population (*i.e.*, the subset of the subjects in the mITT population who did not have serious protocol violations), the baseline HPV clearance rates were 29% for the PDT treatment group and 19% for the placebo group; and the difference is statistically significant ($p = 0.043$). The results demonstrate that the PDT treatment was effective in clearing HPV, especially high-risk HPV16/18.

[00119] In a histopathological analysis, the subjects were classified into their progressive, stable, and improved according to histopathological manifestations. Stable and improved were also collectively referred to as non-progressive. Histological progression was defined as a change in the histopathology of a subject from baseline CIN2 to CIN3. Histological stability was defined as no change in the histopathology of a subject. Histologic improvement was defined as a change in the histopathology of a subject from baseline CIN2 to normal/LSIL or from baseline CIN3 to normal/LSIL/CIN2. Six months after the first treatment, the histological improvement was 54% for the PDT treatment group and 36% for the placebo group, and the difference is statistically significant (p: 0.001); and non-progressors were 79% for the PDT treatment group and 67% for the placebo group; and the difference is statistically significant ($p = 0.017$). Six months after the first treatment, only 7% of the subjects in the PDT treatment progressed; whereas 12% of the subjects in the placebo groups progressed.

TABLE 2

		Treatment	Placebo	p value
mITT population at 6 months		n = 253	n = 129	
Response Rate (RR)		41%	22%	0.0001
HPV Clearance Rate				
	HPV+	28%	20%	0.08
	16+	32%	17%	0.02
	16+/18+	31%	15%	0.01
Histologic Regression Rate		47%	30%	0.0007
Safety Population (6-month period)		n = 266	n = 134	
All TEAEs		57%	56%	
Treatment Related AEs		32%	26%	
TEAEs by Maximum Severity				
	Mild	39%	35%	
	Moderate	16%	20%	
	Severe	1.5%	0.7%	
Serious TEAEs		1.5%	1.5%	
TEAEs Leading to Study Treatment Stopped/Withdrawn/Death		0.0%	0.0%	

[00120] At baseline, 48% (182/382) and 52% (200/382) subjects were diagnosed with cervical CIN2 and CIN3, respectively. The RR in the PDT treatment group was superior to that in the placebo group for both CIN2 and CIN3 subgroups (49% vs. 23%, $p < 0.01$; 34% vs. 21%, $p = 0.07$). The regression rate (histologic normal or LSIL) was also greater after the PDT treatment, with 58% vs. 31% ($p < 0.01$) in the CIN2 subgroup and 38% vs. 28% ($p = 0.21$) in the CIN3 subgroup. Comparing the complete clearance rate of cervical lesion, the PDT treatment group was nearly twice that of the placebo group in the CIN2 subgroup (61% vs. 33%, $p < 0.01$). The same trend was observed in the CIN3 subgroup (43% vs. 36%, $p = 0.47$). These data showed that the PDT treatment group had a higher response/regression rate and greater clearance rate of cervical lesion after merely 1-2 PDT treatments. Thus, the PDT treatment represents an option

for cervical HSIL in women who prefer non-invasive treatment, particularly, those who wish to avoid potential complications associated with surgery upon subsequent pregnancies.

[00121] Additionally, the subjects were analyzed for deep responders, that is, subjects with normal histology and baseline HPV clearance six months after the first treatment. In the baseline HPV-positive mITT population, deep responders were 22% for the PDT treatment group and 12% for the placebo group; and the difference is statistically significant ($p = 0.030$). In the baseline HPV-positive mITT population, the proportions of the subjects who had baseline HPV clearance and normal CIN/LSIL were 25% for the PDT treatment group and 15% for the placebo group; and the difference is statistically significant ($p = 0.031$). In the baseline HPV16/18-positive mITT population, the proportions of the subjects who had baseline HPV clearance and normal CIN/LSIL were 26% for the PDT treatment group and 12% for the placebo group; and the difference is statistically significant ($p = 0.011$).

