

IMPROVE STUDY

Induction with Misoprostol: Oral Mucosa versus Vaginal Epithelium

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NCT clinicaltrials.gov number: NCT 02408315

FDA PIND#: [REDACTED]

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List of Abbreviations

ACOG American Congress of Obstetrics and Gynecology

CRF Case Report Form

DSMB Data Safety Monitoring Board

FDA U. S. Food and Drug Administration

GCP Good Clinical Practice

ICH International Conference on Harmonisation

IOL Induction of Labor

IRB Institutional Review Board

PK Pharmacokinetic

PD Pharmacodynamic

Background

[REDACTED]

[REDACTED]

[REDACTED]

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Rationale and Specific Aims

The primary objective of this proposal is to compare the efficacy and safety of vaginal and buccal misoprostol for women undergoing labor induction at greater than or equal to 37 +0 completed weeks gestation. The secondary objective of this proposal is to assess the PK parameters with these two routes of administration in a subcohort of this trial. The long-term objective of this line of research is to inform providers' clinical decision making for the large number of women having labor induction. By providing robust PK and PD clinical outcomes data for these two routes of administration, clinicians will be informed for evidence-based decisions.

The 3 Specific Aims of this trial are:

1. To compare the efficacy and safety of 25 mcg of misoprostol initially followed by 50mcg thereafter administered by either buccal or vaginal route in a placebo-controlled, double blind RCT. We will recruit women at term undergoing labor induction to accomplish this trial.
2. To compare the PK parameters of 25 mcg and 50 mcg of misoprostol administered by either buccal or vaginal routes. Further, we will analyze the clinical outcomes in Aim 1 based on the PK parameters, controlling for patient characteristics, to assess the impact of PK parameters on clinical success of this drug. In this way, we hope to comment on the strategic dose and individualized dosing model potential for labor induction with misoprostol.

3. To compare the trial participant satisfaction with each route of administration to improve patient-based outcomes. This will be done by administering a satisfaction survey at the end of the trial. As participants will have study drug placed both buccally and vaginally, they will be uniquely able to comment on comfort and preference for route of delivery.

Population and Study procedure

[REDACTED]

Inclusion/Exclusion Criteria

The following are inclusion criteria for the IMPROVE study.

Inclusion Criteria:

- A medical indication for induction of labor at a gestational age between 37 ^{0/7} and 38 ^{6/7} weeks OR an elective or medical indication for induction of labor at a gestational age \geq 39 ^{0/7} completed weeks
- Participant age \geq 14 years old
- Singleton pregnancy
- Modified Bishop score \leq 6
- Vertex fetal presentation by examination or ultrasound
- Any membrane status

Exclusion Criteria:

