

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Regimens of CANDIN for Treatment of Common Warts (Verruca vulgaris)

PROTOCOL # CFW-2D

FINAL

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PROTOCOL APPROVAL

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Varying Regimens of CANDIN for Treatment of Common Warts (Verruca vulgaris)

Protocol number: CFW-2D, Version 5.0

Protocol Final Date: 06Dec2016

The signatures below constitute the approval of this protocol and the attachments, and provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Canadian regulations, U.S. federal regulations and ICH guidelines.



INVESTIGATOR SIGNATURE PAGE

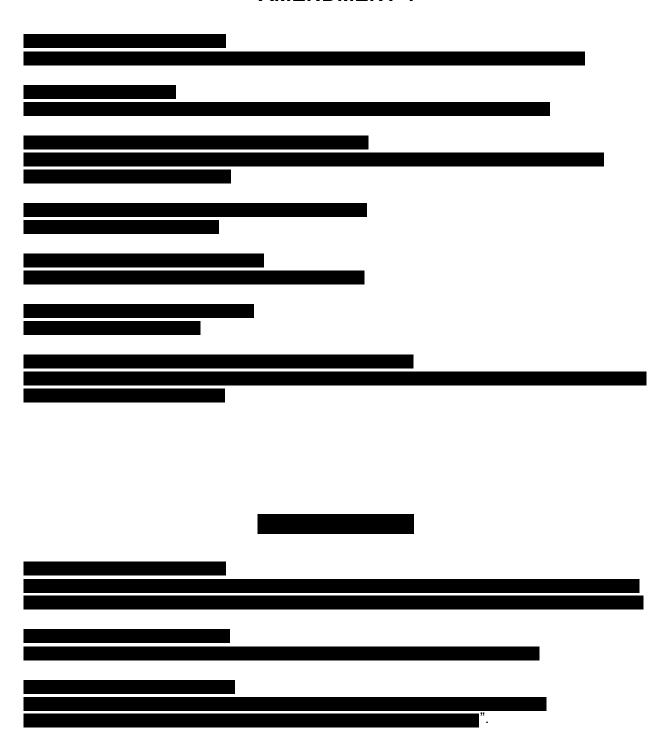
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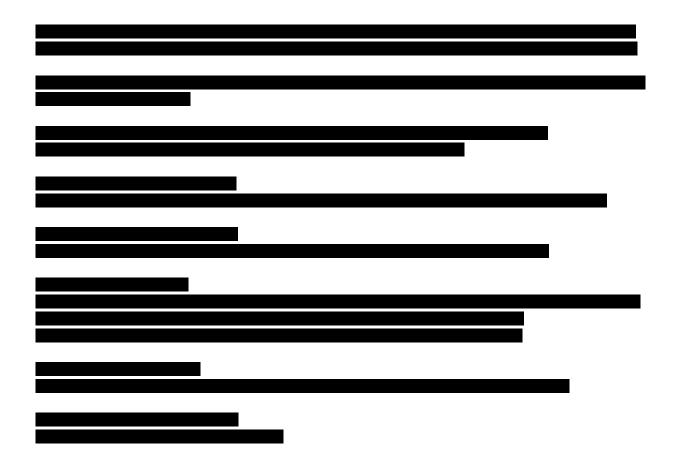
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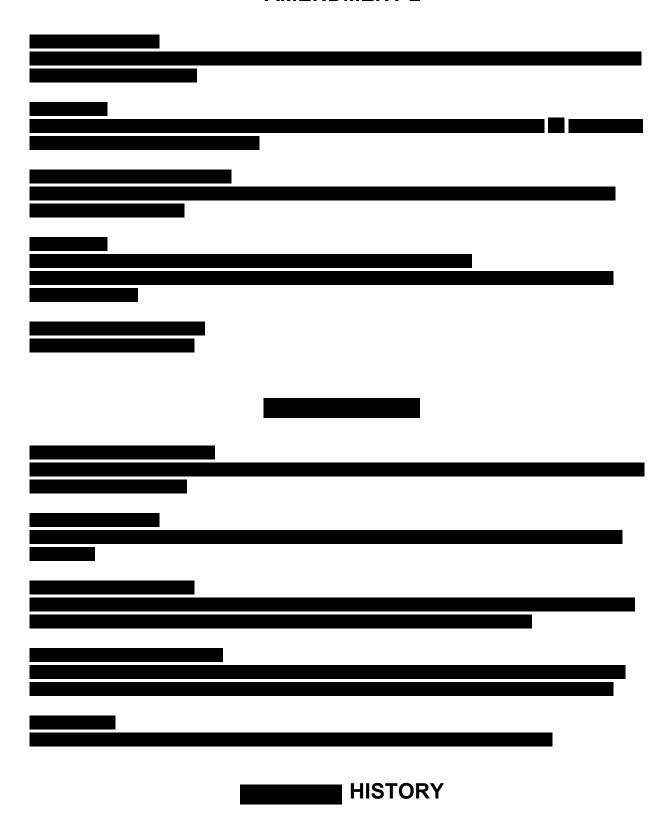
SUMMARY OF CHANGES

AMENDMENT 4





AMENDMENT 2





LIST OF ABBREVIATIONS

AE Adverse Event/Adverse Experience

AIDS Acquired immunodeficiency syndrome

CANDIN Candida albicans Skin Test Antigen for Cellular Hypersensitivity

DNCB Dinitrochlorobenzene

DPCP Diphenylcyclopropenone

DTH Delayed Type Hypersensitivity
eCRF Electronic case report form

GCP Good Clinical Practice

HIV Human immunodeficiency virus

HPV Human Papilloma Virus

ICH International Conference on Harmonization

IRB Institutional Review Board

IUD Intrauterine device

IP Investigational Product

MedDRA Medical Dictionary for Regulatory Activities

OTC Over the counter

REB Research Ethics Board

SAE Serious Adverse Event/Serious Adverse Experience

SOC System Organ Class

S.G. Specific gravity

TEAE Treatment-Emergent Adverse Event

UBG Urobilinogen

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SUMMARY

Title: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study of the Safety

and Efficacy of Varying Regimens of CANDIN for Treatment of Common Warts

(Verruca vulgaris)

Phase: lla

Study Treatment and Administration:

Cohort 1: 0.3 mL of CANDIN (Candida albicans Skin Test Antigen for Cellular

Hypersensitivity) or Placebo administered intralesionally in the largest common

wart

Cohort 2: 0.5 mL of CANDIN or Placebo administered intralesionally in the

largest common wart

Cohort 3: 0.3 mL of CANDIN or Placebo administered intralesionally in up to 4

warts at the same visit (up to 1.2 mL total injected volume)

Population: Approximately 156, male or female subjects aged 18 to 65, with 3 to 20 common

warts on hands, feet (excluding soles), limbs and/or trunk will be included in this

study

Number of Sites: Approximately 15 centers in USA will participate in this study

Study Duration: Subjects will be treated for a maximum of 29 weeks followed by a 16-week

observation period for a total of 45 weeks, excluding the 4-week screening period.

Hypothesis: The null hypothesis for this study is that the CANDIN treatments are not

significantly different from placebo under these experimental conditions

Objectives:

The primary objective is to assess the efficacy of CANDIN treatment in subjects with common warts by evaluating the number and proportion of subjects with the primary injected wart(s) completely resolved.