[00122] Six months after the first treatment, 45% of the subjects in the PDT treatment group had normal histology, 10% had CIN1, 18% had CIN2, and 27% had CIN3. Twelve months after the first PDT treatment, 74% of the subjects in the PDF treatment group had normal histology, 9% had CIN1, 13% had CIN2, and 4% had CIN3. In contrast, six months after the first treatment, 24% of the subjects in the placebo group had normal histology, 13% had CIN1, 26% had CIN2, and 37% had CIN3.

[00123] In the mITT population with high-risk HPV (including HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, and HPV 68), the responder proportions six months after the first treatment were 37% for the PDT treatment group and 20% in the placebo group; and the difference is statistically significant ($p = 0.002$). At 3 and 6 months, the positive rates of different subgroups of HPV in the PDT treatment group were lower than those in the placebo group, suggesting that the PDT treatment group had a faster rate of HPV clearance and that the HPV clearance persisted at 12 months after merely 1-2 treatments. At 12 months, HPV positive rates were still declining substantially in the PDT treatment group.

[00124] In the mITT population, the baseline mean lesion areas as a percentage of the cervical area were 20% for the PDT treatment group and 22% for the placebo group. Six months after

the first treatment, the mean lesion areas were reduced to 7% for the PDT treatment group and 10% for the placebo group. The average reductions in the lesion areas were 67% for the PDT treatment group and 45% for the placebo group; and the difference is statistically significant (p: 0.001).

[00125] In the PDT treatment group, there were 2 subjects aged < 20 years, 125 subjects aged ≥ 20 and < 30 years, 106 subjects aged ≥ 30 and < 40 years, and 20 subjects aged ≥ 40 years. In the placebo group, there were 3 subjects aged < 20 years, 69 subjects aged ≥ 20 and < 30 years, 52 subjects aged ≥ 30 and < 40 years, and 5 subjects aged ≥ 40 years. About 93.7% of all the subjects had HPV infection at enrollment, of which 56.5% were HPV 16 positive and 37.2% were HPV 18 or other types positive. Histopathological analysis results six months after the first treatment are summarized in Table 3, which demonstrates that the histologic regression rates and HPV clearance rates were significantly increased for female subjects of childbearing age between 20 and 40 years old.

TABLE 3

Age		**HPV Clearance Rate (%)**			**Histologic Regression Rate (%)**
		HPV	**HPV 16+**	**HPV 16+/18+**	
≥ 20 Yr and < 30 Yr	Treatment	33.6	37.7	37.6	52.8
	Placebo	24.6	20	18.2	37.7
≥ 30 Yr and < 40 Yr	Treatment	20.6	23	22.2	37.7
	Placebo	10.4	3.8	3.4	19.2

[00126] All subjects in the PDT treatment group were followed for an additional 6 months in an open-label extension period, referred to as extension phase. Study extension endpoints were the proportion of subjects with LSIL histology and non-clearance of baseline HPV at 6 months who became responders at 12 months after first PDT treatment; and the proportion of responders at 6 months with continued regression at 12 months after first PDT treatment. The median follow-up time was 366 days for the extension phase. Of 216 subjects who entered the extension phase, 153 completed the study. Of the 15 subjects who had LSIL histology and non-clearance of baseline HPV at 6 months after first PDT treatment, six subjects (40%) became responders at

12 months after first PDT treatment. Of the 102 responders with the PDT treatment group at 6 months who entered the extension phase.

[00127] In the mITT population, as response and histological regression rates observed at 6 months, the extension phase was consistently observed across subject subgroups by region, age, CIN stage, and HPV status. As shown in Table 4, 55% maintained a response at 12 months after first PDT treatment. Responses were maintained regardless of baseline CIN or HPV status. A trend of increasing HPV clearance over 12 months was observed with the PDT treatment.

TABLE 4. Outcomes During Extension Period in the mITT population.

