

Draft Guidance on Podofilox

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Active ingredient: Podofilox

Form/Route: Gel; Topical

Recommended study: 1 study

Type of study: Bioequivalence (BE) study with clinical endpoint

Design: Randomized, double-blind, parallel, placebo-controlled in vivo

Strength: 0.5%

Subjects: Healthy male or female with external anogenital warts

Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Not Applicable

Bioequivalence based on (90% CI): Clinical endpoint

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Not Applicable.

Additional comments regarding the BE study with a clinical endpoint:

1. The OGD recommends a BE study with a clinical endpoint comparing the podofilox topical gel, 0.5% test product versus the reference listed drug (RLD) and placebo control, with each subject applying the gel to the warts with the applicator tip or finger twice daily for 3 consecutive days, then discontinuing for 4 consecutive days. This one week cycle of treatment is to be repeated until there is no visible wart tissue or for a maximum of four cycles (i.e., study product applied only on study Days 1, 2, 3, 8, 9, 10, 15, 16, 17, 22, 23, and 24). Application on the surrounding normal tissue should be minimized. Care should be taken to allow the gel to dry before allowing the return of opposing skin surfaces to their normal positions. Treatment should be limited to 10 cm² or less of wart tissue and to no more than 0.5 g of the gel per day.
2. The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population with "treatment success" defined as "total disappearance of all warts within all treated areas". The primary endpoint is evaluated at four days (\pm 5 days) after the last day of the last cycle of treatment. Five office visits are recommended: baseline (Day 0), Week 1 (Day 7), Week 2 (Day 14), Week 3 (Day 21) and Week 4 (Day 28).
3. Inclusion Criteria:
 - a. Healthy male or female aged \geq 18 years with a clinical diagnosis of external anogenital warts (i.e., perianal warts and/or external genital warts), two or more distinct external genital warts, and wart area to be treated that is equal to or less than 10 cm². Histological confirmation should be obtained if there is any doubt of the diagnosis.
 - b. Females of childbearing potential may be enrolled if they were practicing a method of birth control with a reliability of at least 90%.

- c. Any female subject with childbearing potential has a negative urine pregnancy test on first day of dosing (study Day 1).
 - d. Negative HIV test within 4 weeks before the first day of dosing (study Day 1).
4. Exclusion Criteria:
- 1. Pregnant or lactating or planning to become pregnant during the study period.
 - 2. Known hypersensitivity or intolerance to podofilox or any component of the formulation.
 - 3. History of previous unsuccessful treatment with any formulation of podofilox.
 - 4. Mucous membrane wart, bowenoid papulosis, squamous cell carcinoma, or active herpes lesion within any treatment area.
 - 5. Primary or secondary immunodeficiency.
 - 6. Local irritation in any treatment area that would interfere with treatment.
 - 7. Use within 4 weeks prior to baseline of any: 1) treatment for anogenital warts, 2) systemic corticosteroid, or 3) systemic immunosuppressive drug.
5. The protocol should include a list of the prescription and over-the-counter drug products that are prohibited during the study, such as:
- a. Any other topical products applied to the treatment area(s).
 - b. Systemic corticosteroid or immunosuppressive drugs.
 - c. Antipruritics, including antihistamines, within 24 hours of study visits.
6. Instruct subjects to wash their hands thoroughly before and after each application of study product and to avoid contact with the eyes. If contact with the eyes occurs, subjects should immediately flush the eyes with copious quantities of water and seek medical advice. Inform subjects that the study product is flammable and to keep it away from open flames.
7. The protocol should clearly define the per-protocol (PP), intent-to-treat (ITT) and safety populations:
- a. The accepted PP population used for bioequivalence evaluation includes all randomized subjects who met all inclusion/exclusion criteria, had no protocol violations that would affect the treatment evaluation, were compliant with applying study product, and returned to the study site for the primary endpoint evaluation at four days (± 5 days) after the last day of the last cycle of treatment. The protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses until treatment success or four cycles of treatment) and specify how compliance will be verified (e.g., by the use of subject diaries).
 - b. The ITT population includes all subjects who are randomized, applied at least one dose of assigned product, and returned for at least one post-baseline evaluation visit.
 - c. The safety population includes all randomized subjects who received study product.
8. Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of external anogenital warts during the study should be discontinued, included in the PP population analysis as treatment failures, and provided with effective treatment. Subjects discontinued prematurely from the study for any other reason should be excluded from the PP population, but included in the ITT population, using Last Observation Carried Forward (LOCF).
9. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