The secondary objectives are:

1. To assess the safety and tolerability of CANDIN



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Endpoints:

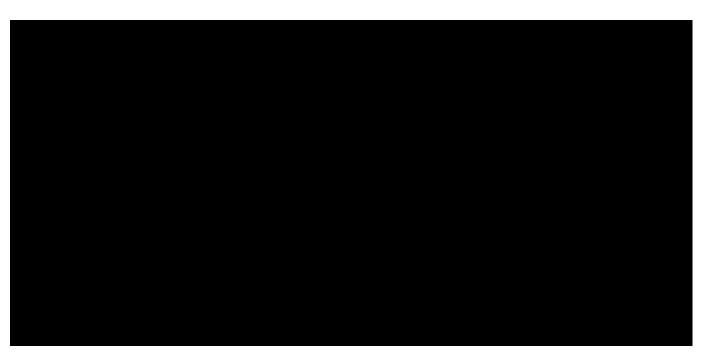
Primary Endpoint:

 The number and proportion of subjects with the primary injected wart(s) completely resolved at any treatment or Follow-up Visit

Secondary Endpoints:

1. Incidence of site injection Adverse Event (AE) for all subjects and Treatment-Emergent Adverse Event (TEAE) for subjects randomized to CANDIN





Overall Study Design

This is a placebo-controlled, double-blind (subject, Investigator, and site staff with the exception of unblinded dedicated staff to handle study medication), phase 2a study with 3 dose cohorts, randomized (concealed) to CANDIN or placebo (3:1). Main study will be up to 20 weeks (10 doses administered every other week) or until a subject has complete resolution of all injectable common warts. Subjects who cannot tolerate dosing every 2 weeks due to a local tolerance issue may be injected at 3-week intervals for up to 10 doses, increasing the length of the study to 29 weeks. Subjects will be followed for 4 months after final injection(s) for evidence of new or reoccurring warts and for safety evaluation.

Inclusion Criteria

Subjects may be eligible if they meet all the following inclusion criteria at the Screening and Baseline Visits unless specified otherwise:

- 1. Men or women between the ages of 18 and 65 years inclusively at time of consent
- 2. Subjects presenting with 3 to 20 injectable common warts (verruca vulgaris) for at least 12 weeks at the time of the Baseline Visit
- 3. Subject's common warts for injection must measure between 3 and 20 mm at Baseline Visit and be located on hands, feet (excluding soles), limbs, and/or trunk. Flat, plantar, facial, periungual, genital warts or warts in region of pre-existing inflammatory condition are excluded from injection
- 4. Subjects enrolled into Cohort 3 must have common warts for injection in at least 2 different anatomical regions defined as: left arm, right arm, left hand, right hand, left leg, right leg, left foot (excluding sole), right foot (excluding sole) and torso
- 5. Subject, male or female is willing to use effective contraceptive method for at least 30 days

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before the Baseline Visit and at least 30 days after the last study drug administration unless not of childbearing potential as defined as post-menopausal for at least 2 years (females) or surgically sterile (tubal ligation, oophorectomy, or hysterectomy for females, and vasectomy for males). The only contraceptive use exceptions would be individuals in exclusive same sex partnerships and individuals who agree to remain non-sexually active for the duration of the study. Acceptable contraceptive methods for subjects include:

- a. Barrier methods, such as condom, sponge or diaphragm, combined with spermicide in foam, gel or cream;
- b. Hormonal contraception (oral, intramuscular, implant or transdermal which includes Depo-Provera, Evra and Nuvaring);
- c. Intrauterine device (IUD)

Female subjects of childbearing potential in a same sex partnership or who are abstinent will still receive pregnancy test as outlined in Appendix A.

6. Mentally and legally capable of giving informed consent prior to any study related procedures

Exclusion Criteria

Subjects will not be eligible if they meet any of the following criteria at the Screening or Baseline Visits unless specified otherwise:

- Presence of systemic or localized diseases, conditions, or medications that could interfere with assessment of safety and efficacy or that compromise immune function including psoriasis
- 2. Subject has been diagnosed with diabetes mellitus
- 3. Subject has a history of keloid formation
- Injectable common wart(s) located in areas with existing dermatologic conditions (such as psoriasis) or with an underlying inflammatory conditions (such as arthritic joints), or tattoos or implants/piercing/hardware or marking that may conceal responses or reactions are excluded from injection
- 5. Existing/planned pregnancy, childbirth in the past six months prior to the Baseline Visit, or breast feeding, or plan on donating eggs or sperm during the study and in the month following the last injection
- Treatment of warts with liquid nitrogen, carbon dioxide, electrodessication, laser, surgery, simple occlusion (e.g. duct tape), salicylic or related acids, OTC treatments, cantharidin, or other treatments (other than immunotherapy or those intended to stimulate immune response) within 4 weeks of the Baseline Visit
- Treatment with immunotherapy (DPCP, DNCB or other), imiquimod, 5-fluorouracil, bleomycin, podophyllin or any other wart immunotherapy or treatment designed to stimulate immune response (except for treatments already listed in exclusion criterion 6) within 12 weeks of the Baseline Visit
- Recalcitrant warts defined as those not successfully treated by five or more treatments

(excluding OTC treatments).

- 9. Abnormal (low < 5 mm or high >25 mm) baseline result to the Delayed Type Hypersensitivity (DTH) test
- 10. Subject has a condition or treatment resulting in being immunocompromised
- 11. Systemic treatment (such as oral or injected) with cimetidine, zinc supplements at a dose higher than 20 mg of elemental zinc daily or an immunosuppressive drug (such as: azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, etanercept, systemic steroids, etc.) within 12 weeks of the Baseline Visit. Note that subjects should not discontinue use of immunosuppressive therapy for the purpose of entering the study as the underlying conditions also could interfere with the study.
- 12. Subject has used any investigational agent within 30 days prior to the Baseline Visit or within 5 half-lives of that investigational agent prior to the Baseline Visit (whichever is longer)
- 13. Previous treatment of warts with any type of intralesional injection with candida extract (including CANDIN)

Statistical Considerations

The primary endpoint is the number and proportion of subjects with complete resolution of the primary injected wart(s). The proportion of subjects with the complete resolution of treated warts will be compared among all treatment groups using the Cochran-Mantel-Haenszel test with a stratification factor of single versus multiple anatomical regions. In addition each active treatment will be compared with the pooled placebo in a similar manner. There will be no adjustment of the type 1 error for multiple comparisons.



Sample Size Determination

A total of approximately 156 subjects will be enrolled into the study with approximately 52 subjects in each active treatment arm and the pooled placebo group. One assumes that the pooled placebo arm has a 24% complete resolution rate and one of the active treatment arms has a complete resolution rate of 70%. The statistical comparison between each active treatment and the pooled placebo will be conducted at the 0.05 significance level. It is assumed that at least 90% of the subjects will either complete the study or reach complete resolution. A sample size of approximately 52 per arm will provide 94% power to detect a statistically significant difference between an active treatment and the pooled placebo. The assumed Nielsen- CFW-2D

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1 BACKGROUND

1.1 Common Warts

Verruca vulgaris, common warts, are caused by the human papilloma virus (HPV). HPV infects epithelial cells and, in the case of common warts, cause proliferation of the fully differentiated epithelium resulting in clinically evident warty papules. Most authors agree that the prevalence of non-genital warts is between 7 and 10% in the US. Young people are preferentially affected, with the peak incidence being reported between the ages of 12 and 16 years. Common warts are least common among infants and the elderly.¹⁻⁷ Common warts occur most frequently on hands and feet, less frequently on limbs, torso or face where flat warts are more common.^{5,7} New common warts frequently regress spontaneously with reports of roughly 60% regressing within two years, and roughly 30% of subjects experiencing spontaneous regression of at least one wart during a nine month period.^{1,2,7,8} However, the remaining roughly 40% may remain for years. While many subjects are instructed to wait and see if the warts resolve spontaneously, warts can bleed, itch, be painful and disfiguring, with 52% of subjects experiencing moderate to severe discomfort and 81% being moderately to extremely embarrassed by the presence of their warts.⁷ Additionally, untreated warts serves as a reservoir for continued shedding of contagious papilloma virus.