	Extension Period
Continued regression at 12 months	
Responders at 12 months — n/N (%)	56/102 (54.9)
95% CI	44.7–64.8
Baseline CIN diagnosis: CIN2	
Responders at 12 months (NRI) — n/N (%)	34/59 (57.6)
95% CI	44.1–70.4
Baseline CIN diagnosis: CIN3	
Responders at 12 months (NRI) — n/N (%)	22/43 (51.2)
95% CI	35.5–66.7
Baseline HPV status: HPV−-	
Responders at 12 months (NRI) — n/N (%)	5/9 (55.6)
95% CI	21.2–86.3
Baseline HPV status: HPV16+	
Responders at 12 months (NRI) — n/N (%)	26/48 (54.2)
95% CI	39.2–68.6
Baseline HPV status: HPV18+/Other+	
Responders at 12 months (NRI) — n/N (%)	25/45 (55.6)
95% CI	40.0–70.4

CI denotes confidence interval.

[00128] Twelve months after the first treatment, more than a half of the subjects who received one PDT treatment showed no progression, 12% showed improvement, 43% showed histological stability, and only 6% showed progression; and almost a half of the subjects who received two

PDT treatments showed no progression, 24% showed improvement, 25% showed histological stability, and only 7% showed progression.

[00129] Those results demonstrate that the PDT treatment benefited the histopathological outcome of HSIL subjects and facilitated the clearance of an HPV infection as well. The results also demonstrate that the PDT treatment was efficacious in treating HSIL with a long-lasting effect.

[00130] Additionally, the PDT treatment was well tolerated. In the PDT treatment group during the first six months after the first treatment, more than two-thirds of the subjects did not report any treatment-related adverse events, about 30% of the subjects reported treatment-related adverse events, and no severe treatment-related adverse events occurred. The proportion of the subjects who experienced treatment-related adverse events was similar between the PDT treatment and placebo groups. The top three treatment-related adverse events in the PDT treatment group were vaginal discharge (13%), abdominal pain (5.6%), and vaginal bleeding (4.5%), all of which were self-limiting. Treatment-related adverse event incidence was 32% with the PDT treatment group and 26% with placebo. All treatment-related adverse events were mild or moderate in severity. No new adverse events were reported during the extension phase.

[00131] The results demonstrate that the PDT treatment has a favorable safety profile in comparison with the current treatment options for HSIL with the risks of an infection, bleeding, cervical stenosis, and pregnancy-related complications. For example, the postoperative delayed bleeding rate after LEEP was close to 70% (Feddersen *et al.*, *Aust. N.Z. J. Obstet. Gynaecol.* **2022**, *62*, 740-7), while the bleeding rate in the PDT treatment was only 4.5% and uncommon and did not require management. The vaginal infection rates after cold knife conization (CKC) and LEEP are 36% and 14%, respectively; whereas the vaginal infection rate was only 1.9% for the PDT treatment. The miscarriage rates for LEEP-to-pregnancy intervals <12 months and ≥12 months are 28% and 13%, respectively. The spontaneous miscarriage rate for the PDT treatment was only 0.8%. The incidence rate of cervical stenosis after cervical circumcision is 1.3%-5.2%, but there was simply no such risk for the PDT treatment.

[00132] All the results demonstrate that the PDT treatment is a long-term and effective non-surgical therapy that is beneficial to clearing an HPV infection, treating cervical epithelial lesions

induced by a persistent HPV infection, preserving cervical tissues, and protecting the normal physiological functions of the cervix. The PDT treatment was easy to follow and did not require patient hospitalization. The safety profile was mild or moderate with a drastically reduced risk of surgery-induced adverse events, thus providing a novel tissue-preserving approach for treatment of cervical HSILs in women of childbearing age.

* * * * *

[00133] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A method of treating, preventing, or ameliorating a cervix disorder or condition in a subject having a cervix with an ectocervix, comprising the steps of:

(i) administering intravaginally to the subject in need thereof a therapeutically effective amount of a semi-solid pharmaceutical composition that comprises hexyl 5-aminolevulinate or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient;

(ii) maintaining the contact of the pharmaceutical composition with the ectocervix for a first predetermined period; and

(iii) irradiating the ectocervix with light having a wavelength ranging from about 600 to about 1,200 nm and a fluence rate/irradiance of no greater than 50 mW/cm^2 for a second predetermined period.

2. The method of claim 1, wherein the semi-solid pharmaceutical composition is administered using an integrated drug- and light-delivery device.