10. Application site reactions such as erythema, dryness, burning/stinging, erosion, edema, pain, itching and bleeding are to be recorded at each visit to allow a comparison between treatment groups. A descriptive analysis comparing the application site reactions for each treatment group is recommended. It is important to ensure that the test product is not worse than the reference product with regard to the expected and unexpected application site reactions.
11. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.
12. If the inactive ingredients are different than those contained in the RLD or in significantly different amounts, then the sponsor is to clearly describe the differences and provide information to show that the differences will not affect the safety, efficacy and/or systemic or local availability of the drug.
13. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.
14. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.
15. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.
16. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
17. To establish bioequivalence, the 90% confidence interval of the difference in the “treatment success” rate between the test product and RLD treatment groups occurring at four days (± 5 days) after the last day of the last cycle of treatment must be within $[-0.20, +0.20]$ for the dichotomous primary endpoint, using the PP study population.
18. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo ($p < 0.05$) with regard to the “treatment success” rate occurring at four days (± 5 days) after the last day of the last cycle of treatment using the ITT study population and LOCF.
19. The following Statistical Analysis Method is recommended for equivalence testing for a dichotomous variable (success/failure):

Equivalence Analysis

Based on the usual method used in OGD for binary outcomes, the 90% confidence interval for the difference in success proportions between test and reference treatment should be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

$$H_0: p_T - p_R < -.20 \text{ or } p_T - p_R > .20$$

versus

$$H_A: -.20 \leq p_T - p_R \leq .20$$

where p_T = success rate of test treatment p_R = success rate of reference treatment.

Let

n_T = sample size of test treatment group

$c n_T$ = number of subjects with success in test treatment group

n_R = sample size of reference treatment group

$c n_R$ = number of subjects with success in reference treatment group

$$\hat{p}_T = c n_T / n_T, \quad \hat{p}_R = c n_R / n_R,$$

$$\text{and se} = \left(\hat{p}_T (1 - \hat{p}_T) / n_T + \hat{p}_R (1 - \hat{p}_R) / n_R \right)^{1/2}.$$

The 90% confidence interval for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = \left(\hat{p}_T - \hat{p}_R \right) - 1.645 \text{ se} - (1/n_T + 1/n_R)/2$$

$$U = \left(\hat{p}_T - \hat{p}_R \right) + 1.645 \text{ se} + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -.20$ and $U \leq .20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

20. Study data should be submitted to the OGD in electronic format.
 - a. A list of file names, with a simple description of the content of each file, should be included.
 - b. Please provide a "pdf" document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.

- d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - e. Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline Bishop Score, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
21. Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- a. Study identifier
 - b. Subject identifier
 - c. Site identifier: study center
 - d. Age
 - e. Age units (years)
 - f. Sex
 - g. Race
 - h. Name of Actual Treatment (exposure): test product, RLD, placebo
 - i. First Dose of Assigned Treatment Date
 - j. First Dose of Assigned Treatment Time
 - k. Last Dose of Assigned Treatment Date
 - l. Last Dose of Assigned Treatment Time
 - m. Duration of Treatment (total number of days from first to last application, inclusive)
 - n. Per Protocol (PP) population inclusion (yes/no)
 - o. Reason for exclusion from PP population
 - p. Intent to Treat (ITT) population inclusion (yes/no)
 - q. Reason for exclusion from ITT population
 - r. Safety population inclusion (yes/no)
 - s. Reason for exclusion from safety population
 - t. Final designation as treatment success (yes/no)
 - u. Treatment compliance : number of missed doses per subject
 - v. Concomitant medication (yes/no)
 - w. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	trt_f_d	trt_f_t	trt_l_d	trt_l_t	EXDUR
101	001	01	20	YEARS	F	1	A	04/1/11	8:00	04/25/11	20:02	24
101	002	01	24	YEARS	F	1	B	04/1/11	9:15	04/25/11	21:15	24