1.2 Treating Common Warts

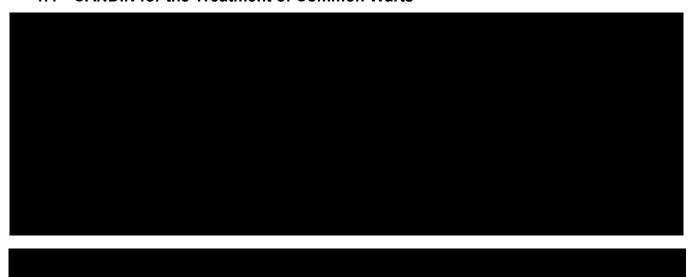




1.3 Candida Albicans Skin Test Antigen for Cellular Hypersensitivity (Candin®)

CANDIN is currently marketed in the United States indicated for use as a recall antigen for detecting DTH by intradermal injection of 0.1 mL. The product may be useful in assessing the cellular immune response in individuals suspected as having decreased immune responses of this type, such as those with AIDS, HIV, and cancer. Local reactions observed in the development of CANDIN for DTH included redness, swelling, pruritus, vesiculation, weeping edema, excoriation, induration, and discoloration of the skin. Immediate hypersensitivity has been observed within 20 minutes of injection characterized as an edematous hive with a surrounding zone of erythema. Up to approximately 20% of subjects had lesions of 10-24 mm diameter and another group of up to approximately 13% had lesions of less than 10 mm diameter.

1.4 CANDIN for the Treatment of Common Warts





2 STUDY HYPOTHESIS AND OBJECTIVE(S)

Hypothesis:

The null hypothesis for this study is that the CANDIN treatments are not significantly different from placebo under these experimental conditions

Objective(s):

The primary objective is to assess the efficacy of CANDIN treatment in subjects with common warts by evaluating the number and proportion of subjects with the primary injected wart(s) completely resolved.

The secondary objectives are:

1. To assess the safety and tolerability of CANDIN



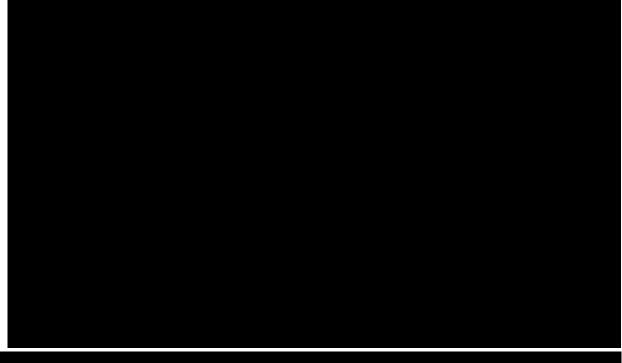
3 STUDY ENDPOINTS

3.1 Primary Endpoint

The number and proportion of subjects with the primary injected wart(s) completely resolved at any treatment or Follow-up Visit.

3.2 Secondary Endpoints

1. Incidence of site injection AE for all subjects and TEAE for subjects randomized to CANDIN





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4 STUDY DESIGN

This is a placebo-controlled, double-blind (subject, Investigator, and site staff with the exception of unblinded dedicated staff to handle study medication), phase 2a study with 3 dose cohorts, randomized (concealed) to CANDIN or placebo (3:1). Main study will be up to 20 weeks (10 doses administered every other week) or until a subject has complete resolution of all injected common warts. Subjects who cannot tolerate dosing every 2 weeks due to a local tolerance issue may be injected at 3-week intervals for up to 10 doses, increasing the length of the study to 29 weeks (+/- study windows). Subjects will be followed for 4 months after final injection(s) for evidence of new or reoccurring warts and for safety evaluation.

5 STUDY POPULATION

Approximately 156, male or female subjects aged 18 to 65 inclusively at the signature of consent with 3 to 20 common warts on hands, feet (excluding soles), limbs and/or trunk will be included in this study in order to complete with approximately 115 subjects. Drop-outs will not be replaced. Additional subjects may be added to ensure approximately 115 subject complete the study in the event an investigator or site discontinues participation in the study

5.1 Inclusion Criteria

Subjects may be eligible if they meet all the following inclusion criteria at the Screening and Baseline Visits unless specified otherwise:

- 1. Men or women between the ages of 18 and 65 years inclusively at time of consent
- 2. Subjects presenting with 3 to 20 injectable common warts (verruca vulgaris) for at least 12 weeks at the time of the Baseline Visit
- 3. Subject's common warts for injection must measure between 3 and 20 mm at Baseline Visit and be located on hands, feet (excluding soles), limbs, and/or trunk. Flat, plantar, facial, periungual, genital warts or warts in region of pre-existing inflammatory condition are excluded from injection
- 4. Subjects enrolled into Cohort 3 must have common warts for injection in at least 2 different anatomic regions defined as: left arm, right arm, left hand, right hand, left leg, right leg, left foot (excluding sole), right foot (excluding sole) and torso
- 5. Subject, male or female is willing to use effective contraceptive method for at least 30 days before the Baseline Visit and at least 30 days after the last study drug administration unless not of childbearing potential as defined as post-menopausal for at least 2 years (females) or surgically sterile (tubal ligation, oophorectomy, or hysterectomy for females, and vasectomy for males). The only contraceptive usage exceptions would be individuals in exclusive same sex partnerships and individuals who agree to remain non-sexually active for the duration of the study. Acceptable contraceptive methods for subjects include:
 - Barrier methods such as condom, sponge or diaphragm combined with spermicide in foam, gel or cream;
 - b. Hormonal contraception (oral, intramuscular, implant or transdermal which includes Depo-Provera, Evra and Nuvaring);
 - c. Intrauterine device (IUD)

Female subjects of childbearing potential in a same sex partnership or who are abstinent will still receive pregnancy test as outlined in Appendix A.

6. Mentally and legally capable of giving informed consent prior to any study related procedures

5.2 Exclusion Criteria

Subjects will not be eligible if they meet any of the following criteria at the Screening and Baseline Visits unless specified otherwise:

- Presence of systemic or localized diseases, conditions, or medications that could interfere
 with assessment of safety and efficacy or that compromise immune function including
 psoriasis
- Subject has been diagnosed with diabetes mellitus
- 3. Subject has a history of keloid formation
- 4. Injectable common wart(s) located in areas with existing dermatologic conditions (such as psoriasis) or with an underlying inflammatory conditions (such as arthritic joints), or tattoos or implants/piercing/hardware or marking that may conceal responses or reactions are excluded from injection.
- Existing/planned pregnancy, childbirth in the past six months prior to the Baseline Visit, or breast feeding, or plan on donating eggs or sperm during the study and in the month following the last injection.
- 6. Treatment of warts with liquid nitrogen, carbon dioxide, electrodessication, laser, surgery, simple occlusion (e.g. duct tape), salicylic or related acids, OTC treatments, cantharidin, or other treatments (other than immunotherapy or those intended to stimulate immune response) within 4 weeks of the Baseline Visit
- 7. Treatment with immunotherapy (DPCP, DNCB or other), imiquimod, 5-fluorouracil, bleomycin, podophyllin or any other wart immunotherapy or treatment designed to stimulate immune response (except for treatments already listed in exclusion criterion 6) within 12 weeks of the Baseline Visit
- 8. Recalcitrant warts defined as those not successfully treated by five or more treatments (excluding OTC treatments).
- Abnormal (low < 5 mm or high >25 mm) baseline result to the Delayed Type Hypersensitivity (DTH) test
- 10. Subject has a condition or treatment resulting in being immunocompromised
- 11. Systemic treatment (such as oral or injected) with cimetidine, zinc supplements at a dose higher than 20 mg of elemental zinc daily or an immunosuppressive drug (such as: azathioprine, 6-mercaptopurine, methotrexate, infliximab, adalimumab, etanercept, systemic steroids, etc.) within 12 weeks of the Baseline Visit. Note that subjects should not discontinue

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use of immunosuppressive therapy for the purpose of entering the study as the underlying conditions also could interfere with the study.