3. The method of claim 1 or 2, wherein the cervix disorder or condition is associated with a human papillomavirus infection.

4. The method of any one of claims 1 to 3, wherein the cervix disorder or condition is a precancerous cervix disorder or condition.

5. The method of claim 4, wherein the precancerous cervix disorder or condition is cervical adenocarcinoma in situ, cervical intraepithelial neoplasia, or squamous intraepithelial lesion.

6. The method of claim 4 or 5, wherein the precancerous cervix disorder or condition is cervical adenocarcinoma in situ.

7. The method of claim 4 or 5, wherein the precancerous cervix disorder or condition is cervical intraepithelial neoplasia.

8. The method of claim 4, 5, or 7, wherein the precancerous cervix disorder or condition is cervical intraepithelial neoplasia 1.

9. The method of claim 4, 5, or 7, wherein the precancerous cervix disorder or condition is cervical intraepithelial neoplasia 2.

10. The method of claim 4, 5, or 7, wherein the precancerous cervix disorder or condition is cervical intraepithelial neoplasia 3.

11. The method of claim 4 or 5, wherein the precancerous cervix disorder or condition is squamous intraepithelial lesion.

12. The method of claim 4, 5, or 11, wherein the precancerous cervix disorder or condition is low-grade squamous intraepithelial lesion.

13. The method of claim 4, 5, or 11, wherein the precancerous cervix disorder or condition is high-grade squamous intraepithelial lesion.

14. The method of any one of claims 4, 5, 11, and 13, wherein the precancerous cervix disorder or condition is histologically confirmed high-grade squamous intraepithelial lesion.

15. The method of any one of claims 4, 5, 11, 13, and 14, wherein the precancerous cervix disorder or condition is histologically confirmed HSIL with neither cervical invasive cancer nor adenocarcinoma in situ.

16. The method of any one of claims 4, 5, 11, and 13, wherein the precancerous cervix disorder or condition is histologically confirmed CIN3 with a lesion area of no more than about 50%.

17. The method of any one of claims 4 to 16, wherein the precancerous cervix disorder or condition is associated with a human papillomavirus infection.

18. The method of any one of claims 4 to 17 wherein the precancerous cervix disorder or condition is associated with a high-risk human papillomavirus infection.

19. The method of any one of claims 4 to 18, wherein the precancerous cervix disorder or condition is associated with an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, or HPV 59 infection.

20. The method of any one of claims 4 to 19, wherein the precancerous cervix disorder or condition is associated with an HPV 16 infection.

21. The method of any one of claims 4 to 19, wherein the precancerous cervix disorder or condition is associated with an HPV 18 infection.

22. The method of any one of claims 1 to 21, wherein the cervix disorder or condition is persistent.

23. The method of any one of claims 1 to 22, wherein the cervix disorder or condition is recurrent.

24. The method of any one of claims 1 to 4, wherein the cervix disorder or condition is a human papillomavirus infection.

25. The method of any one of claims 1 to 4 and 24, wherein the cervix disorder or condition is a high-risk human papillomavirus infection.

26. The method of any one of claims 1 to 4, 24, and 25, wherein the cervix disorder or condition is an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, or HPV 59 infection.

27. The method of any one of claims 1 to 4 and 24 to 26, wherein the cervix disorder or condition is an HPV 16 infection.

28. The method of any one of claims 1 to 4 and 24 to 26, wherein the cervix disorder or condition is an HPV 18 infection.

29. The method of any one of claims 24 to 28, wherein the human papillomavirus infection is persistent.

30. The method of any one of claims 24 to 29, wherein the human papillomavirus infection is recurrent.

31. The method of any one of claims 1 to 3, wherein the cervix disorder or condition is a cancerous cervix disorder or condition.

32. The method of claim 31, wherein the cancerous cervix disorder or condition is cervical cancer.

33. The method of claim 31 or 32, wherein the cancerous cervix disorder or condition is associated with a human papillomavirus infection.

34. The method of any one of claims 31 to 33, wherein the cancerous cervix disorder or condition is associated with a high-risk human papillomavirus infection.