pp	pp_rs	itt	itt_rs	safety	safe_rs	trt_suc	complan	CM	AE
Y		Y		Y		Y	0	Y	N
Y		Y		Y		Y	1	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
SITEID:	Study Site Identifier: study center
AGE:	Age
AGEU:	Age units (years)
SEX:	Sex, e.g., F=Female, U=Unknown
RACE:	Race, e.g., 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=placebo
trt_f_d:	First Application of Assigned Treatment Date, e.g., month/date/year
trt_f_t:	First Application of Assigned Treatment Time, e.g., 24-hour clock
trt_l_d:	Last Application of Assigned Treatment Date, e.g., month/date/year
trt_l_t:	Last Application of Assigned Treatment Time, e.g., 24-hour clock
EXDUR:	Duration of Treatment (total number of days from first to last application, inclusive), e.g., 0, 1 ...24
pp:	Per Protocol (PP) population inclusion, e.g., Y=Yes, N=No
pp_rs:	Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=noncompliant, etc.
itt:	Intent to Treat (ITT) population inclusion, e.g., Y=Yes, N=No
itt_rs:	Reason for exclusion from ITT population, e.g., A=never treated etc.
safety:	Safety population inclusion, e.g., Y=Yes, N=No
safe_rs:	Reason for exclusion from Safety population, e.g., A=never treated, etc.
trt_suc:	Final designation, e.g., Y=Yes (treatment success), N=No (treatment failure)
complan:	Treatment compliance :number of missed doses per subject, e.g., 0, 1 ...24
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

22. Please provide a dataset containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
- Study identifier
 - Subject identifier
 - Name of Actual Treatment (exposure): test product, RLD, placebo control
 - Visit number
 - Visit date
 - Number of days since baseline visit
 - Evaluator: identity of evaluator
 - Total number of anogenital warts within treatment area(s)
 - Total number of external genital warts
 - Total number of perianal warts
 - Skin reaction scores for each sign and symptom evaluated (e.g., erythema, dryness, burning/stinging, erosion, edema, pain, itching, bleeding, etc.)
 - Treatment success (yes/no)
 - Concomitant medication reported during this visit (yes/no)
 - Adverse event reported during this visit (yes/no)
 - Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of dataset containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	anogen	ext_gen	perianal	erythema	dryness	burning	erosion	edema	pain	itching	bleed	trt_suc	CMrpt	AErpt	LBtest
101	1	A	1	2011-07-01	0	JB	4	3	1	1	0	0	1	0	0	0	0	N	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

STUDYID:	Study Identifier
SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBS:	Elapsed Time since Baseline (number of days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
anogen:	Total number of anogenital warts within treatment area(s)
ext_gen:	Total number of external genital warts within treatment area(s)
perianal:	Total number of perianal warts within treatment area(s)
erythema:	Skin reaction erythema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
dryness:	Skin reaction dryness score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
burning:	Skin reaction burning/stinging score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
erosion:	Skin reaction erosion score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
edema:	Skin reaction edema score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
pain:	Skin reaction pain score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
itching:	Skin reaction itching score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
bleed:	Skin reaction bleeding score, e.g. 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), 3=severe (marked, intense)
trt_suc:	Treatment success, e.g., Y=Yes, N=No
CMrpt:	Concomitant Medication reported during this visit, e.g., Y=Yes, N=No
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No
LBtest:	Laboratory Testing performed during this visit, e.g., Y=Yes, N=No

23. These recommendations are specific to this product and may not be appropriate for bioequivalence studies of any other product, including any other dosage form or strength of Podofilox