- 12. Subject has used any investigational agent within 30 days prior to the Baseline Visit or within 5 half-lives of that investigational agent prior to the Baseline Visit (whichever is longer)
- 13. Previous treatment of warts by intralesional injection with any type of candida extract (including CANDIN)

5.3 Discontinuations

Subjects have the right to withdraw from the study at any time for any reason without penalty. The Investigator also has the right to withdraw subjects from the study if he/she feels it is in the best interest of the subject or if the subject is uncooperative or non-compliant. It is understood by all concerned that an excessive rate of withdrawal can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw or if the Investigator decides a subject should be withdrawn, all efforts will be made to complete and report the observations as required in Section 7.6 - Early Termination Visit.

An Early Termination Visit should be completed at the time of the decision to withdraw the subject, or as soon as possible thereafter, and the reason for withdrawal from the study should be documented. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded as the reason for study discontinuation. If this decision is made because of a related SAE, the study drug is to be discontinued and appropriate medical interventions are to be taken. The Investigator will notify the Sponsor immediately. All unresolved, possibly related and related AEs and SAEs will be followed until resolution, or until the Investigator deems the event(s) to be chronic or stable, or until the subject is lost to follow-up.

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be discontinued from the study. If this subject received CANDIN, he/she should come back, if possible within 1 week of the last visit, for safety and efficacy evaluations as required in Section 7.6 - Early Termination Visit.

Reasons for study drug discontinuation include:

- The Investigator decides that the subject should be withdrawn (see above).
- The attending or general physician requests that the subject be withdrawn from the study
- The subject for any reason requires or receives treatment with another therapeutic agent or treatment for their warts. In this case, discontinuation from the study occurs immediately upon introduction of the new agent
- The subject for any reason requires treatment with concomitant medication that is excluded on study.
 In this case, discontinuation from the study occurs immediately upon introduction of the concomitant medication. The Early Termination Visit should occur before the introduction of the concomitant medication if possible.
- The subject is lost to follow-up, in this case, a reasonable attempt to contact the subject and ascertain
 his/her status must be made and these attempts must be documented. The effort will include three or
 more documented attempts then a certified letter requesting the subject contact the site. The

Nielsen- CFW-2D Protocol Final version 5.0: 06Dec2016 Investigator or one of his/her staff members should contact the subject either by telephone, e-mail, or letter to determine as completely as possible the reason for the withdrawal and to schedule the Early Termination Visit. If the subject intends to withdraw from the study, the Early Termination Visit should occur as soon as possible.

- The Sponsor or Regulatory Authorities, for any reason, stops the study. All subjects will be discontinued
 from the study and notified of the reasons for the discontinuation. Subjects may be asked to continue
 with follow-up visits as outlined in Appendix A or to complete the Early Termination Visit.
- The Sponsor, Investigator, or Regulatory Authorities, for any reason, discontinues a site's participation.
 All subjects at that site will be discontinued from the study (unless an alternative, local site is active) and notified of the reasons for the discontinuation. Subjects may be asked to complete the Early Termination Visit and may continue with one or both follow-up visits as outlined in Appendix A.
- Pregnancy at any time during the study. The subject will be followed as outlined in Section 9.4 -Pregnancy Reporting.
- The subject may withdraw from the study for any other reason, including withdrawal of consent. See above.

6 TREATMENT

6.1 Treatment Administered

Subjects who fulfill all the inclusion and none of the exclusion criteria may be accepted in the study. Each subject should read and sign an informed consent form prior to any screening procedures being performed. This study involves a comparison of an intralesional injection of CANDIN with an intralesional injection of placebo (unpreserved normal saline solution) in common warts. Subjects will receive one (Cohorts 1 and 2) or more (Cohort 3) intralesional injections every two weeks (14 +/- 2 days) at the region of the interdigitated base of wart (epidermal/dermal junction) for up to 20 weeks (a maximum of 10 doses per subject) or up to resolution of all injectable warts. Subjects who experience local tolerance issues when dosing is performed at 2-week intervals may be injected at 3-week intervals (21 +/- 2 days) also for a maximum of 10 doses per subject.

Subjects will be included in three cohorts as follows:

- 1. Cohort 1: Approximately 52 subjects will receive 0.3 mL of either CANDIN (n=39) or placebo (n=13) intralesionally in the largest common wart (primary) every second week (14 +/- 2 days) for a maximum of 10 injections. If the primary common wart exhibits a complete response, the second largest injectable common wart of all anatomical regions will be injected with CANDIN at the same dose. If the second largest common wart exhibits a complete response, the third largest of all anatomical regions will be injected. If an injected wart recurs after exhibiting a complete response, it will be re-injected instead of the non-primary injected wart that was injected at the previous visit. This injection strategy will be repeated for a maximum of 10 injections per subject or until all injectable common warts exhibit a complete response, if it occurs before all 10 injections are used.
- 2. **Cohort 2:** Approximately 52 subjects will receive 0.5 mL of either CANDIN (n=39) or placebo (n=13) intralesionally in the largest common wart every second week (14 +/- 2 days) for a maximum of 10 injections. If the primary common wart exhibits a complete

Nielsen- CFW-2D Page 26 of 54 Protocol Final version 5.0: 06Dec2016 response the second largest injectable common wart of all anatomical regions will be injected with CANDIN at the same dose. If the second largest common wart exhibits a complete response the third largest wart of all anatomical regions will be injected. If an injected wart recurs after exhibiting a complete response, it will be re-injected instead of the non-primary injected wart that was injected at the previous visit. This injection strategy will be repeated for a maximum of 10 injections per subject or until all injectable common warts exhibit a complete response, if it occurs before all 10 injections are used.

3. Cohort 3: If the safety data of the 2nd cohort support continuation of the study (defined as medical assessment of the first eight (8) subjects (of cohort 2) completing three (3) injections), the approximately 52 subjects of cohort 3 will receive either 0.3 mL/wart CANDIN (n=39) or placebo (n=13) (total per visit ≤ 1.2 mL). Subjects in cohort 3 must have injectable common warts in at least 2 different anatomic regions. CANDIN or placebo will be injected under the largest wart (primary) per major anatomical region (left or right; arm, hand, leg, foot (excluding sole) or the torso) for a minimum of two (2) and a maximum of four (4) injections per visit every second week (14 +/- 2 days) for a maximum of 10 visits with injections. No more than one wart per anatomical region will be injected on any given visit. If any primary injected wart exhibits a complete response, the next largest injectable common wart will be injected with CANDIN at the same dose (maximum of 4 injections per visit) providing the new injectable wart is not within the same anatomical region as other currently injected warts. If an injected wart recurs after exhibiting a complete response, it will be re-injected instead of the non-primary injected wart that was injected at the previous visit. This injection strategy will be repeated for a maximum total of 10 injection visits per subject or until all injectable common warts exhibit a complete response, if it occurs before the end of the 10 injection visits.

6.2 Materials and Supplies

6.2.1 Study Products

DTH Testing: CANDIN (Candida albicans Skin Test Antigen for Cellular Hypersensitivity) used according to the US approved labeling. CANDIN is a clear, colorless, sterile aqueous solution, pH of 8.0-8.5, packaged in 1 mL multidose glass vials. Each vial delivers 10 x 0.1 mL dose. CANDIN will be provided by Nielsen BioSciences, Inc.

Investigational Product: CANDIN used as the Investigational Product (IP). CANDIN is a clear, colorless, sterile aqueous solution, pH of 8.0-8.5, packaged in 1 mL multidose glass vials. Each vial delivers 10 x 0.1 mL dose. CANDIN will be provided by Nielsen BioSciences, Inc.

Placebo: 0.9% sodium chloride injection, USP, preservative free for injection used as the placebo. It will be provided by Nielsen BioSciences, Inc. Each vial will be used for a single injection (once) since the contents are not preserved.

The Investigator will be responsible for drug accountability. After verification of the drug accountability by the Sponsor, the Investigator will return the remaining study product (used and unused vials) to the Sponsor.