35. The method of any one of claims 31 to 34, wherein the cancerous cervix disorder or condition is associated with an HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, or HPV 59 infection.

36. The method of any one of claims 31 to 35, wherein the cancerous cervix disorder or condition is associated with an HPV 16 infection.

37. The method of any one of claims 31 to 35, wherein the cancerous cervix disorder or condition is associated with an HPV 18 infection.

38. The method of any one of claims 31 to 37, wherein the cancerous cervix disorder or condition is persistent.

39. The method of any one of claims 30 to 37, wherein the cancerous cervix disorder or condition is recurrent.

40. The method of any one of claims 1 to 39, wherein the semi-solid pharmaceutical composition comprises a pharmaceutically acceptable salt of hexyl 5-aminolevulinate, a triglyceride, and a thickener.

41. The method of any one of claims 1 to 40, wherein the semi-solid pharmaceutical composition comprises hexyl 5-aminolevulinate hydrochloride, a triglyceride, and a thickener.

42. The method of any one of claims 1 to 41, wherein the semi-solid pharmaceutical composition comprises hexyl 5-aminolevulinate hydrochloride, a triglyceride, and a thickener.

43. The method of any one of claims 1 to 42, wherein the semi-solid pharmaceutical composition comprises hexyl 5-aminolevulinate hydrochloride in an amount ranging from about 1 to about 10% by weight, a triglyceride in an amount ranging from about 70 to about 85% by weight, and a thickener in an amount ranging from about 10 to about 20% by weight.

44. The method of any one of claims 1 to 43, wherein the semi-solid pharmaceutical composition comprises hexyl 5-aminolevulinate hydrochloride in an amount of about 5% by weight, a triglyceride in an amount of about 77% by weight, and a thickener in an amount of about 18% by weight.

45. The method of any one of claims 40 to 44, wherein the triglyceride is tricaprylin, tricaproin, triheptanoin, caprylic/capric triglyceride, caprylic/capric/linoleic triglyceride, or caprylic/capric/succinic triglyceride.

46. The method of any one of claims 40 to 45, wherein the triglyceride is caprylic/capric triglyceride.

47. The method of any one of claims 40 to 46, wherein the thickener is beeswax, yellow wax, white beeswax, carnauba wax, castor wax, cetyl alcohol, stearyl alcohol, cetostearyl alcohol (cetearyl alcohol), arachidyl alcohol, behenyl alcohol, palmitic acid, or stearic acid.

48. The method of any one of claims 40 to 47, wherein the thickener is stearic acid.

49. The method of any one of claims 1 to 48, wherein the semi-solid pharmaceutical composition comprises hexyl 5-aminolevulinate hydrochloride in an amount of about 5% by weight, caprylic/capric triglycerides in an amount of about 77% by weight, and stearic acid in an amount of about 18% by weight.

50. The method of any one of claims 1 to 49, wherein the pharmaceutical composition has a drop point ranging from about 25 to about 45 °C.

51. The method of any one of claims 1 to 50, wherein the pharmaceutical composition has a drop point ranging from about 35 to about 40 °C.

52. The method of any one of claims 1 to 51, wherein the pharmaceutical composition has a drop point of about 39 °C.

53. The method of any one of claims 1 to 52, wherein the pharmaceutical composition is at least for about six months at 25 ℃ and 60% relative humidity with no less than about 95% of the initial amount of hexyl 5-aminolevulinate remained.

54. The method of any one of claims 1 to 53, wherein the pharmaceutical composition is at least for about nine months at 25 ℃ and 60% relative humidity with no less than about 95% of the initial amount of hexyl 5-aminolevulinate remained.

55. The method of any one of claims 1 to 54, wherein the pharmaceutical composition is at least for about three months at 40 ℃ and 75% relative humidity with no less than about 95% of the initial amount of hexyl 5-aminolevulinate remained.

56. The method of any one of claims 1 to 55, wherein the therapeutically effective amount is ranging from about 10 to about 500 mg hexyl 5-aminolevulinate hydrochloride per treatment.