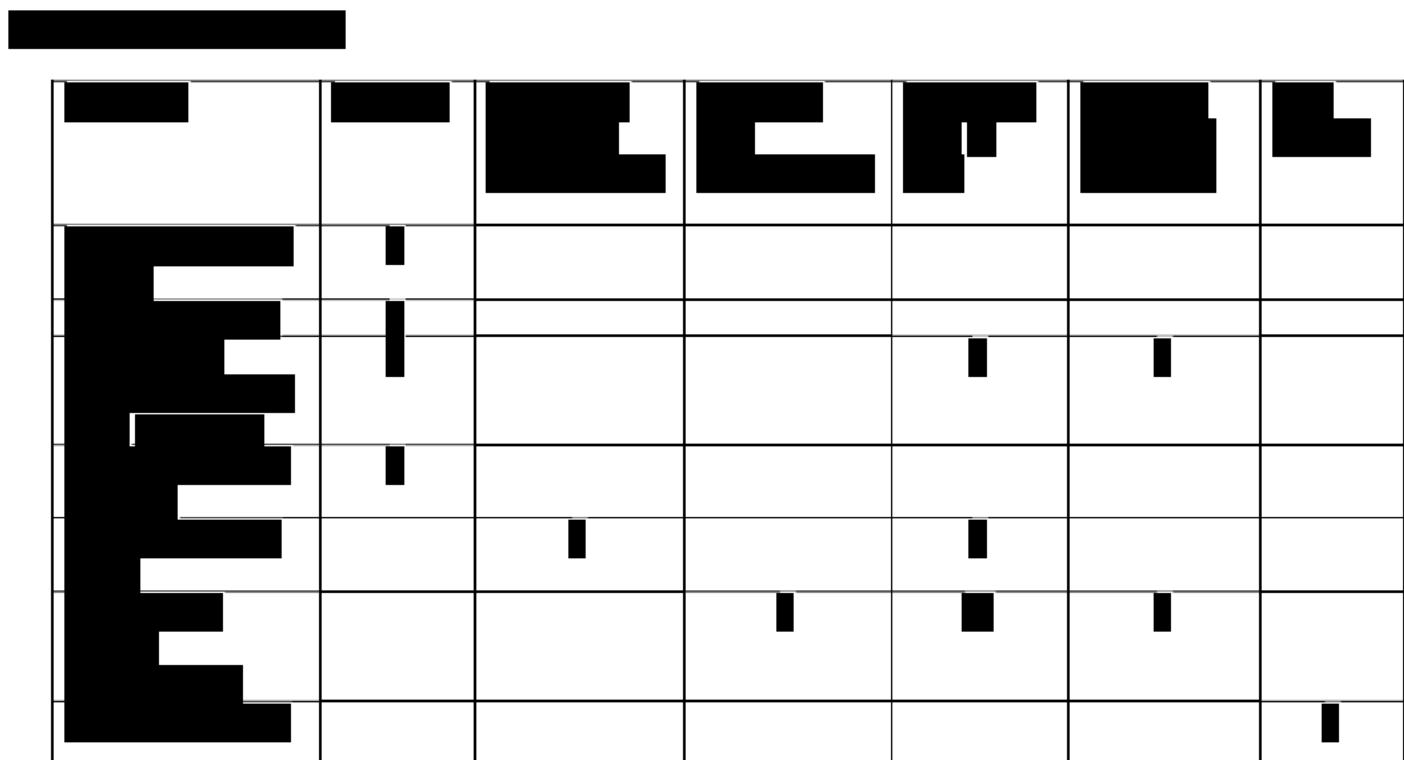
- Elective inductions between 37 0/7 and 38 6/7 are specifically excluded
- Known intrauterine fetal demise
- Any uterine scar including prior cesarean section and myomectomy
- Known major fetal congenital malformations that may impact neonatal health
- Other evidence of fetal compromise (such as Category 2 or 3 tracing) before the induction begins
- Prior induction/cervical ripening methods utilized during this pregnancy
- Allergy to misoprostol
- Known untreated cervical infection (e.g. Gonorrhea, Chlamydia)
- Planned cesarean section due to maternal or fetal condition
- Any other contraindication to labor induction or misoprostol therapy

Enrollment/Randomization and study drug procedures

[REDACTED]







[REDACTED]

[REDACTED]

[REDACTED]

Outcomes

Primary outcomes

Efficacy: Time to delivery- placement of drug to delivery.

Safety: Cesarean delivery for fetal non-reassurance indication

Secondary Outcomes

Efficacy

Vaginal delivery within 24 hours of induction starting

Number of doses needed of Misoprostol

Maximum/total dose of oxytocin utilized for uterine stimulation

Other drugs used for cervical ripening or induction of labor after beginning the study drug

Participant satisfaction

Induction to active labor time (as defined by reaching at least 6 cm per new guidelines)

Safety

Uterine tachysystole and hyperstimulation

Uterine rupture

Maternal or fetal death

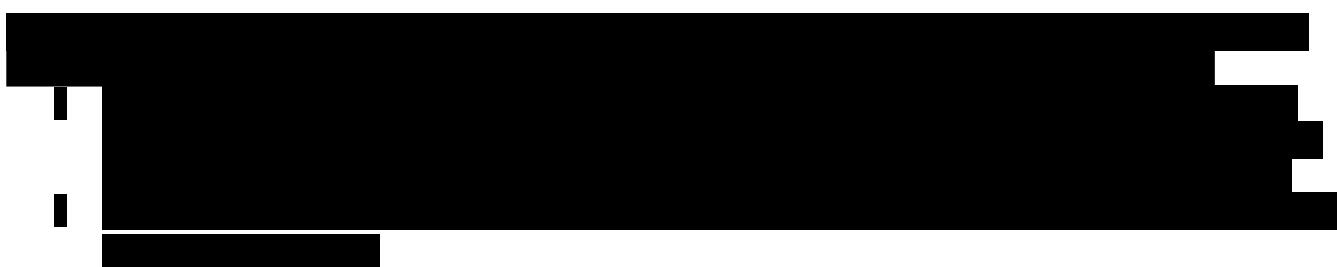
NICU admission and total maternal and newborn hospital days