CANDIN for DTH testing and for use as the IP will be provided by the Sponsor to the Investigator and will be kept on site in a secure temperature controlled refrigerated space (2-8 °C). It will only be dispensed to

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subjects enrolled on the trial under the supervision of the Investigator. Refrigerator temperature will be monitored and recorded in a log. The Investigator is responsible for maintaining accurate records of the dispensing of study medication.
6.2.2 Method of Assignment to Treatment
This is a double-blind study defined as blinding of subjects, investigators, and site personnel not involved in study drug preparation and accountability.
Randomization will be unbalanced (3:1) in favor of CANDIN.
The subjects will be randomly assigned to cohorts first and then to treatment according to the following randomization table. The purpose is to ensure that subject characteristics are as comparable as possible between different cohorts.

used on all subject documentation throughout the study. Numbers will be assigned in ascending order using Sponsor's numbering system. 6.2.4 Breaking of Study Blinding This will be a double-blind study; the Investigators performing the injection, site personnel performing or recording study assessments, site study coordinators, and subjects will remain blinded to active versus control treatment.

The investigational site will assign each subject a subject identifier number during screening that will be

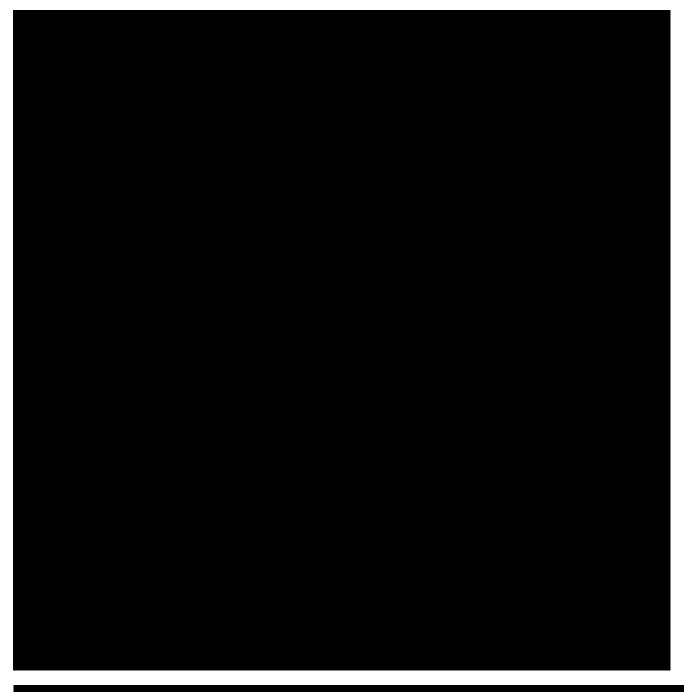


6.2.6 Assessment of Compliance

Since all study drug will be administered on site, compliance will be directly monitored by the study staff.

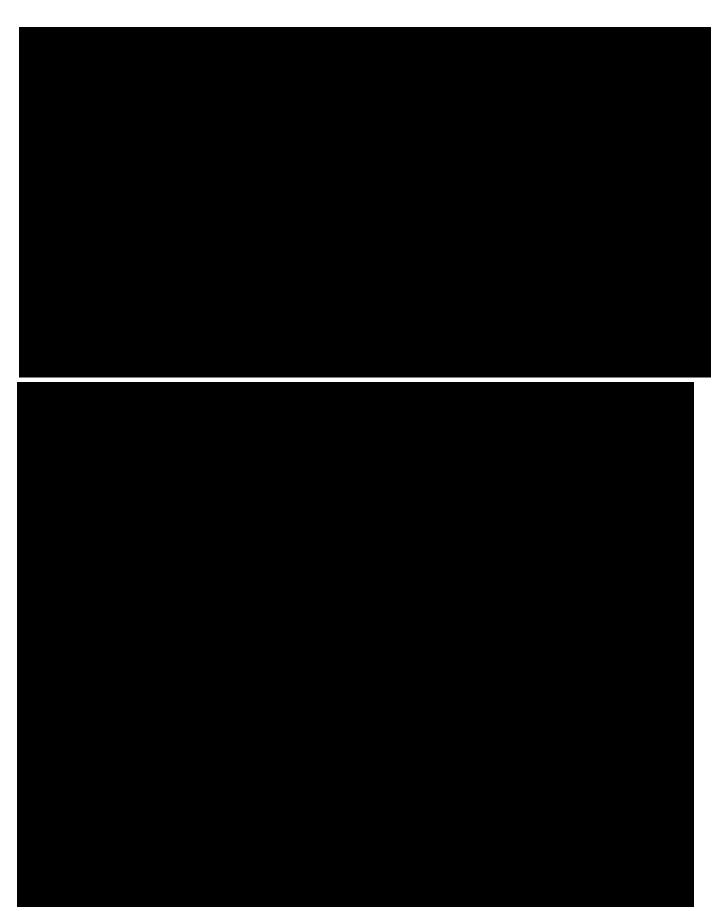
7 STUDY PROCEDURES

7.1 Screening Visits 1 and 2 (Day -30 to Baseline)











7.8 Vital Signs

The following vital signs will be recorded at Screening (V1), Baseline (V3) and Injection (V4-V12) Visits prior to treatment and Efficacy Evaluation Visit (V13) after an approximately 5 minutes resting period in a seated position:

- Systolic and diastolic blood pressure (mm Hg),
- Pulse (bpm),
- Body temperature (°C)

The weight (kg or lbs) and height (cm or inches) will be recorded at the Screening Visit (V1) only.

7.10 Physical Examination

A physical examination will be performed at Screening (V1) and Efficacy Evaluation Visit (V13). The following sites/systems will be included in the physical examination. Each system will be scored as normal/abnormal. Pertinent details must be recorded for any clinically significant findings, in order to be added as medical history or an AE.

- General appearance
- Skin
- Eyes, Ears, Nose, Throat
- Head, Neck, Thyroid
- Lymphatic
- Cardiovascular
- Lungs, Chest
- Abdomen
- Extremities
- Musculoskeletal
- Neurologic



7.12 DTH Challenge

At Screening Visit 1 (V1), the DTH test will be done by administering a single intradermal injection of CANDIN (0.1mL) on the volar surface of the forearm or on the outer aspect of the upper arm, at least 2 cm away from any primary injectable wart(s). The skin should be cleansed with 70% alcohol before applying the skin test. The intradermal injection must be given as superficially as possible causing a distinct, sharply defined bleb. An unreliable reaction may result if the product is injected subcutaneously. The subject will

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be asked to remain in the clinic for 30 minutes after receiving the injection of CANDIN for the DTH test, to assess any immediate reactions. A DTH diary will be handed to the subject, in order to capture any delayed reactions, prior to Screening Visit 2 (V2).

The test should be read on V2 at $(48 \pm 4 \text{ hours post DTH challenge injection that occurred at V1})$ by visually inspecting the test site and palpating the indurated area. Measurements should be made across two diameters. The mean of the longest and midpoint orthogonal diameters of the indurated area should be reported as the DTH response.

The measured DTH response must be between ≥ 5 mm and ≤ 25 mm in diameter to be considered a valid reaction. Responses <5 mm or >25 mm would exclude the subject from the study.



8 EFFICACY EVALUATIONS

8.1 Common Wart Evaluations

In cohort 1 and 2, the largest common wart located on hands, feet (excluding soles), limbs and/or trunk will be selected as the primary injected wart.

In cohort 3, the largest common wart per anatomical region (left or right; arm, hand, leg, foot (excluding sole) or the torso) will be selected as the primary injected wart for a maximum of four warts. For cohort 3, each injected wart must be located on a different anatomical region. Flat, plantar, facial, periungual, or genital warts or warts in region of pre-existing inflammatory condition are excluded.