57. The method of any one of claims 1 to 56, wherein the therapeutically effective amount is ranging from about 75 to about 125 mg hexyl 5-aminolevulinate hydrochloride per treatment.

58. The method of any one of claims 1 to 57, wherein the therapeutically effective amount is about 100 mg hexyl 5-aminolevulinate hydrochloride per treatment.

59. The method of any one of claims 1 to 58, wherein the first predetermined period is ranging from about 0.5 to about 24 hours.

60. The method of any one of claims 1 to 59, wherein the first predetermined period is ranging from about 4 to 6 hours.

61. The method of any one of claims 1 to 60, wherein the first predetermined period is about 5 hours.

62. The method of any one of claims 1 to 61, wherein the wavelength is ranging from about 500 to about 1,000 nm.

63. The method of any one of claims 1 to 62, wherein the wavelength is ranging from about 630 to about 640 nm.

64. The method of any one of claims 1 to 63, wherein the wavelength is about 635 nm.

65. The method of any one of claims 1 to 64, wherein the fluence rate/irradiance is ranging from about 1 to about 50 mW/cm^2.

66. The method of any one of claims 1 to 65, wherein the fluence rate/irradiance is ranging from about 5 to about 10 mW/cm^2.

67. The method of any one of claims 1 to 66, wherein the irradiating step is performed at a fluence rate/irradiance ranging from about 1 to about 50 mW/cm^2.

68. The method of any one of claims 1 to 67, wherein the irradiating step is performed at a fluence rate/irradiance ranging from about 5 to about 10 mW/cm^2.

69. The method of any one of claims 1 to 68, wherein the second predetermined period is ranging from about 0.5 to about 24 hours.

70. The method of any one of claims 1 to 69, wherein the second predetermined period is ranging from about 4 to 5 hours.

71. The method of any one of claims 1 to 70, wherein the second predetermined period is about 4.6 hours.

72. The method of any one of claims 1 to 71, wherein the irradiating step is performed to deliver a fluence in an amount ranging from about 10 to about 500 J/cm^2.

73. The method of any one of claims 1 to 72, wherein the irradiating step is performed to deliver a fluence in an amount ranging from about 100 to about 150 J/cm^2.

74. The method of any one of claims 1 to 73, wherein the irradiating step is performed to deliver a fluence in an amount of about 125 J/cm^2.

75. The method of any one of claims 2 to 74, wherein the device is independently operational while located in the vagina of the subject.

76. The method of any one of claims 2 to 75, wherein the integrated device comprises a housing molded from a resilient material and adapted to be fully inserted and secured in the vagina of the subject, the housing enclosing an LED lamp system and a power source for powering the LED lamp system; wherein the device is independently operational while located in the vagina; and wherein the housing comprises a concave treatment surface that serves as a drug carrying area for delivering the pharmaceutical composition to the cervix.

77. The method of any one of claims 2 to 76, wherein the integrated device comprises:

a housing comprising a separate first housing part for holding a power source for powering a LED lamp system, and a separate second housing part for holding the LED lamp system, wherein:

(a) the first housing part comprises:

a chamber comprising the power source;

an opening part to the chamber, which comprises a first coupling part; and

an electrical coupling passing from the power source to the LED lamp system in the second housing part; and

(b) the second housing part comprises:

a flexible outer portion, which is frustoconical in shape that forms a continuous surface extending away from the first housing part and outwardly from the front of the device;

a concave treatment surface, which serves as a drug carrying area for delivering the pharmaceutical composition to the cervix;

the LED lamp system arranged to emit light from the concave treatment surface onto the cervix; and

a second coupling part;

wherein the first coupling part on the first housing part is arranged to join to and form a seal with the second coupling part on the second housing part, thereby forming a joint and closing the chamber; and

wherein the device, when in use, is fully inserted and secured in the vagina and is independently operational while located in the vagina.

78. The method of any one of claims 2 to 77, wherein the integrated device is a single-use and disposable device.

79. The method of any one of claims 2 to 78, wherein the integrated device automatically switches on the LED lamp system to emit light from the concave treatment surface onto the cervix continuously over the second predetermined time period before automatically shutting down.