Assisted vaginal delivery

Neonatal cord blood gases, Apgar score, birth weight

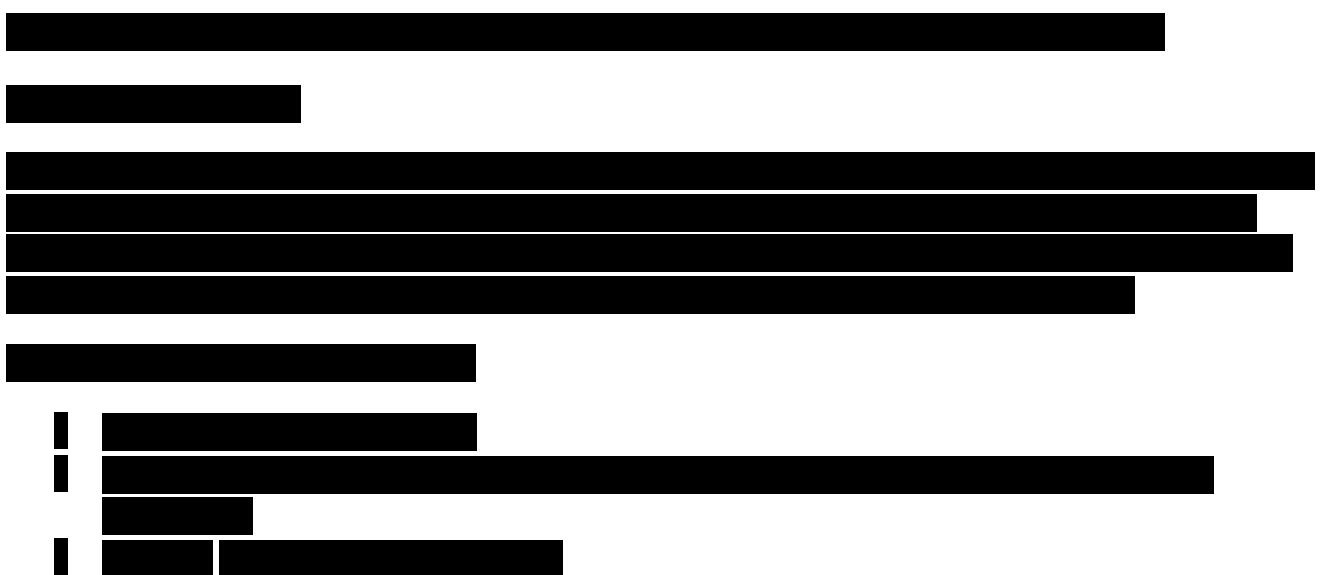
Chorioamnionitis

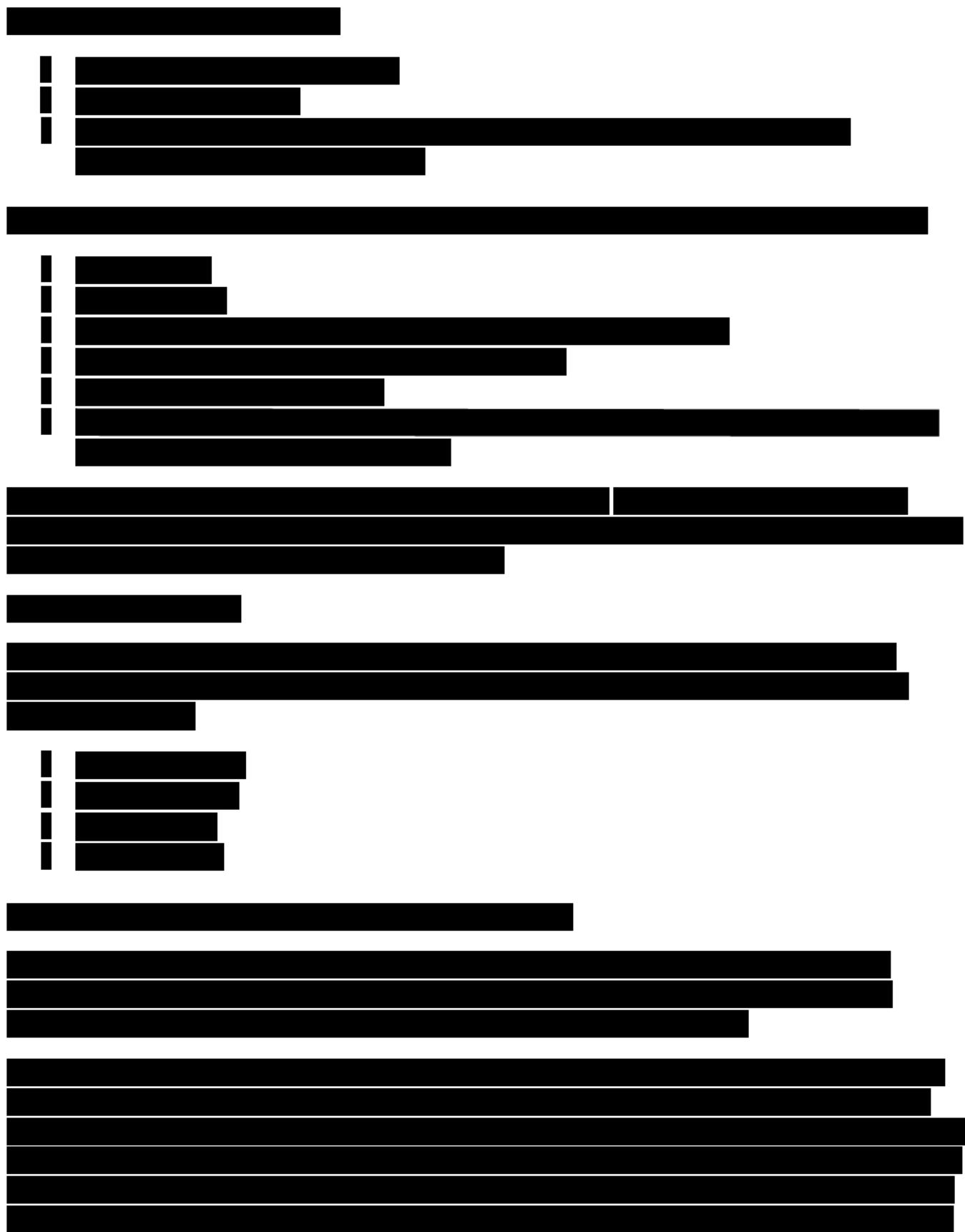
Data Collection



Participant Satisfaction

- Redacted list item





A 4x4 grid of 16 black bars of varying lengths and positions. The bars are arranged as follows:

- Row 1: 4 bars, all at the top of the grid.
- Row 2: 2 bars, both at the top of the grid.
- Row 3: 2 bars, one in the middle-left and one at the top-right.
- Row 4: 4 bars, one in the middle-left, one in the middle-right, one at the bottom-left, and one at the bottom-right.

Statistical Considerations

In our preliminary retrospective analysis of our institutional data over the last 1-2 years, there was just over a 4 hour difference in the time to delivery between the routes of administration. This was confirmed using a survival estimate for the two groups, with buccal misoprostol having a median time to delivery of 16.95 hours and vaginal 12.78 hours. In order to demonstrate a significant difference in a non-inferiority test of two survival curves with a limit of 4.5 hours, we will need 143 women in each group (see table below). We will recruit 300 women total to accommodate up to 5% withdrawals. We do not anticipate loss to follow-up as once women begin an induction, it is extremely rare that induction is terminated. Women remain admitted to labor and delivery until they are discharged after delivery.