8.1.1 Common wart measurement

The visually largest six common warts (including the primary injectable wart(s)) that can be readily identified will be measured at Baseline Visit (V3) and during the study (referred as "measured warts"). Unless the wart location can be easily identified in writing using anatomical terms, these (up to 6) largest common injectable warts will be mapped on transparencies or drawn in the medical chart to ensure it is accurately found at every visit. The mapping process on transparencies will be described in the Study Manual.

Each measured wart will be documented in the source document and reported on the eCRF, with its size, age, treatment history and location. Size will be determined by measuring in mm the longest and orthogonal diameters of the wart using a ruler.

8.1.2 Evaluation of primary injected wart status

The size and status (resolved, partially resolved, or no response) of each primary injected wart will be documented at each visit. Complete resolution of a wart is the absence of visual or measurable presence

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of verruca vulgaris. Complete resolution of all common warts is the absence of any common warts (i.e. wart count = 0).

8.1.3 Evaluation of presence or absence of common warts other than the measured common warts

New warts (those not noted at Baseline Visit (V3)) can be recorded in Progress Notes at any given visit, but are not tracked except as noted in **Section 8.1.4**. If the investigator notes an occurrence of new warts that is considered clinically abnormal or unusual, note as an Adverse Event.

8.1.4 Presence or absence of common warts in designated anatomical areas

At the Baseline Visit (V3) the presence or absence of common warts in the following anatomical areas will be assessed: left arm, right arm, left hand, right hand, left leg, right leg, left foot (excluding sole), right foot (excluding sole) and torso. The presence or absence of common wart in these anatomical areas will also be assessed at Injection Visit V7, Efficacy Evaluation Visit (V13) and Follow-up Visit (V15).

New common warts in anatomical areas will be defined as the presence of common warts at V7, V13 and/or V15 in anatomical area(s) where **NO common warts in that anatomic area were present at Baseline Visit** (V3). New warts in areas that previously were noted to have warts should not be recorded as such in this examination (see Section 8.13).

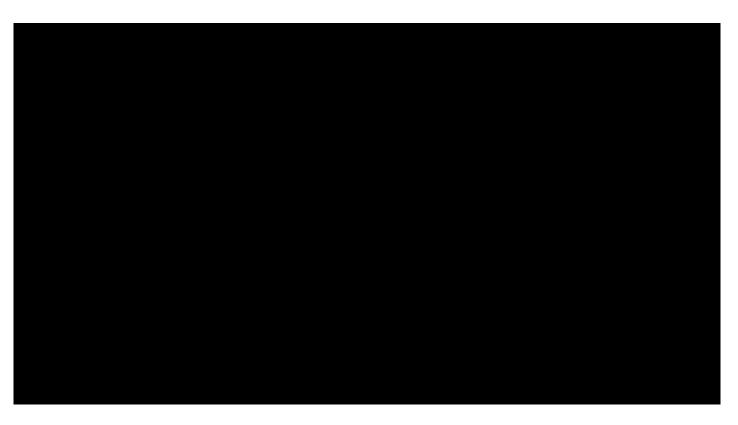
9 SAFETY EVALUATIONS

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the Sponsor of any observation that seems unusual, even if this observation may be considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study.

Safety will be evaluated by collecting AEs and clinically significant changes in safety laboratories or vital signs. The reported AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The number and percentage of subjects with at least one AE will be tabulated. For a given AE, a subject will be counted once even if he or she has experienced multiple episodes for that particular AE. The occurrence of AEs by MedDRA System Organ Class (SOC) and preferred term and the severity and relationship of the AE to the study drug will be summarized using the number and percentage of subjects.

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Study participants will be instructed to contact the Investigator immediately in the event they experience any severe sign or symptom, or feel they need to seek medical attention. For this purpose, they will be provided with an emergency number (available 24 hours daily, 7 days weekly) to report the event and/or seek medical advice and assistance.

9.2 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, without regard to the possibility of a causal relationship with this treatment. Lack of drug effect is not an AE in clinical trials because the purpose of the clinical trial is to establish drug effect.

Any documented pregnancy will be tracked and followed through outcome. While pregnancy itself is not considered an AE or an SAE, any pregnancy complications or elective termination of a pregnancy for medical reasons will be recorded as an AE and evaluated as a possible SAE.

Prior to enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and eCRF. During the study, site personnel will again note any change in the pre-existing condition(s) and the occurrence and nature of any AEs.

CANDIN will be administered in accordance with the US labeled indication for assessment of the subject's DTH response to Candida antigen. AE collection will begin at the time of the DTH injection (Screening Visit 1).

CANDIN administered intralesionally is the investigational product in this study. Treatment-Emergent AEs (TEAEs) will be those arising after the first intralesional wart(s) injection.

If a subject experiences an AE after the informed consent document is signed, but before CANDIN is Nielsen- CFW-2D Page 38 of 54

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administered for assessment of the DTH response, the event will be recorded as a non-treatment emergent AE in the source document. If the subject is randomized, the non-treatment emergent event will also be captured in the eCRF. If the subject screen fails, the event will not be captured in the eCRF or in the clinical database.

AEs reported as related to CANDIN administered for assessment of the DTH response will be described in the source document and assessed for expectedness and regulatory reportability using the Candin package insert. If the subject is randomized, the AE related to Candin for the DTH assessment will also be captured in the eCRF.

Injection site AEs may be captured from either subject diaries or during Treatment and Follow-up Visits. In all cases, causality and severity of injection site TEAEs are assessed by Investigator as described in Sections 9.2.1 and 9.2.2, respectively.

All unresolved, at least possibly related AEs and SAEs will be followed until resolution or until the Investigator deems the event to be chronic or the event to be stable or until the subject is lost to follow-up.

For subjects randomized to receive study drug, all AEs and SAEs will be described in the source documents and in the eCRF.

Abnormal laboratory values or test results should not be reported as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE include the following:

- Test result is associated with accompanying symptoms;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy;
- Test result is considered to be an AE by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

9.2.1 Adverse Events Causality

The Investigator will establish causality of the AE to experimental treatment. The Investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: temporal relationship of the onset of the AE, relative to the experimental treatment is not reasonable or another cause can explain the occurrence of the AE.
- <u>Unlikely related</u>: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable; however, an alternative explanation is more likely.
- Possibly related: temporal relationship of the onset of the AE, relative to experimental treatment is reasonable; however, follows no known response pattern to the treatment, and an alternative cause seems more likely or there is sufficient uncertainty about the cause of the event.

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- Probably related: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable, and follows a known response pattern to the treatment, but a potential alternative cause may be present.
- <u>Related</u>: temporal relationship of the onset of the AE, relative to the experimental treatment is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

9.2.2 Adverse Events Severity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The severity of AEs at the injection site will be estimated using the table below from the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (see below).²⁰ The following definitions are to be used to rate the severity of AEs that are not at the injection site:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.
- <u>Moderate</u>: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.
- <u>Severe</u>: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary. Note-severe intensity of an AE such as injection site pain does not necessarily mean that it is a SAE (see Section 9.3)

The following definitions from the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials will be used to rate the severity of an injection site AE.

Local Reaction to	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life
Injection				Threatening (Grade 4)
Pain	Does not interfere with	Repeated use of non-	Any use of narcotic	Emergency room visit or
	activity	narcotic pain reliever	pain reliever by	hospitalization
		>24 h or interferes with	physician or prevents	
		normal daily activity	normal daily activity	
Tenderness	Mild discomfort to	Discomfort with	Significant discomfort	Emergency room visit or
	touch	movement	at rest	hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1—10 cm	>10 cm	Necrosis or severe
				exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does	5.1—10 cm or	>10 cm or prevents	Necrosis
	not interfere with	interferes with normal	normal daily activity	
	normal daily activity	daily activity		

^{*}In addition to grading the measure local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

9.3 Serious Adverse Events

If a subject experiences a SAE after the informed consent document is signed, but before CANDIN is administered for assessment of the DTH response, the event will be recorded as a non-treatment emergent SAE in the source document. If the subject is randomized, the non-treatment emergent SAE will also be captured in the source and reported in the CRF. If the subject screen fails, the SAE will not be reported in

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^{**}Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

the eCRF.

