

Draft Guidance on Dinoprostone

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Active ingredient: Dinoprostone

Form/Route: Gel; Endocervical

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 mg/3 gm (single dose)

Subjects: Pregnant female patients at or near term with a medical or obstetrical indication for the induction of labor.

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 dinoprostone endocervical gel, 0.5 mg/3 gm test product versus the reference listed drug (RLD) and placebo control, with each subject receiving a single dose administered into the cervical canal just below the level of the internal os with the primary endpoint evaluation occurring 12 hours after dosing of the assigned product.
- 2) The recommended primary endpoint of the study is the proportion of subjects in the per protocol (PP) population identified as “treatment success” occurring during the 12-hour observation period after dosing of the assigned product. A “treatment success” is defined as attainment of an increase of at least 3 in a Bishop score during the 12-hour observation period, the attainment of a Bishop score of ≥ 6 during the 12-hour observation period, or vaginal delivery occurring during the 12-hour observation period. It is recommended that the same individual perform the Bishop Score assessment at baseline, at 6 hours after dosing, and at 12 hours after dosing.
- 3) Inclusion Criteria:
 - a. Pregnant women aged ≥ 18 years.
 - b. Medical or obstetrical indication for induction.
 - c. Singleton pregnancy at ≥ 37 weeks gestation
 - d. Cephalic presentation.
 - e. Parity ≤ 3 .

- f. Fetal reactive non-stress test.
- g. Bishop score ≤ 4 on admission.

Bishop score¹				
Parameter\Score	0	1	2	3
Dilation	0 cm	1-2 cm	3-4 cm	5-6 cm
Effacement	0-30%	40-50%	60-70%	$\geq 80\%$
Fetal Station	-3	-2	-1 to 0	+1 to +2
Consistency	Firm	Medium	Soft	-
Position	Posterior	Mid.	Anterior	-

- 4) Stratify treatment groups by parity (i.e., nulliparous versus multiparous) to ensure similar proportions of nulliparous and multiparous women in each of the three treatment groups.
- 5) Exclusion Criteria:
 - a. Subject with hypersensitivity to prostaglandins or constituent of the gel.
 - b. Subject in whom oxytocic drugs are generally contraindicated or where prolonged contractions of the uterus are considered inappropriate, such as:
 - cases with a history of cesarean section or major uterine surgery
 - cases in which cephalopelvic disproportion is present
 - cases in which there is a history of difficult labor and/or traumatic delivery
 - non-vertex presentation
 - cases with hyperactive or hypertonic uterine patterns
 - cases of fetal distress where delivery is not imminent
 - in obstetric emergencies where the benefit-to-risk ratio for either the fetus or the mother favors surgical intervention
 - c. Subject with placenta previa or unexplained vaginal bleeding during this pregnancy.
 - d. Subject for whom vaginal delivery is not indicated, such as vasa previa or active herpes genitalia.
 - e. Premature rupture of membranes.
 - f. History of asthma, glaucoma, or raised intraocular pressure.
 - g. Renal or hepatic dysfunction.
 - h. Prior attempts at cervical softening or induction of labor in the present pregnancy
 - i. Subject already receiving intravenous oxytocic drugs.
 - j. Fetal death in-utero.
 - k. Spontaneous labor.
- 6) Caution should be taken so as not to administer the study product above the level of the internal os. Careful vaginal examination will reveal the degree of effacement which will regulate the size of the shielded endocervical catheter to be used. That is, the 20 mm endocervical catheter should be used if no effacement is present, and the 10 mm catheter should be used if the cervix is 50% effaced. Placement of the RLD into the extra-amniotic space has been associated with uterine hyperstimulation.
- 7) Dinoprostone should be administered by physicians in a hospital that can provide immediate intensive care and acute surgical facilities. During use, uterine activity and fetal status should be carefully monitored either by auscultation or electronic fetal monitoring to detect possible evidence of undesired responses, e.g., hypertonus, sustained uterine contractility, or fetal distress. The character of the cervix (dilation and effacement) should be evaluated when appropriate. In

¹ Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol.* 1964 Aug; 24 (2): 266-8.

cases where there is a history of hypertonic uterine contractility or tetanic uterine contractions, it is recommended that uterine activity and the state of the fetus should be continuously monitored. The possibility of uterine rupture should be borne in mind when high-tone myometrial contractions are sustained. Feto-pelvic relationships should be carefully evaluated before use of study product.

- 8) Vaginal irritation should be evaluated at baseline and 12 hours after administering the dose of assigned product and compared between treatment groups. The protocol could use a scoring system and pre-specify definitions for various degrees of vaginal irritation.
- 9) 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 meet all inclusion/exclusion criteria, have no protocol violations that would affect the treatment evaluation, receive a single dose of the assigned product with the final evaluation completed at 12 hours after dosing of the assigned product OR vaginal delivery occurred prior to 12 hours after dosing. The protocol should specify how compliance will be verified, e.g., data collected on case report form for date and times of dosing, delivery method (i.e., vaginal delivery, Cesarean section) and delivery date and time.
 - b. The ITT population includes all subjects who are randomized, receive a single dose of assigned product, and undergo at least one Bishop score assessment after dosing.
 - c. The safety population includes all randomized subjects who receive at least one dose of study product.
- 10) Subjects who discontinue early from the study should be excluded from the PP population, but included in the ITT population, using LOCF.
- 11) Treatment groups should also be compared with regard to the number of subjects with hypertonicity, fetal distress, and other potentially treatment-related obstetrical adverse events.
- 12) Delivery mode (i.e., vaginal delivery, Cesarean section) and delivery date and time should be recorded for each subject and compared between treatment groups.
- 13) 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.
- 14) 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.
- 15) 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.
- 16) 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.