Non-inferiority test for two exponential survival curves (Nquery), 80% power at a .05 significance level:

Limit	4 hours	4.25 hours	4.5 hours	5 hours
Maximum follow-up	60 hours	60 hours	60 hours	60 hours
Denominator lambda	.0409	.0409	.0409	.0409
Median survival (buccal)	16.95	16.95	16.95	16.95
Median survival (vaginal)	12.95	12.7	12.45	11.95
Non-inferiority limit on hazard ratio	1.309	1.335	1.361	1.418
N per group	187	163	143	111
Total number of events (vaginal births required)	341	296	260	203
N per group if Null hypothesis is true	183	158	139	108

We plan to analyze the primary outcome using survival curve analysis due to the possibility of cesarean delivery truncating the time to delivery. All outcomes will be compared using an intent-to-treat methodology. Discrete outcomes will be compared using chi-square testing and continuous variables will use appropriate parametric and nonparametric tests.

PK analysis will follow standard techniques for comparison of standard parameters and will be fitted to the most appropriate compartmental model. Our investigator team has the expertise to perform these analyses and has a large body of experience with pregnancy pharmacology studies.

Privacy/Confidentiality Issues

[REDACTED]

Follow-up and Record Retention

[REDACTED]

Appendix A: Administration of Study Drug and Placebo

[REDACTED]

[REDACTED]

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