CANDIN will be administered in accordance with the US labeled indication for assessment of the subject's DTH response to Candida antigen. SAEs reported as related to Candin administered for the DTH assessment will be described in the source document and assessed for expectedness and regulatory reportability using the Candin package insert. If the subject is randomized, the SAE related to Candin administered for the DTH assessment will also be captured in the eCRF.

All SAEs occurring following wart injections and up to 30 days following the last wart injection will be captured in the source document and reported in the CRF.

A SAE (event/experience) or reaction is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires in-subject hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

9.3.1 SAE Reporting:

Any SAE, related or not, occurring during the study as described above must be reported as soon as possible using the SAE form provided and followed by fax within **24 hours** of awareness to:



For each SAE received, the Sponsor will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. The Sponsor will manage the expedited

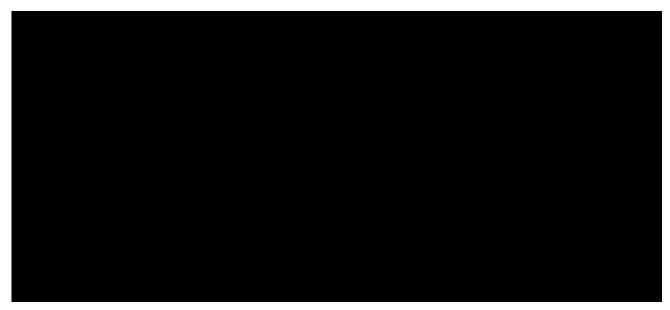
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reporting of relevant safety information to concerned health authorities and competent authorities in accordance with local laws and regulations.

The Sponsor will assess the expectedness of each SAE to the study treatment. The current Investigator's Brochure will be used as the reference document to assess expectedness of the event to study drug.

9.4 Pregnancy Reporting

If a female subject or if a female partner of a male subject becomes pregnant during the study, the subject should inform the study site as soon as possible. No additional treatments shall be administered until a serum pregnancy test is performed and confirmed. Upon confirmation of the pregnancy, the female subject will be discontinued from the treatment portion of the study, and requested to continue with the follow-up visits. Any confirmed pregnancy will be tracked and followed through outcome. While pregnancy itself is not considered an AE or an SAE, any pregnancy complications or elective termination of a pregnancy for medical reasons will be recorded as an AE and evaluated as a possible SAE. All pregnancies should be reported to the Sponsor and Ethics Committee.



9.6 Laboratory Tests

All laboratory tests procedures will be referenced in the Central Laboratory Manual.

9.6.1 Pregnancy Test

A urine and serum pregnancy test will be performed at the first Screening Visit (V1) for females of childbearing potential. Samples will be sent to a central laboratory. Pregnancy testing not required for women of non-childbearing potential defined as post-menopausal for at least 2 years or surgically sterile (tubal ligation, oophorectomy, or hysterectomy).

A urine pregnancy test will be performed at the DTH challenge if performed at an additional visit after Screening Visit (V1), at Baseline Visit (V3) and at every other visit during the injection period (Visits 5, 7, 9, 11) and Efficacy Evaluation Visit (V13) at the investigative site for all females of childbearing potential. Urine pregnancy testing not required for women of non-childbearing potential defined as post-menopausal for at least 2 years or surgically sterile (tubal ligation, oophorectomy, or hysterectomy).

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9.6.2 Clinical Chemistry Analysis
The following clinical chemistry analyses will be performed at the first Screening and Efficacy Evaluation
9.6.3 Clinical Haematology Analysis
A complete blood count
will be performed at the Screening and Efficacy Evaluation Visits (Vis 1 and 13). Samples will be sent to a central laboratory for analysis and reporting.
9.6.4 Urinalysis
Routine urinalysis including blood (
will be performed at the Screening and Effica Evaluation Visits (Visits 1 and 13). Samples will be sent to a central laboratory for analysis and reporting
The following microscopic analysis will be performed when relevant for any positive results:
9.7 Stopping Rules
The following are Stopping Rules that will be applied to individual subjects or treatment cohorts. In addition to the Stopping Rules, the Investigator may discontinue treatment of any subject in which addition treatments are judged to be unsafe or intolerable.
9.7.1 Individual Stopping Rules
9.7.1.1 Immediate Reactions Following DTH or Intralesional Injection
Subjects will remain in the clinic for safety monitoring after DTH or intralesional injection for a minimum 30 minutes after dosing in the event they experience signs and/or symptoms of immediate hypersensitiv and/or anaphylaxis.

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9.7.1.2 Local Reactions

The following reactions occurring within 7 days following the injection of Investigational Product, as judged by the Investigator based upon the subject diary entries, discussion with subject, and the scale in Protocol Section 9.2.2, also judged by Investigator as possibly, probably, or definitely related to the Study Drug:

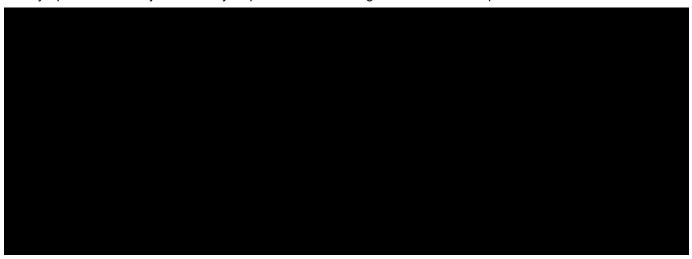
- Pain (Severity Grade 4)
- Tenderness (Severity Grade 4)
- Erythema/Redness (Severity Grade 4)
- Induration/Swelling (Severity Grades 3-4)

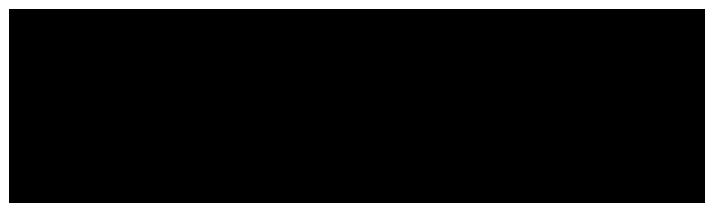
If a subject fails to contact the Investigator about the occurrence of a severity Grade 4 local reaction, the Investigator and Medical and Safety Monitor will investigate this event to characterize the severity and grade of the event, before recommending the stopping of the subject.

9.7.1.3 Serious Adverse Events (SAE)

A serious adverse event as defined in Protocol Section 9.3 and is judged as possibly, probably, or definitely related to Study Drug.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes





9.7.2.3 Serious Adverse Events (SAE)

A serious adverse event as defined in Protocol Section 9.3 and is judged as possibly, probably, or definitely related to Study Drug.

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in 9.3.

10 DATA QUALITY ASSURANCE/SITE MONITORING

During the study, monitoring visits will be conducted at regular intervals as detailed in the Monitoring Plan. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities.

The site may be audited and/or monitored by a quality assurance officer named by the Sponsor and/or regulatory authorities may wish to perform on-site audits. The Investigator will be given notice before an audit occurs and will be expected to cooperate with any audit, provide assistance and documentation (including source data) as requested.

11 DATA COLLECTION AND RETENTION

Subject data will be entered in the eCRFs by site personnel. The Data Management Plan (DMP) will define and document the processes and procedures used to ensure consistent, efficient and effective data collection, transfer, storage, quality, and reporting for the study.

The Investigator will maintain source documents for each subject in the study, consisting of case and visit notes (clinical medical records) containing demographic and medical information and the results for any tests or assessments. All information on the eCRFs must be traceable to these source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The data collected will be encoded and stored electronically in a database system. AEs will be coded using MedDRA and summarized by SOC, Preferred Term, and treatment group. Summaries by severity and by relationship to study drug will also be included. SAE and discontinuations due to AE will be summarized separately. Concomitant medications will be coded using the World Health Organization Drug Dictionary Nielsen- CFW-2D

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12 CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must assure that the subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject enrolment log relating codes with the names of subjects. The Investigator should maintain documents not for submission to Sponsor e.g., subjects' written consent forms, in strict confidence.

