Training Sign-in Sheet

Misopess Phase III Study

Miso-Obs-303: The EXPEDITE Study

STUDY DESIGN

Protocol Version: Final, Revision 01
Date: 26 July 2010

Miso-Obs-303: The *EXPEDITE* Study

A phase III, double-blind, randomized, multicenter study of Exogenous Prostaglandin comparing the Efficacy and safety of the Misoprostol Vaginal Insert (MVI) 200 mcg to the Dinoprostone vaginal insert for reducing Time to vaginal delivery in pregnant women at tErm

The EXPEDITE Study

- Randomized, double-blind
  - Misoprostol Vaginal Insert 200 mcg (MVI 200) or Dinoprostone vaginal insert 10 mg (DVI) (Cervidil)
  - Stratified by parity (60% nullips, 40% parous)
- Women requiring cervical ripening and induction of labor
- 1,350 subjects (675 per treatment group)
  - Approximately 35 sites

Primary Objectives / Endpoints

Demonstrate time to vaginal delivery is shorter in MVI 200 than DVI

- Measured by time to vaginal delivery *during first hospital admission*

Demonstrate rate of cesarean is not greater in MVI 200 than DVI

- Measured by the incidence of cesarean delivery *during first hospital admission*

Secondary Endpoints

- Time to any delivery mode
- Time to active labor
- Proportion of subjects with:
  - Pre-delivery oxytocin
  - Vaginal delivery within 12 & 24 hours
  - Any delivery within 12 & 24 hours
  - Cervical ripening success at 12 hours
- Overall safety

Tertiary Endpoints

Pharmacoeconomics, comparing MVI to DVI for:

- Duration in L&D suite
- Duration of pre-delivery oxytocin administration
- Duration of hospital stay for subject and neonate
- Proportion of subjects/neonates admitted to ICU/NICU
- Proportion of subjects/neonates requiring antibiotics
- Proportion of subjects with failed inductions (discharged undelivered)

Study Population: Inclusion/Exclusion Criteria

Study Population: Inclusion Criteria

- Written informed consent
- Women at ≥36 weeks 0 days inclusive gestation
- Age ≥18 years
- Candidate for pharmacologic IOL
- Single, live, vertex fetus
- Parity ≤3
  - Parity = one or more births, live or still births after 24 weeks 0 days gestation
- BMI ≤50 at time of entry into the study
- **Baseline modified Bishop score ≤4**

Modified Bishop Score

DOCUMENT all five elements:

- **Station**
- **Dilatation**
- **Effacement…**

REMEMBER

- **CONSISTENCY** (Firm; Average; Soft)
- **POSITION** (Posterior; Mid, Anterior)

Modified Bishop Score

Points:	0	1	2	3
Dilation	<1 cm	1-2 cm	>2-4 cm	>4 cm
Station	– 3	– 2	– 1; 0	+1; +2
Consistency	Firm	Average	Soft	
Position	Posterior	Mid; anterior		
Length of cervix	>4 cm	>2–4 cm	1 – 2 cm	<1 cm

(Calder & Embrey, 1974)

Corresponding effacement measurement	0-30%	40-50%	60-70%	≥ 80%

(Cunningham, Gant, Leveno, et al, 2001)

Maximum mBS is 12:

- 3 for Dilation
- 3 for Station
- 2 for Consistency
- 1 for Position
- 3 for Length of Cervix

Study Population: Exclusion Criteria

- Women in active labor
- Administration of ANY of the following within 7 days prior to study drug administration:
  - Oxytocin
  - Any cervical ripening or labor inducing agents (including mechanical methods)
  - Tocolytic drug
    - Magnesium sulfate permitted if prescribed for preeclampsia or gestational hypertension

Exclusion Criteria (continued):

- Amnioinfusion or other treatment of non-reassuring fetal **status** at ANY time prior to induction attempt
- Any evidence of fetal compromise at baseline e.g.,
  - Failed non-stress or stress test
  - Meconium staining
  - Diagnosis or history of non-reassuring fetal status
  - Fetal growth restriction (<10%), polyhydramnios and oligohydramnios are NOT considered evidence of fetal compromise and ARE permitted