- 17) 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 and to maintain adequate blinding of evaluators. When possible, the investigator should not be able to identify the treatment.
- 18) 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.
- 19) It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.
- 20) To establish bioequivalence, the 90% confidence interval of the difference in the "treatment success" rate between the test product and RLD treatment groups at 12 hours after dosing of the assigned product must be within [-0.20, +0.20] for the dichotomous primary endpoint, using the PP study population.
- 21) 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 12 hours after dosing of the assigned product, using the intent-to-treat (ITT) study population and Last Observation Carried Forward (LOCF).
- 22) 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

cn_T = number of subjects with success in test treatment group

n_R = sample size of reference treatment group

cn_R = number of subjects with success in reference treatment group

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

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

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.

- 23) Study data should be submitted to the OGD in electronic format.
- A list of file names, with a simple description of the content of each file, should be included.
 - 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).
 - 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.
 - 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).
 - 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.
- 24) Please provide a summary dataset containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
- Study identifier
 - Subject identifier
 - Site identifier: study center
 - Age
 - Age units (years)
 - Sex
 - Race

- h. Name of Actual Treatment (exposure): test product, RLD, placebo
- i. Dose of Assigned Treatment Date
- j. Dose of Assigned Treatment Time
- k. Duration of Treatment (total exposure in hours)
- l. Per Protocol (PP) population inclusion (yes/no)
- m. Reason for exclusion from PP population
- n. Intent to Treat (ITT) population inclusion (yes/no)
- o. Reason for exclusion from ITT population
- p. Safety population inclusion (yes/no)
- q. Reason for exclusion from safety population
- r. Bishop Score prior to dosing, e.g. at baseline
- s. Bishop Score at 6 hours after dosing
- t. Bishop Score at 12 hours after dosing
- u. Bishop Score increased by ≥ 3 points within 12 hours after dosing (yes/no)
- v. Bishop Score increased to ≥ 6 within 12 hours after dosing (yes/no)
- w. Method of Delivery (vaginal delivery/Cesarean section)
- x. Delivery Date
- y. Delivery Time
- z. Vaginal Delivery occurred within 12 hours after dosing (yes/no)
- aa. Final designation as treatment success/treatment failure (yes/no)
- bb. Vaginal Irritation at baseline
- cc. Vaginal Irritation at 12 hours after dosing
- dd. Treatment compliance (yes/no)
- ee. Concomitant medication (yes/no)
- ff. 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_d	trt_t	EXDUR	PP	pp_rs	itt	itt_rs
101	001	01	20	YEARS	F	1	A	04/16/11	8:00	12	Y		Y	
101	002	01	24	YEARS	F	1	B	04/17/11	9:15	12	Y		Y	

safety	safe_rs	bish_b	bish_6	bish_12	bish_≥3	bish_≥6	deliv_m	deliv_d	deliv_t	vag_d_12	trt_suc	irr_b	irr_12	complan	CM	AE
Y		4	5	6	N	Y	V	04/17/11	7:05	Y	Y	0	1	Y	Y	N
Y		3	5	7	Y	Y	C	04/18/11	6:10	Y	Y	0	2	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
SITEID:	Study Site Identifier
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_d:	Dose of Assigned Treatment Date, e.g., month/day/year
trt_t:	Dose of Assigned Treatment Time, e.g., 24-hour clock
EXDUR:	Duration of Treatment (total exposure in hours)
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.
bish_b:	Bishop Score prior to dosing (at baseline), e.g., integer ranging from 0 to 13
bish_6:	Bishop Score at 6 hours after dosing, e.g., integer ranging from 0 to 13
bish_12:	Bishop Score at 12 hours after dosing, e.g., integer ranging from 0 to 13
bish_≥3:	Bishop Score increased by ≥ 3 points within 12 hours after dosing, e.g., Y=Yes, N=No
bish_≥6:	Bishop Score increased to ≥ 6 within 12 hours after dosing, e.g., Y=Yes, N=No
deliv_m:	Delivery Method, e.g., V=vaginal delivery, C=Cesarean section
deliv_d:	Delivery Date (e.g., month/day/year)
deliv_t:	Delivery Time (e.g., 24-hour clock)
vag_d_12:	Vaginal Delivery occurred within 12 hours after dosing, e.g., Y=Yes, N=No
trt_suc:	Final designation, e.g., Y=Yes (treatment success), N=No (treatment failure)
irr_b:	Vaginal Irritation at baseline, e.g., 0=none; 1=minimal; 2=moderate; 3=severe
irr_12:	Vaginal Irritation at 12 hours after dosing e.g., 0=none; 1=minimal; 2=moderate; 3=severe
complan:	Treatment compliance (received single dose of study product), e.g., Y=Yes, N=No
CM:	Concomitant medication, e.g., Y=Yes, N=No
AE:	Adverse event(s) reported, e.g., Y=Yes, N=No

25) 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 Dinoprostone.