13 INVESTIGATOR'S FILES/RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: Investigator Study File and Subject Clinical Source Documents.

The Investigator must keep these two categories of documents on file according to country-specific regulation, but no less than US FDA requirements, after completion or discontinuation of the study. After that period of time, the Sponsor will be contacted for long term disposition (Sponsor storage or disposal).



14.2 Analysis Populations

Three populations will be used for the summaries and analyses of the study data. These populations are defined as follows:

Intent-to-Treat (ITT): The ITT Population will consist of all randomized subjects who receive at least one intralesional dose of study medication.

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14.3 Subject Disposition

Subject disposition will be summarized by treatment and overall for the Randomized Population.

14.4 Demographic and Baseline Characteristic

Demographic and relevant baseline characteristics will be presented and summarized descriptively by cohort/treatment for the ITT Populations. Additional summary of demographic and baseline characteristics may be specified in the SAP, if deemed necessary.

14.5 Statistical Analysis

General Considerations

<u>Baseline</u>: Baseline refers to the last measurement collected prior to the first dose of randomized study medication at Visit 3 (Day 1).

<u>Placebo</u>: The placebo data from the three cohorts will be assessed for comparability. If the data appear comparable they will be pooled into one placebo group for analyses.

<u>Significance Testing</u>: All statistical testing will be conducted at an α =0.05 significance level. There will be no adjustment of the significance level for multiple comparisons.

14.5.1 Efficacy analysis

14.5.1.1 Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint is the number and proportion of subjects with the primary injected wart(s) with complete resolution, which will be compared among all treatment groups by using the Cochran-Mantel-Haenszel test with a stratification factor of single versus multiple anatomical regions. Each active treatment will be compared with the pooled placebo in a similar manner.





14.5.2 Safety Analysis

The analysis of safety data will be performed for the ITT Population unless otherwise stated. The primary safety endpoint is the incidence of TEAEs defined as any new AEs or existing AEs that have worsened during or following the first wart(s) injection with CANDIN (Visit 3) through final Follow-up Visit (V15) or Early Termination/Withdrawal. Other safety endpoints include vital signs, physical exams and laboratory measures.

14.5.2.1 Analysis of Adverse Events

TEAEs (those arising after the first intralesional wart injection in this study) will be summarized by treatment, SOC, and preferred term defined by MedDRA. The number of events and number of events by severity, the number of subjects, and the percent of subjects who experienced at least one TEAE will be presented for each SOC and for each preferred term by treatment group. TEAEs that lead to early withdrawals and serious TEAEs will be summarized in the same manner. Additional details will be provided in the SAP. Injection site TEAEs will be analysed separately from other TEAEs.

DTH-related AEs will be analysed separately by Sponsor and Medical Monitor to determine FDA reportability.

14.5.2.2 Analysis of Laboratory Measures

All laboratory results will be listed by treatment, subject, and visit, including scheduled and unscheduled measurements. Laboratory assessments that are outside of normal ranges will be flagged.

Baseline values, the values at each visit, and changes from baseline values will be summarized for each of the quantitative laboratory assessments by treatment.

Shift tables of laboratory results will be used to summarize changes from Baseline to the end of the Follow up Visit (V15) or Early Termination.

14.5.2.3 Analysis of Vital Signs and Physical Examinations

Vital signs at Baseline (Visit 3, Day 1), each scheduled visit, and changes from baseline values will be summarized by treatment. Physical exam findings will be listed.



15 ETHICS

15.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013) and that are consistent with "Good Clinical Practice" ICH Tripartite Guideline (July 2002) and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

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15.2 Ethical Review

This protocol (and any amendment) as well as appropriate consent procedures and related documents (advertisement, subjects' cards, etc.), will be reviewed and approved by the REB/IRB. This Board must operate in accordance with the current Federal regulations. A letter or certification of approval will be sent by the Investigator to the Sponsor prior to initiation of the study, and also whenever subsequent modifications to the protocol are made.

15.3 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason.

If new safety information results in significant changes in the risk/benefice assessment or any new information that may affect willingness to continue to participate, the consent form should if necessary be updated by the Sponsor or Sponsor's representative and be reviewed by the REB/IRB. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and asked to give their consent to continue in the study.





18 APPENDIX A Study Flow Chart

		ening sits	Baseline Visit (Day 1)				Injec	tions V	/isits²				Efficacy Evaluation Visit ¹⁰	Follow-up Visits	
Visit	V1 ¹⁴	V21	V3 ¹	V4	V5	V6	V 7	V8	V9	V10	V11	V12	V13 ¹⁴	V14	V15
Window (days)	-30d to -2d	±4h ⁵			± 2d						± 3d	± 3d	± 7d		
PROCEDURES															
Informed Consent	Х														
Inclusion/Exclusion Criteria	Х		Х												
Demographics	Х														
Medical and Surgical History	Х		Х												
Blood Draw for Safety Labs ¹⁴	Х												Х		
Urinalysis	Х												Х		
Pregnancy Test ³	Х		Х		Х		Х		Х		Х		Х		
Vital Signs (Includes weight and height at <u>screening</u>)	Х		Х	Х	Х	Х	Х	х	Х	х	х	Х	Х		
Physical Examination	Х												Х		
Full Body Dermatologic Examination to identify the presence of any wart type			х				X						Х		х
Presence or absence of common warts in designated anatomical areas			х				х						Х		х
Evaluation of presence or absence of common warts other than the measured			х										Х	х	х

		ening sits	Baseline Visit (Day 1)				Efficacy Evaluation Visit ¹⁰	Follow-up Visits							
Visit	V1 ¹⁴	V2 ¹	V3 ¹	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13 ¹⁴	V14	V15
Window (days)	-30d to -2d	±4h ⁵			1			± 2d	•	•			± 3d	± 3d	± 7d
and mapped injectable common warts															
Common warts measurement and mapping (up to 6 injectable common warts including all primary injectable warts)			х	X	x	х	X	x	x	х	x	X	х	х	х
Evaluation of primary injected wart(s) status				Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х
Selection of primary injectable wart(s) ⁹			Х												
Selection and Mapping of non-primary common wart(s) for injection ⁸				х	Х	Х	Х	х	х	х	х	Х			
DTH Challenge Injection (30-min observation period)	X ¹³														
DTH Evaluation		Х													
Blood Draw for Biomarkers Evaluation	X ⁶				X ^{6, 12}								X ⁶		
Randomization			Х												
Intralesional Injection (30-min observation period)			Х	Х	Х	Х	Х	х	х	х	х	Х			
Give Subject Diary/Device	X ⁷		Х	Х	Х	Х	Х	Х	Х	Х	Х	Х			
Review/Retrieve Subject Diary		X ⁷		Х	Х	Х	Х	Х	х	Х	Х	Х	Х		
Retain Diary Device													Х		
Medical Photographs ⁴			Х		Х		Х				Х		Х	Х	Х

		ening sits	Baseline Visit (Day 1)				Injec	tions V	isits²				Efficacy Evaluation Visit ¹⁰	Follow-up Visits	
Visit	V1 ¹⁴	V2 ¹	V3 ¹	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13 ¹⁴	V14	V15
Window (days)	-30d to -2d	±4h ⁵						± 2d					± 3d	± 3d	± 7d
Hypopigmentation and Scarring Assessments ¹¹			Х	Х	Х	Х	Х	Х	Х	х	Х	Х	×	Х	Х
Concomitant Medications	Х	Х	Х	Х	Х	Χ	Х	Х	Х	Х	Х	Х	Х	Х	Х
Adverse Events	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х	Х