Exclusion Criteria (continued):

- Diagnosed congenital anomalies, NOT including polydactyly
- Ruptured membranes ≥48 hours prior to study drug administration
- Signs and symptoms of chorioamnionitis
- Fever (oral or aural temperature >99.5°F/ 37.5°F)
- Any unexplained vaginal bleeding at any time after 24 weeks 0 days gestation

Exclusion Criteria (continued):

- Any condition in which vaginal delivery is contraindicated
- Known or suspected allergy to misoprostol, dinoprostone, other prostaglandins or any of the excipients
- Any condition urgently requiring delivery
- Unable to comply with the protocol

No eligibility waivers will be permitted

Schedule of Events
SCREENING

SCREENING (continued):

- Perform/Review EFM/CTG monitoring for at least 15 minutes prior to insertion of study drug to confirm:

Category I FHR and

No uterine contractile pattern indicative of active labor

Schedule of Events

STUDY DRUG

Description, Storage, Randomization, Administration and Discontinuation

Study Drug: Description

MVI 200

Comprised of three components

- Hydrogel polymer base
- 200 mcg **reservoir dose** of misoprostol
- Inert woven polyester retrieval tape in which the polymer is contained

Sustained release of misoprostol for up to 24 hours

- **Released at a controlled rate** (approximately 8 mcg/hr)

Half-life approximately 30-45 minutes

DVI

Comprised of three components

- Hydrogel polymer base
- 10 mg reservoir dose of dinoprostone
- Inert woven polyester retrieval tape in which the polymer is contained

Sustained release of misoprostol for up to 24 hours

- Released at a controlled rate (approximately 0.3 mg/hr)

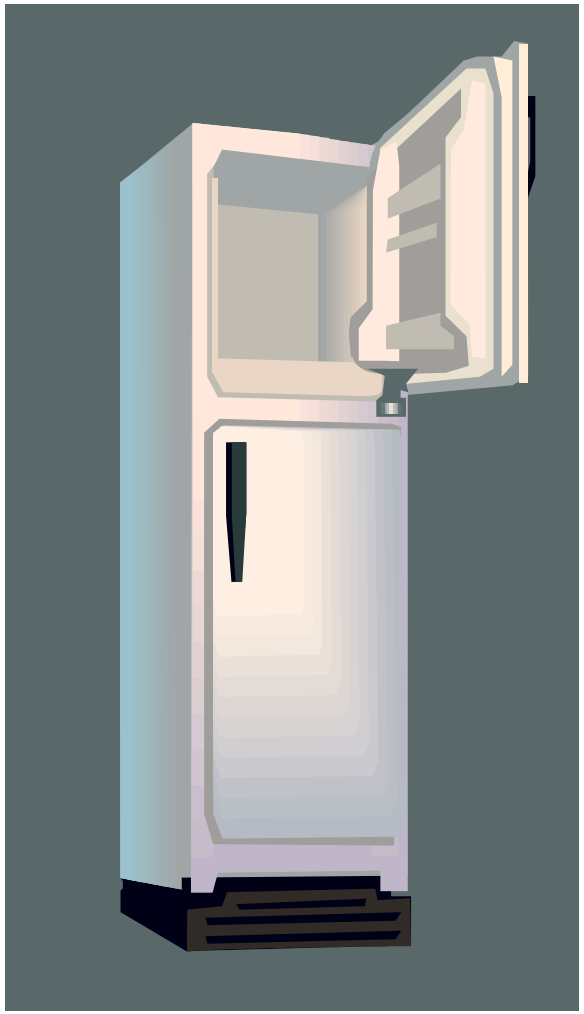
Labeled in US for 12 hours treatment/ EU for 24 hours

- FDA agreed to 24 hour dosing for this study

Study Drug: Description

Study Drug: Storage

- Frozen storage required (-20°C to -10°C)
- May be removed and returned to freezer multiple times
  - Total time outside freezer cannot be >24 hours
  - Document removal/ return times

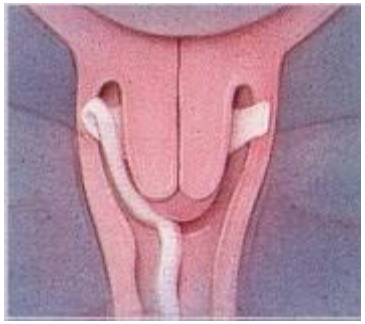


Study Drug: Randomization

- Inform pharmacy of qualifying study patient and parity
  - Pharmacy takes next Subject ID sachet in **sequential order**
    - **Nulliparous** inserts: ID number begin with "**1**####"
    - **Parous** inserts: ID number will begin with "**2**####"
  - **Correct numerical order maintains randomization**
  - No need to let drug thaw
  - Room temp transport from Pharmacy to L&D acceptable

Study Drug: Administration

- Insert study drug
  - Place high into the posterior vaginal fornix
    - Minimal amount of water-soluble lubricant allowed
  - Turn 90° so it lies transversely
  - Subject should remain in bed for 30 minutes following insertion to allow insert to swell



DOCUMENT the date and time of insertion, save duplicate study drug label

Events Requiring Study Drug Discontinuation

- Any Category II or III FHR Patterns
- Uterine Tachysystole with late decelerations, bradycardia or prolonged decelerations
- Tocolysis
- Intrapartum resuscitation (amnioinfusion or tocolysis)
- **Thick or fresh meconium** in amniotic fluid
- Antepartum hemorrhage
- Fetal acidosis (scalp pH<7.20)
- Uterine rupture

Study Drug Removal Data Capture

STUDY DRUG REMOVAL:	
Date & Time Study Drug removed:	_____ / _____ / 20___ ____: ____ Mon / dd / yyyy hh:mm
or	
Primary Reason for Study Drug Removal:	
____	Onset of Active Labor (progressive cervical dilatation to 4 cm with any frequency of contractions ***or*** rhythmic, firm, adequate quality uterine contractions causing progressive cervical change occurring at a frequency of 3 or more in 10 minutes and lasting 45 seconds or more)
____	Study drug in situ for 24 hours
____	Intrapartum Adverse Event (complete Intrapartum AE page)
____	Non-AE Category II FHR
____	Non-AE Uterine Tachysytole
____	Study drug fell out
____	Maternal request
____	OTHER (specify): _____

These would fall under "**investigator's judgment**", however, we want to track how many times investigators remove study drug based on these specific reasons.

Schedule of Events

TREATMENT PERIOD

Treatment Period: Throughout Treatment

- **Continuous EFM/CTG Monitoring**
- **Vaginal exams to obtain modified Bishop Score**
  - 6, **12**, 18 and 24 hours after study drug insertion if delivery has not occurred
    - Required even if insert removed, subject is in active labor and/or CS planned
  - Reposition study drug at each assessment (in posterior vaginal fornix)
- **DOCUMENT all five elements: Station, Dilatation, Effacement…**

REMEMBER

- **CONSISTENCY** (Firm; Average; Soft)
- **POSITION** (Posterior; Mid, Anterior)

Throughout Treatment (continued)

- Date, time and method of rupture of membranes

Date and time of onset of active labor

At Study Drug Removal:

Date, time and REASON for study drug removal

- If study drug fell out and exact date and time unknown, record date and time the insert was discovered to have fallen out.

Oxytocin use

- **Permitted after removal of study drug**
- **Must wait at least 30 minutes after study drug removal**
- Recommend low-dose protocol
- If study drug insert removed for active labor, carefully assess need for oxytocin

Treatment Period (continued)

At/After Delivery:

- Mode of delivery
- Date and time of delivery
  - Neonatal weight in grams
- Apgar score at 1 and 5 minutes after delivery
- Date and time of subject's (mother) discharge from L&D unit
  - First induction attempt only